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Diagnostics, Risk Factors, Treatment and Outcomes of Acute Kidney Injury in a New Paradigm

Edited by
Wisit Cheungpasitporn, Charat Thongprayoon and Wisit Kaewput

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About the Special Issue Editors

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Editorial

Diagnostics, Risk Factors, Treatment and Outcomes of Acute Kidney Injury in a New Paradigm

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Abstract: Acute kidney injury (AKI) is a common clinical condition among patients admitted in the hospitals. The condition is associated with both increased short-term and long-term mortality. With the development of a standardized definition for AKI and the acknowledgment of the impact of AKI on patient outcomes, there has been increased recognition of AKI. Two advances from past decades, the usage of computer decision support and the discovery of AKI biomarkers, have the ability to advance the diagnostic method to and further management of AKI. The increasingly widespread use of electronic health records across hospitals has substantially increased the amount of data available to investigators and has shown promise in advancing AKI research. In addition, progress in the finding and validation of different forms of biomarkers of AKI within diversified clinical environments and has provided information and insight on testing, etiology and further prognosis of AKI, leading to future of precision and personalized approach to AKI management. In this this article, we discussed the changing paradigms in AKI: From mechanisms to diagnostics, risk factors, and management of AKI.

Keywords: acute kidney injury; acute renal failure; biomarkers; critical care; renal replacement therapy; risk factors outcomes; predictors

1. Introduction

Acute kidney injury (AKI) is a highly complicated clinical disorder that is widely characterized by rapid rate of reduced rate of glomerular filtration (GFR), demonstrated by a rise in serum creatinine (SCr) concentration or oliguria, or both [1–5]. AKI is common among hospitalized patients, affecting approximately 10%–20% of hospitalized patients, of whom 10% require renal replacement therapy (RRT) [6–11]. Among critically ill patients, the incidence of AKI has been reported as high as 45–50% [2,12]. AKI is associated with significant morbidity, mortality, extra cost incurred in the

hospitalization process, longer stay in the hospital, and long-term consequences, including chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [13–16]. In the United States, AKI is associated with high hospitalization costs that range from $5.4 to $24.0 billion [17]. Overall mortality rate at 30 days post AKI is as high as 24% [18]. Each year, around 1.7 million people are globally thought to die from AKI [19].

In the recent years, there has been significant progress in the discovery and validation of AKI biomarkers in a number of clinical settings and has provided information and insight on diagnosis, prognosis as well as etiology of AKI [20]. Furthermore, the increasingly widespread use of electronic health records (EHR) across hospitals has substantially increased the amount of data available to investigators and has shown promise in advancing AKI research [21,22]. In this this article, we discussed the changing paradigms in AKI: from mechanisms to diagnostics, risk factors, and management of AKI.

2. Definition of AKI, Persistent AKI, and Renal Recovery after AKI

2.1. Definition of AKI

In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) [23] gave out guidelines on the management of AKI to make the diagnosis process of the condition standardized and the severity of the disease based on absolute or relative increases in SCr and further progressive extent of oliguria, which built off of the RIFLE criteria [24] and the AKIN criteria [25], Table 1. KDIGO describe AKI as a condition that comprise of one or more of the following: (1) an increase in SCr level ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h, or (2) an increase in SCr level to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, or (3) a urine volume of less than <0.5 mL/kg/h for 6 h or longer.

Table 1. KDIGO criterion for diagnosis and staging of AKI [23].

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR 0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL OR initiation of replacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

2.2. Baseline SCr, Adjust SCr for Fluid Balance, and Body Weights for Urine Output Criterion

Establishing the baseline SCr is very much important in AKI diagnosis and classification [26,27]. Inaccurate determination of the baselines SCr can lead into misclassification of AKI and additionally impact the overall prognostication of the outcomes associated to AKI [28]. SCr at the outpatient is actually a very vigorous assessment of the renal function. The process is so robust such that it is more effective at the outpatient compared to the inpatients. This is mainly because it usually represents a kind of steady state and is not altered by the index critical condition of the illness [29]. When several preadmission SCr measurements are available, the use of minimum value of the preadmission SCr as the baseline SCr can detect more AKI cases, but also provides the better predictive ability for sixty day mortality [26] (Figure 1).

In clinical practice, it is very common that baseline outpatient SCr is unavailable [30]. While the Acute Dialysis Quality Initiative (ADQI) has recommended backward estimation of baseline SCr by applying the Modification of Diet in Renal Disease (MDRD) formula, making the assumption of an estimated GFR value of 75 mL/min/1.73 m^2 (SCrGFR-75) for patients with no available baseline SCr [24], the European Renal Best Practice (ERBP) proposes the usage of the initial documented SCr value on hospital admission (SCrADM) as the baseline SCr when baseline outpatient SCr values are not available [31].

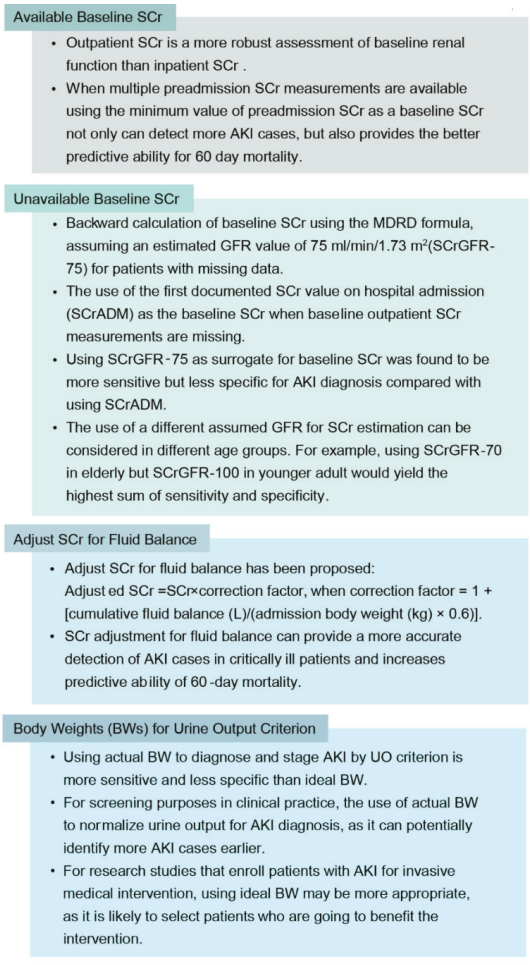

Figure 1. Baseline SCr, Adjust SCr for Fluid Balance, and Body Weights for Urine Output Criterion.

The types of strategies have their own shortcomings [24,31]. While backward calculation can lead to misclassification of AKI, especially in the early stages [32], the use of SCrADM as the baseline SCr can be inaccurate in patients who might be suffering from community-acquired AKI, as the SCr might had already escalated before the time of hospitalization [30,33]. In addition, using SCrGFR-75 as surrogate for baseline SCr was established to be more sensitive but less specific for AKI diagnosis compared with the use of SCrADM [30].

In clinical practice, prevention of AKI and subsequent timely treatment may improve the outcomes of the patient with AKI. Therefore, for the stratification risk purposes within the clinical undertakings, we highly encourage the application of SCrGFR-75 for the diagnosis of AKI, as it has the ability to properly identify more AKI cases. On the other hand, using SCrADM may be suitable for research studies, as it would be more likely to enroll patients who are going to benefit from the intervention [30]. Furthermore, since GFR decreases with age, the use of SCrGFR-75 might result in over-AKI classification in the elderly [34], therefore use of a different assumed GFR for SCr estimation could be considered in different age groups. For instance, applying SCrGFR-70 among the elderly and SCrGFR-100 for the younger adult would generate high amount of sensitivity together with specificity [30,34].

Among perioperative and intensive care unit (ICU) settings, volume overload is very common. It can cause the dilution and masking SCr increments, which may result in a delay in AKI diagnosis in critically ill patients [35]. Adjust SCr for fluid balance has been proposed with the following formula: adjusted SCr = SCr × correction factor, when correction factor = 1 + [cumulative fluid balance (L)/(admission body weight (kg) × 0.6)] [35–37]. SCr adjustment for fluid balance can provide a more accurate detection of AKI cases in critically ill patients and increases predictive ability of sixty day mortality [35].

Given the definition of AKI is currently based on absolute or relative changes in SCr and weight-adjusted hourly urine output [23], body weight (BW) is an essential factor and used when normalizing the UO for weight and time. Using actual BW to diagnose and stage AKI by UO criterion is more sensitive and less specific than ideal BW [38]. Thus, the choice of using ABW or IBW for AKI diagnosis and classification depends on the purpose of the AKI definition. In clinical practice, AKI prevention and early treatment of AKI may help improve patient outcomes. Therefore, for screening purposes in clinical practice, we suggest the use of ABW to normalize UO for AKI diagnosis, as it can potentially identify more patients with AKI earlier. Conversely, for research studies, using IBW may be more appropriate, as it is likely to select patients who are going to benefit the treatment [38].

2.3. Persistent AKI and Renal Recovery after AKI

Recently, the term "persistent AKI (pAKI)" has been proposed and is described as AKI diagnosis together with an increase in SCr that persisted through hospital discharge [39–45]. pAKI could be highly relevant endpoint for some additional further studies in the future [39]. As AKI which resolve very rapidly still has worse outcomes when compared to the patients who are not suffering from AKI, the overall outcome of transient AKI had been reported to be significantly better when comparison is made to pAKI [39–45]. pAKI is closely linked with more severe outcomes among patients when comparison is made to transient AKI, such as development of progressive CKD, increased mortality among those hospitalized, and reduced long-term survival [39–45].

The effects of renal recovery following AKI condition on the outcomes have recently been described [39,46,47], when complete renal recovery is defined as no AKI at patient discharge (comparing the SCr at discharge to the SCr at baseline). On the other hand, partial renal recovery is defined as AKI that is not complete renal recovery, and without the need for renal replacement therapy at discharge. No renal recovery is defined as a need for renal replacement therapy at discharge [39,46,47].

The Acute Disease Quality Initiative 16 Workgroup recently published a consensus report that placed more emphasis on the importance of renal recovery following AKI [46]. Recovery of renal function after AKI has been shown to be an independent determinant of morbidity and mortality in patients who are hospitalized, including those who are within ICU, or those who had undergone a process of cardiac surgery [40,48–50].

3. Causes and Diagnosis of AKI

The main causes of AKI are divided into three categories: Prerenal, intrinsic renal and postrenal (Figure 2).

AKI can have many different causes as shown in Figure 2, such as decreased kidney perfusion, parenchymal kidney diseases, acute tubular necrosis (ATN), and obstruction of the urinary tract. Articles on detailed specific causes of AKI have been published in our current special issue "Diagnostics, Risk Factors, Treatment and Outcomes of Acute Kidney Injury in a New Paradigm" (https://www.mdpi.com/journal/jcm/special_issues/acute_kidney_injury) [3,51–88]. Reported incidence of AKI is different among different patient populations as shown in Table 2.

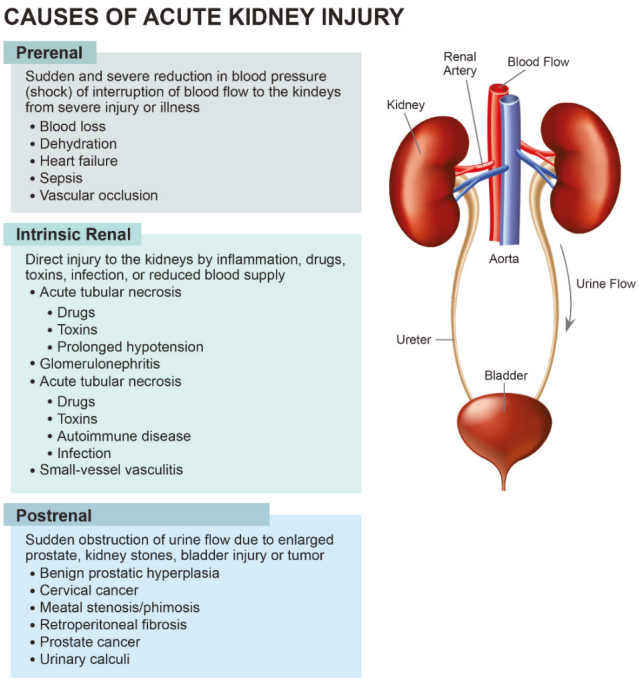

Figure 2. Causes of AKI.

Table 2. Reported incidence of AKI is different among different patient populations [6–11,59,65,70,72,89–104].

Patient Populations/Settings	Incidence of AKI
- General hospitalized patients	10%–20%
- ICU	20%–50%
- Cardiac surgery	30%–50%
- Transcatheter Aortic Valve Replacement	28%
- Sepsis	16%–25%
- Acute respiratory distress syndrome	44%–50%
- Extracorporeal Membrane Oxygenation	
o AKI	63%
o Severe AKI requiring RRT	45%
- Liver transplantation	
o AKI	41%
o Severe AKI requiring RRT	8%
- Lung transplantation	53%
o AKI	9%
o Severe AKI requiring RRT	
- Cardiac Transplantation	47%
o AKI	12%
o Severe AKI requiring RRT	
- Hematopoietic Stem Cell Transplantation	55%
o AKI	8%
o Severe AKI requiring RRT	
- Total Hip Arthroplasty	6%
o AKI	0.5%
- Severe AKI requiring RRT	

AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy.

In patients with AKI from some other causes, urinalysis, dipstick, sediment, albuminuria and total proteinuria; and the presence or absence of hematuria, pyuria, renal tubular epithelial cells, and granular and cellular casts, chemistries, and serologic evaluation can be helpful in identifying the cause of AKI, as shown in Table 3. Imaging studies are usually performed to evaluate the presence of hydronephrosis, defined as dilatation of the renal collecting system due to obstruction [1].

Table 3. Diagnostic tests in patients with AKI [1,105,106].

Diagnostic Test	Findings	Pathologic Condition (s)
Urinalysis with microscopy	Hyaline cast	Prerenal azotemia
	Muddy brown cast	ATN
	Dysmorphic RBC & RBC casts	GN
	WBC casts	AIN
	Crystals	Crystal induced nephropathy, drugs, nephrolithiasis
	Monomorphic RBCs, WBCs	UTI, Nephrolithiasis, Genitourinary tumors etc
	Protein	GN, Monoclonal gammopathy
CBC with peripheral smear	Anemia, Schistocytes, low platelets	TMA
Serum osmolality	Osmolar gap & severe metabolic acidosis	Toxin
Creatinine kinase	>5000 IU/L	Rhabdomyolysis
Serologic tests	HIV antibody	HIV associated nephropathy, HIV induced immunocomplex kidney disease
	Hepatitis serology	Membranous GN, MPGN
	ANA, dsDNA	Lupus nephritis
	C- ANCA, P- ANCA	ANCA vasculitis
	Rheumatoid factor, Cryoglobulins	Cryoglobulinemia, MPGN
	Anti—GBM antibody	Good pasture syndrome
	ASO	Infection related GN
	Low Complement levels	Lupus, Infection related GN, atheroemboli, MPGN, shunt nephritis
Fractional excretion of sodium (FeNa) *	<1%	Prerenal azotemia
Fractional Excretion of urea (Fe Urea)	<35%	Prerenal azotemia
POCUS (Volume Assessment)	IVC diameter ↓ (>50% w/inspiration)	Hypovolemia
Renal USG	Hydronephrosis, Hydroureter	Nephrolithiasis, Retroperitoneal fibrosis, BPH, Phimosis, Ureteral obstruction
	Renal vein thrombosis	Hypercoagulable state
Renal biopsy	Variable	GN, ATN, AIN, crystal induced nephropathy
Newer biomarkers	↑ NGAL, KIM 1, (TIMP-2)·(IGFBP7) **	"Damage biomarkers" increased much before rise in creatinine

ATN: Acute tubular necrosis, GN- Glomerulonephritis, AIN: Acute interstitial nephritis, UTI: Urinary tract infection, ANA: Antinuclear antibody, ANCA: Antinuclear cytoplasmic antibody, GBM: Glomerular basement membrane, MPGN: Membranoproliferative glomerulonephritis, ASO: Anti Streptolysin, POCUS: Point of care ultrasound, IVC: Inferior vena cava, NGAL: neutrophil gelatinase–associated lipocalin, KIM-1: Kidney injury molecule -1, TIMP 2-Tissue inhibitor of metalloproteinases-2, IGFBP7: Insulin like growth factor-binding protein 7. Notes: UA dipstick ++ for blood but no RBCs - Suspect rhabdomyolysis. If urine protein creatinine ratio quite elevated but urine dipstick with low grade proteinuria - Suspect multiple myeloma. BUN out of proportion to Cr - Suspect GI bleeding, high dose steroids, high protein feeding. Urine eosinophils have low sensitivity (30.8%) and specificity (68.2%) for AIN[1] so not diagnostic of AIN. * FeNa is affected in CKD, diuretics, contrast administration, acute GN and Rhabdomyolysis so is not quite reliable in cause of AKI diagnosis. ** FDA approved in 2014.

Furosemide "stress test" (administration of 1 mg/kg of IV furosemide with 1:1 replacement of urine output with saline) can be used to assess prognosis: Patients with <200 mL of urine output over the subsequent 2 h are at greater risk for progression to a higher AKI stage or to the need for RRT [107,108].

4. Biomarkers of Acute Kidney Injury (AKI)

SCr level does not detect AKI promptly and increased SCr and oliguria may not occur for several hours after the onset of an acute decline in GFR [1]. In addition, the rise in SCr (and decrease in estimated GFR) may be delayed in patients with low muscle mass or volume overload and faster in those with high muscle mass or volume depletion [1,109].

Within the last few years, the discovery and further validation of the special biomarkers of the kidney injury has attracted great attention [110]. Several biomarkers like Cystatin C and further neutrophil gelatinase-associated lipocalin have consequently been recommended for the purpose of diagnosis, severity grouping and more essential, the modification in the AKI outcome [1]. Novel biomarkers are under investigation to determine whether they may enable earlier detection of decreased GFR and complications of AKI [3,111], as shown in Table 4.

Table 4. Characteristics of selected novel biomarkers for acute kidney injury [112–127].

Novel Biomarkers	Specimen	Type	Representation	Study Population
NGAL	Serum, urine	Upregulated protein	Distal tubules	Cardiac surgery, Critically ill, CRS, KT
KIM-1	Urine	Upregulated protein	Proximal tubules	Cardiac surgery, KT
L-FABP	Urine	Upregulated protein	Proximal tubules	Cardiac surgery, Critically ill
IL-10	Urine	Cytokine	Inflammatory cascades	Cardiac surgery
IL-18	Urine	Cytokine	Inflammatory cascades	Cardiac surgery, Critically ill, KT
Urine Cystatin C	Serum, urine	Functional	Proximal tubules (urine), glomerular (serum)	Critically ill
NAG	Urine	Enzyme	Proximal tubules	Critically ill, KT
IGFBP7	Urine	Upregulated protein	Proximal tubules	Critically ill, cardiac surgery
TIMP-2	Urine	Upregulated protein	Proximal tubules	Critically ill, cardiac surgery
Calprotectin	Urine	Upregulated protein	Renal inflammation	Hospitalized patients
AGT	Urine	Enzyme	Renin-angiotensin activation	Heart failure
microRNA	Urine	RNA fragment	Proximal and distal tubules	Cardiac surgery

AGT, angiotensinogen; CRS, cardiorenal syndrome; IGFBP, insulin-like growth factor-bind protein 7; IL, interleukin; KIM-1, Kidney injury molecule-1; KT, kidney transplantation; L-FABP, liver fatty acid; LMWP, low-molecular weight protein; NAG, N-acetyl-b-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinase 2.

5. Risk Factors

While diabetics with baseline CKD represent the highest risk patient population for AKI development [128], overall reported risk factors for AKI from the literature include older age, history of diabetes, hypertension, congestive heart failure, peripheral vascular disease, sepsis, use of nephrotoxic drugs, higher severity of disease scores, use of vasopressors/inotropes, high risk surgery, emergency surgery, hemodynamic instability, use of intra-aortic balloon pump, anemia requiring blood transfusion, and longer time in cardiopulmonary bypass pump [129–132], Table 5.

Table 5. Risk factors for AKI [129–132].

Modifiable	Non-Modifiable
• Anemia/Blood transfusion	• Chronic kidney disease
• Hypertension	• Chronic liver disease
• Hypercholesterolemia	• Congestive heart failure
• Hypoalbuminemia	• Diabetes mellitus
• Infection/Sepsis	• Older age
• Mechanical ventilator	• Peripheral vascular disease
• Nephrotoxic agents	
• Use of vasopressors/inotropes	
• High risk surgery	
• Emergency surgery	
• Hemodynamic instability	
• Use of intra-aortic balloon pump	
• Longer time in cardiopulmonary bypass pump	

6. Outcomes and Mortality Risk among Patients with AKI

AKI is associated with significant morbidity and mortality [13–15]. Patients with AKI who fail to recover their renal function, have been reported to be having 47% hospital mortality. In addition, among those who are discharged from the hospital alive, 1-year patient survival is only 77% [47]. Mortality risk among patients with AKI in different patient populations are demonstrated in Table 6. In addition to increased mortality, AKI is also associated with an increased risk of cardiovascular mortality and major cardiovascular events, particularly heart failure and acute myocardial infarction [133].

Table 6. Mortality outcomes of acute kidney injury in different patients' population from selected studies [59,70,90,92,134–150].

Patient Populations	Odds Ratio (95% CI) for Mortality
Acute coronary syndrome	4.1 (3.3–5.0)
Cardiac surgery	6.27 (3.6–11.0)
TAVR	18.0 (6.3–52.0)
ECMO	3.7 (2.9–4.9)
Liver transplantation	3.0 (2.3–3.8)
Cirrhosis	2.6 (1.5–4.7)
Lung transplantation	1.5 (1.1–1.9)
Stem cell transplantation	3.0 (2.1–4.5)
Heart transplantation	2.7 (1.6–3.3)
Critically ill patients	1.4 to 2.5
Rhabdomyolysis	3.3 (1.1–9.7)
Cardiorenal syndrome	4.9 (3.7–6.5)
Burn patients	11.3 (7.3–17.4)
Ischemic stroke	2.5 (1.5–4.1)
Cancer	3.0 (2.3–3.9)
COPD	1.8 (1.6–2.0)
Malnutrition	2.0 (1.5–2.7)
Gastrointestinal bleeding	2.6 to 4.9

COPD, chronic obstructive pulmonary disease; ECMO, extra-corporal membrane oxygenation; NSAID, non-steroidal anti-inflammatory disease; TAVR, transcatheter aortic valve.

Irrespective of cause, the severity of AKI is related to the risk for complications [1]. Complications of AKI result from impaired excretory, endocrine, and metabolic kidney functions. Decreased GFR and tubular function lead to retained water and solutes, manifested by volume overload, hyperkalemia, high an- ion gap metabolic acidosis, hyponatremia, hyperphosphatemia, hypermagnesemia, encephalopathy, pericarditis, pruritus, and bleeding due to platelet dysfunction [1]. Drug toxicity is common because of

altered pharmacokinetics and pharmacodynamics. Complications may occur in other organ systems throughout the course of disease; multiple organ failure is associated with the highest mortality. Such form of injuries are mainly recorded in close to 20% of the patients who have been hospitalized, with the great complications recorded to comprise of drug toxicity, uremic complications, disorders of the electrolyte and subsequently volume overload. Incomplete recovery may lead to new onset or worsening of CKD [1].

7. AKI Prevention and Management of AKI

7.1. AKI Prevention

Since severe AKI is associated with a high mortality rate and there are currently no effective targeted pharmacotherapies available for AKI, all the relevant measures that are undertaken for the purpose of preventing AKI (Table 7).

Table 7. AKI prevention measures.

General Measures	
Identify patients at risk	- Personal risks: older age, history of CKD, diabetes, dementia, coronary artery disease. - Related to clinical scenario: reason for admission, severity of illness, ICU stay, and recurrent hospitalizations.
Use of Clinical decision support systems (CDSS)	- Electronic-based alert systems in the hospitals have shown to improve the detection of AKI.
Maintain euvolemia	- Use intravenous fluids if hypovolemia is anticipated in clinical settings such as poor oral intake, vomiting, diarrhea, polyuria, etc. - Avoid starches for volume resuscitation - Avoid volume overload by discontinuing fluids when appropriate.
Avoid nephrotoxic medications.	- Discontinue medications such as NSAIDs - Avoid ACE/ARB inhibitors (controversial) which affect the hemodynamics of the kidneys. - Avoid nephrotoxic antibiotics such as aminoglycosides, amphotericin and vancomycin. If their use is necessary, monitor levels if appropriate. - Utilize minimal dose and for the shortest time possible.
Judicious use of contrasted studies	- Outweigh risks vs. benefits of contrasted studies. Intra-arterial pose a higher risk than intravenous contrasted studies.
Avoid hypotension	- Decrease in renal blood flow is a known risk factor for AKI. It is therefore imperative to keep MAP >65 (target 65–70 mmHg), and a higher target (80–85 mmHg) in chronically hypertensive patients. - If vasopressors are too be used in the ICU, norepinephrine should be the first-choice to protect kidney function.
Renal function monitoring	- Monitor SCr as often as necessary, depending on the risk factors and clinical scenario. - Monitor fluid input and urinary output.
Specific Clinical Scenarios	
Patients undergoing a procedure needing IV contrast use	- Discontinue nephrotoxic medications - IV hydration with intravenous isotonic saline at a rate of 1 to 1.5 mL per kilogram per hour for 12 h before and up to 24 h after the procedure. A shorter protocol for patients undergoing urgent procedures comprises an intravenous infusion of isotonic saline for 1 to 3 h before and 6 h after the procedure. - Recent data does not support the use of IV bicarbonate or N-acetyl cysteine. - Utilize low-osmolar or iso-osmolar contrast media. - Minimize contrast volume (<350 mL or <4 mL per kilogram)
Traumatic and non-traumatic rhabdomyolysis	- Early and aggressive volume expansion with isotonic solutions aimed at increasing urine flow (about 200–300 mL/h). - Use of bicarbonate is not evidence based and might precipitate metastatic tissue calcification and ionized hypocalcemia - Use of diuretics is not generally recommended.

Table 7. *Cont.*

General Measures	
Patients undergoing cardiac surgery	Preoperative: - Perform pre-operative AKI stratification. - Delay elective surgeries if current AKI and delay 24–72 h after contrast use. - Discontinue ACE/ARB (controversial) - Discontinue NSAIDs. - Limited use of blood transfusions. - Correcting hypoalbuminemia with exogenous albumin preoperatively may play a role in preventing AKI. - Use of balanced crystalloid solutions guided by measures of fluid responsiveness. Intraoperative - Cold perfusion of the kidneys during aortic aneurysm repair - Avoidance of hyperthermia. - Pulsatile Cardiopulmonary bypass. - Avoidance of hemodilution. - Use of volatile anesthetics. - Minimization of aortic manipulation. - Techniques to prevent procedure-related atheroembolism. Postoperative - Low tidal volume strategy. - General measures mentioned above. - Glucose control (target 127–179 mg/dL).

AKI; acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; ACE, angiotensin converting enzyme; ARB, angiotensin-receptor blocker; MAP, mean arterial pressure; IV, intravenous.

Fluid composition has also been the subject of substantial investigation. The use of hydroxyethyl starch has been shown to result in increased rates of AKI especially in patients with sepsis [151,152], while on the other hand, saline has been demonstrated to increase the risks associated with dialysis, mortality and continuous renal dysfunction when compared to the fluids that are very similar to the relevant physiological ones like the Ringer's lactate solution [153,154].

General measures undertaken to limit the risk comprise of the prevention as well as the treatment of volume depletion and avoidance of nephrotoxic drugs [155]. IV isotonic fluids before, during, and after intra-arterial administration of iodinated radiocontrast media may reduce risk for contrast-induced AKI [98,156–158]. Monitoring therapeutic levels of nephrotoxic drugs, such as vancomycin, aminoglycosides, and calcineurin inhibitors, can reduce risk for AKI. KDIGO suggests additional measures to reduce the risk for nephrotoxicity of aminoglycosides and amphotericin B [1].

While the data on discontinuation of the continued angiotensin-converting enzyme inhibitors (ACEIs) as well as the angiotensin-receptor blockers (ARBs) during the period of acute illness to prevent AKI is controversial [159,160], some other nephrotoxic drugs need to be avoided especially among people who are suffering from CKD, such as nonsteroidal anti-inflammatory drugs (NSAIDs) [161]. Contrast-associated AKI is becoming less frequent because of reduced toxicity and lesser amounts of contrast media used for imaging techniques. However, prevention measures should still be considered for individual patients, especially in patients with CKD [2].

7.2. Management of AKI

The timely identification of the at risk patents, timely diagnosis and early treatment of all the AKI cases are essential part of the general management of individual patients who might be suffering from AKI. The initial principle of AKI management is specifically to treat its causative factor or trigger, such as treating infection in sepsis-associated AKI. The second principle of management and specific treatments according to the underlying cause of AKI syndromes such as hepatorenal syndrome, cardiorenal syndrome, glomerulonephritis, interstitial nephritis, vasculitis, and multiple myeloma, etc.. Currently, there are currently no effective pharmacotherapies for treating ATN. The specific treatments for these specific types of kidney injuries are not focus of this review. The third principle is based on ensuring that there is avoidance of any additional insults of AKI. There is need to optimize hemodynamics that are systemic based, so that even in the absence of some other triggers, additional damage is not

experienced and correct perfusion pressure and renal perfusion are adequately maintained. The fourth principle is to apply provide supportive care to prevent and treat complications.

RRT are a spectrum of dialysis modalities employed in management of renal dysfunction. They are broadly classified as continuous, intermittent and hybrid variants. Continuous renal replacement therapies (CRRT) are ideally used in hemodynamically unstable patients to allow steady solute and volume shifts. CRRT further categorized based on principles of clearances [162] to four types. Slow continuous ultra-filtration (SCUF) aims at filtration of plasma water in patients with refractory volume overload while no significant solute clearances are achieved. The other three modalities are continuous veno-venous hemofiltration (CVVH) (convection), continuous veno-venous hemodialysis (CVVHD) (diffusion) and continuous veno-venous hemodiafiltration (CVVHDF) (diffusion and convection) [163–166]. Peritoneal dialysis, a slow efficient continuous modality is an acceptable alternative to extra corporeal modalities [167]. Intermittent hemodialysis (iHD) is routinely prescribed for 3 to 4 h three times a week and supports rapid clearances of small molecules and toxic drugs [168]. Hybrid therapies include sustained low-efficiency dialysis (SLED), prolonged intermittent renal replacement therapy (PIRRT), extended daily dialysis with filtration (EDDf) and accelerated veno-venous hemofiltration (AVVH) [169]. Hybrid modalities tend to blend features of intermittent and continuous modalities with objectives to enhance hemodynamic stability while minimizing the disadvantages of continues modalities [170].

Even though CRRT has multiple potential advantages, no randomized control studies (RCT) have proven survival benefit of any specific modality [171,172]. In a metanalysis by Nash et al. including 21 studies comparing iHD, SLED and CRRT modalities failed to demonstrate mortality difference or superior renal recovery of one over other groups [173]. Friedrich et al. performed a systematic review involving 19 RCTS, compared outcomes among hemofiltration and hemodialysis in patients with AKI and were unsuccessful in achieving survival advantages of one therapy over other. However, hemofiltration group had a trend towards increased clearance of inflammatory molecules including cytokines [174].

Currently, recommended effluent CRRT dose for clinical practices is 20 to 25 mL/kg/h. Multiple studies were conducted comparing different doses. The prospective randomized study by Ronco et al. involving critically ill AKI patients comparing three different doses (20 mL/kg/h, 35 mL/kg/h and 45 mL/kg/h) reported inferior survival rates in in lower dose group (20 mL/kg/h) compared to higher (35 mL/kg/h and 45 mL/kg/h) [175]. However, the land mark RCTs, VA/NIH Acute Renal Failure Trial Network (ATN trial) [176] by Palevsky et al. (35 mL/kg/h vs. 20 mL/kg/h) and RENAL study by Bellamo et al. (40 mL/kg/h vs. 25 mL/kg/h) [177] were ineffective in decreasing mortality, or improving renal recovery at higher dose compared to lower. In a metanalysis by Clark et al, including 4 RCTs comparing high volume hemofiltration (>50 mL/kg/h) (HVHF) to standard volume hemofiltration (SVHF) among septic AKI patients did not demonstrate any difference in 28-day mortality. Even though vasopressor requirements were lower among HVHF group, they sustained significant adverse effects including hypokalemia, hypophosphatemia, metabolic alkalosis, excessive micronutrient loss [178].

Significant controversies exist regarding the timing of initiation of RRT and are still a topic of debate. HEROICS study, a prospective randomized multicenter trial including post-cardiac surgery septic shock patients compared early HVHF (80 mL/kg/h) to delayed CVVHDF with no difference in outcomes (30 day mortality) [179]. The Artificial Kidney Initiation In Kidney Injury (AKIKI) trial and Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL- ICU) trials are randomized multicenter studies involving critically ill AKI patients with KDIGO stage3 compared early (Immediately after randomization or within 12 h) vs. delayed initiation of RRT, (refractory to medical management or >48 h) were unsuccessful in demonstrating outcome benefits in early group as compared to delayed [180,181]. The Effect of Early vs. Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN) study did report a 15% reduction in 90-day mortality in early initiation group, however this study suffered serious criticism including single centered study with significant number of post cardiac surgical patients, RRT initiation

at KDIGO stage 2 and less than 24 h difference in initiation of RRT among both groups [182].The current evidence suggests no tremendous benefit of early initiation of RRT but is associated with complications. Therefore, the timing of initiation of RRT should be individualized based on judicious examination, disease acuity and medical necessity [183]. The two large ongoing multicenter RCTS, AKIKI-2 [184] and START- AKI [185] trials might further shed some light on Ideal timing of RRT.

8. Potential Directions and Future Scope

Two advances from past decades, the usage of the computer decision intelligence and the discovery of AKI biomarkers, have the great ability to generally improve the approach applied in diagnosis and further treatment of AKI. For instance, in the instance of AKI, electronic, the automated diagnostic strategy tend to create great opportunity to initiate predictive strategies, subsequently optimize the relevant AKI alerts, and subsequently trace AKI events across various associations, as well as the relevant managerial datasets [186]. In addition, dynamic and multidimensional approach to AKI, using AKI biomarkers over time, will be presented as a versatile theoretic construct usable to characterize and phenotype AKI itself, refining the precision of diagnosis and making possible the ability to track different aspects of the injury as they change over time, potentially leading to a modern and personalized approach to AKI [187] (Figure 3).

Population Age	Maker
Variable	Age Specific Maker Panels
Location	**Marker**
Glomerulus	Real-time GFR
Tubular Epithelium	Urine biomarker panel
Vasa recta	Renal oximetry
Collecting Duct	Kinetic Urine Output
Etiology	**Marker**
Perfusion / Reperfusion	Real-time GFR
Apoptosis / Necrosis / Autophagy	Biomaker profile
Inflammation / Oxidative Stress	Bioenergetics panel
Chloride Transport	Furosemide Stress Test
Severity / Progression	**Marker**
Low	Negative renal angina
Moderate	Renal angina+ / Stable Biomakers
Progressive / High	Renal angina+ / Rising Biomakers

Figure 3. Future of biomarkers of AKI. Abbreviations: GFR, glomerular filtration rate.

9. Conclusions

Based on the mere fact that presently there is absence of effective pharmacotherapies that are usable for AKI, all measures geared toward preventing the condition should be taken seriously. Two advances from past decades, the usage of computer decision intelligence support and the discovery of AKI biomarkers, have the great ability to in a sustainable way improve the general diagnostic strategy to AKI and its further treatment. The advances in developments and future progress in AKI biomarkers over time can lead to future of precision and personalized approach to AKI management.

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References

1. Levey, A.S.; James, M.T. Acute Kidney Injury. *Ann. Intern. Med.* **2017**, *167*, ITC66–ITC80. [CrossRef] [PubMed]
2. Ronco, C.; Bellomo, R.; Kellum, J.A. Acute kidney injury. *Lancet* **2019**, *394*, 1949–1964. [CrossRef]
3. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef] [PubMed]
4. Jadlowiec, C.; Smith, M.; Neville, M.; Mao, S.; Abdelwahab, D.; Reddy, K.; Moss, A.; Aqel, B.; Taner, T. Acute Kidney Injury Patterns following Transplantation of Steatotic Liver Allografts. *J. Clin. Med.* **2020**, *9*, 954. [CrossRef]
5. Manohar, S.; Kompotiatis, P.; Thongprayoon, C.; Cheungpasitporn, W.; Herrmann, J.; Herrmann, S.M. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: Meta-analysis. *Nephrol. Dial. Transplant.* **2019**, *34*, 108–117. [CrossRef]
6. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Erickson, S.B. Admission hyperphosphatemia increases the risk of acute kidney injury in hospitalized patients. *J. Nephrol.* **2018**, *31*, 241–247. [CrossRef]
7. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Kashani, K. U-shape association of serum albumin level and acute kidney injury risk in hospitalized patients. *PLoS ONE* **2018**, *13*, e0199153. [CrossRef]
8. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Harrison, A.M.; Erickson, S.B. Elevated admission serum calcium phosphate product as an independent risk factor for acute kidney injury in hospitalized patients. *Hosp. Pract.* **2019**, *47*, 73–79. [CrossRef]
9. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Erickson, S.B. Admission calcium levels and risk of acute kidney injury in hospitalised patients. *Int. J. Clin. Pract.* **2018**, *72*, e13057. [CrossRef]
10. Cheungpasitporn, W.; Thongprayoon, C.; Harrison, A.M.; Erickson, S.B. Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients. *Clin. Kidney J.* **2016**, *9*, 51–56. [CrossRef]
11. Cheungpasitporn, W.; Thongprayoon, C.; Erickson, S.B. Admission hypomagnesemia and hypermagnesemia increase the risk of acute kidney injury. *Ren. Fail.* **2015**, *37*, 1175–1179. [CrossRef] [PubMed]
12. Li, P.K.; Burdmann, E.A.; Mehta, R.L. Acute kidney injury: Global health alert. *Kidney Int.* **2013**, *83*, 372–376. [CrossRef] [PubMed]
13. Cerdá, J.; Liu, K.D.; Cruz, D.N.; Jaber, B.L.; Koyner, J.L.; Heung, M.; Okusa, M.D.; Faubel, S. Promoting Kidney Function Recovery in Patients with AKI Requiring RRT. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 1859–1867. [CrossRef] [PubMed]
14. Silver, S.A.; Long, J.; Zheng, Y.; Chertow, G.M. Cost of Acute Kidney Injury in Hospitalized Patients. *J. Hosp. Med.* **2017**, *12*, 70–76. [CrossRef]
15. Hansrivijit, P.; Lertjitbanjong, P.; Thongprayoon, C.; Cheungpasitporn, W.; Aeddula, N.R.; Salim, S.A.; Chewcharat, A.; Watthanasuntorn, K.; Srivali, N.; Mao, M.A.; et al. Acute Kidney Injury in Pediatric Patients on Extracorporeal Membrane Oxygenation: A Systematic Review and Meta-analysis. *Medicines* **2019**, *6*, 109. [CrossRef] [PubMed]
16. Thongprayoon, C.; Cheungpasitporn, W.; Shah, I.K.; Kashyap, R.; Park, S.J.; Kashani, K. Long-term Outcomes and Prognostic Factors for Patients Requiring Renal Replacement Therapy ater Cardiac Surgery. *Mayo Clin. Proc.* **2015**, *90*, 857–864. [CrossRef] [PubMed]
17. Silver, S.A.; Chertow, G.M. The Economic Consequences of Acute Kidney Injury. *Nephron* **2017**, *137*, 297–301. [CrossRef]
18. Selby, N.M.; Kolhe, N.V.; McIntyre, C.W.; Monaghan, J.; Lawson, N.; Elliott, D.; Packington, R.; Fluck, R.J. Defining the cause of death in hospitalised patients with acute kidney injury. *PLoS ONE* **2012**, *7*, e48580. [CrossRef]

19. Mehta, R.L.; Cerdá, J.; Burdmann, E.A.; Tonelli, M.; García-García, G.; Jha, V.; Susantitaphong, P.; Rocco, M.; Vanholder, R.; Sever, M.S.; et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): A human rights case for nephrology. *Lancet* **2015**, *385*, 2616–2643. [CrossRef]
20. Charlton, J.R.; Portilla, D.; Okusa, M.D. A basic science view of acute kidney injury biomarkers. *Nephrol. Dial. Transplant.* **2014**, *29*, 1301–1311. [CrossRef]
21. Sutherland, S.M.; Chawla, L.S.; Kane-Gill, S.L.; Hsu, R.K.; Kramer, A.A.; Goldstein, S.L.; Kellum, J.A.; Ronco, C.; Bagshaw, S.M. Utilizing electronic health records to predict acute kidney injury risk and outcomes: Workgroup statements from the 15(th) ADQI Consensus Conference. *Can. J. Kidney Health Dis.* **2016**, *3*, 11. [CrossRef] [PubMed]
22. Cheungpasitporn, W.; Kashani, K. Electronic Data Systems and Acute Kidney Injury. *Contrib. Nephrol.* **2016**, *187*, 73–83. [PubMed]
23. Kellum, J.A. KDIGO clinical practice guideline for acute kidney injury, Section 2: AKI Definition. *Kidney Int. Suppl.* **2012**, *2*, 19–36.
24. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P. Acute Dialysis Quality Initiative w. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, R204–R212. [CrossRef]
25. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef]
26. Thongprayoon, C.; Cheungpasitporn, W.; Kittanamongkolchai, W.; Srivali, N.; Ungprasert, P.; Kashani, K. Optimum methodology for estimating baseline serum creatinine for the acute kidney injury classification. *Nephrology* **2015**, *20*, 881–886. [CrossRef]
27. Acosta-Ochoa, I.; Bustamante-Munguira, J.; Mendiluce-Herrero, A.; Bustamante-Bustamante, J.; Coca-Rojo, A. Impact on Outcomes across KDIGO-2012 AKI Criteria according to Baseline Renal Function. *J. Clin. Med.* **2019**, *8*, 1323. [CrossRef]
28. Siew, E.D.; Ikizler, T.A.; Matheny, M.E.; Shi, Y.; Schildcrout, J.S.; Danciu, I.; Dwyer, J.P.; Srichai, M.; Hung, A.M.; Smith, J.P.; et al. Estimating baseline kidney function in hospitalized patients with impaired kidney function. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 712–719. [CrossRef]
29. Siew, E.D.; Matheny, M.E.; Ikizler, T.A.; Lewis, J.B.; Miller, R.A.; Waitman, L.R.; Go, A.S.; Parikh, C.R.; Peterson, J.F. Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury. *Kidney Int.* **2010**, *77*, 536–542. [CrossRef]
30. Thongprayoon, C.; Cheungpasitporn, W.; Harrison, A.; Kittanamongkolchai, W.; Ungprasert, P.; Srivali, N.; Akhoundi, A.; Kashani, K.B. The comparison of the commonly used surrogates for baseline renal function in acute kidney injury diagnosis and staging. *BMC Nephrol.* **2016**, *17*, 6. [CrossRef]
31. Ad-hoc working group of ERBP; Fliser, D.; Laville, M.; Covic, A.; Fouque, D.; Vanholder, R.; Juillard, L.; Van Biesen, W. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: Part 1: Definitions, conservative management and contrast-induced nephropathy. *Nephrol. Dial. Transplant.* **2012**, *27*, 4263–4272.
32. Pickering, J.W.; Endre, Z.H. Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 1165–1173. [CrossRef] [PubMed]
33. Hsu, C.Y.; Ordoñez, J.D.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Go, A.S. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int.* **2008**, *74*, 101–107. [CrossRef] [PubMed]
34. Spoorenberg, S.M.; Meijvis, S.C.; Navis, G.; Bos, W.J. Age- and gender-adjusted eGFR to estimate baseline creatinine for RIFLE criteria. *NDT Plus.* **2011**, *4*, 365–366. [CrossRef]
35. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Ungprasert, P.; Kittanamongkolchai, W.; Kashani, K. The impact of fluid balance on diagnosis, staging and prediction of mortality in critically ill patients with acute kidney injury. *J. Nephrol.* **2016**, *29*, 221–227. [CrossRef]
36. Liu, K.D.; Thompson, B.T.; Ancukiewicz, M.; Steingrub, J.S.; Douglas, I.S.; Matthay, M.A.; Wright, P.; Peterson, M.W.; Rock, P.; Hyzy, R.C.; et al. Acute kidney injury in patients with acute lung injury: Impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit. Care Med.* **2011**, *39*, 2665–2671. [CrossRef]

37. Macedo, E.; Bouchard, J.; Soroko, S.H.; Chertow, G.M.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Mehta, R.L. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit. Care* **2010**, *14*, R82. [CrossRef]
38. Thongprayoon, C.; Cheungpasitporn, W.; Akhoundi, A.; Ahmed, A.H.; Kashani, K.B. Actual versus ideal body weight for acute kidney injury diagnosis and classification in critically ill patients. *BMC Nephrol.* **2014**, *15*, 176. [CrossRef]
39. Kellum, J.A. Persistent Acute Kidney Injury. *Crit. Care Med.* **2015**, *43*, 1785–1786. [CrossRef]
40. Perinel, S.; Vincent, F.; Lautrette, A.; Dellamonica, J.; Mariat, C.; Zeni, F.; Cohen, Y.; Tardy, B.; Souweine, B.; Darmon, M. Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients: Results of a Multicenter Cohort Study. *Crit. Care Med.* **2015**, *43*, e269–e275. [CrossRef]
41. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Srivali, N.; Kittanamongkolchai, W.; Harrison, A.; Greason, K.L.; Kashani, K.B. Persistent acute kidney injury following transcatheter aortic valve replacement. *J. Card. Surg.* **2017**, *32*, 550–555. [CrossRef] [PubMed]
42. Goldberg, A.; Kogan, E.; Hammerman, H.; Markiewicz, W.; Aronson, D. The impact of transient and persistent acute kidney injury on long-term outcomes after acute myocardial infarction. *Kidney Int.* **2009**, *76*, 900–906. [CrossRef] [PubMed]
43. Choi, J.S.; A Kim, Y.; Kim, M.J.; Kang, Y.U.; Kim, C.S.; Bae, E.H.; Ma, S.K.; Ahn, Y.; Jeong, M.H.; Kim, S.W. Relation between transient or persistent acute kidney injury and long-term mortality in patients with myocardial infarction. *Am. J. Cardiol.* **2013**, *112*, 41–45. [CrossRef] [PubMed]
44. Wi, J.; Ko, Y.G.; Kim, J.S.; Kim, B.K.; Choi, D.; Ha, J.W.; Hong, M.K. Impact of contrast-induced acute kidney injury with transient or persistent renal dysfunction on long-term outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Heart* **2011**, *97*, 1753–1757. [CrossRef]
45. Kim, C.S.; Bae, E.H.; Ma, S.K.; Kweon, S.S.; Kim, S.W. Impact of Transient and Persistent Acute Kidney Injury on Chronic Kidney Disease Progression and Mortality after Gastric Surgery for Gastric Cancer. *PLoS ONE* **2016**, *11*, e0168119. [CrossRef]
46. Chawla, L.S.; Bellomo, R.; Bihorac, A.; Goldstein, S.L.; Siew, E.D.; Bagshaw, S.M.; Bittleman, D.; Cruz, D.; Endre, Z.H.; Fitzgerald, R.L.; et al. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat. Rev. Nephrol.* **2017**, *13*, 241–257. [CrossRef]
47. Kellum, J.A.; Sileanu, F.E.; Bihorac, A.; Hoste, E.A.; Chawla, L.S. Recovery after Acute Kidney Injury. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 784–791. [CrossRef]
48. Bagshaw, S.M. Epidemiology of renal recovery after acute renal failure. *Curr. Opin. Crit. Care* **2006**, *12*, 544–550. [CrossRef]
49. Pannu, N.; James, M.; Hemmelgarn, B.; Klarenbach, S. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 194–202. [CrossRef]
50. Swaminathan, M.; Hudson, C.C.; Phillips-Bute, B.G.; Patel, U.D.; Mathew, J.P.; Newman, M.F.; Milano, C.A.; Shaw, A.; Stafford-Smith, M. Impact of early renal recovery on survival after cardiac surgery-associated acute kidney injury. *Ann. Thorac. Surg.* **2010**, *89*, 1098–1104. [CrossRef]
51. Wajda, J.; Dumnicka, P.; Sporek, M.; Maziarz, B.; Kolber, W.; Ząbek-Adamska, A.; Ceranowicz, P.; Kuźniewski, M.; Kuśnierz-Cabala, B. Does Beta-Trace Protein (BTP) Outperform Cystatin C as a Diagnostic Marker of Acute Kidney Injury Complicating the Early Phase of Acute Pancreatitis? *J. Clin. Med.* **2020**, *9*, 205. [CrossRef] [PubMed]
52. Antal, O.; Ștefănescu, E.; Mleșnițe, M.; Bălan, A.M.; Caziuc, A.; Hagău, N. Hemodynamic Predictors for Sepsis-Induced Acute Kidney Injury: A Preliminary Study. *J. Clin. Med.* **2020**, *9*, 151. [CrossRef] [PubMed]
53. Lee, K.H.; Sol, I.S.; Park, J.T.; Kim, J.H.; Shin, J.W.; Park, M.; Lee, J.; Kim, Y.H.; Kim, K.W.; Shin, J.I.; et al. Continuous Renal Replacement Therapy (CRRT) in Children and the Specialized CRRT Team: A 14-Year Single-Center Study. *J. Clin. Med.* **2019**, *9*, 110. [CrossRef] [PubMed]
54. Lee, C.-C.; Chang, C.-H.; Cheng, Y.-L.; Kuo, G.; Chen, S.-W.; Li, Y.-J.; Chen, Y.; Tian, Y.-C. Diagnostic Performance of Cyclophilin A in Cardiac Surgery-Associated Acute Kidney Injury. *J. Clin. Med.* **2019**, *9*, 108. [CrossRef] [PubMed]
55. Rubin, S.; Orieux, A.; Clouzeau, B.; Rigothier, C.; Combe, C.; Gruson, D.; Boyer, A. The Incidence of Chronic Kidney Disease Three Years after Non-Severe Acute Kidney Injury in Critically Ill Patients: A Single-Center Cohort Study. *J. Clin. Med.* **2019**, *8*, 2215. [CrossRef] [PubMed]

56. Wu, C.-K.; Wu, C.-L.; Su, T.-C.; Kou, Y.R.; Kor, C.-T.; Lee, T.-S.; Tarng, D.-C. Renal Tubular TRPA1 as a Risk Factor for Recovery of Renal Function from Acute Tubular Necrosis. *J. Clin. Med.* **2019**, *8*, 2187. [CrossRef]
57. Averdunk, L.; Fitzner, C.; Levkovich, T.; Leaf, D.E.; Sobotta, M.; Vieten, J.; Ochi, A.; Moeckel, G.; Marx, G.; Stoppe, C.; et al. Secretory Leukocyte Protease Inhibitor (SLPI)-A Novel Predictive Biomarker of Acute Kidney Injury after Cardiac Surgery: A Prospective Observational Study. *J. Clin. Med.* **2019**, *8*, 1931. [CrossRef]
58. Wu, V.C.; Chueh, S.J.; Chang, J.T.; Hsu, B.G.; Ostermann, M.; Chu, T.S. Acute Kidney Injury and Septic Shock-Defined by Updated Sepsis-3 Criteria in Critically Ill Patients. *J. Clin. Med.* **2019**, *8*, 1731. [CrossRef]
59. Lertjitbanjong, P.; Thongprayoon, C.; Cheungpasitporn, W.; O'Corragain, O.A.; Srivali, N.; Bathini, T.; Watthanasuntorn, K.; Aeddula, N.R.; Salim, S.A.; Ungprasert, P.; et al. Acute Kidney Injury after Lung Transplantation: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 1731. [CrossRef]
60. Lee, H.-J.; Bae, J.; Kwon, Y.; Jang, H.S.; Yoo, S.; Jeong, C.W.; Kim, J.-T.; Kim, W.H. General Anesthetic Agents and Renal Function after Nephrectomy. *J. Clin. Med.* **2019**, *8*, 1530. [CrossRef]
61. Yoon, H.-K.; Lee, H.-J.; Yoo, S.; Park, S.-K.; Kwon, Y.; Jun, K.; Jeong, C.W.; Kim, W.H. Acute Kidney Injury Adjusted for Parenchymal Mass Reduction and Long-Term Renal Function after Partial Nephrectomy. *J. Clin. Med.* **2019**, *8*, 1482. [CrossRef] [PubMed]
62. Fabbian, F.; Savriè, C.; De Giorgi, A.; Cappadona, R.; Simone, D.; Boari, B.; Storari, A.; Gallerani, M.; Manfredini, R.; De Giorgi, A.; et al. Acute Kidney Injury and In-Hospital Mortality: A Retrospective Analysis of a Nationwide Administrative Database of Elderly Subjects in Italy. *J. Clin. Med.* **2019**, *8*, 1371. [CrossRef]
63. Doyle, J.; Sarnowski, A.; Saadat, F.; Samuels, T.L.; Huddart, S.; Quiney, N.; Dickinson, M.C.; McCormick, B.; Debrunner, R.; Preece, J.; et al. Does the Implementation of a Quality Improvement Care Bundle Reduce the Incidence of Acute Kidney Injury in Patients Undergoing Emergency Laparotomy? *J. Clin. Med.* **2019**, *8*, 1265. [CrossRef] [PubMed]
64. Wu, M.J.; Tsai, S.F.; Lee, C.T.; Wu, C.Y. The Predictive Value of Hyperuricemia on Renal Outcome after Contrast-Enhanced Computerized Tomography. *J. Clin. Med.* **2019**, *8*, 1003. [CrossRef] [PubMed]
65. Thongprayoon, C.; Cheungpasitporn, W.; Lertjitbanjong, P.; Aeddula, N.R.; Bathini, T.; Watthanasuntorn, K.; Srivali, N.; Mao, M.A.; Kashani, K. Incidence and Impact of Acute Kidney Injury in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 981. [CrossRef]
66. Ortiz-Soriano, V.; Donaldson, K.; Du, G.; Li, Y.; Lambert, J.; Cleland, D.; Thornton, A.; Fanucchi, L.C.; Huaman, M.A.; Neyra, J.A. Incidence and Cost of Acute Kidney Injury in Hospitalized Patients with Infective Endocarditis. *J. Clin. Med.* **2019**, *8*, 927. [CrossRef]
67. Kim, H.-J.; Park, H.-S.; Go, Y.-J.; Koh, W.U.; Kim, H.; Song, J.-G.; Ro, Y.-J. Effect of Anesthetic Technique on the Occurrence of Acute Kidney Injury after Total Knee Arthroplasty. *J. Clin. Med.* **2019**, *8*, 778. [CrossRef]
68. Kim, N.Y.; Hong, J.H.; Koh, D.H.; Lee, J.; Nam, H.J.; Kim, S.Y. Effect of Diabetes Mellitus on Acute Kidney Injury after Minimally Invasive Partial Nephrectomy: A Case-Matched Retrospective Analysis. *J. Clin. Med.* **2019**, *8*, 468. [CrossRef]
69. Oh, T.K.; Song, I.A.; Jeon, Y.T.; Jo, Y.H. Fluctuations in Serum Chloride and Acute Kidney Injury among Critically Ill Patients: A Retrospective Association Study. *J. Clin. Med.* **2019**, *8*, 447. [CrossRef]
70. Thongprayoon, C.; Kaewput, W.; Thamcharoen, N.; Bathini, T.; Watthanasuntorn, K.; Lertjitbanjong, P.; Sharma, K.; Salim, S.A.; Ungprasert, P.; Wijarnpreecha, K.; et al. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 372. [CrossRef]
71. Vilander, L.M.; Vaara, S.T.; Kaunisto, M.A.; Pettilä, V. Common Inflammation-Related Candidate Gene Variants and Acute Kidney Injury in 2647 Critically Ill Finnish Patients. *J. Clin. Med.* **2019**, *8*, 342. [CrossRef] [PubMed]
72. Kaewput, W.; Thongprayoon, C.; Rangsin, R.; Mao, M.A.; Satirapoj, B.; Cheungpasitporn, W. The association between renal function and neurological diseases in type 2 diabetes: A multicenter nationwide cross-sectional study. *Hosp. Pract.* **2019**, *47*, 46–52. [CrossRef] [PubMed]
73. Kim, W.H.; Lee, H.C.; Lim, L.; Ryu, H.G.; Jung, C.W. Intraoperative Oliguria with Decreased SvO_2 Predicts Acute Kidney Injury after Living Donor Liver Transplantation. *J. Clin. Med.* **2018**, *8*, 29. [CrossRef] [PubMed]
74. Oh, T.K.; Song, I.A.; Cho, Y.J.; Lim, C.; Jeon, Y.T.; Bae, H.J.; Jo, Y.H. Preadmission Statin Therapy Is Associated with a Lower Incidence of Acute Kidney Injury in Critically Ill Patients: A Retrospective Observational Study. *J. Clin. Med.* **2018**, *8*, 25. [CrossRef] [PubMed]

75. Kim, J.-S.; Kim, Y.J.; Ryoo, S.M.; Sohn, C.H.; Seo, D.W.; Ahn, S.; Lim, K.S.; Kim, W. One–Year Progression and Risk Factors for the Development of Chronic Kidney Disease in Septic Shock Patients with Acute Kidney Injury: A Single-Centre Retrospective Cohort Study. *J. Clin. Med.* **2018**, *7*, 554. [CrossRef]
76. Zelt, J.G.E.; Mielniczuk, L.M.; Liu, P.P.; Dupuis, J.-Y.; Chih, S.; Akbari, A.; Sun, L. Utility of Novel Cardiorenal Biomarkers in the Prediction and Early Detection of Congestive Kidney Injury Following Cardiac Surgery. *J. Clin. Med.* **2018**, *7*, 540. [CrossRef]
77. Marouli, D.; Stylianou, K.; Papadakis, E.; Kroustalakis, N.; Kolyvaki, S.; Papadopoulos, G.; Ioannou, C.; Papaioannou, A.; Daphnis, E.; Georgopoulos, D.; et al. Preoperative Albuminuria and Intraoperative Chloride Load: Predictors of Acute Kidney Injury following Major Abdominal Surgery. *J. Clin. Med.* **2018**, *7*, 431. [CrossRef]
78. Kee, Y.K.; Kim, D.; Kim, S.-J.; Kang, D.-H.; Choi, K.B.; Oh, H.J.; Ryu, D.-R. Factors Associated with Early Mortality in Critically Ill Patients following the Initiation of Continuous Renal Replacement Therapy. *J. Clin. Med.* **2018**, *7*, 334. [CrossRef]
79. Lee, H.-C.; Yoon, H.-K.; Nam, K.; Cho, Y.J.; Kim, T.K.; Kim, W.H.; Bahk, J.-H. Derivation and Validation of Machine Learning Approaches to Predict Acute Kidney Injury after Cardiac Surgery. *J. Clin. Med.* **2018**, *7*, 322. [CrossRef]
80. Douvris, A.; Zeid, K.; Hiremath, S.; Brown, P.A.; Sood, M.M.; Arkoub, R.A.; Malhi, G.; Clark, E. Safety Lapses Prior to Initiation of Hemodialysis for Acute Kidney Injury in Hospitalized Patients: A Patient Safety Initiative. *J. Clin. Med.* **2018**, *7*, 317. [CrossRef]
81. Chen, Y.-Y.; Wu, V.-C.; Huang, W.-C.; Yeh, Y.-C.; Wu, M.-S.; Huang, C.-C.; Wu, M.-S.; Fang, J.-T.; Wu, C.-J.; Nsarf, T.; et al. Norepinephrine Administration Is Associated with Higher Mortality in Dialysis Requiring Acute Kidney Injury Patients with Septic Shock. *J. Clin. Med.* **2018**, *7*, 274. [CrossRef] [PubMed]
82. Shiao, C.-C.; Kan, W.-C.; Wang, J.-J.; Lin, Y.-F.; Chen, L.; Chueh, E.; Huang, Y.-T.; Chiang, W.-P.; Tseng, L.-J.; Wang, C.-H.; et al. Risk of Incident Non-Valvular Atrial Fibrillation after Dialysis-Requiring Acute Kidney Injury. *J. Clin. Med.* **2018**, *7*, 248. [CrossRef] [PubMed]
83. Wu, C.-H.; Chang, H.-M.; Wang, C.-Y.; Chen, L.; Chen, L.W.; Lai, C.-H.; Kuo, S.-W.; Wang, H.-C.; Wu, V.-C. Long-Term Outcomes in Patients with Incident Chronic Obstructive Pulmonary Disease after Acute Kidney Injury: A Competing-Risk Analysis of a Nationwide Cohort. *J. Clin. Med.* **2018**, *7*, 237. [CrossRef] [PubMed]
84. Awdishu, L.; Connor, A.I.; Bouchard, J.; Macedo, E.; Chertow, G.M.; Mehta, R.L. Use of Estimating Equations for Dosing Antimicrobials in Patients with Acute Kidney Injury Not Receiving Renal Replacement Therapy. *J. Clin. Med.* **2018**, *7*, 211. [CrossRef]
85. Wu, V.-C.; Shiao, C.-C.; Chi, N.-H.; Wang, C.-H.; Chueh, J.S.; Liou, H.-H.; Spapen, H.; Honore, P.M.; Chu, T.-S. Outcome Prediction of Acute Kidney Injury Biomarkers at Initiation of Dialysis in Critical Units. *J. Clin. Med.* **2018**, *7*, 202. [CrossRef]
86. Selby, A.R.; Hall, R.G. Utilizing the Patient Care Process to Minimize the Risk of Vancomycin-Associated Nephrotoxicity. *J. Clin. Med.* **2019**, *8*, 781. [CrossRef]
87. Chen, J.J.; Fan, P.C.; Kou, G.; Chang, S.W.; Chen, Y.T.; Lee, C.C.; Chang, C.H. Meta-Analysis: Urinary Calprotectin for Discrimination of Intrinsic and Prerenal Acute Kidney Injury. *J. Clin. Med.* **2019**, *8*, 74. [CrossRef]
88. Abassi, Z.; Rosen, S.; Lamothe, S.; Heyman, S.N. Why Have Detection, Understanding and Management of Kidney Hypoxic Injury Lagged Behind those for the Heart? *J. Clin. Med.* **2019**, *8*, 267. [CrossRef]
89. Case, J.; Khan, S.; Khalid, R.; Khan, A. Epidemiology of acute kidney injury in the intensive care unit. *Crit. Care Res. Pract.* **2013**, *2013*, 479730. [CrossRef]
90. Thongprayoon, C.; Lertjitbanjong, P.; Hansrivijit, P.; Crisafio, A.; Mao, M.A.; Watthanasuntorn, K.; Aeddula, N.R.; Bathini, T.; Kaewput, W.; Cheungpasitporn, W. Acute Kidney Injury in Patients Undergoing Cardiac Transplantation: A Meta-Analysis. *Medicines* **2019**, *6*, 108. [CrossRef]
91. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Kittanamongkolchai, W.; Greason, K.L.; Kashani, K.B. Incidence and risk factors of acute kidney injury following transcatheter aortic valve replacement. *Nephrology* **2016**, *21*, 1041–1046. [CrossRef] [PubMed]
92. Kanduri, S.R.; Cheungpasitporn, W.; Thongprayoon, C.; Bathini, T.; Kovvuru, K.; Garla, V.; Medaura, J.; Vaitla, P.; Kashani, K.B. Incidence and Mortality of Acute Kidney Injury in Patients Undergoing Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-analysis. *QJM Int. J. Med.* **2020**. [CrossRef] [PubMed]

93. Lagny, M.-G.; Jouret, F.; Koch, J.-N.; Blaffart, F.; Donneau, A.-F.; Albert, A.; Roediger, L.; Krzesinski, J.-M.; Defraigne, J.-O. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. *BMC Nephrol.* **2015**, *16*, 76. [CrossRef] [PubMed]
94. Vives, M.; Hernandez, A.; Parramon, F.; Estanyol, N.; Pardina, B.; Muñoz, A.; Alvarez, P.; Hernandez, C. Acute kidney injury after cardiac surgery: Prevalence, impact and management challenges. *Int. J. Nephrol. Renovasc. Dis.* **2019**, *12*, 153–166. [CrossRef] [PubMed]
95. Mårtensson, J.; Bellomo, R. Sepsis-Induced Acute Kidney Injury. *Crit. Care Clin.* **2015**, *31*, 649–660. [CrossRef] [PubMed]
96. Panitchote, A.; Mehkri, O.; Hastings, A.; Hanane, T.; Demirjian, S.; Torbic, H.; Mireles-Cabodevila, E.; Krishnan, S.; Duggal, A. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann. Intensive Care* **2019**, *9*, 74. [CrossRef]
97. Darmon, M.; Clec'H, C.; Adrie, C.; Argaud, L.; Allaouchiche, B.; Azoulay, E.; Bouadma, L.; Garrouste-Orgeas, M.; Haouache, H.; Schwebel, C.; et al. Acute respiratory distress syndrome and risk of AKI among critically ill patients. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 1347–1353. [CrossRef]
98. Wijarnpreecha, K.; Thongprayoon, C.; Edmonds, P.J.; Cheungpasitporn, W. Associations of sugar- and artificially sweetened soda with nonalcoholic fatty liver disease: A systematic review and meta-analysis. *QJM* **2016**, *109*, 461–466. [CrossRef]
99. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Ungprasert, P.; Kittanamongkolchai, W.; Greason, K.L.; Kashani, K.B. Acute kidney injury after transcatheter aortic valve replacement: A systematic review and meta-analysis. *Am. J. Nephrol.* **2015**, *41*, 372–382. [CrossRef]
100. Thongprayoon, C.; Cheungpasitporn, W.; Lin, J.; Mao, M.A.; Qian, Q. Acute kidney injury in octogenarians after heart valve replacement surgery: A study of two periods over the last decade. *Clin. Kidney J.* **2017**, *10*, 648–654. [CrossRef]
101. Thongprayoon, C.; Cheungpasitporn, W.; Thamcharoen, N.; Ungprasert, P.; Kittanamongkolchai, W.; Mao, M.A.; Sakhuja, A.; Greason, K.L.; Kashani, K.B. Association of frailty status with acute kidney injury and mortality after transcatheter aortic valve replacement: A systematic review and meta-analysis. *PLoS ONE* **2017**, *12*, e0177157. [CrossRef] [PubMed]
102. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Kittanamongkolchai, W.; Sakhuja, A.; Greason, K.L.; Kashani, K.B. The association between renal recovery after acute kidney injury and long-term mortality after transcatheter aortic valve replacement. *PLoS ONE* **2017**, *12*, e0183350. [CrossRef] [PubMed]
103. Sakhuja, A.; Kashani, K.; Schold, J.; Cheungpasitporn, W.; Soltesz, E.; Demirjian, S. Hospital procedure volume does not predict acute kidney injury after coronary artery bypass grafting-a nationwide study. *Clin. Kidney J.* **2017**, *10*, 769–775. [CrossRef] [PubMed]
104. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Harrison, A.M.; Gunderson, T.M.; Kittanamongkolchai, W.; Greason, K.L.; Kashani, K.B. AKI after Transcatheter or Surgical Aortic Valve Replacement. *J. Am. Soc. Nephrol.* **2016**, *27*, 1854–1860. [CrossRef]
105. Muriithi, A.K.; Nasr, S.H.; Leung, N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1857–1862. [CrossRef]
106. Nguyen, M.T.; Maynard, S.E.; Kimmel, P.L. Misapplications of commonly used kidney equations: Renal physiology in practice. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 528–534. [CrossRef]
107. Chawla, L.S.; Davison, D.; Brasha-Mitchell, E.; Koyner, J.L.; Arthur, J.; Shaw, A.; Tumlin, J.; A Trevino, S.; Kimmel, P.L.; Seneff, M.G. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit. Care* **2013**, *17*, R207. [CrossRef]
108. Koyner, J.L.; Davison, D.L.; Brasha-Mitchell, E.; Chalikonda, D.M.; Arthur, J.; Shaw, A.; Tumlin, J.A.; Trevino, S.A.; Bennett, M.R.; Kimmel, P.L.; et al. Furosemide stress test and biomarkers for the prediction of AKI severity. *J. Am. Soc. Nephrol.* **2015**, *26*, 2023–2031. [CrossRef]
109. Thongprayoon, C.; Cheungpasitporn, W.; Kashani, K. Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients. *J. Thorac. Dis.* **2016**, *8*, E305–E311. [CrossRef]
110. Kashani, K.; Cheungpasitporn, W.; Ronco, C. Biomarkers of acute kidney injury: The pathway from discovery to clinical adoption. *Clin. Chem. Lab Med.* **2017**, *55*, 1074–1089. [CrossRef]
111. Capasso, A.; Benigni, A.; Capitanio, U.; Danesh, F.R.; Di Marzo, V.; Gesualdo, L.; Grandaliano, G.; Jaimes, E.A.; Malyszko, J.; Perazella, M.A.; et al. Summary of the International Conference on Onco-Nephrology: An emerging field in medicine. *Kidney Int.* **2019**, *96*, 555–567. [CrossRef] [PubMed]

112. Parikh, C.R.; Coca, S.G.; Thiessen-Philbrook, H.; Shlipak, M.G.; Koyner, J.L.; Wang, Z.; Edelstein, C.L.; Devarajan, P.; Patel, U.D.; Zappitelli, M.; et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J. Am. Soc. Nephrol.* **2011**, *22*, 1748–1757. [CrossRef] [PubMed]
113. Siew, E.D.; Ware, L.B.; Bian, A.; Shintani, A.; Eden, S.K.; Wickersham, N.; Cripps, B.; Ikizler, T.A. Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. *Kidney Int.* **2013**, *84*, 786–794. [CrossRef] [PubMed]
114. Srisawat, N.; Wen, X.; Lee, M.; Kong, L.; Elder, M.; Carter, M.; Unruh, M.; Finkel, K.; Vijayan, A.; Ramkumar, M.; et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 1815–1823. [CrossRef]
115. Damman, K.; Masson, S.; Hillege, H.L.; Maggioni, A.P.; Voors, A.A.; Opasich, C.; Van Veldhuisen, D.J.; Montagna, L.; Cosmi, F.; Tognoni, G.; et al. Clinical outcome of renal tubular damage in chronic heart failure. *Eur. Heart J.* **2011**, *32*, 2705–2712. [CrossRef]
116. Hall, I.E.; Yarlagadda, S.G.; Coca, S.G.; Wang, Z.; Doshi, M.; Devarajan, P.; Han, W.K.; Marcus, R.J.; Parikh, C.R. IL-18 and urinary NGAL predict dialysis and graft recovery after kidney transplantation. *J. Am. Soc. Nephrol.* **2010**, *21*, 189–197. [CrossRef]
117. Nauta, F.L.; Bakker, S.J.L.; Van Oeveren, W.; Navis, G.; Van Der Heide, J.J.H.; Van Goor, H.; De Jong, P.E.; Gansevoort, R.T. Albuminuria, proteinuria, and novel urine biomarkers as predictors of long-term allograft outcomes in kidney transplant recipients. *Am. J. Kidney Dis.* **2011**, *57*, 733–743. [CrossRef]
118. Zhang, W.R.; Garg, A.X.; Coca, S.G.; Devereaux, P.J.; Eikelboom, J.; Kavsak, P.; McArthur, E.; Thiessen-Philbrook, H.; Shortt, C.; Shlipak, M.; et al. Plasma IL-6 and IL-10 Concentrations Predict AKI and Long-Term Mortality in Adults after Cardiac Surgery. *J. Am. Soc. Nephrol.* **2015**, *26*, 3123–3132. [CrossRef]
119. Arthur, J.; Hill, E.G.; Alge, J.; Lewis, E.C.; Neely, B.A.; Janech, M.G.; Tumlin, J.A.; Chawla, L.S.; Shaw, A. Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. *Kidney Int.* **2014**, *85*, 431–438. [CrossRef]
120. Parikh, C.R.; Abraham, E.; Ancukiewicz, M.; Edelstein, C.L. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J. Am. Soc. Nephrol.* **2005**, *16*, 3046–3052. [CrossRef]
121. Nejat, M.; Pickering, J.W.; Walker, R.J.; Westhuyzen, J.; Shaw, G.M.; Frampton, C.M.; Endre, Z.H. Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. *Crit. Care* **2010**, *14*, R85. [CrossRef] [PubMed]
122. Doi, K.; Negishi, K.; Ishizu, T.; Katagiri, D.; Fujita, T.; Matsubara, T.; Yahagi, N.; Sugaya, T.; Noiri, E. Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. *Crit. Care Med.* **2011**, *39*, 2464–2469. [CrossRef] [PubMed]
123. Bell, M.; Larsson, A.; Venge, P.; Bellomo, R.; Martensson, J. Assessment of cell-cycle arrest biomarkers to predict early and delayed acute kidney injury. *Dis. Markers* **2015**, *2015*, 158658. [CrossRef] [PubMed]
124. Meersch, M.; Schmidt, C.; Van Aken, H.; Martens, S.; Rossaint, J.; Singbartl, K.; Goerlich, D.; Kellum, J.A.; Zarbock, A. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS ONE* **2014**, *9*, e93460. [CrossRef] [PubMed]
125. Heller, F.; Frischmann, S.; Grunbaum, M.; Zidek, W.; Westhoff, T.H. Urinary calprotectin and the distinction between prerenal and intrinsic acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 2347–2355. [CrossRef] [PubMed]
126. Yang, X.; Chen, C.; Tian, J.; Zha, Y.; Xiong, Y.; Sun, Z.; Chen, P.; Li, J.; Yang, T.; Ma, C.; et al. Urinary Angiotensinogen Level Predicts AKI in Acute Decompensated Heart Failure: A Prospective, Two-Stage Study. *J. Am. Soc. Nephrol.* **2015**, *26*, 2032–2041. [CrossRef]
127. Du, J.; Cao, X.; Zou, L.; Chen, Y.; Guo, J.; Chen, Z.; Hu, S.-S.; Zheng, Z. MicroRNA-21 and risk of severe acute kidney injury and poor outcomes after adult cardiac surgery. *PLoS ONE* **2013**, *8*, e63390. [CrossRef]
128. Leblanc, M.; Kellum, J.A.; Gibney, R.T.; Lieberthal, W.; Tumlin, J.; Mehta, R. Risk factors for acute renal failure: Inherent and modifiable risks. *Curr. Opin. Crit. Care* **2005**, *11*, 533–536. [CrossRef]
129. Cheungpasitporn, W.; Thongprayoon, C.; Kashani, K. Transcatheter Aortic Valve Replacement: A Kidney's Perspective. *J. Ren. Inj. Prev.* **2016**, *5*, 1–7. [CrossRef]

130. Cartin-Ceba, R.; Kashiouris, M.; Plataki, M.; Kor, D.J.; Gajic, O.; Casey, E.T. Risk factors for development of acute kidney injury in critically ill patients: A systematic review and meta-analysis of observational studies. *Crit. Care Res. Pract.* **2012**, *2012*, 691013. [CrossRef]
131. Cheungpasitporn, W.; Thongprayoon, C.; Kashani, K. Updates on the risk factors of acute kidney injury after transcatheter aortic valve replacement. *J. Ren. Inj. Prev.* **2017**, *6*, 16–17. [CrossRef] [PubMed]
132. Thongprayoon, C.; Cheungpasitporn, W.; Gillaspie, E.A.; Greason, K.L.; Kashani, K.B. Association of blood transfusion with acute kidney injury after transcatheter aortic valve replacement: A meta-analysis. *World J. Nephrol.* **2016**, *5*, 482–488. [CrossRef] [PubMed]
133. Odutayo, A.; Wong, C.X.; Farkouh, M.; Altman, U.G.; Hopewell, S.; Emdin, C.A.; Hunn, B.H. AKI and Long-Term Risk for Cardiovascular Events and Mortality. *J. Am. Soc. Nephrol.* **2017**, *28*, 377–387. [CrossRef] [PubMed]
134. Pickering, J.W.; Blunt, I.R.H.; Than, M.P. Acute Kidney Injury and mortality prognosis in Acute Coronary Syndrome patients: A meta-analysis. *Nephrology* **2018**, *23*, 237–246. [CrossRef]
135. Shi, Q.; Hong, L.; Mu, X.; Zhang, C.; Chen, X. Meta-analysis for outcomes of acute kidney injury after cardiac surgery. *Medicine* **2016**, *95*, e5558. [CrossRef]
136. Giordana, F.; D'Ascenzo, F.; Nijhoff, F.; Moretti, C.; D'Amico, M.; Biondi-Zoccai, G.; Sinning, J.M.; Nickenig, G.; Van Mieghem, N.M.; Chieffo, A.; et al. Meta-analysis of predictors of all-cause mortality after transcatheter aortic valve implantation. *Am. J. Cardiol.* **2014**, *114*, 1447–1455. [CrossRef]
137. Abdul Salim, S.; Tran, H.; Thongprayoon, C.; Fülöp, T.; Cheungpasitporn, W. Comparison of drug-coated balloon angioplasty versus conventional angioplasty for arteriovenous fistula stenosis: Systematic review and meta-analysis. *J. Vasc. Access* **2019**. [CrossRef]
138. De Carvalho, J.R.; Villela-Nogueira, C.A.; Luiz, R.R.; Guzzo, P.L.; Rosa, J.M.D.S.; Rocha, E.; Coelho, H.S.M.; Perez, R.D.M. Acute kidney injury network criteria as a predictor of hospital mortality in cirrhotic patients with ascites. *J. Clin. Gastroenterol.* **2012**, *46*, e21–e26. [CrossRef]
139. Mandelbaum, T.; Scott, D.J.; Lee, J.; Mark, R.G.; Malhotra, A.; Waikar, S.S.; Howell, M.D.; Talmor, D. Outcome of critically ill patients with acute kidney injury using the Acute Kidney Injury Network criteria. *Crit. Care Med.* **2011**, *39*, 2659–2664. [CrossRef]
140. Wongrakpanich, S.; Kallis, C.; Prasad, P.; Rangaswami, J.; Rosenzweig, A. The Study of Rhabdomyolysis in the Elderly: An Epidemiological Study and Single Center Experience. *Aging Dis.* **2018**, *9*, 1–7. [CrossRef]
141. Vandenberghe, W.; Gevaert, S.; Kellum, J.A.; Bagshaw, S.M.; Peperstraete, H.; Herck, I.; Decruyenaere, J.; Hoste, E. Acute Kidney Injury in Cardiorenal Syndrome Type 1 Patients: A Systematic Review and Meta-Analysis. *Cardiorenal. Med.* **2016**, *6*, 116–128. [CrossRef] [PubMed]
142. Folkestad, T.; Brurberg, K.G.; Nordhuus, K.M.; Tveiten, C.K.; Guttormsen, A.B.; Os, I.; Beitland, S. Acute kidney injury in burn patients admitted to the intensive care unit: A systematic review and meta-analysis. *Crit. Care* **2020**, *24*, 2–11. [CrossRef] [PubMed]
143. Arnold, J.; Ng, K.P.; Sims, D.; Gill, P.; Cockwell, P.; Ferro, C. Incidence and impact on outcomes of acute kidney injury after a stroke: A systematic review and meta-analysis. *BMC Nephrol.* **2018**, *19*, 283. [CrossRef] [PubMed]
144. Juwon, L.; Jang, G.; Kim, S.; Kim, D.; Lee, J.; Park, H.; Lee, J.; Kim, S.; Kim, Y.; Kim, S.Y.; et al. Outcomes of acute kidney injury patients with and without cancer. *Ren. Fail.* **2015**, *37*, 332–337. [CrossRef] [PubMed]
145. Barakat, M.F.; McDonald, H.I.; Collier, T.J.; Smeeth, L.; Nitsch, D.; Quint, J.K. Acute kidney injury in stable COPD and at exacerbation. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2015**, *10*, 2067–2077. [CrossRef] [PubMed]
146. Fiaccadori, E.; Lombardi, M.; Leonardi, S.; Rotelli, C.F.; Tortorella, G.; Borghetti, A. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: A prospective cohort study. *J. Am. Soc. Nephrol.* **1999**, *10*, 581–593. [PubMed]
147. Bai, Z.; Primignani, M.; Guo, X.; Zheng, K.; Li, H.; Qi, X. Incidence and mortality of renal dysfunction in cirrhotic patients with acute gastrointestinal bleeding: A systematic review and meta-analysis. *Expert Rev. Gastroenterol. Hepatol.* **2019**, *13*, 1181–1188. [CrossRef]
148. Fiaccadori, E.; Maggiore, U.; Clima, B.; Melfa, L.; Rotelli, C.; Borghetti, A. Incidence, risk factors, and prognosis of gastrointestinal hemorrhage complicating acute renal failure. *Kidney Int.* **2001**, *59*, 1510–1519. [CrossRef]

149. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Harrison, A.; Kittanamongkolchai, W.; Greason, K.L.; Kashani, K.B. Transapical versus transfemoral approach and risk of acute kidney injury following transcatheter aortic valve replacement: A propensity-adjusted analysis. *Ren. Fail.* **2017**, *39*, 13–18. [CrossRef]
150. Thongprayoon, C.; Cheungpasitporn, W.; Gillaspie, E.A.; Greason, K.L.; Kashani, K.B. The risk of acute kidney injury following transapical versus transfemoral transcatheter aortic valve replacement: A systematic review and meta-analysis. *Clin. Kidney J.* **2016**, *9*, 560–566. [CrossRef]
151. Perner, A.; Haase, N.; Guttormsen, A.B.; Tenhunen, J.; Klemenzson, G.; Åneman, A. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N. Engl. J. Med.* **2012**, *367*, 124–134. [CrossRef] [PubMed]
152. Patel, A.; Pieper, K.; Myburgh, J.A.; Perkovic, V.; Finfer, S.; Yang, Q.; Li, Q.; Billot, L. Reanalysis of the Crystalloid versus Hydroxyethyl Starch Trial (CHEST). *N. Engl. J. Med.* **2017**, *377*, 298–300. [CrossRef] [PubMed]
153. Semler, M.W.; Self, W.H.; Wanderer, J.P.; Ehrenfeld, J.M.; Wang, L.; Byrne, D.W.; Stollings, J.L.; Kumar, A.B.; Hughes, C.G.; Hernandez, A.; et al. Balanced Crystalloids versus Saline in Critically Ill Adults. *N. Engl. J. Med.* **2018**, *378*, 829–839. [CrossRef] [PubMed]
154. Self, W.H.; Semler, M.W.; Wanderer, J.P.; Wang, L.; Byrne, D.W.; Collins, S.P.; Slovis, C.M.; Lindsell, C.J.; Ehrenfeld, J.M.; Siew, E.D.; et al. Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N. Engl. J. Med.* **2018**, *378*, 819–828. [CrossRef]
155. Cheungpasitporn, W.; Thongprayoon, C.; Brabec, B.A.; Edmonds, P.J.; O'Corragain, O.A.; Erickson, S.B. Oral hydration for prevention of contrast-induced acute kidney injury in elective radiological procedures: A systematic review and meta-analysis of randomized controlled trials. *N. Am. J. Med. Sci.* **2014**, *6*, 618–624. [CrossRef]
156. Cheungpasitporn, W.; Thongprayoon, C.; A Mao, M.; A Mao, S.; D'Costa, M.R.; Kittanamongkolchai, W.; Kashani, K.B. Contrast-induced acute kidney injury in kidney transplant recipients: A systematic review and meta-analysis. *World J. Transplant.* **2017**, *7*, 81–87. [CrossRef]
157. Thongprayoon, C.; Cheungpasitporn, W.; Srivali, N.; Erickson, S.B. Admission serum magnesium levels and the risk of acute respiratory failure. *Int. J. Clin. Pract.* **2015**, *69*, 1303–1308. [CrossRef]
158. Thamcharoen, N.; Thongprayoon, C.; Edmonds, P.J.; Cheungpasitporn, W. Periprocedural Nebivolol for the Prevention of Contrast-Induced Acute Kidney Injury: A Systematic Review and Meta-analysis. *N. Am. J. Med. Sci.* **2015**, *7*, 446–451. [CrossRef]
159. Cheungpasitporn, W.; Thongprayoon, C.; Srivali, N.; O'Corragain, O.A.; Edmonds, P.; Ungprasert, P.; Kittanamongkolchai, W.; Erickson, S.B. Preoperative renin-angiotensin system inhibitors use linked to reduced acute kidney injury: A systematic review and meta-analysis. *Nephrol. Dial. Transplant.* **2015**, *30*, 978–988. [CrossRef]
160. Tomson, C.; Tomlinson, L.A. Stopping RAS Inhibitors to Minimize AKI: More Harm than Good? *Clin. J. Am. Soc. Nephrol.* **2019**, *14*, 617–619. [CrossRef]
161. Ungprasert, P.; Cheungpasitporn, W.; Crowson, C.S.; Matteson, E.L. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. *Eur. J. Intern. Med.* **2015**, *26*, 285–291. [CrossRef] [PubMed]
162. O'Reilly, P.; Tolwani, A. Renal replacement therapy III: IHD, CRRT, SLED. *Crit. Care Clin.* **2005**, *21*, 367–378. [CrossRef] [PubMed]
163. Tolwani, A. Continuous renal-replacement therapy for acute kidney injury. *N. Engl. J. Med.* **2012**, *367*, 2505–2514. [CrossRef]
164. Cerdá, J.; Ronco, C. Modalities of continuous renal replacement therapy: Technical and clinical considerations. *Semin. Dial.* **2009**, *22*, 114–122. [CrossRef] [PubMed]
165. Kellum, J.A.; Mehta, R.L.; Angus, D.C.; Palevsky, P.; Ronco, C. The first international consensus conference on continuous renal replacement therapy. *Kidney Int.* **2002**, *62*, 1855–1863. [CrossRef] [PubMed]
166. Cerda, J.; Sheinfeld, G.; Ronco, C. Fluid overload in critically ill patients with acute kidney injury. *Blood Purif.* **2010**, *29*, 331–338. [CrossRef] [PubMed]
167. Tandukar, S.; Palevsky, P.M. Continuous Renal Replacement Therapy: Who, When, Why, and How. *Chest* **2019**, *155*, 626–638. [CrossRef]
168. Ronco, C.; Bellomo, R.; Ricci, Z. Continuous renal replacement therapy in critically ill patients. *Nephrol. Dial. Transplant.* **2001**, *16*, 67–72. [CrossRef]

169. Schwenger, V.; Weigand, M.A.; Hoffmann, O.; Dikow, R.; Kihm, L.P.; Seckinger, J.; Miftari, N.; Schaier, M.; Hofer, S.; Haar, C.; et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury—A randomized interventional trial: The RElnal Replacement Therapy Study in Intensive Care Unit PatiEnts. *Crit. Care* **2012**, *16*, R140. [CrossRef]
170. Villa, G.; Neri, M.; Bellomo, R.; Cerda, J.; De Gaudio, A.R.; De Rosa, S.; Garzotto, F.; Honore, P.M.; Kellum, J.A.; Lorenzin, A.; et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: Practical applications. *Crit. Care* **2016**, *20*, 283. [CrossRef]
171. Lins, R.L.; Elseviers, M.M.; Van Der Niepen, P.; Hoste, E.; Malbrain, M.L.; Damas, P.; Devriendt, J. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: Results of a randomized clinical trial. *Nephrol. Dial. Transplant.* **2009**, *24*, 512–518. [CrossRef] [PubMed]
172. Vinsonneau, C.; Camus, C.; Combes, A.; De Beauregard, M.A.C.; Klouche, K.; Boulain, T.; Pallot, J.-L.; Chiche, J.-D.; Taupin, P.; Landais, P.; et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* **2006**, *368*, 379–385. [CrossRef]
173. Nash, D.M.; Przech, S.; Wald, R.; O'Reilly, D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *J. Crit. Care* **2017**, *41*, 138–144. [CrossRef] [PubMed]
174. Friedrich, J.O.; Wald, R.; Bagshaw, S.M.; Burns, K.E.; Adhikari, N.K. Hemofiltration compared to hemodialysis for acute kidney injury: Systematic review and meta-analysis. *Crit. Care* **2012**, *16*, R146. [CrossRef]
175. Ronco, C.; Bellomo, R.; Homel, P.; Brendolan, A.; Dan, M.; Piccinni, P.; La Greca, G. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* **2000**, *356*, 26–30. [CrossRef]
176. Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury. *N. Engl. J. Med.* **2008**, *359*, 7–20. [CrossRef]
177. Bellomo, R.; Cass, A.; Cole, L.; Finfer, S.; Gallagher, M.P.; Billot, L.; McArthur, C.; McGuinness, S.; Myburgh, J.; Norton, R.; et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N. Engl. J. Med.* **2009**, *361*, 1627–1638.
178. Clark, E.; Molnar, A.O.; Joannes-Boyau, O.; Honoré, P.M.; Sikora, L.; Bagshaw, S.M. High-volume hemofiltration for septic acute kidney injury: A systematic review and meta-analysis. *Crit. Care* **2014**, *18*, R7. [CrossRef]
179. Combes, A.; Cozic, N.; Guidon, C.; Thiranos, J.-C.; Rigal, J.-C.; Benhaoua, H.; Abry, B.; Chastre, J.; Bréchot, N.; Amour, J.; et al. Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock. The HEROICS Study. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 1179–1190. [CrossRef]
180. Gaudry, S.; Hajage, D.; Schortgen, F.; Martin-Lefevre, L.; Pons, B.; Boulet, E.; Boyer, A.; Chevrel, G.; Lerolle, N.; Carpentier, D.; et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N. Engl. J. Med.* **2016**, *375*, 122–133. [CrossRef]
181. Barbar, S.D.; Clere-Jehl, R.; Bourredjem, A.; Hernu, R.; Montini, F.; Bruyère, R.; Lebert, C.; Bohé, J.; Badie, J.; Eraldi, J.-P.; et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N. Engl. J. Med.* **2018**, *379*, 1431–1442. [CrossRef] [PubMed]
182. Zarbock, A.; Kellum, J.A.; Schmidt, C.; Van Aken, H.; Wempe, C.; Pavenstädt, H.; Boanta, A.; Gerß, J.; Meersch, M. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* **2016**, *315*, 2190–2199. [CrossRef] [PubMed]
183. Zhang, Z. No "optimal timing" of renal-replacement therapy in critically ill patients with acute kidney injury. *Ann. Transl. Med.* **2018**, *23*. [CrossRef] [PubMed]
184. Gaudry, S.; Hajage, D.; Martin-Lefevre, L.; Louis, G.; Moschietto, S.; Beauport, D.T.; La Combe, B.; Pons, B.; De Prost, N.; Besset, S.; et al. The Artificial Kidney Initiation in Kidney Injury 2 (AKIKI2): Study protocol for a randomized controlled trial. *Trials* **2019**, *20*, 726. [CrossRef]
185. Smith, O.M.; Wald, R.; Adhikari, N.K.; Pope, K.; Weir, M.A.; Bagshaw, S.M. Standard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury: Study Protocol for a Multi-National, Multi-Center, Randomized Controlled Trial. *Can. J. Kidney Health Dis.* **2019**, *6*, 320.

186. Sutherland, S.M. Electronic Health Record-Enabled Big-Data Approaches to Nephrotoxin-Associated Acute Kidney Injury Risk Prediction. *Pharmacotherapy* **2018**, *38*, 804–812. [CrossRef] [PubMed]
187. Basu, R.K. Dynamic Biomarker Assessment: A Diagnostic Paradigm to Match the AKI Syndrome. *Front. Pediatr.* **2019**, *7*, 535. [CrossRef]

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Perspective

Why Have Detection, Understanding and Management of Kidney Hypoxic Injury Lagged behind Those for the Heart?

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Abstract: The outcome of patients with acute myocardial infarction (AMI) has dramatically improved over recent decades, thanks to early detection and prompt interventions to restore coronary blood flow. In contrast, the prognosis of patients with hypoxic acute kidney injury (AKI) remained unchanged over the years. Delayed diagnosis of AKI is a major reason for this discrepancy, reflecting the lack of symptoms and diagnostic tools indicating at real time altered renal microcirculation, oxygenation, functional derangement and tissue injury. New tools addressing these deficiencies, such as biomarkers of tissue damage are yet far less distinctive than myocardial biomarkers and advanced functional renal imaging technologies are non-available in the clinical practice. Moreover, our understanding of pathogenic mechanisms likely suffers from conceptual errors, generated by the extensive use of the wrong animal model, namely warm ischemia and reperfusion. This model parallels mechanistically type I AMI, which properly represents the rare conditions leading to renal infarcts, whereas common scenarios leading to hypoxic AKI parallel physiologically type II AMI, with tissue hypoxic damage generated by altered oxygen supply/demand equilibrium. Better understanding the pathogenesis of hypoxic AKI and its management requires a more extensive use of models of type II-rather than type I hypoxic AKI.

Keywords: acute kidney injury; myocardial infarction; ischemia; biomarkers; management; diversity outcome

1. Introduction

Despite the high incidence of acute kidney injury (AKI) and its association with an alarming increase in morbidity and mortality, the therapeutic approaches for AKI are still disappointing and rely mainly on supportive measures [1,2]. This deficiency stems from the poor understanding of the pathogenesis of AKI and due to the delayed detection of AKI, as this syndrome is often asymptomatic during its early stages. Concerning the latter, the diagnosis of AKI is challenging since it mainly relies on serum creatinine (Scr), which suffers from major limitations as reliable biomarker for measurement of kidney function [3]. Specifically, in the setting of AKI, the time relationship between changes in SCr and concomitant changes in GFR does not allow accurate estimation regarding timing and reversibility of renal injury and the severity of kidney dysfunction, thus delaying diagnosis and intervention [3].

As opposed to the lack of breakthroughs in the diagnosis and management of AKI, great leaps took place in the setup of acute myocardial infarction (AMI). Mortality following AMI declined dramatically

over the last 40 years and post-MI morbidity and mortality improved substantially, thanks to the early detection of evolving myocardial hypoxic injury and the achievement of myocardial salvage by the prompt restoration of coronary blood flow, first with early thrombolysis, and later with immediate or delayed coronary interventions and surgery. Currently, early mortality among patients treated for acute ST-elevation MI (STEMI) is about 4%, some 80% lower than a few decades ago, underscoring the importance of early detection of AMI and of prompt intervention to restore regional blood flow.

Renal parenchymal hypoxia plays a pivotal role in various conditions leading to AKI, and a major clinical challenge is its early detection and the differentiation between hypoxic injury and other factors leading to AKI.

The aim of this review is to compare the clinical tools available for the timely detection of incipient or evolving acute hypoxic organ damage in the heart and kidney and to analyze the causes leading to the lack of advances in the diagnosis and management of hypoxic AKI, as compared with the outstanding clinical achievements in ischemic myocardial injury. This review will encompass the physiologic complexity of acute hypoxic kidney dysfunction, as compared with the heart, and as summarized in Table 1 putting side-by-side clinical features and available techniques detecting real-time organ injury. We shall further underscore what we believe are basic misconceptions regarding hypoxic AKI that have for decades diverted interventional efforts in the attempt to prevent or amend AKI in the wrong direction.

Table 1. Types of acute kidney injury (AKI) and acute myocardial infarction (AMI)-similarities and differences.

	Type I Ischemic AKI	Type II Hypoxic AKI	Type I AMI	Type II AMI
Pathophysiology	Ischemia and reperfusion	Altered oxygen supply/demand balance	Ischemia and reperfusion	Altered oxygen supply/demand balance
Tissue blood supply	ceases	Maintained or reduced	ceases	Maintained or reduced
Workload and oxygen consumption	ceases	continued/enhanced	Rapidly declines	enhanced
Clinical scenario	Rare Renal infarct	Common Hypotension, CKD, diabetes, NSAIDs, iodinated contrast media, osmotic dieresis etc.	AMI Due to ruptured plaque	Increased workload in the presence of coronary stenosis (hypotension, anemia, tachycardia etc.)
Symptoms	Flank pain, hematuria	None related to AKI	Chest pain and accompanying complaints	Chest pain and accompanying complaints
Immediate evidence of functional impairment	None if unilateral/segmental	None	Occasionally evidence of impaired circulation and heart failure	Occasionally evidence of impaired circulation and heart failure
Rapid functional diagnostic tools	None	None	Echocardiography (ECG)	Echocardiography (ECG)
Specific biomarkers	Available and sensitive, limited specificity †	Available, limited specificity and sensitivity †	Highly specific and sensitive in detecting injury	Highly specific and sensitive in detecting injury

† Specificity is limited especially in the presence of pre-existing renal disease and in aged patients. Tubular segment-type-specificity of the various biomarkers require panel assays. CKD: Chronic kidney diseases; NSAIDs: Non-steroidal anti-inflammatory drugs.

2. Comparing the Pathogenesis of Renal and Cardiac Hypoxic Injury

Myocardial ischemia is caused by interrupted blood supply, either as an acute coronary occlusion (caused by a ruptured plaque within an atheromatous plaque), or as a chronic narrowing of the coronary lumen, mostly due to an atheromatous plaque. The former clinical scenario leads to what is called Type I AMI, reflecting organ ischemia (i.e., anoxia due to total cessation of regional blood flow), whereas chronic narrowing of the coronary lumen leads to a transient and usually reversible regional hypoxia with an anginal syndrome (typically characterized by reversible pain), appearing whenever oxygen demand surpasses the restricted oxygen supply, for instance during

exercise or tachycardia, and resolving as oxygen demand declines. If severe and protracted enough, myocardial hypoxia related to anginal syndrome may evolve into frank tissue injury, termed Type II MI [4]. The myocardium is characterized by an oxygenation gradient, with pO_2 declining from the sub-pericardial to the innermost sub-endocardial regions, especially in regions with coronary stenosis, whenever oxygen demand/supply balance is altered: for instance when diastolic intraventricular pressure increases, undermining sub-endocardial myocardial blood flow and oxygen supply [5–7]. Consequently, a trans-myocardial gradient of hypoxia-induced response appears, such as enhanced expression of hypoxia-inducible factors (HIF) specifically in subendocardial regions [8], or ultimate myocardial injury, first manifested at the innermost portions of the myocardium and spreads outwards as hypoxia persists or intensifies. Intermediate degrees of sub-lethal hypoxia may invoke functional impairment, with altered myocyte contraction and relaxation, myocardial hibernation and apoptosis, whereas prolonged ischemia invokes tissue necrosis and a local inflammatory response [9,10]. Adaptive responses to chronic hypoxia such as the development of collateral microcirculation, as happens in patients with multi-vessel disease, often mitigate the outcome of acute vessel occlusion, leading to subtler tissue damage, in the form of limited subendothelial necrosis (often presented as non-Q wave myocardial infarction). By contrast, acute coronary occlusion due to ruptured plaque without prior chronic hypoxia, as occurs in young smokers with a single vessel disease, is usually manifested as STEMI, with en-block trans-mural myocardial infarction that spreads from the sub-endocardial myocardium outwards along time as ischemia persists. Rapid restoration of regional blood flow by thrombolysis, endovascular interventions (transluminal angioplasty and stenting) or with bypass operations provide myocardial salvage and may restrict the spread of necrosis. Cellular mechanisms of injury are beyond the scope of this short review but the outcome of ischemia and subsequent reperfusion in these settings are the consequence of energy store depletion and access formation of free-radicals, leading to the impairment of vital cellular functions and irreversible structural damage.

As compared with the heart, the kidney presents with only a few uncommon clinical conditions that physiologically mimic Type I AMI with extensive ischemia and reperfusion injury. Acute main- or segmental renal arterial occlusion, for instance due to arterial emboli, is one example. Functional impairment may be subtle in these instances, reflecting enhanced filtration in remnant nephrons, unless an embolus affects a single functioning kidney, or in the presence of a-priori renal failure without functional reserve [11]. Acute global renal ischemia with AKI may develop also in kidneys harvested for transplantation or during cross-clamping of the aorta or cardiopulmonary bypass operations, where the organ is subjected to cold ischemia-reperfusion injury. Acute global warm renal ischemia with AKI may also very rarely develop due to profound and protracted shock in post-partum settings [12], or as shown in Figure 1, following prolonged pulseless cardiorespiratory resuscitation with the use of huge amounts of catecholamines [13].

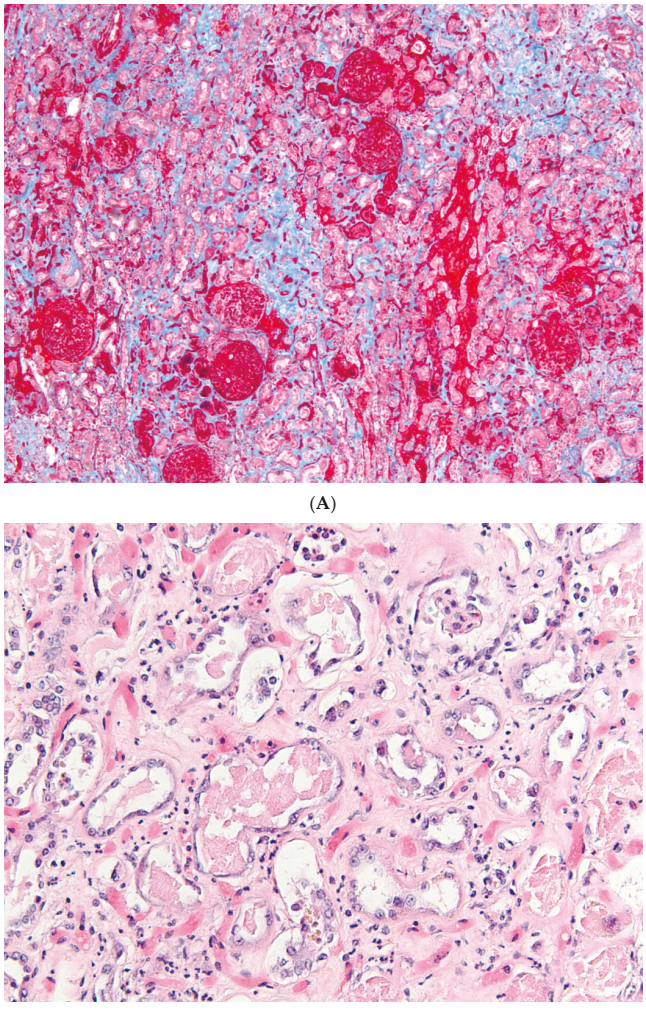
However, most cases of hypoxic AKI encountered in the clinical practice are not associated with total or near-total cessation of renal blood flow, and is believed to represent a Type II organ injury pattern, reflecting imbalanced regional renal oxygen supply and consumption, especially in regions which are a-priori physiologically hypoxic. As with the heart, the renal parenchymal oxygenation profile is also non-homogenous, with a cortico-medullary oxygen gradient and an inner medullary pO_2 as low as 20 mmHg under normal physiologic conditions [14]. Physiological medullary hypoxia reflects very limited blood supply (some 10% of total renal blood flow, delivered by vasa recta), medullary oxygen shunts across descending and ascending vasa recta, and intense regional tubular transport and oxygen consumption. Medullary physiologic hypoxia is the price paid for the construction of the countercurrent urine concentrating apparatus and the very low regional blood flow required for the generation of medullary hyperosmolality. Complex mechanisms are designed to maintain safe oxygen levels in the medulla by the regulation and matching of regional blood flow and oxygen consumption for tubular transport. Prostaglandins, nitric oxide and adenosine are key regulators of these mechanisms [15]. Additional physiologic factors that affect distal tubular transport activity and oxygen consumption are glomerular filtration rate (GFR) and the extent of proximal tubular

reabsorption. Enhanced GFR and diminished proximal tubular transport increase distal tubular transport workload, while reduced GFR and enhanced proximal tubular reabsorption reduce oxygen consumption by distal tubular segments and may paradoxically improve medullary oxygenation [16]. Renal oxygenation profile may diversely be affected in the cortex and medulla. For instance, controlled moderate hypotension (with reduced cortical oxygenation but maintained vasa recta blood flow) may result in declined cortical oxygenation, while medullary pO_2 paradoxically increases as tubular transport workload diminishes. By contrast, medullary oxygenation eventually declines when mean blood pressure falls below 60–65 mmHg, as vasa recta blood flow and medullary oxygen delivery eventually decline [17]. The term "renal angina syndrome" has been proposed to describe the situation of the renal medulla, which functions on the verge of hypoxia, comparable to the myocardial anginal syndrome. Pre-renal failure exists in this setup, when mean blood pressure is kept above 60–65 mmHg, without structural damage or tubular functional defects. As medullary hypoxia intensifies with a further decline of blood pressure, tubular injury and dysfunction develops, with an activation of tubulo-glomerular feedback mechanisms that reduce GFR. Indeed, this condition of transformation from pre-renal failure to hypoxic AKI has been termed "acute renal success", with renal parenchymal injury remaining limited and often undetected in biopsies (Figure 2) thanks to reduced GFR, as long as medullary blood supply is not critically diminished [15].

As opposed to the rare scenarios leading to total cessation of blood flow with ischemic injury, there is a host of clinical conditions leading to renal parenchymal hypoxia and to the propensity to develop hypoxic AKI due to imbalanced regional oxygen supply and consumption. Chronic kidney disease leads to renal hypoxia through rarefication of microvasculature, interstitial fibrosis and increased workload imposed on remnant nephrons [18,19]. The diabetic kidney is also hypoxic, reflecting both altered medullary flow, combined with enhanced tubular transport and oxygen requirements [20,21]. As detailed above, all conditions leading to reduced renal perfusion may affect the renal parenchymal oxygenation profile. Administration of hypertonic saline [22], mannitol [23] or SGLT2 inhibitors [24,25] increase distal solute delivery and may intensify transport workload and medullary hypoxia. Inhibition of prostaglandins synthesis with non-steroidal anti-inflammatory agents or altered nitric oxide production invokes profound medullary hypoxia by both the selective reduction of vasa recta blood flow and augmentation of sodium transport in medullary thick ascending limbs (mTALs) [26]. Likewise, iodinated contrast agents cause intense medullary hypoxia by reducing vasa recta flow and enhancing tubular transport [27]. Other nephrotoxins may induce hypoxic injury by the reduction of regional blood flow alone (cyclosporine, heme-containing molecules) or in association with enhancement of tubular transport (amphotericin) [26]. Near-drowning in seawater is an archetype of renal oxygenation imbalance, due to both reduced renal oxygen supply (because of systemic hypoxemia, intense sympathetic activity and perhaps a transient hypotension) and enhanced oxygen consumption (with large amounts of absorbed hypertonic saline profoundly enhancing solute delivery for re-uptake in the distal nephron) [28]. Worth noting is that we often induce predictable iatrogenic type II hypoxic AKI in justified clinical settings such as coronary interventions using iodinated contrast media in very high-risk patients with cardiogenic shock. Yet, understanding this disorder might reduce it by measures aimed to maintain renal oxygen balance, as outlined in Future Challenges.

Unlike the homogenous myocardium, renal morphology is highly complex and tubular segments and other parenchymal components differ in their ability to cope with hypoxic stress. The proximal tubule is highly susceptible to hypoxic injury since it cannot tolerate prolonged anaerobic glycolysis. By contrast, mTALs are capable to endure prolonged hypoxia as long as transport activity stops, but rapidly develop hypoxic damage in proportion to oxygen consumption for ion transport [29,30]. Transport activity also intensifies hypoxic injury to S3 segments [31], while collecting ducts are highly resistant to hypoxia and are able to express large amounts of HIF in response to intensified ambient hypoxia [32]. In the outer medulla, seemingly tubular segments compete with each other on sparse oxygen availability, and excess tubular transport in on segment intensify damage in others [33]. A further complicating factor is the often complex and multifactorial nature of renal

parenchymal injury and dysfunction, with renal hypoxic injury act in concert with direct tubular toxicity (as with amphothericin, or in hemo/myoglobinuric renal failure), or with altered renal hemodynamics (for instance in sepsis) [26]. It is, therefore, often impossible to assess the independent impact of hypoxia on AKI in these settings.



(**A**)

(**B**)

Figure 1. Renal cortical morphology of type I ischemic AKI. Resuscitation was initiated in a 71 years old patient with AMI who remained pulseless for an hour before the restoration of effective cardiac rhythm. The patient's blood pressure was only briefly maintained by intravenous pressors, but he subsequently developed intractable cardiogenic shock and anuria, dying 5 days after the initial incident. Autopsy findings resemble renal morphology following prolonged WIR in rodents: In (**A**) changes of ischemic hemorrhagic necrosis are shown, superimposed on renal parenchymal tissue with fibrotic changes. Proximal tubules are illustrated in high-power photograph (**B**). The tubular epithelium is flattened and shows extensive regenerative changes and formation of casts. Scattered polymorphonuclear infiltration is also noted. (Masson's trichrome and H&E, original magnifications ×40 and ×200, respectively).

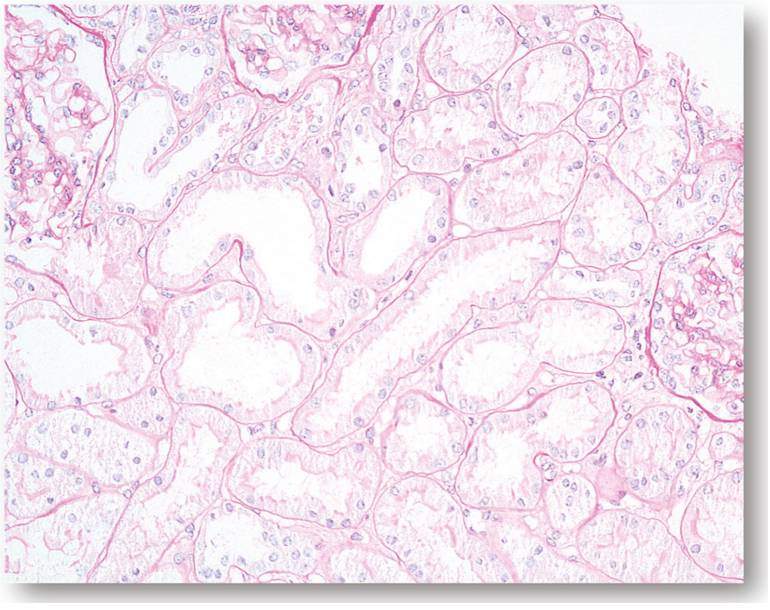


Figure 2. Renal cortical morphology of type II hypoxic acute kidney injury (AKI). A 18 year old male who presented with a one-day history of nausea and copious vomiting, accompanied by low-back and lower abdominal pain for which he took ibuprofen. The previous day he had consumed a fifth of Jack Daniels, smoked marijuana and played drums all night. Initial creatinine upon admission was 6.0 mg/dL with laboratory evidence of mild rhabdomyolysis (creatine kinase 2025u, normal 90–250u). Anuric AKI developed, requiring a single hemodialysis. Biopsy, obtained at peak creatinine of 14.7 mg/dL on 7th day shows maintained cortical parenchyma. (Periodic Acid-Schiff (PAS), original magnification ×200).

In conclusion, renal ischemia, i.e., total cessation of renal blood flow is a rare form of hypoxic AKI that resembles Type I AMI, with tissue ischemia and reperfusion injury. By contrast, in most cases, renal parenchymal- and particularly medullary hypoxic injury may develop whenever oxygen supply/demand balance is disrupted, resembling pathophysiologically Type II AMI in patients with fixed stenotic coronary arteries [4]. We propose using the terminology of type I and type II hypoxic AKI, for these two different conditions, respectively.

3. Conceptual Errors in the Understanding of Hypoxic AKI

For decades, renal warm ischemia-reperfusion has been adopted by nephrologists as the representative of hypoxic AKI. Extensive research and large budgets have been invested in studying rodent models of ischemia generated by arterial cross-clamping of the renal artery for 30 and up to 60 min in mice and rats, respectively, followed by reperfusion. These models of ischemia and reperfusion (type I hypoxic AKI) parallel animal models of Type I AMI. Morphologic characteristics of tissue injury in these AKI models are ischemic time-dependent extensive proximal tubular injury predominantly in the outer stripe of the outer medulla, accompanied by congestion and substantial inflammation [34], with renal functional impairment grossly proportional to the extent of injury. Medullary thick limb injury in these models does not occur since tubular transport ceases upon cross-clamping, and is low during reperfusion, likely because of reduced GFR and downstream solute delivery [35]. Renal morphology in these models resembles en-bloc necrosis and inflammation, noted in the uncommon clinical cases of global renal ischemia, as shown in Figure 1.

As outlined above, this injury mechanism with global organ ischemia does not physiologically mimic type II hypoxic AKI, where near-complete cessation of renal blood flow does not occur. Over the years models of hypoxic AKI were constructed, both in isolated perfused kidneys and in intact animals in vivo, based on medullary oxygen imbalance, where renal oxygen supply and tubular transport persist throughout the induction of injury [36,37]. Tubular hypoxic stress and injury in these models is principally noted in mTALs and to a lesser extent in S3 segments in the outer medulla, ranging from stabilization of HIF signals, through apoptosis or reversible phases of cell injury (nuclear pyknosis, mitochondrial swelling) to frank necrosis with cell membrane disruption. Injury gradient is evident, most prominent in the inner layers of the outer medulla and in the interbundle zone, most remote from vasa recta and oxygen supply [32,38,39]. In these models tissue injury may be focal, without prominent inflammation, and with functional impairment (reduced GFR) often out-of-proportion to the very limited focal tubular injury. We believe that such models are physiologically relevant to type II hypoxic AKI, with limited tubular injury as in Figure 2. Using the warm ischemia-reperfusion AKI models for years has been a formidable obstacle in the development of clinically relevant therapeutic strategies, treating animals with an artificial disease that is irrelevant to the human scenario [36,40].

4. Clinical Presentation of Hypoxic Cardiac vs. Renal Injury

Myocardial ischemia is most often manifested immediately with chest pain and accompanying complains, such as radiating pain, nausea and vomiting, cold perspiration, shortness of breath and doom feeling. Angina pectoris is initiated or aggravated by physical activity and enhanced myocardial oxygen demand. Yet, some patients, especially elderly and diabetic individuals might undergo painless myocardial ischemia or hypoxia due to altered sensorium.

As opposed to protean overt symptoms in most cases of myocardial injury, clinical symptoms in the clinical settings of hypoxic AKI are most often absent, likely since tissue injury in subtle and focal, and out of proportion to the extent of functional impairment. Rare exceptions are type I hypoxic injury due to acute total or segmental renal infarction that may be manifested as flank pain mimicking renal colic. Gradual renal artery stenosis may be revealed among patients during the evaluation of secondary hypertension, and symptoms of severe hypertension or pulmonary congestion may develop in the case of renal arterial occlusion of a single functioning kidney or in the rare cases of bilateral renal ischemia.

5. Detection and Assessment of Myocardial Hypoxic Injury

A large and easily accessible arsenal of diagnostic tools is available in the clinical practice for the immediate detection of myocardial hypoxia. Myocardial ischemia can be detected in real time as it evolves by typical electrocardiographic changes and by altered regional wall motion, easily sensed by echocardiography, which also helps ruling out major differential diagnoses. Dynamics in these parameters can be assessed in type II ischemia during enhanced workload and oxygen consumption, with exercise test or its equivalents. Myocardial perfusion can be identified by radiolabled scans and by MRI, and tissue injury can be validated by the detection of released myocardial constituents, such as troponin isoforms, myoglobin and others. The extent of myocardial necrosis grossly correlates with the rise in these biomarkers of cardiac muscle injury. With all these technologies myocardial hypoxia or ischemia is usually easily detected and intravascular lesions can be located and managed by non-invasive and invasive coronary imaging and interventions.

Altogether, cardiologists possess reliable and readily available diagnostic tools that provide immediate assessment of cardiac function and indices of tissue injury, studies that can be performed repeatedly with grossly clear-cut threshold definitions of myocyte injury.

6. Detection of Hypoxic Renal Injury

Delayed involvement of nephrologists is an important obstacle in achieving real-time identification, appropriate management and improved outcome of AKI. Furthermore, comparable

tools for the prompt and timely diagnosis of AKI in general and specifically of hypoxic renal injury are unfortunately lacking. The parameters used by AKIN or RIFLE criteria for grading of AKI stages [41,42], namely the rates of urine output and rise in plasma creatinine, are non-specific and non-immediate upon injury. The clinical scenario and the presence of orthostatic hypotension may suggest pre-renal failure, and renal Doppler-ultrasound can rule out post-renal causes and assess renal vascular resistance, and may identify features of chronic renal disease. Urinalysis and microscopy may help detecting glomerulopathies and might identify typical features of acute tubular necrosis or crystal nephropathy. Analysis of urine osmolality, sodium and creatinine, and their corresponding plasma values further may help differing pre-renal failure from tubular injury. Yet, often results are within a very wide gray zone with low specificity, and these parameters are markedly affected by the use of fluids and diuretics and in the presence of pre-existing renal disease. Enhancement imaging with iodine-containing- or gadolinium-based contrast agents is associated with the risk of further renal injury or nephrogenic systemic fibrosis, respectively.

Novel technologies currently under development provide non-enhanced imaging of renal morphology, function, microcirculation and oxygenation [43]. Additional promising diagnostic tools are biomarkers of renal tissue injury [44]. The potential use of these two advanced tools in the early detection of AKI in general and in are briefly discussed below.

7. Biomarkers of Acute Kidney Injury

The great development in molecular biology during recent decades has led to a major advance in the search for novel biomarkers for early detection of AKI [45], as evident by the discovery of several key biomarkers of myocardial injury with various specificity and sensitivity, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), netrin-1 and IL18 [45–48]. NGAL is one of the most prominently up-regulated genes in the kidney after AKI, particularly in distal nephron segments and damaged renal tubule [45,46]. This biomarker is increased in urine and plasma early after renal ischemia in mouse and rat models [49], and following cardiopulmonary bypass, radiocontrast administration, sepsis, and kidney transplantation, specifically in patients who subsequently developed AKI [50]. Meta-analysis of data from 19 studies, which included more than 2500 patients, revealed that rises in serum or urine NGAL levels are diagnostic for AKI [51]. As opposed to NGAL, KIM-1 is a biomarker for proximal tubular injury, and is a hallmark of toxic and ischemic proximal tubular injury [46,47]. Double labeling immunohistochemistry in various experimental and human renal diseases revealed that KIM-1-positive tubules are associated with macrophages and areas with increased expression of α-smooth muscle actin (α-SMA), a marker of myofibroblast transformation [46,52,53]. Interleukin 18 (IL-18), a pro-inflammatory cytokine belonging to the IL-1 superfamily has been reported to mediate experimental ischemic proximal tubular injury and its accompanied pro-inflammatory responses [54]. IL-18 is produced by phagocytes attracted to injured proximal tubules, activated by caspase 1, and excreted into the urine upon renal ischemic injury [54]. Although IL-18 was found to be a helpful biomarker for early detection of AKI, it is less sensitive than NGAL [55,56]. Most recently additional two cycle arrest biomarkers were added to the growing list of AKI biomarkers, namely, insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), with the potential to provide new mechanistic insights into the pathogenesis of AKI on one hand and the ability for early detection of this clinical setting, on the other [48,57].

Despite the expectations from these novel biomarkers to be sensitive, practical, and accurate in predicting AKI, the results were not unambiguous. Indeed, some of these biomarkers show unequivocal ability to predict AKI in certain settings as mentioned above. However, many of them suffer from drawbacks mainly due to broad range of its predictive accuracy. Moreover, the circulatory concentration profile of most biomarkers is adversely affected by the fluid balance and diuretic therapy. Though this concern regarding urinary biomarkers could be overcome by correcting their excretion to urinary creatinine, in certain clinical settings the creatinine kinetics is dramatically altered as the

case in critical ill patients where most of the AKI cases are witnessed. Additional concern is the fact the most of the tested biomarkers are present in the circulation and their excretion in the urine does not necessarily reflect renal origin/damage. For instance, NGAL is expressed by several cell types, including endothelial cells, smooth muscle cells and macrophages in atherosclerotic plaques, where it assumedly plays a role in the pathogenesis of atherosclerosis, endothelial dysfunction, inflammatory processes and extracellular matrix remodeling [58]. Moreover, since the urinary origin of the various biomarkers are cell-specific, and AKI could be due various aetiologies, i.e., ischemia, nephrotoxicity, inflammation and renal outflow obstruction, with differential involvement of cell types, it is unlikely that a single biomarker would predict AKI reliably, the mechanisms underlying AKI or the identity of the damaged renal cells: proximal, distal, collecting duct epithelial cells, or interstitial cells [48]. Support for the use of combined biomarkers to improve their predictability value came from a study in adult patients who underwent CPB surgery, where using urinary biomarkers KIM-1, NAG, and NGAL predicted AKI 3 h from the operation by 0.65 for KIM-1; 0.63 for NAG; and 0.65 for NGAL [59]. When two biomarker was applied, the sensitivity of AKI prediction 3 h from surgery was enhanced to 0.78 [60], and escalated even to a higher specificity (0.94) when four biomarkers were used [59]. Finally, the specificity and sensitivity of most of these biomarkers are deleteriously affected by confounding factors as the presence background diseases such as CKD, cancer, heart failure, atherosclerosis or inflammation, which may cause false positive diagnosis [45]. This may explain the high specificity and sensitivity of the initial results where the reliability of theses biomarkers were tested in children who underwent CPB or radiocontrast administration [45,46], as compared with the lower accuracy when the studies were repeated in adult patients (usually with background diseases) who underwent similar clinical procedures [48].

In sum, the AKI biomarkers field is evolving. Despite their advantage as noninvasive and reasonable specificity for renal injury, more comprehensive studies are still requested to determine their clinical application.

8. Renal Functional Imaging

Although determination of vital organs function and dysfunction still largely relies on biochemical analysis of blood/serum and/or urine, imaging of these organs is evolving rapidly and holds great promise for improving detection of structural, functional and even molecular changes in these tissues [61]. The kidney is of special interest yet challenging, as it has unique anatomic and ultrastructural features. Specifically, the multi functions of the kidney require different types of epithelial cells, regional blood flow and oxygen consumption along the nephron and the cortical and medullary tissues. Therefore, development of functional imaging is crucial for diagnosis of physiological and pathophysiological alterations in the kidney.

Historically, renal perfusion and oxygenation under various conditions was determined either invasively via laser-Doppler flowmeter and oxygen microelectrodes [17,23,33] or indirectly via measurement of urinary pO_2 [22]. Subsequently, imaging of renal perfusion and GFR were developed, with arterial spin labeling (ASL), an MRI methodology applied to determine total RBF [62]. ASL uses magnetically tagged water with a radiofrequency pulse. Briefly, a control image is obtained without contrast, followed by a radiofrequency pulse of the blood before it enters the kidney. The labeled image is then subtracted from the baseline image, generating a map of the signal difference created by the perfused blood [63]. Although initially ASL was not considered sensitive, upgrading imaging acquisition techniques improved its performance, where it can currently discriminate between medulla and cortex according to meta-analysis of 53 studies [64]. For instance, ASL allows detecting early renal damage following cardiopulmonary bypass procedures, where the incidence of AKI may reach up to one third of patients [50,65]. As cardiopulmonary bypass-induced AKI was associated with renal hypoperfusion and vasoconstriction, ASL was sensitive enough to detect reduced RBF and GFR [49]. This methodology was found to be valid in kidney-transplanted patients with delayed graft function [66]. Similarly, ASL exhibited high sensitivity in detecting impaired regional blood perfusion

along kidney injury and histological changes in correlation with the severity of the renal insult in experimental models of AKI induced by ischemic/reperfusion for 35–45 min [67]. Moreover, ASL detected long term outcome of renal remodeling and hypo perfusion/remodeling or full recovery a few weeks after the AKI induction [61,67].

In the last two decades, blood oxygen level-dependent (BOLD) MRI and related technologies provided the most striking advance in non-invasive measurement of intra renal oxygenation profile in humans and in experimental animals [61,68]. Bold MRI uses the different properties of oxygenated and non-oxygenated hemoglobin, where the latter is magnetic, to determine tissue oxygen levels [61]. Several studies have shown that R2* relaxation rate is inversely correlated with tissue pO_2 and can be mapped throughout BOLD MRI of the kidneys [69–71]. Specifically, using BOLD MRI revealed that administration of furosemide to normal subjects significantly decreased outer medullary R2* [72], indicating improved oxygenation, in agreement with findings with oxygen microelectrodes [23]. Yet it did not cause such reduction in patients with CKD and among hypertensive subjects, although basal R2* was comparable in the three studied groups [72]. Despite the increasing popularity of this convenient method, there are several confounding factors that may adversely affect its reliability, such as fluid balance, salt intake, smoking, and pulmonary function [69]. Respiratory gating is also required to overcome kidney motion-related artifacts. Dynamic contrast-enhanced (DCE) MRI is an additional imaging approach aimed at measuring GFR and renal blood flow, using gadolinium-based contrast agents [73,74]. For this purpose, serial images of the kidney are obtained as the contrast is filtered and used to calculate GFR. The DCE MRI method was found to be superior to other MRI techniques that use radionuclides for the measurements of GFR [75]. Finally, hemodynamic response imaging (HRI), a non-enhanced functional MRI method, provides insights regarding renal perfusion and vascular reactivity in response to alternating hypercapnia and hyperoxia [76,77].

Sodium MRI provides an additional unique capability of the assessment of outer medullary function. In healthy state and especially in pre-renal impairment, this gradient reflects the efficient concentrating mechanism generated in part by avid sodium transport across mTALs. Disruption of the normal cortico-medullary sodium gradient that appears within a few hours following the disruption of medullary oxygenation balance is a very early indicator of medullary hypoxic injury, when morphologic indices of tubular damage are still very focal and perhaps reversible, and plasma creatinine hardly rises [78]. This finding likely goes together with increased fractional sodium excretion and the transformation from highly concentrated urine to isosthenuria [79]. Thus, renal sodium MRI might provide the equivalent of the detection of compromised myocardium with segmental wall-motion disturbances by stress-echocardiography.

These wonderful non-invasive tools alone or in combination provide tremendous insight about real-time changes in renal structure, hemodynamics, glomerular filtration, oxygenation and function. Unfortunately, while they may serve as advanced experimental probes, their clinical use is limitted, as they are not available in most institutes. Furthermore, most patients requiring diagnostic evaluation of AKI are in critical care settings, connected to monitoring and life-maintaining equipment that preclude bedside usage of MRI. A more feasible and promising technology for the early real-time detection of evolving medullary hypoxia and for assessing the risk of hypoxic AKI is a continuous determination of urinary pO_2 at the catheter tip, as recently shown in the settings of cardiac surgery [80].

Imaging that enables the detection of injured tissues is another exciting plausible technology to be studied [81]. Focal tubular apoptosis and necrosis were traced by a specific small molecule in evolving hypoxic and septic models of AKI [82]. Radiolabeling of this molecule enables detection by PET, and has been used to spot apoptotic malignant cells in response to chemotherapy or the development of neuronal damage. However, the renal clearance of this compound currently precludes its use in the assessment of tissue damage in AKI. In that respect, recently introduced advanced Doppler ultrasound technologies provide fine assessment of the renal microcirculation at the bedside [83] and may be clinically more applicable.

9. Future Challenges

Current technologies enable the precise mapping of hypoxic regions (such as BOLD MRI in vivo, or immunostaining for HIF isoforms or for pimonidazole adducts in kidney samples) and the detection of renal parenchymal injury in animal models with biomarkers. To better appreciate the pathophysiology and the impact of interventions, such endpoints should be included in experimental settings in whole animal studies, in parallel with precise morphology, since looking only at parameters of glomerular filtration, or even of tubular function may not suffice. For instance, the use of loop diuretics in clinical trials for the prevention of hypoxic AKI induced by radiocontrast agents has been abandoned as plasma creatinine increased [84]. Likely, the rise in creatinine reflected insufficient volume replacement and pre-renal failure [85], while in fact medullary oxygenation and tubular viability have been improved [38,86]. In later clinical trials in high-risk patients, large fluid replacements combined with furosemide attenuated the risk of radiocontrast-induced nephropathy [87]. Most importantly, the correlation of urine biomarker levels with the extent and distribution of tubular injury has not been studied in depth. As mentioned above, some urine biomarkers, such as KIM-1 are generated by proximal tubular segments while others, such as NGAL originate from distal segments. Precise quantitation of injury at specified nephron segments at various locations within the renal parenchyma, as well as the extent of chronic fibrotic changes and the renal distribution of hypoxia (with pimonidazole) and hypoxia-response (HIF detection) can be achieved in perfusion-fixed thin section preparations in experimental models of AKI [88,89]. It is about time to try and correlate the extent of tubular injury at different segments with their corresponding cell-specific biomarkers in order to validate the sensitivity and specificity of these biomarkers in animal models of acute- and acute on chronic AKI. Such studies may improve our understanding of human AKI and may direct us in the generation of appropriate panels of biomarkers to appropriate for varied clinical conditions, for instance biomarkers for proximal tubular injury for suspected aminoglycoside nephrotoxicity, or a panel of distal tubular biomarkers following near drowning, or in AKI following the administration of SGLT2 antagonists.

Most non-invasive functional imaging techniques are not applicable for patients in critical care settings, and their use is restricted to animal studies and to human studies under ambulatory settings. Further development is needed of technologies that will enable bedside mapping of renal oxygenation profile and of real-time renal functional parameters.

10. Conclusions

The detection, prevention and successful treatment of hypoxic AKI have only moderately been advanced over recent decades, as compared to the substantial achievements in the diagnosis and management of ischemic heart disease. Disorders of renal parenchymal oxygenation are much more compound than those of the heart muscle. Furthermore, nephrology lags far behind cardiology in the diagnosis and management of hypoxic injury because of the lack of clinical symptoms and overt early physiologic signs, and the absence of diagnostic tools that provide immediate and highly specific results during the evolution of kidney injury. Changes in urine volume and the pattern of the rise in creatinine are non-specific and often retarded crude indices of renal dysfunction. Novel biomarkers provide new tools for the early detection of renal parenchymal injury, yet, the heterogeneity of damage patterns affecting different tubular segments in various toxic and hypoxic insults may differently affect some segment-specific biomarkers. There is no available human data regarding the correlation of biomarker levels and tissue injury extent and pattern, and such data should be evaluated in animal studies. The specificity and sensitivity of biomarkers in the detection of acute-on-chronic renal injury need improvement. Functional imaging is a fantastic experimental tool, but its availability and potential use in the clinical practice are currently limited.

The pathogenesis of AKI is often complex, with direct nephrotoxicity, hypoxia, altered microcirculation and other factors playing in concert. Differentiation between the causative factors is therefore principally based on clinical judgment and the assessment of the individual contribution of

hypoxia may be based only on hypoxia mapping by functional imaging or by the determination of urine pO_2.

Differing between type I and type II organ injury pattern should be based principally on the clinical scenario, both for the heart and kidney. Yet, this distinction, easily confirmed by angiography in AMI, might not be possible to establish unequivocally for AKI.

Finally, nephrologists lag behind cardiologists regarding hypoxic AKI also because of conceptual errors. Research projects have failed to distinguish between conditions with protracted renal warm ischemia and reperfusion, and those with maintained renal blood flow and transport activity but imbalanced oxygen supply and expenditure. We propose to differently address these conditions as type I and type II hypoxic AKI, terms physiologically parallel to type I and type II AMI. Whereas type I AKI is infrequent and rarely presents with renal functional impairment, most research studies use type I ischemic AKI animal models, which bear little relevance to the far more frequent conditions leading to type II hypoxic AKI. Better understanding and advances in the management of hypoxic AKI will require more studies using animal models of type II-, rather than type I renal parenchymal hypoxic injury.

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References

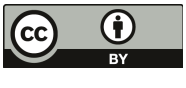
1. Bonventre, J.V.; Yang, L. Cellular pathophysiology of ischemic acute kidney injury. *J. Clin. Investig.* **2011**, *121*, 4210–4221. [CrossRef] [PubMed]
2. Schrier, R.W.; Wang, W.; Poole, B.; Mitra, A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J. Clin. Investig.* **2004**, *114*, 5–14. [CrossRef] [PubMed]
3. Moran, S.M.; Myers, B.D. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int.* **1985**, *27*, 928–937. [CrossRef] [PubMed]
4. Smilowitz, N.R.; Naoulou, B.; Sedlis, S.P. Diagnosis and Management of Type II Myocardial Infarction: Increased Demand for a Limited Supply of Evidence. *Curr. Atheroscler. Rep.* **2015**, *17*, 478. [CrossRef] [PubMed]
5. Bache, R.J.; Dai, X.Z. Myocardial oxygen consumption during exercise in the presence of left ventricular hypertrophy secondary to supravalvular aortic stenosis. *J. Am. Coll. Cardiol.* **1990**, *15*, 1157–1164. [CrossRef]
6. Watanabe, H.; Ohtsuka, S.; Kakihana, M.; Sugishita, Y. Decreased aortic compliance aggravates subendocardial ischaemia in dogs with stenosed coronary artery. *Cardiovasc. Res.* **1992**, *26*, 1212–1218. [CrossRef] [PubMed]
7. Nagao, N.; Yamasaki, Y.; Kawanami, S.; Kamitani, T.; Sagiyama, K.; Higo, T.; Ide, T.; Takemura, A.; Ishizaki, U.; Fukushima, K.; et al. Quantification of myocardial oxygenation in heart failure using blood-oxygen-level-dependent T2* magnetic resonance imaging: Comparison with cardiopulmonary exercise test. *Magn. Reson. Imaging* **2017**, *39*, 138–143. [CrossRef] [PubMed]
8. May, D.; Gilon, D.; Djonov, V.; Itin, A.; Lazarus, A.; Gordon, O.; Rosenberger, C.; Keshet, E. Transgenic system for conditional induction and rescue of chronic myocardial hibernation provides insights into genomic programs of hibernation. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 282–287. [CrossRef] [PubMed]
9. Frangogiannis, N.G.; Smith, C.W.; Entman, M.L. The inflammatory response in myocardial infarction. *Cardiovasc. Res.* **2002**, *53*, 31–47. [CrossRef]
10. Buja, L.M. Myocardial ischemia and reperfusion injury. *Cardiovasc. Pathol.* **2005**, *14*, 170–175. [CrossRef] [PubMed]
11. Hazanov, N.; Somin, M.; Attali, M.; Beilinson, N.; Thaler, M.; Mouallem, M.; Maor, Y.; Zaks, N.; Malnick, S. Acute renal embolism: Forty-four cases of renal infarction in patients with atrial fibrillation. *Medicine (Baltimore)* **2004**, *83*, 292–299. [CrossRef] [PubMed]

12. Matlin, R.A.; Gary, N.E. Acute cortical necrosis. Case report and review of the literature. *Am. J. Med.* **1974**, *56*, 110–118. [CrossRef]
13. Rosen, S.; Stillman, I.E. Acute Tubular Necrosis Is a Syndrome of Physiologic and Pathologic Dissociation. *J. Am. Soc. Nephrol.* **2008**, *19*, 871–875. [CrossRef] [PubMed]
14. Brezis, M.; Rosen, S. Hypoxia of the Renal Medulla-Its Implications for Disease. *N. Engl. J. Med.* **1995**, *332*, 647–655. [CrossRef] [PubMed]
15. Heyman, S.N.; Evans, R.G.; Rosen, S.; Rosenberger, C. Cellular adaptive changes in AKI: mitigating renal hypoxic injury. *Nephrol. Dial. Transplant.* **2012**, *27*, 1721–1728. [CrossRef] [PubMed]
16. Stillman, I.E.; Brezis, M.; Heyman, S.N.; Epstein, F.H.; Spokes, K.; Rosen, S. Effects of salt depletion on the kidney: changes in medullary oxygenation and thick ascending limb size. *J. Am. Soc. Nephrol.* **1994**, *4*, 1538–1545. [PubMed]
17. Brezis, M.; Heyman, S.N.; Epstein, F.H. Determinants of intrarenal oxygenation. II. Hemodynamic effects. *Am. J. Physiol.* **1994**, *267*, F1063–F1068. [CrossRef] [PubMed]
18. Nangaku, N.; Rosenberger, C.; Heyman, S.N.; Eckardt, K.U. Regulation of hypoxia-inducible factor in kidney disease. *Clin. Exp. Pharmacol. Physiol.* **2013**, *40*, 148–157. [CrossRef] [PubMed]
19. Heyman, S.N.; Khamaisi, M.; Rosen, S.; Rosenberger, C. Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. *Am. J. Nephrol.* **2008**, *28*, 998–1006. [CrossRef] [PubMed]
20. Franzén, S.; Palm, F. Endothelin type A receptor inhibition normalises intrarenal hypoxia in rats used as a model of type 1 diabetes by improving oxygen delivery. *Diabetologia* **2015**, *58*, 2435–2442. [CrossRef] [PubMed]
21. Heyman, S.N.; Rosenberger, C.; Rosen, S.; Khamaisi, M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? *BioMed Res. Int.* **2013**, *2013*, 123589. [CrossRef] [PubMed]
22. Washington, J.A., 2nd; Holland, J.M. Urine oxygen tension: effects of osmotic and saline diuresis and of ethacrynic acid. *Am. J. Physiol.* **1966**, *210*, 243–250. [CrossRef] [PubMed]
23. Brezis, M.; Agmon, Y.; Epstein, F.H. Determinants of intrarenal oxygenation. I. Effects of diuretics. *Am. J. Physiol.* **1994**, *267*, F1063–F1068. [CrossRef] [PubMed]
24. O'Neill, J.; Fasching, A.; Pihl, L.; Patinha, D.; Franzén, S.; Palm, F. Acute SGLT inhibition normalizes O_2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. *Am. J. Physiol. Renal Physiol.* **2015**, *309*, F227–F234. [CrossRef] [PubMed]
25. Szalat, A.; Perlman, A.; Muszkat, M.; Khamaisi, M.; Abassi, Z.; Heyman, S.N. Can SGLT2 Inhibitors Cause Acute Renal Failure? Plausible Role for Altered Glomerular Hemodynamics and Medullary Hypoxia. *Drug Saf.* **2018**, *41*, 239–252. [CrossRef] [PubMed]
26. Rosenberger, C.; Rosen, S.; Heyman, S.N. Renal parenchymal oxygenation and hypoxia adaptation in acute kidney injury. *Clin. Exp. Pharmacol. Physiol.* **2006**, *33*, 980–988. [CrossRef] [PubMed]
27. Heyman, S.N.; Rosen, S.; Rosenberger, C. Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 288–296. [CrossRef] [PubMed]
28. Heyman, S.N.; Gorelik, Y.; Zorbavel, D.; Rosenberger, C.; Abassi, Z.; Rosen, S. Near drowning: New perspectives for human hypoxic AKI. *Nephrol Dial. Transplant.* **2019**. [CrossRef] [PubMed]
29. Brezis, M.; Shanley, P.; Silva, P.; Spokes, K.; Lear, S.; Epstein, F.H.; Rosen, S. Disparate mechanisms for hypoxic cell injury in different nephron segments. Studies in the isolated perfused rat kidney. *J. Clin. Investig.* **1985**, *76*, 1796–1806. [CrossRef] [PubMed]
30. Brezis, M.; Rosen, S.; Silva, P.; Epstein, F.H. Transport activity modifies thick ascending limb damage in the isolated perfused kidney. *Kidney Int.* **1984**, *25*, 65–72. [CrossRef] [PubMed]
31. Shanley, P.F.; Brezis, M.; Spokes, K.; Silva, P.; Epstein, F.H.; Rosen, S. Transport-dependent cell injury in the S3 segment of the proximal tubule. *Kidney Int.* **1986**, *29*, 1033–1037. [CrossRef] [PubMed]
32. Rosenberger, C.; Rosen, S.; Shina, A.; Bernhardt, W.; Wiesener, M.S.; Frei, U.; Eckardt, K.U.; Heyman, S.N. Hypoxia-inducible factors and tubular cell survival in isolated perfused kidneys. *Kidney Int.* **2006**, *70*, 60–70. [CrossRef] [PubMed]
33. Heyman, S.N.; Rosen, S.; Epstein, F.H.; Spokes, K.; Brezis, M.L. Loop diuretics reduce hypoxic damage to proximal tubules of the isolated perfused rat kidney. *Kidney Int.* **1994**, *45*, 981–985. [CrossRef] [PubMed]
34. Shanley, P.F.; Rosen, M.D.; Brezis, M.; Silva, P.; Epstein, F.H.; Rosen, S. Topography of focal proximal tubular necrosis after ischemia with reflow in the rat kidney. *Am. J. Pathol.* **1985**, *122*, 462–468.

35. Heyman, S.N. Proximal tubular injury attenuates outer medullary hypoxic damage: studies in perfused rat kidneys. *Exp. Nephrol.* **2001**, *10*, 259–266. [CrossRef] [PubMed]
36. Heyman, S.N.; Rosen, S.; Rosenberger, C. Critical assessment of experimental models of acute renal failure. *Crit. Care Nephrol.* **2009**, *169*, 237–250.
37. Heyman, S.N.; Rosen, S.; Rosenberger, C. Animal models of renal dysfunction: acute kidney injury. *Expert Opin. Drug Discov.* **2009**, *4*, 629–641. [CrossRef] [PubMed]
38. Heyman, S.N.; Brezis, M.; Epstein, F.H.; Spokes, K.; Silva, P.; Rosen, S. Early renal medullary hypoxic injury from radiocontrast and indomethacin. *Kidney Int.* **1991**, *40*, 632–642. [CrossRef] [PubMed]
39. Heyman, S.N.; Brezis, M.; Reubinoff, C.A.; Greenfeld, Z.; Lechene, G.; Epstein, F.H.; Rosen, S. Acute renal failure with selective medullary injury in the rat. *J. Clin. Investig.* **1988**, *82*, 401–412. [CrossRef] [PubMed]
40. Heyman, S.N.; Rosenberger, C.; Rosen, S. Experimental ischemia-reperfusion: Biases and mythsthe proximal vs. distal hypoxic tubular injury debate revisited. *Kidney Int.* **2010**, *77*, 9–16. [CrossRef] [PubMed]
41. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P.; Acute Dialysis Quality Initiative Workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, R204–R212. [PubMed]
42. Bagga, A.; Bakkaloglu, A.; Devarajan, P.; Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Joannidis, M.; et al. Improving outcomes from acute kidney injury: Report of an initiative. *Pediatr. Nephrol.* **2007**, *22*, 1655–1658. [CrossRef] [PubMed]
43. Ronco, C. Acute kidney injury: from clinical to molecular diagnosis. *Crit. Care* **2016**, *20*, 201–204. [CrossRef] [PubMed]
44. Cox, E.F.; Buchanan, C.E.; Bradley, C.R.; Prestwich, B.; Mahmoud, H.; Taal, M.; Selby, N.M.; Francis, S.T. Multiparametric renal magnetic resonance imaging: Validation, interventions, and alterations in chronic kidney disease. *Front. Physiol.* **2017**, *8*, 696. [CrossRef] [PubMed]
45. Devarajan, P. Review: Neutrophil gelatinase-associated lipocalin: A troponin-like biomarker for human acute kidney injury. *Nephrology (Carlton)* **2010**, *15*, 419–428. [CrossRef] [PubMed]
46. Vaidya, V.S.; Ferguson, M.A.; Bonventre, J.V. Biomarkers of acute kidney injury: early diagnosis, pathogenesis, and recovery. *Annu. Rev. Pharmacol. Toxicol.* **2008**, *48*, 463–493. [CrossRef] [PubMed]
47. Vanmassenhove, J.; Vanholder, R.; Nagler, E.; Van Biesen, W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: An in-depth review of the literature. *Nephrol. Dial. Transplant.* **2013**, *28*, 254–273. [CrossRef] [PubMed]
48. Beker, B.M.; Corleto, M.G.; Fieiras, C.; Musso, C.G. Novel acute kidney injury biomarkers: Their characteristics, utility and concerns. *Int. Urol. Nephrol.* **2018**, *50*, 705–713. [CrossRef] [PubMed]
49. Mishra, J.; Qing, M.A.; Prada, A.; Mitsnefes, M.; Zahedi, K.; Yang, J.; Barasch, J.; Devarajan, P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J. Am. Soc. Nephrol.* **2003**, *14*, 2534–2543. [CrossRef] [PubMed]
50. Mishra, J.; Dent, C.; Tarabishi, R.; Mitsnefes, M.M.; Ma, Q.; Kelly, C.; Ruff, S.M.; Zahedi, K.; Shao, M.; Bean, J.; et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* **2005**, *365*, 1231–1238. [CrossRef]
51. Haase, M.; Bellomo, R.; Devarajan, P.; Schlattmann, P.; Haase-Fielitz, A.; Bagshaw, S.M.; Bogle, R.; Changchun, C.; Constantin, J.M.; Cruz, D.; et al. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. *Am. J. Kidney Dis.* **2009**, *54*, 1012–1024. [CrossRef] [PubMed]
52. Ichimura, T.; Asseldonk, E.J.; Humphreys, B.D.; Gunaratnam, L.; Duffield, J.S.; Bonventre, J.V. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. *J. Clin. Investig.* **2008**, *118*, 1657–1668. [CrossRef] [PubMed]
53. Ichimura, T.; Bonventre, J.V.; Bailly, V.; Wei, H.; Hession, C.A.; Cate, R.L.; Sanicola, M. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *J. Biol. Chem.* **1998**, *273*, 4135–4142. [CrossRef] [PubMed]
54. Melnikov, V.Y.; Ecder, T.; Fantuzzi, G.; Siegmund, B.; Lucia, M.S.; Dinarello, C.A.; Schrier, R.W.; Edelstein, C.L. Impaired IL-18 processing protects caspase-1-deficient mice from ischemic acute renal failure. *J. Clin. Investig.* **2001**, *107*, 1145–1152. [CrossRef] [PubMed]

55. Gan, J.; Zhou, X. Comparison of urine neutrophil gelatinase-associated lipocalin and interleukin-18 in prediction of acute kidney injury in adults. *Medicine (Baltimore)* **2018**, *97*, e12570. [CrossRef] [PubMed]
56. Liu, Y.; Guo, W.; Zhang, J.; Xu, C.; Yu, S.; Mao, Z.; Wu, J.; Ye, C.; Mei, C.; Dai, B. Urinary interleukin 18 for detection of acute kidney injury: A meta-analysis. *Am. J. Kidney Dis.* **2013**, *62*, 1058–1067. [CrossRef] [PubMed]
57. Jia, H.M.; Huang, L.F.; Zheng, Y.; Li, W.X. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: A meta-analysis. *Crit. Care* **2017**, *21*, 77. [CrossRef] [PubMed]
58. Hemdahl, A.L.; Gabrielsen, A.; Zhu, C.; Eriksson, P.; Hedin, U.; Kastrup, J.; Thorén, P.; Hansson, G.K. Expression of neutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 136–142. [CrossRef] [PubMed]
59. Elmedany, S.M.; Naga, S.S.; Elsharkawy, R.; Mahrous, R.S.; Elnaggar, A.I. Novel urinary biomarkers and the early detection of acute kidney injury after open cardiac surgeries. *J. Crit. Care* **2017**, *40*, 171–177. [CrossRef] [PubMed]
60. Ghatanatti, R.; Teli, A.; Tirkey, S.S.; Bhattacharya, S.; Sengupta, G.; Mondal, A. Role of renal biomarkers as predictors of acute kidney injury in cardiac surgery. *Asian Cardiovasc. Thorac. Ann.* **2014**, *22*, 234–241. [CrossRef] [PubMed]
61. Buddenkotte, J.; Steinhoff, M. Recent advances in understanding and managing. *F1000 Res.* **2018**, *7*, 1–10. [CrossRef] [PubMed]
62. Petcharunpaisan, S. Arterial spin labeling in neuroimaging. *World J. Radiol.* **2010**, *2*, 384–398. [CrossRef] [PubMed]
63. Nery, F.; Gordon, I.; Thomas, D. Non-Invasive Renal Perfusion Imaging Using Arterial Spin Labeling MRI: Challenges and Opportunities. *Diagnostics (Basel)* **2018**, *8*, 2. [CrossRef] [PubMed]
64. Odudu, A.; Nery, F.; Harteveld, A.A.; Evans, R.G.; Pendse, D.; Buchanan, C.E.; Francis, S.T.; Fernández-Seara, M.A. Arterial spin labelling MRI to measure renal perfusion: a systematic review and statement paper. *Nephrol. Dial. Transplant.* **2018**, *33*, ii15–ii21. [CrossRef] [PubMed]
65. O'Neal, J.B.; Shaw, A.D.; Billings, F.T. Acute kidney injury following cardiac surgery: Current understanding and future directions. *Crit. Care* **2016**, *20*, 187. [CrossRef] [PubMed]
66. Hueper, K.; Gueler, F.; Bräsen, J.H.; Gutberlet, M.; Jang, M.S.; Lehner, F.; Richter, N.; Hanke, N.; Peperhove, M.; Martirosian, P.; et al. Functional MRI detects perfusion impairment in renal allografts with delayed graft function. *Am. J. Physiol. Ren. Physiol.* **2015**, *308*, F1444–F1451. [CrossRef] [PubMed]
67. Hueper, K.; Gutberlet, M.; Rong, S.; Hartung, D.; Mengel, M.; Lu, X.; Haller, H.; Wacker, F.; Meier, M.; Gueler, F. Acute Kidney Injury: Arterial Spin Labeling to Monitor Renal Perfusion Impairment in Mice-Comparison with Histopathologic Results and Renal Function. *Radiology* **2014**, *270*, 117–124. [CrossRef] [PubMed]
68. Prasad, P.V.; Priatna, A.; Spokes, K.; Epstein, F.H. Changes in intrarenal oxygenation as evaluated by BOLD MRI in a rat kidney model for radiocontrast nephropathy. *J. Magn. Reson. Imaging* **2001**, *13*, 744–747. [CrossRef] [PubMed]
69. Pruijm, M.; Mendichovszky, I.A.; Liss, P.; Van der Niepen, P.; Textor, S.C.; Lerman, L.O.; Krediet, C.T.P.; Caroli, A.; Burnier, M.; Prasad, P.V. Renal blood oxygenation level-dependent magnetic resonance imaging to measure renal tissue oxygenation: a statement paper and systematic review. *Nephrol. Dial. Transplant.* **2018**, *33*, ii22–ii28. [CrossRef] [PubMed]
70. Prasad, P.V.; Edelman, R.R.; Epstein, F.H. Noninvasive evaluation of intrarenal oxygenation with BOLD MRI. *Circulation* **1996**, *94*, 3271–3275. [CrossRef] [PubMed]
71. Prasad, P.V.; Chen, Q.; Goldfarb, J.W.; Epstein, F.H.; Edelman, R.R. Breath-hold R2 mapping with a multiple gradient-recalled echo sequence: Application to the evaluation of intrarenal oxygenation. *J. Magn. Reson. Imaging* **1997**, *7*, 1163–1165. [CrossRef] [PubMed]
72. Textor, S.C.; Glockner, J.F.; Lerman, L.O.; Misra, S.; McKusick, M.A.; Riederer, S.J.; Grande, J.P.; Gomez, S.I.; Romero, J.C. The Use of Magnetic Resonance to Evaluate Tissue Oxygenation in Renal Artery Stenosis. *J. Am. Soc. Nephrol.* **2008**, *19*, 780–788. [CrossRef] [PubMed]
73. Zhang, J.L.; Morrell, G.; Rusinek, H.; Sigmund, E.E.; Chandarana, H.; Lerman, L.O.; Prasad, P.V.; Niles, D.; Artz, N.; Fain, S.; et al. New magnetic resonance imaging methods in nephrology. *Kidney Int.* **2014**, *85*, 768–778. [CrossRef] [PubMed]

74. Bokacheva, L.; Rusinek, H.; Chen, Q.; Oesingmann, N.; Prince, C.; Kaur, M.; Kramer, E.; Lee, V.S. Quantitative determination of Gd-DTPA concentration in T1-weighted MR renography studies. *Magn. Reson. Med.* **2007**, *57*, 1012–1018. [CrossRef] [PubMed]
75. Bokacheva, L.; Rusinek, H.; Zhang, J.L.; Chen, Q.; Lee, V.S. Estimates of glomerular filtration rate from MR renography and tracer kinetic models. *J. Magn. Reson. Imaging* **2009**, *29*, 371–382. [CrossRef] [PubMed]
76. Milman, Z.; Heyman, S.N.; Corchia, N.; Edrei, Y.; Axelrod, J.H.; Rosenberger, C.; Tsarfati, G.; Abramovitch, R. Hemodynamic response magnetic resonance imaging: Application for renal hemodynamic characterization. *Nephrol. Dial. Transplant.* **2013**, *28*, 1150–1156. [CrossRef] [PubMed]
77. Milman, Z.; Axelrod, J.H.; Heyman, S.N.; Nachmansson, N.; Abramovitch, R. Assessment with unenhanced MRI techniques of renal morphology and hemodynamic changes during acute kidney injury and chronic kidney disease in mice. *Am. J. Nephrol.* **2014**, *39*, 268–278. [CrossRef] [PubMed]
78. Maril, N.; Margalit, R.; Rosen, S.; Heyman, S.N.; Degani, H. Detection of evolving acute tubular necrosis with renal 23Na MRI: Studies in rats. *Kidney Int.* **2006**, *69*, 765–768. [CrossRef] [PubMed]
79. Kleeman, C.R.; Maxwell, M.H.; Witlin, S. Functional isosthenuria; an isolated reversible renal tubular defect. *AMA Arch. Intern. Med.* **1958**, *101*, 1023–1028. [CrossRef] [PubMed]
80. Zhu, M.Z.L.; Martin, A.; Cochrane, A.D.; Smith, J.A.; Thrift, A.G.; Harrop, G.K.; Ngo, J.P.; Evans, R.G. Urinary hypoxia: an intraoperative marker of risk of cardiac surgery-associated acute kidney injury. *Nephrol Dial Transplant.* **2018**, *33*, 2191–2201. [CrossRef] [PubMed]
81. Reshef, A.; Shirvan, A.; Akselrod-Ballin, A.; Wall, A.; Ziv, I. Small-Molecule Biomarkers for Clinical PET Imaging of Apoptosis. *J. Nucl. Med.* **2010**, *51*, 837–840. [CrossRef] [PubMed]
82. Damianovich, M.; Ziv, I.; Heyman, S.N.; Rosen, S.; Shina, A.; Kidron, D.; Aloya, T.; Grimberg, H.; Levin, G.; Reshef, A.; et al. *ApoSense*: A novel technology for functional molecular imaging of cell death in models of acute renal tubular necrosis. *Eur. J. Nucl. Med. Mol. Imaging* **2006**, *33*, 281–291. [CrossRef] [PubMed]
83. Correas, J.M.; Anglicheau, D.; Joly, D.; Gennisson, J.L.; Tanter, M.; Hélénon, O. Ultrasound-based imaging methods of the kidney-recent developments. *Kidney Int.* **2016**, *90*, 1199–1210. [CrossRef] [PubMed]
84. Solomon, R.; Werner, C.; Mann, D.; D'Elia, J.; Silva, P. Effects of Saline, Mannitol, and Furosemide on Acute Decreases in Renal Function Induced by Radiocontrast Agents. *N. Engl. J. Med.* **1994**, *331*, 1416–1420. [CrossRef] [PubMed]
85. Weinstein, J.M.; Heyman, S.; Brezis, M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron* **1992**, *62*, 413–415. [CrossRef] [PubMed]
86. Heyman, S.N.; Brezis, M.; Greenfeld, Z.; Rosen, S. Protective Role of Furosemide and Saline in Radiocontrast-Induced Acute Renal Failure in the Rat. *Am. J. Kidney Dis.* **1989**, *14*, 377–385. [CrossRef]
87. Briguori, C.; Visconti, G.; Focaccio, A.; Airoldi, F.; Valgimigli, M.; Sangiorgi, G.M.; Golia, B.; Ricciardelli, B.; Condorelli, G. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II). *Circulation* **2011**, *124*, 1260–1269. [CrossRef] [PubMed]
88. Goldfarb, M.; Rosenberger, C.; Abassi, Z.; Shina, A.; Zilbersat, F.; Eckardt, K.U.; Rosen, S.; Heyman, S.N. Acute-on-chronic renal failure in the rat: Functional compensation and hypoxia tolerance. *Am. J. Nephrol.* **2006**, *26*, 22–33. [CrossRef] [PubMed]
89. Rosenberger, C.; Heyman, S.N.; Rosen, S.; Shina, A.; Goldfarb, M.; Griethe, W.; Frei, U.; Reinke, P.; Bachmann, S.; Eckardt, K.U. Up-regulation of HIF in experimental acute renal failure: Evidence for a protective transcriptional response to hypoxia. *Kidney Int.* **2005**, *67*, 531–542. [CrossRef] [PubMed]



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Impact on Outcomes across KDIGO-2012 AKI Criteria According to Baseline Renal Function

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Abstract: Acute kidney injury (AKI) and Chronic Kidney Disease (CKD) are global health problems. The pathophysiology of acute-on-chronic kidney disease (AoCKD) is not well understood. We aimed to study clinical outcomes in patients with previous normal (pure acute kidney injury; P-AKI) or impaired kidney function (AoCKD) across the 2012 Kidney Disease Improving Global Outcomes (KDIGO) AKI classification. We performed a retrospective study of patients with AKI, divided into P-AKI and AoCKD groups, evaluating clinical and epidemiological features, distribution across KDIGO-2012 criteria, in-hospital mortality and need for dialysis. One thousand, two hundred and sixty-nine subjects were included. AoCKD individuals were older and had higher comorbidity. P-AKI individuals fulfilled more often the serum creatinine (SCr) ≥ 3.0× criterion in AKI-Stage3, AoCKD subjects reached SCr ≥ 4.0 mg/dL criterion more frequently. AKI severity was associated with in-hospital mortality independently of baseline renal function. AoCKD subjects presented higher mortality when fulfilling AKI-Stage1 criteria or SCr ≥ 3.0× criterion within AKI-Stage3. The relationship between mortality and associated risk factors, such as the net increase of SCr or AoCKD status, fluctuated depending on AKI stage and stage criteria sub-strata. AoCKD patients that fulfil SCr increment rate criteria may be exposed to more severe insults, possibly explaining the higher mortality. AoCKD may constitute a unique clinical syndrome. Adequate staging criteria may help prompt diagnosis and administration of appropriate therapy.

Keywords: acute kidney injury; chronic kidney disease; AKI staging

1. Introduction

Acute kidney injury (AKI) is a global public health problem [1]. Using the 2012 Kidney Disease: Improving Global Outcomes AKI definition (KDIGO-2012) [2], one in five adults and one in three children worldwide experience AKI during a hospital episode of care [3]. AKI implicates a great burden in morbidity and mortality, increases sanitary costs [4,5], and affects long-term outcomes, including cardiovascular events and survival [6–9]. It is a clinical syndrome with a variety of aetiologies [10], once instituted, the treatment is mostly supportive [11,12], and the best approach remains prevention [13–15]. Based on the KDIGO definition of Chronic Kidney Disease (CKD) [16] its prevalence approximates 8–16% worldwide [17], affecting one in nine Americans and more than 300 million persons globally [18]. AKI is more prevalent in (and a significant risk factor for) patients with impaired renal function [2]; AKI, in turn, may act as a promoter of progression of the underlying CKD [2,19–23].

This evidence has led to a renewed interest in an old clinical concept: Acute on chronic renal failure, coined by Lim et al. in 1969 [24] and currently referred to as acute on chronic kidney disease

(AoCKD) and its pathophysiology [23,25–29]. Few studies compare patients directly with prior normal (pure acute kidney injury [P-AKI]) and impaired renal function (AoCKD) during an AKI episode: Some conclude that patients with previous CKD bare worst clinical and renal outcomes [30–34], while others conclude that it could be protective against the negative consequences of AKI [35–38].

The most frequently used AKI classifications: RIFLE [39], AKIN [40] and KDIGO-2012 [2] do not discriminate patients with or without previous CKD, so the same criteria are used interchangeably in these individuals; therefore, a knowledge gap exists in the evaluation and staging of AoCKD. We hypothesized that AKI affects individuals with baseline normal and impaired renal function in a different way; in order to verify this theory we examined the distribution of patients in the strata defined by KDIGO-2012 criteria, and the relationship of AKI severity with short-term outcomes, such as in-hospital mortality and initiation of renal replacement therapy (RRT) between P-AKI and AoCKD subjects.

2. Experimental Section

All consecutive hospitalized patients treated by nephrologists in a 762-bed teaching institution, with a diagnosis of AKI by KDIGO-2012 criteria (Table 1), during a three-year period (June 2012 through May 2015) were reviewed.

Table 1. KDIGO-2012 acute kidney injury (AKI) classification and criteria.

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline	<0.5 mL/kg/h for 6–12 h
	OR	
	≥0.3 mg/dL increase	
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥ 12 h
3	3.0 times baseline	<0.3 mL/kg/h for ≥ 24 h
	OR	OR
	Increase in serum creatinine to ≥4.0 mg/dL	Anuria for ≥ 12 h
	OR	
	Initiation of renal replacement therapy	
	OR	
	In patients <18 years. Decrease in eGFR to <35 mL/min/1.73 m^2	

Inclusion criteria: Age ≥ 18 years, admission for >2 or and ≤91 days and rise in serum creatinine (SCr) sustained at least for 24 h. Exclusion criteria: History of solid organ transplantation, hospital readmission less than 3 months before or after index hospitalization, patients without baseline SCr, end-stage renal disease (previous RRT) or estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 calculated by the four item Modification of Diet in Renal Disease formula (MDRD-4) [41] and pregnant and puerperal women (Figure 1). Previous and later hospitalizations were searched even if a nephrologist was not consulted and included as a new index hospitalization if they met the inclusion criteria.

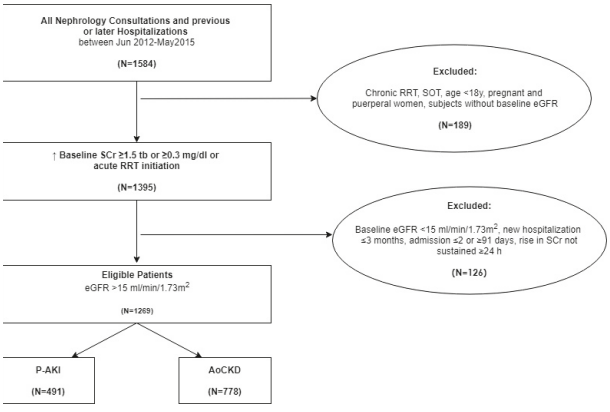

Figure 1. Study flow chart for inclusion and exclusion criteria. RRT: Renal replacement therapy; SOT: Solid organ transplantation; Tb: Times baseline. SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; P-AKI: Pure acute kidney injury; AoCKD: Acute on chronic kidney disease.

We designed a retrospective cohorts study. The study conforms to the STROBE statement for reporting observational studies. Patients were divided in two groups: P-AKI (baseline eGFR ≥60 mL/min/1.73 m^2) and AoCKD (baseline eGFR ≥15 and <60 mL/min/1.73 m^2 for more than three months) (16). We defined baseline SCr as the lowest value in the six months prior to hospitalization, and when it was not available, we searched the 12 previous months [42]. Community-acquired AKI was defined as a SCr ≥ 1.5× increment at hospital admission [43]. We used the KDIGO-2012 stage associated with the peak SCr reached during hospitalization.

We registered several epidemiological and clinical features, intensive care unit (ICU) admission and hospitalization in medical or surgical units. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Área de Salud Valladolid Este (CINV 14–45); because of the anonymous and non-interventional nature of the study, they waived the need for informed consent.

Our primary objective was to compare the rate of in-hospital mortality across every criterion of the KDIGO-2012 AKI classification between groups. Our secondary objectives included comparing the rate of initiation of RRT, length of hospital stay (LOS), time to nephrology consultation, and dialysis-dependence at discharge in both groups.

Patient demographics are summarized using mean and standard deviations (SD) or median (25th–75th percentile) for continuous variables and counts with percentages for binary variables, as appropriate and according to data distribution. Normal distribution of data was analyzed using a Kolmogorov-Smirnov test. Continuous data was analyzed using Mann-Whitney U tests (between P-AKI and AoCKD) or Kruskal-Wallis tests among P-AKI and CKD stage 3a (CKD-3a), 3b (CKD-3b) and 4 (CKD-4). Binary data were analyzed using the Chi-square test. A two-sided p-value ≤ 0.05 was considered statistically significant.

We used a Cox proportional hazards model, unadjusted and adjusted for age and Charlson Index (modeled as continuous variables), gender, ICU admission and comorbidities: Hypertension, diabetes, coronary artery disease, chronic heart failure, peripheral artery disease and chronic hepatic disease to study in-hospital survival rates. We tested the proportionality assumption of the Cox models using Schoenfeld residual plots. Age and ICU admission were considered as time-dependent covariates. No collinearity was found between the independent variables included in the model. The adjusted Cox model for in-hospital mortality according to AKI severity and baseline renal function was used to create survival curves.

Statistical analysis was carried out using the Statistical Package for Social Sciences software, version 20.0 (SPSS, IBM, Armonk, NY, USA), GraphPad Prism, version 7.04 for Windows (GraphPad Software, La Jolla California USA) and Microsoft Excel 2013 (Microsoft, Inc. Redmond, WA, USA).

3. Results

3.1. Demographic Characteristics of Patients

We revised all 1584 nephrology consultations and previous or later hospitalizations during the study period; 1269 cases met inclusion criteria (Figure 1), 491 in the P-AKI group and 778 in the AoCKD group.

Characteristics and comparison between groups are shown in Table 2. Individuals in the AoCKD group were older, had higher mean Charlson Index [44] and suffered hypertension, diabetes and cardiovascular disease at a significantly higher rate. Twenty-one patients of the AoCKD (3%) presented a baseline SCr ≥ 4.0 mg/dL. Patients in the P-AKI group were admitted to the ICU more frequently. The distribution across every KDIGO-2012 AKI stage and criterion between P-AKI and AoCKD patients, is shown in Table 2. The proportion of patients who developed AKI stage 1 (ST1) was higher among the AoCKD group; while AKI stage 2 (ST2) was more frequent in the P-AKI group. The criterion used to reach AKI stage 3 (ST3) differed between groups: Most P-AKI patients suffered a ≥ 3.0× increase in SCr from baseline, while the majority of AoCKD patients reached an SCr ≥ 4 mg/dL. The rate of initiation of RRT was similar between groups. In general, we found no statistically significant difference between groups in reaching ST3 (all criteria) (Table 2). We analyzed differences of peak value and SCr net increase (NI)—defined as the difference between peak and baseline SCr values-among P-AKI and AoCKD subjects that fulfilled a specific AKI criterion. Distribution of peak SCr and SCr NI values differed in P-AKI and AoCKD subjects when fulfilling the increment of SCr 1.5–1.9 times baseline criterion (Median peak SCr, P-AKI 1.45 mg/dL vs. AoCKD 2.81 mg/dL, U = 547.5, $p < 0.001$; Median SCr NI, P-AKI 0.57 mg/dL vs. AoCKD 1.2 mg/dL, U = 1045.5, $p < 0.001$), the ST2 criterion (Median peak SCr, P-AKI 2.24 mg/dL vs. AoCKD 3.32 mg/dL, U = 511, $p < 0.001$; Median SCr NI, P-AKI 1.28 mg/dL vs. AoCKD 1.87 mg/dL, U = 921.5, $p < 0.001$), the increment of SCr 3.0 times baseline criterion (Median peak SCr, P-AKI 4.66 mg/dL vs. AoCKD 6.8 mg/dL, U = 8161, $p < 0.001$; Median SCr NI, P-AKI 3.81 mg/dL vs. AoCKD 5.24 mg/dL, U = 10,090.5, $p < 0.001$) or the SCr ≥4.0 mg/dL criterion (Median peak SCr, P-AKI 6.05 mg/dL vs. AoCKD 5.64 mg/dL, U = 23,786, $p = 0.071$; Median SCr NI, P-AKI 5.13 mg/dL vs. AoCKD 3.26 mg/dL, U = 12,110, $p < 0.001$).

Table 2. Baseline Characteristics of AKI and AoCKD Groups and Distribution across KDIGO-2012 Criteria.

	ALL	P-AKI	AoCKD	p Value[1]	AoCKD			p Value[2]
					CKD-3A	CKD-3B	CKD-4	
N	**1269**	**491**	**778**		**221**	**282**	**275**	
Male sex—No. (%)	883 (70)	339 (69)	544 (70)	0.739	162 (73)	198 (70)	184 (67)	0.476
Age (years)—Median (IQR)	75 (65–81)	71 (61–79)	77 (69–83)	<0.001	76 (69–82)	78 (70–83)	77 (67–83)	<0.001
HTN—No. (%)	1125 (89)	395 (80)	730 (94)	<0.001	206 (93)	268 (95)	256 (93)	<0.001
DM—No. (%)	536 (42)	158 (32)	378 (49)	<0.001	96 (43)	145 (51)	137 (50)	<0.001
CAD—No. (%)	385 (30)	107 (22)	278 (36)	<0.001	73 (33)	105 (37)	100 (36)	<0.001
CHF—No. (%)	491 (39)	140 (29)	351 (45)	<0.001	94 (43)	146 (52)	111 (40)	<0.001
PAD—No. (%)	392 (31)	108 (22)	284 (37)	<0.001	89 (40)	112 (40)	83 (30)	<0.001
CHD—No. (%)	231 (18)	37 (8)	36 (5)	0.03	11 (5)	14 (5)	11 (4)	0.171
Charlson Comorbidity Index (SD)	4 (3–6)	4 (2–6)	5 (3–6)	<0.001	4 (3–6)	5 (3–6)	6 (4–7)	<0.001
Unit of Admission								
Medical Unit—No. (%)	808 (64)	180 (37)	281 (36)	0.845	91 (41)	110 (39)	80 (29)	0.025
ICU—No. (%)	241 (19)	117 (24)	124 (16)	<0.001	44 (20)	42 (15)	38 (14)	0.001
AKI Type								
Community Acquired—No. (%)	870 (69)	160 (33)	239 (31)	0.485	74 (34)	90 (32)	75 (27)	0.396
KDIGO-2012 AKI Stage 1 (global)—No. (%)	506 (40)	169 (34)	337 (43)	0.002	115 (53)	145 (51)	77 (28)	<0.001
≥0.3 mg/dL	506 (40)	169 (34)	337 (43)	0.002	115 (53)	145 (51)	77 (28)	<0.001
SCr 1.5–1.9×	264 (21)	115 (23)	149 (19)	0.068	59 (27)	70 (25)	20 (7)	<0.001
KDIGO-2012 AKI Stage 2 (SCr 2.0–2.9×)—No. (%)	158 (13)	88 (18)	70 (9)	<0.001	42 (19)	27 (10)	1 (0.4)	<0.001
KDIGO-2012 AKI Stage 3 (global)—No. (%)	605 (48)	234 (48)	371 (48)	0.992	60 (28)	112 (39)	199 (72)	<0.001
SCr ≥ 3.0×	354 (28)	229 (47)	125 (16)	<0.001	46 (21)	54 (19)	25 (9)	<0.001

Table 2. *Cont.*

	ALL	P-AKI	AoCKD	p Value[1]	AoCKD			p Value[2]
					CKD-3A	CKD-3B	CKD-4	
N	**1269**	**491**	**778**		**221**	**282**	**275**	
SCr ≥ 4.0 mg/dL	503 (40)	150 (31)	353 (45)	<0.001	48 (22)	108 (38)	197 (71)	<0.001
Initiation RRT	167 (13)	62 (13)	105 (14)	0.656	16 (7)	24 (9)	65 (24)	<0.001
Baseline SCr (mg/dL)	1.4 (1–2)	0.9 (0.7–1.1)	1.9 (1.5–2.5)	<0.001	1.4 (1.2–1.5)	1.8 (1.6–2)	2.7 (2.4–3.2)	<0.001
Peak SCr (mg/dL)	3.4 (2.2–5.2)	2.5 (1.5–4.5)	3.7 (2.6–5.5)	<0.001	2.6 (2–3.8)	3.4 (2.6–4.9)	5 (3.9–6.7)	<0.001
SCr Net Increase (mg/dL)	1.6 (0.7–3.3)	1.6 (0.6–3.6)	1.7 (0.9–3)	0.232	1.2 (0.7–2.4)	1.6 (0.8–3.2)	2.2 (1.2–3.5)	<0.001
Discharge SCr (mg/dL)	1.9 (1.3–2.9)	1.2 (0.9–1.7)	2.4 (1.7–3.5)	<0.001	1.7 (1.4–2.2)	2.3 (1.8–2.8)	3.6 (2.7–4.9)	<0.001

Data are expressed as mean ± standard deviation (SD), median and interquartilic range (IQR) or number (percentage). P-AKI, pure acute kidney injury; AoCKD, acute on chronic kidney disease; HTN, Hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CHF, chronic heart failure; PAD, peripheral arterial disease; CHD, chronic hepatic disease; ICU, intensive care unit; AKI, acute kidney injury; SCr, serum creatinine; RRT, renal replacement therapy. p Value[1]: Comparison of P-AKI vs. AoCKD (all patients). p Value[2]: Comparison of P-AKI vs. AoCKD stages.

3.2. In-Hospital Mortality

279 (22%) patients died during hospitalization. We found no statistically significant difference in global mortality rates between groups. More patients died in the ST3 category in both groups compared to the other KDIGO-2012 AKI categories (Table 3).

Table 3. Primary and secondary endpoints. Mortality rates of subjects that met each KDIGO stage/criterion within P-AKI/AoCKD groups.

	ARF	AoCKD	*p* Value
N	**491**	**778**	
Primary Endpoint			
In-Hospital Mortality—No. (%)	100 (20.4)	179 (23)	0.15
Secondary Endpoints			
Initiation of RRT—No. (%)	62 (12.6)	105 (13.5)	0.36
Length of Hospital Stay (days)	12 (7–25)	12 (7–21)	0.08
Time to Nephrology Consultation (days)	4 (1–8)	3 (1–6)	<0.001
Dialysis Dependence at Discharge—No. (%)	7 (1.4)	40 (5.1)	<0.001
In-Hospital Mortality	**ARF**	**AoCKD**	***p* Value**
KDIGO-2012 AKI Stage 1 (global)	10 (5.9)	44 (13.1)	0.014
≥0.3 mg/dL	10 (5.9)	44 (13.1)	0.014
SCr 1.5–1.9×	7 (6.1)	26 (17.4)	0.006
KDIGO-2012 AKI Stage 2	21 (23.9)	12 (17.1)	0.302
KDIGO-2012 AKI Stage 3 (global)	69 (29.5)	123 (33.2)	0.345
SCr 3.0×	67 (29.3)	50 (40)	0.04
SCr ≥ 4.0 mg/dL	41 (27.3)	116 (32.9)	0.221
Initiation RRT	24 (38.7)	39 (37.1)	0.84

Data are expressed as mean ± SD or number (percentage). P-AKI: Pure acute kidney injury; AoCKD: Acute on chronic kidney disease; RRT: Renal replacement therapy; AKI: Acute kidney injury; SCr: Serum creatinine.

We studied the distribution of all in-hospital deaths across each KDIGO-2012 AKI criterion in both groups (Table 3). AoCKD presented a higher death rate compared to P-AKI when fulfilling any ST1 criteria or the SCr ≥ 3.0× criterion within ST3 stage. Although the percentage of deaths associated with ST3 was similar between groups, its association with each criterion varied: RRT initiation was the ST3 criterion associated with the highest mortality rate among P-AKI patients, while SCr ≥ 3.0× was the criterion linked to the highest death rate in AoCKD subjects. The percentage of deaths associated with the SCr ≥ 4.0 mg/dL criterion in the P-AKI group was lower when compared to AoCKD subjects (Table 3).

The Cox proportional hazard model, using P-AKI ST1 individuals as the reference group, showed that AoCKD ST3 patients had significantly worse in-hospital survival, with an adjusted hazard ratio (HR) of 4.8 and 95% confidence interval (CI) of 2.5–9.2 ($p < 0.001$), followed by P-AKI ST3 subjects, P-AKI ST2 and AoCKD ST2 patients. In-hospital mortality of those with AoCKD ST1 did not significantly differ from that of P-AKI ST1 individuals (Figures 2 and 3). Other determinants that showed an association to in-hospital mortality were older age (HR: 1.001; 95% CI: 1–1.001; $p = 0.001$), Charlson Index (HR: 1.16; 95% CI: 1.1–1.23; $p < 0.001$), ICU admission (HR: 1.04; 95% CI: 1.03–1.05; $p < 0.001$) and CHF (HR: 1.5; 95% CI: 1.15–1.96; $p = 0.003$).

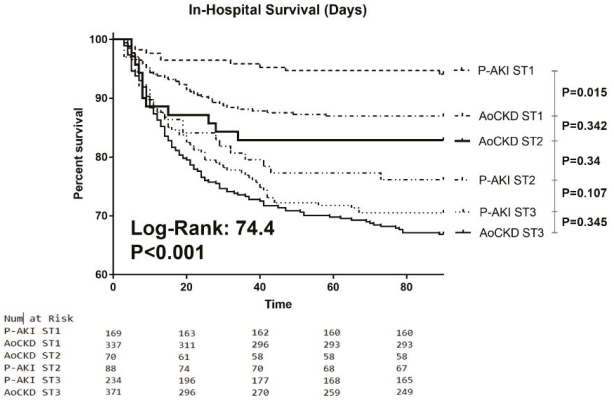

Figure 2. Kaplan-Meier curves. In-hospital survival curves stratified by baseline renal function and AKI severity. P-AKI: Pure Acute kidney injury. AoCKD: Acute-on-chronic kidney disease. AKI: Acute kidney injury. ST1: AKI stage 1. ST2: AKI stage 2. ST3: AKI stage 3.

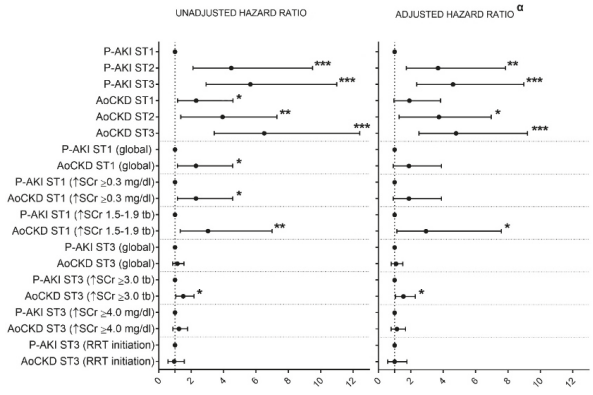

Figure 3. Unadjusted and adjusted hazard ratios (95% confidence interval) for death. P-AKI: Pure acute kidney injury. AoCKD: Acute-on-chronic kidney disease. AKI: Acute kidney injury. ST1: AKI stage 1. ST2: AKI stage 2. ST3: AKI stage 3. SCr: Serum creatinine. Tb: Times baseline. RRT: Renal replacement therapy. α: Models including P-AKI/AoCKD status, age, intensive care unit admission (considered as time-dependent variables), gender, Charlson Index, and comorbidity (hypertension, diabetes, coronary artery disease, chronic heart failure, peripheral arterial disease and chronic hepatic disease). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

We also built Cox proportional hazards models to study the effect of fulfilling specific ST1 and ST3 criterion among groups. AoCKD patients presented significantly higher unadjusted mortality HR compared to P-AKI subjects when fulfilling any ST1 stage criterion or the ST3 SCr ≥ 3.0× criterion (Figure 3). After adjustment, only AoCKD individuals who reached ST1 through the SCr ≥ 1.5–1.9× criterion and those that attained ST3 fulfilling the SCr ≥3.0× criterion showed a significantly higher HR for death compared with P-AKI individuals. The AoCKD group showed a small, but not statistically significant, increase in the risk of in-hospital mortality when fulfilling the SCr ≥ 0.3 mg/dL criterion within ST1 or the SCr ≥ 4.0 mg/dL criterion within ST3 (Figure 3). To further investigate the effect of baseline kidney function and its modification during AKI on in-hospital mortality, we added related variables to the analysis. Peak SCr and SCr NI were, as expected, highly correlated variables ($r = 0.953$, $p < 0.001$). SCr NI and baseline eGFR were added to our model as independent variables. Models simultaneously, including baseline eGFR and P-AKI/AoCKD status, were not considered due

to multicollinearity. In a global model, including all patients (Figure 4), SCr NI was an independent risk factor for in-hospital mortality, whereas baseline eGFR or P-AKI/AoCKD status were not. This approach was also tested in specific AKI strata that were associated with higher mortality rates among AoCKD patients, namely cases with SCr rise by 1.5–1.9 times or ≥3.0 times baseline (Figure 4). SCr NI proved to be independently associated with mortality among patients that reached an SCr rise 1.5–1.9 times baseline. Conversely, that association was not found among between subjects that suffered an SCr rise ≥ 3.0 times baseline, while in this group, AoCKD status was directly correlated with in-hospital death.

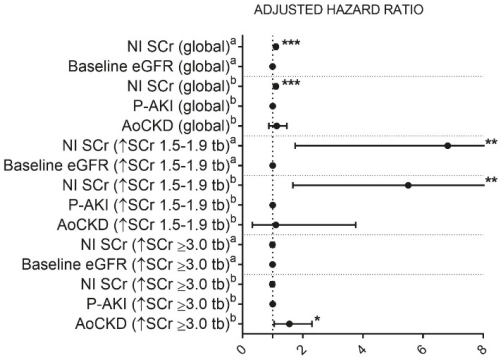

Figure 4. Adjusted hazard ratios (95% confidence interval) for death. NI: Net increase. SCr: Serum creatinine. eGFR: Estimated glomerular filtration rate. P-AKI: Pure acute kidney injury. AoCKD: Acute-on-chronic kidney disease. Tb: Times baseline. a: Models including SCr NI, baseline eGFR, age, Intensive care unit admission (considered as time-dependent variables), gender, Charlson Index, and comorbidity (hypertension, diabetes, coronary artery disease, chronic heart failure, peripheral arterial disease and chronic hepatic disease. b: Models including SCr NI, P-AKI/AoCKD status, age, intensive care unit admission (considered as time-dependent variables), gender, Charlson Index, and comorbidity (hypertension, diabetes, coronary artery disease, chronic heart failure, peripheral arterial disease and chronic hepatic disease. * $p < 0.05$; ** $p < 0.01$; *** $p < 001$.

Mean survival time was significantly higher among ST1 P-AKI individuals when compared to ST1 AoCKD subjects (86.2 ± 16.5 vs. 80.5 ± 24.9 days, $p < 0.01$). ST3 P-AKI patients with an SCr ≥ 3.0× had a better in-hospital survival time compared to AoCKD individuals (69.9 ± 32.5 vs. 61.3 ± 37.1 days, $p < 0.05$) (Figure 5).

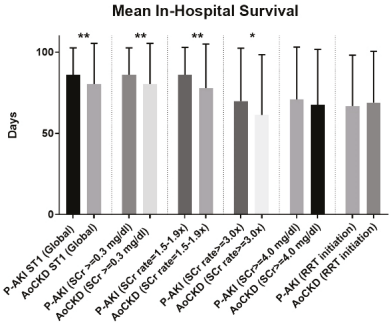

Figure 5. Mean in-hospital survival time (days) by baseline renal function and KDIGO AKI stage and criteria. P-AKI: Pure acute kidney injury. AoCKD: Acute-on-chronic kidney disease. AKI: Acute kidney injury. ST1: AKI stage 1. ST2: AKI stage 2. ST3: AKI stage 3. SCr: Serum creatinine. RRT: Renal replacement therapy. * $p < 0.05$; ** $p < 0.01$.

3.3. Secondary Outcomes

We found no statistically significant difference between groups in need of RRT. The severity of AKI was directly associated with LOS in both groups, but we found no differences in LOS between P-AKI and AoCKD patients. AoCKD group presented a significantly lower time to nephrology consultation compared to P-AKI and a higher dialysis-dependence at discharge (Table 3).

4. Discussion

We found that patients with previous impaired renal function were older and had a higher Charlson's Index, showing that AoCKD individuals differ in their baseline characteristics from the P-AKI group. In addition, we found that the distribution of patients across KDIGO-2012 criteria is different between groups; AKI severity is related with worse short-term outcomes, independently of baseline SCr, and that fulfilling a specific KDIGO-2012 AKI criterion, even within the same AKI stage, is associated with an increased risk of in-hospital death in patients with AoCKD.

In our sample, ST1 was the most common stage reached by CKD-3a and CKD-3b patients, while P-AKI and CKD-4 subjects most frequently reached ST3. The apparent predisposition of individuals with advanced CKD to suffer severe AKI could be due to the increasingly higher baseline SCr associated with CKD-4, which enables reaching the SCr ≥ 4 mg/dL criterion, and thus, ST3, even in the presence of mild insults. A recent study by Hatakeyama et al., [45] also described a higher incidence of ST3 among patients with P-AKI or advanced CKD stages compared to CKD-3a individuals. The percentage of patients in the ST2 stage was surprisingly low in both groups (Table 2). This is not a rare finding; an even lower percentage of patients in the ST2 category was found in individuals from a general (34) and cardiac surgery ICU [46]; the authors propose that this could be explained by the automatic classification of all patients that require RRT as ST3. The path followed by P-AKI and AoCKD individuals to reach a specific AKI stage was also different: Within ST3, the most common criterion fulfilled by AoCKD patients, regardless of CKD stage, was SCr ≥ 4.0 mg/dL, while P-AKI individuals fulfilled more frequently the SCr ≥ 3.0× criterion.

We observed no differences in overall in-hospital mortality rates between groups; but it was significantly higher among AoCKD/ST1 and AoCKD/ST3 subjects compared to P-AKI subjects within that same stage, although only if ST3 was attained through reaching an SCr ≥ 3.0× in the latter group. Peak SCr and SCr NI were significantly higher among AoCKD compared to P-AKI patients in these stages. Lack of differences in mortality between P-AKI and AoCKD individuals for ST2 may be due to the low prevalence of severe CKD among AoCKD subjects—defined as CKD-3b or CKD-4-in this specific stratum. However, within strata associated with higher mortality among AoCKD subjects, such as those with SCr rise by 1.5–1.9 times or ≥3 times vs. baseline, we observed no differences in severe CKD prevalence between AoCKD survivors and non-survivors (1.5–1.9 times baseline, survivors—56.1%, non-survivors—76.9%, $p = 0.128$; three times baseline, survivors—65.3%, non-survivors—56%, $p = 0.336$), indicating a complex relationship between mortality, CKD severity, SCr values and other risk factors among this subpopulation.

When compared with P-AKI/ST1 patients (reference group), patients with AoCKD/ST3 presented the highest adjusted HR for in-hospital death, followed by P-AKI/ST3, P-AKI/ST2 and AoCKD/ST2 patients. We found that AKI severity was associated with higher in-hospital mortality in a stepwise incremental fashion, regardless of baseline renal function; we found no significant differences in adjusted mortality HR within ST3 subjects among those that received RRT or not or those who fulfilled the SCr ≥ 4.0 mg/dL criterion or not. AoCKD patients that reached ST1 or ST3 while fulfilling the SCr ≥ 1.5–1.9× or SCr ≥ 3.0× criteria, respectively, presented a higher adjusted HR of death compared to P-AKI patients. This differential effect on mortality appears among those AoCKD individuals that fulfilled specific AKI criteria that require not a net increase in SCr values, but an increased rate of this parameter with respect to its baseline values. To further support the notion of a differential effect of risk factors, such as AoCKD status or a net increase of SCr in each AKI stratum, we found that SCr NI was closely associated with in-hospital mortality when studying the whole spectrum of AKI.

However, if we specifically analyzed the subset of patients that suffered a rise of SCr ≥ 3.0 times baseline, that relationship was no longer found while AoCKD status appeared as an independent risk factor for in-hospital death.

Our results are consistent with previous works: For example, Sawhney et al., [47] observed a higher mortality associated with AKI severity, regardless of baseline eGFR; Zhou et al., [31] reported that AKI severity in patients with decompensated heart failure, assessed using the RIFLE classification, was directly correlated with mortality rates both in P-AKI and AoCKD, but the latter group showed more comorbidities and higher risk of death than P-AKI individuals; Machado et al., [46] also described an increased risk of death associated with AKI severity in patients with preoperatively increased SCr who underwent cardiac surgery. Conversely, higher in-hospital mortality in P-AKI, but not in AoCKD patients, has been linked to AKI severity using the RIFLE and KDIGO-2012 classifications in other studies [35–38]. Some of these works are based on specific populations, such as the critically ill, describing similar mortality rates in both groups compared to our findings [34,36]. In these settings, the severity of illness could modify the course and outcomes of AKI, explaining the higher mortality observed in P-AKI subjects. Moreover, some of these studies included considerably younger patients in both groups, e.g., Prakash et al., [37]. Our population consists of elderly patients that suffer more frequently relevant comorbid conditions; this could explain the effect of AKI on the excess mortality in AoCKD individuals. We found a similar rate for need of RRT in both groups; irrespective of baseline renal function, these patients showed higher in-hospital mortality (Table 3). Dialysis-dependence at discharge was less frequent in the P-AKI group, regardless of AKI severity. Moreover, approximately 30% of AoCKD were dialysis-dependent at discharge, a lower percentage than that previously described in the literature [32,36], which may be linked to the higher in-hospital mortality observed in this group in our sample. P-AKI patients were admitted more frequently to the ICU; in both groups, AKI severity was directly correlated with admission to the ICU. AKI severity was associated with higher LOS in the P-AKI group, but not in the AoCKD group. This is probably due to AKI severity being intrinsically associated with severity of illness in P-AKI, but not in AoCKD patients.

The present study has several strengths: The study provides a novel approach regarding the influence of each KDIGO-2012 AKI criterion over outcomes in P-AKI and AoCKD patients. All patients have a baseline SCr value to calculate eGFR and the rate of SCr increments; data were obtained prior to the index hospitalization, thus, avoiding the use of surrogate values for calculating baseline renal function. Our cohort consists a heterogeneous sample of hospitalized patients with AKI, not restricted to critically ill or those with a specific condition, such as advanced heart failure, allowing a more reliable representation of a nephrologist day-to-day clinical activity; this increases the generalizability of results not limited to a specific clinical setting. We used standardized and updated definitions of AKI and CKD, following currently available KDIGO guidelines and recorded extensive data on comorbid conditions, which allowed us to adjust for these factors when considering outcomes.

We also acknowledge several important limitations: This is a retrospective single-center study of patients that were treated at least once by the nephrology department, which could lead to a selection bias toward higher AKI severity in both groups, but this circumstance could drive to increased specificity. Extensive efforts were undertaken to adjust for potential confounding, but residual confounding is still possible. Comorbid conditions, such as diabetes, hypertension or coronary artery disease, were considered as dichotomic variables, so there may be residual confounding by severity of these comorbidities. We did not use the urine output criterion. We used only SCr and no other biomarkers for diagnosing and staging AKI. We could not differentiate between true AoCKD and progression of primary renal disease (no biomarkers, few renal biopsies). Follow up was limited to the length of admission to reduce potential bias associated with differential losses to follow up between groups.highlighted.

5. Conclusions

To our knowledge, this is the first study that compares the in-hospital outcomes of patients with previous normal and impaired renal function through KDIGO-2012 stages and criteria. The results showed that AKI KDIGO-2012 classification predicted in-hospital mortality in both P-AKI and AoCKD patients, but we found a differential effect of AKI KDIGO-2012 criteria on outcomes among AoCKD patients compared to P-AKI subjects. Several authors have proposed that certain specific conditions, such as CKD or advanced age, should be taken into account while applying AKI classifications [35,48]. RIFLE, AKIN and/or KDIGO-2012 were designed for and tested in patients with previously normal renal function, but considering the different outcomes observed among P-AKI and AoCKD subjects within the same AKI stage and criterion maybe one size does not fit all AKI patients. We consider that AoCKD may constitute a separate clinical syndrome, and due to the increasing prevalence of CKD, the development of adequate staging criteria for AoCKD could help prompt the diagnosis and administration of appropriate therapy.

Author Contributions: Conceptualization and methodology, I.A.-O., J.B.-B., A.M.-H. and A.C.-R.; formal analysis, I.A.-O. and A.C.-R.; investigation, I.A.-O., data curation, I.A.-O. and A.C.-R.; writing—original draft preparation, I.A.-O. and A.C.-R.; writing—review and editing, I.A.-O., J.B.-M. and A.C.-R.; supervision, J.B.-M., J.B.-B. and A.M.-H.

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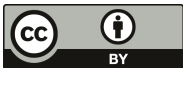
Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sawhney, S.; Fraser, S.D. Epidemiology of AKI: Utilizing Large Databases to Determine the Burden of AKI. *Adv. Chronic. Kidney Dis.* **2017**, *24*, 194–204. [CrossRef] [PubMed]
2. Kidney Disease: Improving Global Outcomes (KDIGO); Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
3. Susantitaphong, P.; Cruz, D.N.; Cerda, J.; Abulfaraj, M.; Alqahtani, F.; Koulouridis, I.; Jaber, B.L.; Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: A meta-analysis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1482–1493. [CrossRef] [PubMed]
4. Lameire, N.H.; Bagga, A.; Cruz, D.; de Maeseneer, J.; Endre, Z.; Kellum, J.A.; Liu, K.D.; Mehta, R.L.; Pannu, N.; van Biesen, W.; et al. Acute kidney injury: An increasing global concern. *Lancet* **2013**, *382*, 170–179. [CrossRef]
5. Collister, D.; Pannu, N.; Ye, F.; James, M.; Hemmelgarn, B.; Chui, B.; Manns, B.; Klarenbach, S. Alberta Kidney Disease Network. Health Care Costs Associated with AKI. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1733–1743. [CrossRef] [PubMed]
6. Murugan, R.; Kellum, J.A. Acute kidney injury: What's the prognosis? *Nat. Rev. Nephrol.* **2011**, *7*, 209–217. [CrossRef]
7. Chawla, L.S.; Amdur, R.L.; Shaw, A.D.; Faselis, C.; Palant, C.E.; Kimmel, P.L. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 448–456. [CrossRef]
8. Omotoso, B.A.; Abdel-Rahman, E.M.; Xin, W.; Ma, JZ.; Scully, K.W.; Arogundade, F.A.; Balogun, R.A. Acute kidney injury (AKI) outcome, a predictor of long-term major adverse cardiovascular events (MACE). *Clin. Nephrol.* **2016**, *85*, 1–11. [CrossRef]
9. Odutayo, A.; Wong, C.X.; Farkouh, M.; Altman, D.G.; Hopewell, S.; Emdin, C.A.; Hunn, B.H. AKI and Long-Term Risk for Cardiovascular Events and Mortality. *J. Am. Soc. Nephrol.* **2017**, *28*, 377–387. [CrossRef]
10. Chawla, L.S. Disentanglement of the acute kidney injury syndrome. *Curr. Opin. Crit. Care.* **2012**, *18*, 579–584. [CrossRef]
11. Palevsky, P.M. Renal replacement therapy in acute kidney injury. *Adv. Chronic. Kidney Dis.* **2013**, *20*, 76–84. [CrossRef] [PubMed]
12. Brienza, N.; Giglio, M.T.; Dalfino, L. Protocoled resuscitation and the prevention of acute kidney injury. *Curr. Opin. Crit. Care.* **2012**, *18*, 613–622. [CrossRef] [PubMed]

13. Alsabbagh, M.M.; Asmar, A.; Ejaz, N.I.; Aiyer, R.K.; Kambhampati, G.; Ejaz, A.A. Update on clinical trials for the prevention of acute kidney injury in patients undergoing cardiac surgery. *Am. J. Surg.* **2013**, *206*, 86–95. [CrossRef] [PubMed]
14. Chopra, T.A.; Brooks, C.H.; Okusa, M.D. Acute Kidney Injury Prevention. *Contrib. Nephrol.* **2016**, *187*, 9–23. [CrossRef] [PubMed]
15. Hayes, W. Stop adding insult to injury-identifying and managing risk factors for the progression of acute kidney injury in children. *Pediatr. Nephrol.* **2017**, *32*, 2235–2243. [CrossRef] [PubMed]
16. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int. Suppl.* **2013**, *3*, 1–150.
17. Jha, V.; Garcia-Garcia, G.; Iseki, K.; Li, Z.; Naicker, S.; Plattner, B.; Saran, R.; Wang, A.Y.; Yang, C.W. Chronic kidney disease: Global dimension and perspectives. *Lancet* **2013**, *382*, 260–272. [CrossRef]
18. Quaggin, S.E. Kindling the Kidney. *N. Engl. J. Med.* **2016**, *374*, 281–283. [CrossRef]
19. Hsu, C.Y.; Ordonez, J.D.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Go, A.S. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int.* **2008**, *74*, 101–107. [CrossRef]
20. Bedford, M.; Farmer, C.; Levin, A.; Ali, T.; Stevens, P. Acute Kidney Injury and CKD: Chicken or Egg? *Am. J. Kidney Dis.* **2012**, *59*, 485–491. [CrossRef]
21. Palevsky, P.M. Chronic-on-acute kidney injury. *Kidney Int.* **2012**, *81*, 430–431. [CrossRef] [PubMed]
22. Heung, M.; Steffick, D.E.; Zivin, K.; Gillespie, B.W.; Banerjee, T.; Hsu, C.Y.; Powe, N.R.; Pavkov, M.E.; Williams, D.E.; Saran, R.; et al. Centers for Disease Control and Prevention CKD Surveillance Team. Acute Kidney Injury Recovery Pattern and Subsequent Risk of CKD: An Analysis of Veterans Health Administration Data. *Am. J. Kidney Dis.* **2016**, *67*, 742–752. [CrossRef] [PubMed]
23. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef] [PubMed]
24. Lim, P.; Khoo, O.T. Hypermagnesaemia in Presence of Magnesium Depletion in Acute-on-chronic Renal Failure. *Br. Med. J.* **1969**, *1*, 414–416. [CrossRef] [PubMed]
25. He, L.; Wei, Q.; Liu, J.; Yi, M.; Liu, Y.; Liu, H.; Sun, L.; Peng, Y.; Liu, F.; Venkatachalam, M.A.; et al. AKI on CKD: Heightened injury, suppressed repair, and the underlying mechanisms. *Kidney Int.* **2017**, *92*, 1071–1083. [CrossRef] [PubMed]
26. Zager, R.A. Progression of Acute Kidney Injury to Chronic Kidney Disease: Clinical and Experimental Insights and Queries. *Nephron. Clin. Pract.* **2014**, *127*, 46–50. [CrossRef] [PubMed]
27. Zager, R.A. 'Biologic memory' in response to acute kidney injury: Cytoresistance, toll-like receptor hyper-responsiveness and the onset of progressive renal disease. *Nephrol. Dial. Transplant.* **2013**, *28*, 1985–1993. [CrossRef] [PubMed]
28. Goldfarb, M.; Rosenberger, C.; Abassi, Z.; Shina, A.; Zilbersat, F.; Eckardt, K.U.; Rosen, S.; Heyman, S.N.; Source, AJ. Acute-on-chronic renal failure in the rat: Functional compensation and hypoxia tolerance. *Am. J. Nephrol.* **2006**, *26*, 22–33. [CrossRef] [PubMed]
29. Singh, P.; Rifkin, D.E.; Blantz, R.C. Chronic kidney disease: An inherent risk factor for acute kidney injury? *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 1690–1695. [CrossRef]
30. Grams, M.E.; Sang, Y.; Ballew, S.H.; Gansevoort, R.T.; Kimm, H.; Kovesdy, C.P.; Naimark, D.; Oien, C.; Smith, D.H.; Coresh, J.; et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex with Acute Kidney Injury. *Am. J. Kidney Dis.* **2015**, *66*, 591–601. [CrossRef]
31. Zhou, Q.; Zhao, C.; Xie, D.; Xu, D.; Bin, J.; Chen, P.; Liang, M.; Zhang, X.; Hou, F. Acute and acute-on-chronic kidney injury of patients with decompensated heart failure: Impact on outcomes. *BMC Nephrol.* **2012**. [CrossRef] [PubMed]
32. Hsu, C.Y.; Chertow, G.M.; McCulloch, C.E.; Fan, D.; Ordoñez, J.D.; Go, A.S. Nonrecovery of Kidney Function and Death after Acute on Chronic Renal Failure. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 891–898. [CrossRef] [PubMed]
33. Pannu, N.; James, M.; Hemmelgarn, B.R.; Dong, J.; Tonelli, M.; Klarenbach, S. Modification of outcomes after acute kidney injury by the presence of CKD. *Am. J. Kid. Dis.* **2011**, *58*, 206–213. [CrossRef] [PubMed]
34. Neyra, J.A.; Mescia, F.; Li, X.; Adams-Huet, B.; Yessayan, L.; Yee, J.; Toto, R.D.; Moe, O.W. Impact of acute kidney injury and CKD on adverse outcomes in critically ill septic patients. *Kidney Int. Rep.* **2018**, *3*, 1344–1353. [CrossRef] [PubMed]

35. Pan, H.C.; Wu, P.C.; Wu, V.C.; Yang, Y.F.; Huang, T.M.; Shiao, C.C.; Chen, T.C.; Tarng, D.C.; Lin, J.H.; Yang, W.S.; et al. A nationwide survey of clinical characteristics, management, and outcomes of acute kidney injury (AKI)-patients with and without preexisting chronic kidney disease have different prognoses. *Medicine (Baltimore)* **2016**, *95*, e4987. [CrossRef] [PubMed]
36. Khosla, N.; Soroko, S.B.; Chertow, G.M.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.; Mehta, R.L.; Program to Improve Care in Acute Renal Disease (PICARD). Preexisting chronic kidney disease: A potential for improved outcomes from acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1914–1919. [CrossRef] [PubMed]
37. Prakash, J.; Rathore, S.S.; Arora, P.; Ghosh, B.; Singh, T.B.; Gupta, T.; Mishra, R.N. Comparison of clinical characteristics of acute kidney injury versus acute-on-chronic renal failure: Our experience in a developing country. *Hong Kong J. Nephrol.* **2015**, *17*, 14e20. [CrossRef]
38. Ali, T.; Khan, I.; Simpson, W.; Prescott, G.; Townend, J.; Smith, W.; Macleod, A. Incidence and outcomes in acute kidney injury: A comprehensive population-based study. *J. Am. Soc. Nephrol.* **2007**, *18*, 1292–1298. [CrossRef] [PubMed]
39. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P.; ADQI Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, R204–R212. [CrossRef]
40. Ronco, C.; Levin, A.; Warnock, D.G.; Mehta, R.; Kellum, J.A.; Shah, S.; Molitoris, B.A.; AKIN Working Group. Improving outcomes from acute kidney injury (AKI): Report on an initiative. *Int. J. Artif. Organs.* **2007**, *30*, 373–376. [CrossRef]
41. Levey, A.S.; Bosch, J.P.; Lewis, J.B.; Greene, T.; Rogers, N.; Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* **1999**, *130*, 461–470. [CrossRef] [PubMed]
42. Siew, E.D.; Ikizler, T.A.; Matheny, M.E.; Shi, Y.; Schildcrout, J.S.; Danciu, I.; Dwyer, J.P.; Srichai, M.; Hung, A.M.; Smith, J.P.; et al. Estimating Baseline Kidney Function in Hospitalized Patients with Impaired Kidney Function. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 712–719. [CrossRef] [PubMed]
43. Der Mesropian, P.J.; Kalamaras, J.S.; Eisele, G.; Phelps, K.R.; Asif, A.; Mathew, R.O. Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: A retrospective analysis. *Clin. Nephrol.* **2014**, *81*, 81–174. [CrossRef] [PubMed]
44. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic. Dis.* **1987**, *40*, 373–383. [CrossRef]
45. Hatakeyama, Y.; Horino, T.; Nagata, K.; Matsumoto, T.; Terada, Y.; Okuhara, Y. Transition from acute kidney injury to chronic kidney disease: A single centre cohort study. *Clin. Exp. Nephrol.* **2018**, *22*, 1281–1293. [CrossRef] [PubMed]
46. Machado, M.N.; Nakazone, M.A.; Maia, L.N. Acute kidney injury based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine undergoing cardiac surgery. *Rev. Bras. Cir. Cardiovasc.* **2014**, *29*, 299–307. [CrossRef]
47. Sawhney, S.; Marks, A.; Fluck, N.; Levin, A.; Prescott, G.; Black, C. Intermediate and long-term outcomes of survivors of acute kidney injury episodes: A large population-based cohort study. *Am. J. Kid. Dis.* **2017**, *69*, 18–28. [CrossRef] [PubMed]
48. Chao, C.T.; Wu, VC.; Lai, C.F.; Shiao, C.C.; Huang, T.M.; Wu, P.C.; Tsai, I.J.; Hou, C.C.; Wang, W.J.; Tsai, H.B.; et al. Advanced age affects the outcome-predictive power of RIFLE classification in geriatric patients with acute kidney injury. *Kidney Int.* **2012**, *82*, 920–927. [CrossRef]



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Hemodynamic Predictors for Sepsis-Induced Acute Kidney Injury: A Preliminary Study

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Abstract: The aim of our study was to assess the association between the macrohemodynamic profile and sepsis induced acute kidney injury (AKI). We also investigated which minimally invasive hemodynamic parameters may help identify patients at risk for sepsis-AKI. We included 71 patients with sepsis and septic shock. We performed the initial fluid resuscitation using local protocols and continued to give fluids guided by the minimally invasive hemodynamic parameters. We assessed the hemodynamic status by transpulmonary thermodilution technique. Sequential organ failure assessment (SOFA score) (AUC 0.74, 95% CI 0.61–0.83, $p < 0.01$) and cardiovascular SOFA (AUC 0.73, 95% CI 0.61–0.83, $p < 0.01$) were found to be predictors for sepsis-induced AKI, with cut-off values of 9 and 3 points respectively. Persistent low stroke volume index (SVI) ≤ 32 mL/m^2/beat (AUC 0.67, 95% CI 0.54–0.78, $p < 0.05$) and global end-diastolic index (GEDI) < 583 mL/m^2 (AUC 0.67, 95% CI 0.54–0.78, $p < 0.05$) after the initial fluid resuscitation are predictive for oliguria/anuria at 24 h after study inclusion. The combination of higher vasopressor dependency index (VDI, calculated as the (dobutamine dose × 1 + dopamine dose × 1 + norepinephrine dose × 100 + vasopressin × 100 + epinephrine × 100)/MAP) and norepinephrine, lower systemic vascular resistance index (SVRI), and mean arterial blood pressure (MAP) levels, in the setting of normal preload parameters, showed a more severe vasoplegia. Severe vasoplegia in the first 24 h of sepsis is associated with a higher risk of sepsis induced AKI. The SOFA and cardiovascular SOFA scores may identify patients at risk for sepsis AKI. Persistent low SVI and GEDI values after the initial fluid resuscitation may predict renal outcome.

Keywords: sepsis-induced AKI; advanced hemodynamic monitoring

1. Introduction

Sepsis is still an important cause of morbidity and mortality in the intensive care unit (ICU) [1]. The combination of acute kidney injury (AKI) and sepsis carries an even higher mortality; sepsis-induced AKI was found to be a significant independent factor for mortality [2]. Sepsis is the leading cause of AKI in critically ill patients with a reported incidence of around 42.1% [3].

The pathophysiology of sepsis AKI is multifactorial, involving hemodynamic, microcirculatory, and inflammatory mechanisms [4]. Fluid management is a fundamental step in the management of this condition; it was already demonstrated that a successful goal-directed therapy decreases the risk of developing sepsis AKI [5].

Early identification and optimal management of patients at risk for sepsis AKI may lower the associated morbidity and mortality. The altered macrohemodynamic profile is one of the multiple triggers for sepsis induced AKI. The central role of the hemodynamic management in the prevention and treatment of patients with or at risk of sepsis AKI was already stated [6], but there is only limited research regarding the ability of the hemodynamic parameters in identifying the risk of AKI in the septic setting [7–9].

Advanced hemodynamic monitoring may be an essential tool in diagnosing the hemodynamic alterations and in achieving hemodynamic coherence [10,11]. Transpulmonary thermodilution technique was proven to be a reliable tool in assessing the hemodynamic status and in guiding fluid resuscitation in the critically ill [12,13]. By measuring cardiac output (CO) and its components (preload, afterload, and contractility) and by tailoring our interventions accordingly, we may improve diagnosis, treatment, and outcome.

The aim of our study was to find advanced hemodynamic parameters that may help in the early identification of patients at risk of developing sepsis AKI.

2. Patients and Methods

This prospective observational study was carried out between 2016 and 2017, in a mixed surgical and medical ICU of a university hospital. The protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy of Cluj-Napoca (no 119/6.03.2015). We obtained individual informed consent from each patient or from next of kin before data acquisition.

2.1. Study Patients

Seventy-one consecutive septic patients [14,15], recruited in the emergency department (ED) or hospital ward, were included in this study. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, clinically defined as a qSOFA (quick sequential organ failure assessment) > 2, in the presence of suspected infection [15]. Organ dysfunction was defined as an acute change in total sequential organ failure assessment (SOFA) score of 2 points or greater secondary to infection [15]. Septic shock was defined by persisting hypotension requiring vasopressors to maintain a MAP of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation [15].

All patients included in this study had no previous history of acute kidney disease or end-stage renal disease with oliguria or anuria, and had a normal urinary output prior to this hospital admission.

Patients were excluded if aged ≥80, previously known with cardiac failure NYHA III or IV, significant aortic valvular disease, severe pulmonary hypertension or cor pulmonale, hepatic failure, renal failure, known vascular disease, severe anaemia with no consent for red blood cells (RBCs) transfusion, or prone position. We used these complex exclusion criteria in order to avoid all factors that could bias the hemodynamics of the patients [16–19]. Both spontaneous breathing and mechanically ventilated patients were included in the study.

2.2. Data Collection

Time zero (T_0) was defined as the time of study inclusion in the intensive care unit (ICU). H_3, H_6, and H_{24} were defined as the 3rd, 6th, and 24th hour after study inclusion. Sepsis onset was defined as the moment when the patient with suspected infection met at least two points from the qSOFA or SOFA scores [15]; the time interval between sepsis onset and study inclusion time (T_0) was less than two hours.

Fluid resuscitation in this time interval was carried out following local protocols (Supplemental Material 1A). Protocol compliance was achieved in all patients.

From T_0 to H_3 fluid resuscitation was carried out according to the same local protocols (Supplemental Material 1A). Starting with the 3rd h (H_3) to the 24th h (H_{24}) after study inclusion, all patients continued to be resuscitated using minimally invasive hemodynamic monitoring parameters

obtained through transpulmonary thermodilution techniques (EV1000, Edwards Lifesciences©, Irvine, CA, USA) and the local protocol (Supplemental Material 1B). Calibrations in the first 24 h were performed at H_3, H_6, and H_{24}, and at any time the vasoactive infusion was adjusted. Static hemodynamic parameters and clinical features were also used in the monitoring process. Compliance to the fluid resuscitation protocol was achieved in all patients.

We used the vasopressor dependency index (VDI), to express the relationship between the vasopressor infusion dose and MAP. VDI is calculated as following: ((dobutamine dose × 1) + (dopamine dose × 1) + (norepinephrine dose × 100) + (vasopressin × 100) + (epinephrine × 100))/MAP [20]. Epinephrine, norepinephrine, dobutamine, and dopamine are expressed as μg/kg/min and vasopressin as units/min.

We defined vasoplegia as the syndrome of pathological low systemic vascular resistance, manifested clinically through the need for vasopressors in order to maintain a blood pressure ≥65 mm Hg in the absence of hypovolemia [21].

Sequential organ failure assessment (SOFA), cardiovascular SOFA, and acute physiology and chronic health evaluation (APACHE II) scores were used to classify the illness severity [22,23], while the kidney disease improving global outcomes (KDIGO) and acute kidney injury network (AKIN) urinary output criteria were used to define sepsis related AKI [24,25]. The rationale for choosing this clinical parameter at the expense of creatinine levels was due to the early and high sensitivity in predicting AKI [26].

We defined AKI as oliguria or anuria which persisted 24 h after sepsis diagnosis, after adequate fluid resuscitation was performed and obstruction was ruled out [25].

According to the renal outcome at 24 h, we separated the patients in two groups: the oliguric/anuric group, 19 patients (oliguric/anuric patients at 24 h after enrollment) and the normal urinary output group, 49 patients (patients which were with normal diuresis both at the time of study inclusion and 24 h later and the patients which were initially oliguric/anuric but restored normal diuresis by the 24th h after enrollment). This stratification was performed after the exclusion of patients with mortality < 24 h and patients with continuous renal replacement therapies (CRRT).

2.3. Statistical Analysis

For the statistical analysis we used IBM SPSS Statistics (version 23.0, IBM Corp, Armonk, NY, USA) MedCalc statistical software (version 17.9, MedCalc Software, Ostend, Belgium) Microsoft Excel (2013, Microsoft Corporation, Redmond, WA, USA), and GraphPad Prism (6, GraphPad Software, La Jolla, CA, USA). Continuous variables were expressed as mean ± SD and categorical variables as numbers or percentages. For descriptive statistics we used tables and graphs. To compare means we used the Wilcoxon signed rank test and Mann–Whitney U test and independent samples t-test. Proportions were compared using the two-proportion Z-Test; Receiver operating characteristic (ROC) curve analysis was used to determine predicting factors and cutoff points; odds ratio (OR) and relative risk (RR) were used as measures of association; a $p < 0.05$ was considered to be statistically significant.

3. Results

All 71 patients were included in the statistical analysis. Their demographic and physiologic characteristics are shown in Table 1.

By the 3rd h after study inclusion (H_3) most of the macro hemodynamic parameters were in the targeted range (Supplemental Material 2). An improvement in microcirculation was also noted, as shown by the reduction in the number of patients with increased capillary refill time (CRT, $p < 0.05$ at 6 hours and $p < 0.01$ at 24 h), the reduction in the number of patients presenting oliguria/anuria ($p < 0.05$ at H_3 and $p < 0.01$ at H_6 and H_{24}), and the reduction in serum lactate level (for the septic shock patients, $p < 0.0001$ at H_{24}) (Supplemental Material 2). We considered the fluid resuscitation to be appropriate as we noticed an improvement in these macro- and micro-hemodynamic parameters.

Table 1. Clinical and demographic characteristics of the patients included in the study.

	All Patients Included in the Study	Oliguric/Anuric Group	Normal Urinary Output Group	*p* Value *
Number of patients N	71	19	52	
Age Mean ± SD	62.6 ± 14.7	61.4 ± 10.7	62.9 ± 15.1	0.57
Weight (actual) kg Mean ± SD	82.5 ± 20.0	88.5 ± 21.4	79.9 ± 19.6	0.14
Body Surface Area Mean ± SD	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.09
Diagnosis N (%)				
Sepsis	37 (52.1)	13 (68.4)	21 (40.4)	0.03
Septic shock	34 (47.9)	6 (31.6)	31 (59.6)	0.03
Type of sepsis N (%)	N (%)			
Medical	26 (36.6)	8 (42.1)	19 (36.5)	0.66
Surgical	45 (63.4)	11 (57.9)	33 (63.5)	0.66
Ventilation N (%)	N (%)			
Mechanically ventilated	49 (69)	18 (94.7)	31 (59.6)	0.04
Spontaneous ventilation	22 (31)	1 (5.3)	21 (40.4)	0.04
PEEP for Mechanically ventilated at study inclusion (T_0) Mean ± SD	5.7 ± 1.1	6 ± 1.2	5.5 ± 0.9	0.16
SOFA Score at study inclusion (T_0) Mean ± SD points	9.5 ± 3.2	11.3 ± 2.9	8.8 ± 3.2	0.02
SOFA Score without renal SOFA at study inclusion (T_0) Mean ± SD points	7.1 ± 2.5	8.2 ± 2.2	6.8 ± 2.6	0.06
Cardiovascular SOFA at study inclusion (T_0) Mean ± SD points	2.8 ± 1.4	3.4 ± 1.2	2.5 ± 1.3	0.03
APACHE II Score at study inclusion (T_0) Mean ± SD points	21.9 ± 8.6	23.3 ± 8.5	20.8 ± 8.4	0.17
Heart Rate at study inclusion (T_0) Mean ± SD beats/min	105.0 ± 20.6	108.5 ± 19.2	101.6 ± 18.0	0.15
Mean arterial blood pressure (MAP) at study inclusion (T_0) Mean ± SD mm Hg	75.2 ± 13.6	74.3 ± 16.4	75.8 ± 12.8	0.68
Lactate at study inclusion (T_0) Mean ± SD mmol/l	2.52 ± 2.2	4.1 ± 2.0	3.5±2.3	0.12
Norepinephrine at study inclusion (T_0) Mean ± SD mcg/kg/min	0.09 ± 0.1	0.18 ± 0.1	0.06 ± 0.07	0.001
VDI Mean ± SD at study inclusion (T_0)	0.14 ± 0.2	0.26 ± 0.27	0.08 ± 0.1	0.001
Creatinine Mean ± SD at study inclusion (T_0) μmol/l	218.3 ± 192.7	291.7 ± 226.3	192.76 ± 179.5	0.06
Urea Mean ± SD at study inclusion (T_0) mmol/l	16.4 ± 12.0	20.3 ± 13.7	14.6 ± 11.2	0.09

* *p* value between the oliguric/anuric group and the normal urinary output group.

The incidence of sepsis induced AKI in our study was 27.9%, as shown by the number of oliguric/anuric vs. normal urinary output patients (19 vs. 49).

When we compared the SOFA and cardiovascular SOFA scores at T_0 among the two groups we found statistically significant differences ($p < 0.05$).

The ROC curve analysis for the SOFA score identified a cutoff point of >9 points (AUC 0.74, SE 0.06, 95% CI 0.61–0.83, $p < 0.01$) and a cutoff point of >3 for the cardiovascular SOFA for identifying patients at risk of oliguria/anuria (AUC 0.73, SE 0.06, 95% CI 0.61–0.83, $p < 0.01$). The graphical representation is shown in Figure 1.

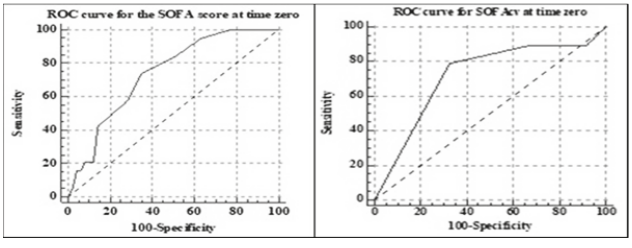

Figure 1. Receiver operating characteristic (ROC) curve analysis for Sequential organ failure assessment (SOFA) and cardiovascular SOFA at time zero.

If we compare the total fluid load (from T_0 to the H_{24}) among the two groups, we can observe that the anuric/oliguric patients received more fluids compared to the normal urinary output group (113.43 ± 72.73 versus 88.02 ± 50.06 (Figure 2A).

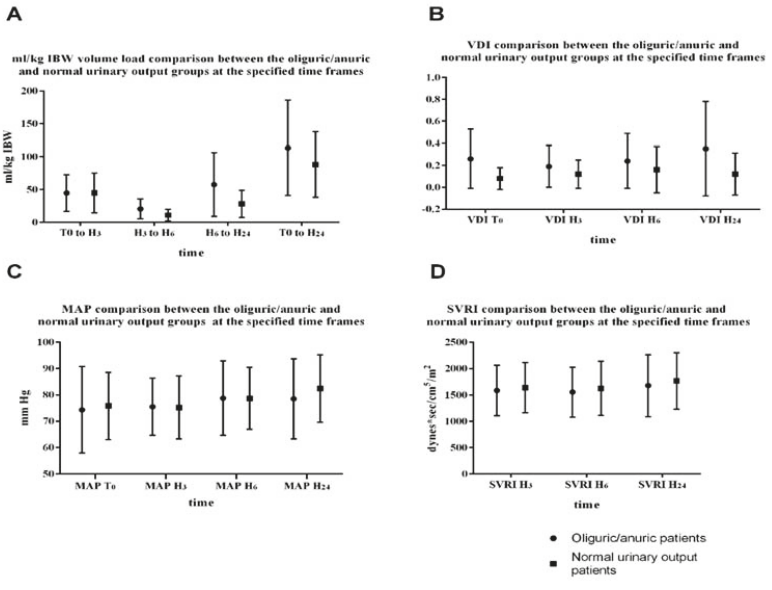

Figure 2. Comparison between the poor and normal urinary output groups at the specified time frames. (**A**) Fluid load, (**B**) vasopressor dependency index, (**C**) mean arterial blood pressure, (**D**) systemic vascular resistance index.

From T_0 to H_3 the fluid load was similar among the two groups (Figure 2A). Still the 3rd h minimally invasive hemodynamic evaluation showed a statistically significant lower stroke volume index (31.5 ± 9.3 compared to 37.0 ± 9.6, $p = 0.03$) and global end diastolic index (565.8 ± 133.6 versus 661.8 ± 158.4, $p = 0.03$) in the oliguric/anuric group compared to the normal urinary output group. The ROC curve analysis showed a cutoff point of 32 mL/m^2/beat for SVI (AUC 0.67, SE 0.07, 95% CI 0.54–0.78, $p < 0.05$) and a cutoff value of 583 mL/m^2 for GEDI (AUC 0.67, SE 0.07, 95% CI 0.54–0.78, $p < 0.05$) as predictive for oliguria/anuria at 24 h after study inclusion (Figure 3). There were no statistically significant differences in the MAP and SVRI among the two groups, even though the patients in the oliguric/anuric group had statistically significant more norepinephrine ($p < 0.001$, at T_0, and $p < 0.02$ at H_{24}, Table 2) and statistically significant higher VDI levels ($p < 0.001$, at T_0, and $p < 0.01$ at H_{24}, Table 2). Both the difference in norepinephrine infusion and the higher VDI were suggestive for a more severe vasoplegia in the oliguric/anuric.

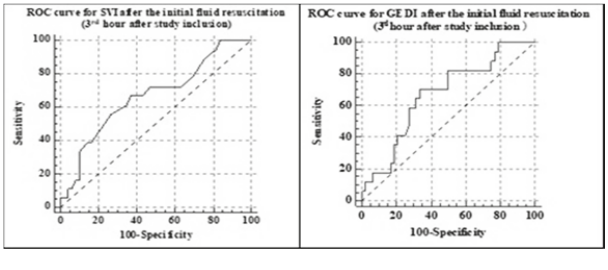

Figure 3. ROC curve analysis for the stroke volume index (SVI) and global end diastolic index (GEDI) after the initial fluid resuscitation.

Table 2. The hemodynamic parameters of the two groups of patients.

	T_0			H_3			H_6			H_{24}		
	Oliguric/ Anuric Group	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**
SOFA Mean ± SD points	11.3 ± 2.9	8.8 ± 3.2	0.02	not calculated at the 3rd h			10.1 ± 3.1	8.4 ± 3.6	0.11	10.0 ± 2.5	7.2 ± 3.6	0.02
SOFAcv Mean ± SD points	3.4 ± 1.2	2.5 ± 1.3	0.03				3.0 ± 1.6	2.8 ± 1.5	0.22	3.0 ± 1.6	2.3 ± 1.5	0.03
SOFAr Mean ± SD points	3.1 ± 1.4	1.9 ± 1.6	0.03				2.8 ± 1.5	1.3 ± 1.5	0.01	2.7 ± 1.3	1.1 ± 1.3	0.00
SOFAp Mean ± SD points	2.4 ± 1.2	1.8 ± 1.2	0.02				2.2 ± 1.2	1.0 ± 1.0	0.18	2.1 ± 0.9	1.6 ± 1.0	0.12
APACHE II Mean ± SD points	23.3 ± 8.5	20.8 ± 8.4	0.17				not calculated at 6th h			not calculated at 24th h		
SBD Mean ± SD mm Hg	121.1 ± 23.9	117.5 ± 19.9	0.53	124.2 ± 18.5	123.0 ± 17.9	0.80	126.1 ± 17.3	127.9 ± 18.5	0.70	130.5 ± 17.9	130.1 ± 20.0	0.93
DBP Mean ± SD mm Hg	57.7 ± 14.5	55.6 ± 10.0	0.67	58.0 ± 11.9	55.0 ± 11.9	0.34	60.5 ± 12.0	56.5 ± 11.7	0.21	60.4 ± 12.3	59.5 ± 13.3	0.80
MAP Mean ± SD mm Hg	74.3 ± 16.4	75.8 ± 12.8	0.68	75.4 ± 10.9	75.2 ± 11.9	0.94	78.7 ± 14.1	78.6 ± 11.7	0.97	78.5 ± 15.2	82.4 ± 12.7	0.29
Heart rate Mean ± SD beats/min	108.5 ± 19.2	101.5±17.9	0.15	101.7 ± 18.7	96.5 ± 18.3	0.26	100.1 ± 21.0	98.1 ± 19.5	0.90	101.1 ± 14.9	95.5±17.4	0.25
CVP Mean ± SD mm Hg	8.5 ± 4.2	6.8 ± 4.7	0.08	10.7 ± 3.9	7.6 ± 4.9	0.006	11.2 ± 3.7	8.2 ± 4.9	0.01	7.7 ± 3.9	8.3 ± 4.6	0.96
CI Mean ± SD l/min	not monitored at time 0			3.2 ± 0.8	3.5 ± 0.9	0.20	3.1 ± 0.8	3.7 ± 0.9	0.03	3.2 ± 0.6	3.5 ± 0.7	0.23
SVI Mean ± SD mL/m^2/beat				31.5 ± 9.4	37.0 ± 9.6	0.03	34.1 ± 12.2	38.0 ± 10.0	0.27	33.1 ± 8.6	38.0 ± 10.4	0.07
GEDI Mean ± SD mL/kg				565.8 ± 133.6	661.8 ± 158.4	0.037	530.9 ± 199.3	651.9 ± 203.0	0.07	605.1 ± 120.6	707.4 ± 153.6	0.009
ITBI Mean ± SD mL/m^2				754.5 ± 215.6	764.6 ± 153.0	0.15	761.9 ± 247.0	858.3 ± 262.2	0.20	776.4 ± 247.8	931.4 ± 229.8	0.009
ELWI Mean ± SD mL/kg				7.9 ± 2.0	8.7 ± 3.3	0.88	8.88 ± 3.03	8.9 ± 4.0	0.49	8.8 ± 2.2	8.5 ± 3.0	0.45
GEF Mean ± SD				23.6 ± 8.7	22.3 ± 5.8	0.91	23.6 ± 9.8	22.7 ± 6.2	0.96	22.7 ± 7.0	21.1 ± 6.2	0.64
SVRI Mean ± SD dynes * sec/cm^5/m^2				1584.4 ± 477.4	1638.9 ± 476.4	0.97	1554.3 ± 472.3	1623.7 ± 512.1	0.85	1678.0 ± 588.0	1765.6 ± 536.0	0.69
Norepinephrine Mean ± SD mcg/kg/min	0.18 ± 0.19	0.06 ± 0.07	0.001	0.14 ± 0.14	0.08 ± 0.08	0.08	0.17 ± 0.16	0.10 ± 0.12	0.11	0.24 ± 0.30	0.12 ± 0.19	0.02
VDI Mean ± SD	0.26 ± 0.27	0.08 ± 0.1	0.001	0.19 ± 0.19	0.12 ± 0.13	0.14	0.24 ± 0.25	0.16 ± 0.21	0.19	0.35 ± 0.43	0.12 ± 0.19	0.01
Creatinine Mean ± SD) µmol/L	291.7 ± 226.3	192.76 ± 179.5	0.06	not monitored at these time frames						249.3 ± 191.8	184.8 ± 165.3	0.14
Urea Mean ± SD mmol/L	20.32 ± 13.7	14.6 ± 11.28	0.09							19.0 ± 10.7	15.3 ± 11.6	0.11
Mean urinary output Mean ± SD mL/kg/hour										0.12 ± 0.12	1.26 ± 0.75	<0.001
Lactate (septic shock patients) mean ± SD mmol/L	4.1 ± 2.0	3.5 ± 2.3	0.12	3.6 ± 2.0	3.6 ± 3.4	0.08	3.5 ± 1.5	3.7 ± 3.4	0.18	2.2 ± 1.2	2.5 ± 2.7	0.18

Table 2. *Cont.*

	T_0			H_3			H_6			H_{24}		
	Oliguric/ Anuric Group	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**	**Oliguric/ Anuric Group**	**Normal Urinary Output Group**	***p* Value**
Lactate clearance ≥ 10% (septic shock patients) %	not monitored between time of presentation and time zero			53.8	44.4	0.60	53.8	44.4	0.60	84.6	94.4	0.36
Capilary refill time > 3 sec %	31.60	16.30	0.16	26.30	10.10	0.09	21.10	6.2%	0.06	5.30	4.10	0.08

T_0: time zero, time of study inclusion; H_3, H_6, H_{24}: 3rd, 6th, and 24th h transpulmonary thermodilution calibrations performed in Ev1000. SOFAcv: cardiovascular SOFA; SOFAr: renal SOFA; SOFAp: pulmonary SOFA; SBD: systolic blood pressure; DBP: dyastolic blood pressure; MAP: mean arterial blood pressure; CVP: central venous pressure; CI: cardiac index; SVI: stroke volume index; GEDI: global end-dyastolic index; ITBI: intrathoracic blood index; ELWI: extravscular lung water index; GEF: global ejection fraction; SVRI: systemic vascular resistance index; VDI: vasopressor dependency index.

Patients who had an SVI lower than the cutoff value had a higher risk of remaining oliguric/anuric at 24 h than the patients with normal SVI (OR = 3.44, 95% CI 1.1–10.76, $p = 0.03$); the calculated relative risk (RR) was 2.46 (CI 1.05–5.79, $p = 0.03$).

The renal outcome upon discharge or at 28 days after admission showed a higher creatinine level in the anuric/oliguric group compared to the normal urinary output group (164.4 µmol/L ± 255.1 vs. 95.4 µmol/L ± 70.0, $p = 0.14$). The number of ICU days among the two groups showed no statistically significant difference (19.3 ± 14.4 in the oliguric/anuric group compared to 17.4 ± 13.9 in the normal urinary output group, $p = 0.70$).

The all-cause mortality for all patients included in the study was 30.9%. The all-cause mortality within the normal urinary output patients was 22.4%, while in the oliguric/anuric patients was 52.63%. The odds ratio was 3.84, 95% CI 1.24–11.80, $p = 0.01$; the RR was 2.43, 95% CI 1.19–4.59, $p = 0.01$.

4. Discussion

The main finding of our study is the fact that renal outcome in patients with sepsis and septic shock may be predicted by severe vasoplegia in the first 24 h of sepsis. A persistent low SVI (≤32 mL/m^2/beat) and low GEDI (<583 mL/kg) after the initial fluid resuscitation are also predictive for sepsis AKI. There are few studies which investigate the relationship between hemodynamics and progression of AKI during early phases of sepsis, and, from our knowledge, there are no studies which focus on the predicting value of vasoplegia, SVI or GEDI [7,8].

The cutoff values found on the ROC curves analysis for the stroke volume index and global end-diastolic volume are lower than the normal values specified by the manufacturer. The association between a low SVI and a low GEDI is suggestive for a low preload. Therefore, we may argue that the patients in the oliguric/anuric group did not receive enough fluids. But as shown in Figure 2A, not only they received similar amounts of fluids in the initial fluid resuscitation, but in the next few hours, they were given more fluids, in the attempt to restore normal GEDI, SVI, and urinary output. If we add the fact that patients in the oliguric/anuric group were having both statistically higher VDI and norepinephrine infusion rates to maintain the SVRI in clinically acceptable ranges (Table 2), and also a significantly higher pulmonary SOFA at time 0 ($p < 0.05$, Table 2), we may state that these patients were having a more severe vasoplegia with both enhanced vascular compliance and capillary leakage [27,28]. This group of patients has a high risk for fluid overload, a status associated with increased mortality in sepsis.

A high SOFA score (>9 points) and a high cardiovascular SOFA (>3 points) at time zero may be predictors for sepsis AKI. The cutoff values found for the SOFA and cardiovascular SOFA may represent tools for screening the septic patients at risk for AKI. The ease in obtaining these scores made them efficient screening methods for sepsis and septic complications [15,29].

We used only the urine output criterion to define AKI at 24 h after study inclusion. The rationale for choosing this clinical parameter at the expense of creatinine levels was due to the early and high sensitivity in predicting AKI [26]. Kellum et al. demonstrated that AKI defined by isolated oliguria (no SC criteria present) was surprisingly frequent and was associated with a long-term morbidity and mortality [30]. In their study they also emphasized that some of the critically ill patients may have fluid overload with impact on the measured serum creatinine levels [30]. The mean values of creatinine among the two groups at admission and 24 h later (as shown in Table 2) are higher in the oliguric/anuric group compared to the normal urinary output group, but don't show statistically significant differences.

The incidence of sepsis induced AKI found in our study was lower compared to other studies [2,5,31]. This could be since we stratified the patients according to the 24 h renal outcome, including only patients with stage 2 and 3 AKIN and KDIGO acute kidney injury scores. This could be a limitation of our study.

All-cause mortality for the patients included in the study was 30.9%, similar to the one found in other significant research on the subject [3,32]. AKI is known to be an independent risk factor for

in-hospital mortality [2]. Our research showed that patients which developed AKI had twice the mortality rate of septic patients without AKI, in concordance with other important works [33,34]. A possible limitation in our study was the fact that we did not calculate mortality with adjustments for SOFA or APACHE II scores.

The renal outcome at 28 day or upon discharge among survivors was similar in the two studied groups, but a larger study is needed in order to confirm these findings. The number of ICU days among the two groups showed no statistically significant difference (19.3 ± 14.4 in the oliguric/anuric group compared to 17.4 ± 13.9 in the normal urinary output group, $p = 0.70$), but due to the small sample size, further research is needed to confirm this result.

Our study has several limitations. Due to the complex exclusion criteria, which had the purpose of reducing the bias generated by the hemodynamic monitoring (e.g., severe valvular diseases may impair the results of the transpulmonary thermodilution hemodynamic monitoring parameters), our results cannot be extrapolated to all septic patients. Moreover, the sample size was also limited, and the study is underpowered; more research is needed in order to confirm these results.

The lack of temporal relationship as AKI onset after sepsis onset is probably the biggest weakness in research method.

Another limitation of our study is related to the ROC AUC values which are modest, especially in the context of the multiple factors involved in the onset and persistence of oliguria and sepsis related AKI. Furthermore, the differences in baseline characteristics and number of patients in the two groups are possible factors for further errors. The results obtained through a case control experimental design, matched for selected baseline factors, could support the results obtained in this observational study; further research is needed.

5. Conclusions

Severe vasoplegia in the first 24 h of sepsis is associated with a higher risk of sepsis induced AKI. The SOFA and cardiovascular SOFA may help identify patients at risk for sepsis-induced AKI. Renal outcome in patients with sepsis and septic shock may be predicted by a persistent low SVI ($\leq$32 nmL/m^2/beat) and low GEDI (<583 mL/kg) after the initial fluid resuscitation. Further research is needed to confirm these results.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/1/151/s1, Supplemental Material 1A: Fluid resuscitation protocol in the absence of advanced hemodynamic monitoring, Supplemental Material 1B: Fluid resuscitation protocol guided by advanced hemodynamic monitori, Supplemental Material 2: The hemodynamic parameters of the patients included in the study.

Author Contributions: Conceptualization, N.H. and O.A.; Methodology, N.H. and O.A.; Software, O.A. and A.C.; Validation, N.H.; Formal analysis, O.A.; Investigation, O.A., E.Ș., M.M., A.M.B.; Resources, O.A.; Data curation, O.A.; Writing—original draft preparation, O.A.; Writing—review and editing, N.H. and O.A.; Visualization, O.A.; Supervision, N.H. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare that there is no conflict of interest regarding the authorship of the present paper.

Statement of Ethics: Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (Ethics Committee of the University of Medicine and Pharmacy of Cluj-Napoca no 119/6.03.2015) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

References

1. Sakhuja, A.; Kumar, G.; Gupta, S.; Mittal, T.; Taneja, A.; Nanchal, R.S. Acute Kidney Injury Requiring Dialysis in Severe Sepsis. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 951–957. [CrossRef]
2. Oppert, M.; Engel, C.; Brunkhorst, F.M.; Bogatsch, H.; Reinhart, K.; Frei, U.; Eckardt, K.U.; Loeffler, M.; John, S.; German Competence Network Sepsis (Sepnet). Acute renal failure in patients with severe sepsis and septic shock-a significant independent risk factor for mortality: Results from the German Prevalence Study. *Nephrol. Dial. Transplant.* **2008**, *23*, 904–909. [CrossRef]
3. Bagshaw, S.M.; George, C.; Bellomo, R.; Committee, A.D.M. ANZICS Database Management Committee. Early acute kidney injury and sepsis: A multicentre evaluation. *Crit. Care* **2008**, *12*, R47. [CrossRef]
4. Montomoli, J.; Donati, A.; Ince, C. Acute Kidney Injury and Fluid Resuscitation in Septic Patients: Are We Protecting the Kidney? *Nephron Clin. Pract.* **2019**, *143*, 170–173. [CrossRef]
5. Plataki, M.; Kashani, K.; Cabello-Garza, J.; Maldonado, F.; Kashyap, R.; Kor, D.J.; Gajic, O.; Cartin-Ceba, R. Predictors of acute kidney injury in septic shock patients: An observational cohort study. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 1744–1751. [CrossRef]
6. Prowle, J.R.; Bellomo, R. Sepsis-associated acute kidney injury: Macrohemodynamic and microhemodynamic alterations in the renal circulation. *Semin. Nephrol.* **2015**, *35*, 64–74. [CrossRef]
7. Poukkanen, M.; Wilkman, E.; Vaara, S.T.; Pettilä, V.; Kaukonen, K.M.; Korhonen, A.M.; Uusaro, A.; Hovilehto, S.; Inkinen, O.; Laru-Sompa, R.; et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: Data from the prospective observational FINNAKI study. *Crit. Care* **2013**, *17*, R295. [CrossRef] [PubMed]
8. Badin, J.; Boulain, T.; Ehrmann, S.; Skarzynski, M.; Bretagnol, A.; Buret, J.; Benzekri-Lefevre, D.; Mercier, E.; Runge, I.; Garot, D.; et al. Relation between mean arterial pressure and renal function in the early phase of shock: A prospective, explorative cohort study. *Crit. Care.* **2011**, *15*, R135. [CrossRef] [PubMed]
9. Vallabhajosyula, S.; Sakhuja, A.; Geske, J.B.; Kumar, M.; Kashyap, R.; Kashani, K.; Jentzer, J.C. Clinical profile and outcomes of acute cardiorenal syndrome type-5 in sepsis: An eight-year cohort study. *PLoS ONE* **2018**, *13*, e0190965. [CrossRef] [PubMed]
10. Ince, C. Personalized physiological medicine. *Crit. Care.* **2017**, *21* (Suppl. 3), 308. [CrossRef]
11. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for acute kidney injury. Section 2: AKI definition. *Kidney Int. Suppl.* **2012**, *2*, 19–36.
12. Teboul, J.L.; Saugel, B.; Cecconi, M.; De Backer, D.; Hofer, C.K.; Monnet, X.; Perel, A.; Pinsky, M.R.; Reuter, D.A.; Rhodes, A.; et al. Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med.* **2016**, *42*, 1350–1359. [CrossRef] [PubMed]
13. Taton, O.; Fagnoul, D.; De Backer, D.; Vincent, J.L. Evaluation of cardiac output in intensive care using a noninvasive arterial pulse contour technique (Nexfin1) compared with echocardiography. *Anaesthesia* **2013**, *68*, 917–923. [CrossRef] [PubMed]
14. Dellinger, R.P.; Levy, M.M.; Rhodes, A.; Annane, D.; Gerlach, H.; Opal, S.M.; Sevransky, J.E.; Sprung, C.L.; Douglas, I.S.; Jaeschke, R.; et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* **2013**, *39*, 165–228. [CrossRef] [PubMed]
15. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 801–810. [CrossRef]
16. Iwakiri, Y.; Shah, V.; Rockey, D.C. Vascular pathobiology in chronic liver disease and cirrhosis – Current status and future directions. *J. Hepatol.* **2014**, *61*, 912–924. [CrossRef]
17. Varin, R.; Mulder, P.; Tamion, F.; Richard, V.; Henry, J.P.; Lallemand, F.; Lerebours, G.; Thuillez, C. Improvement of endothelial function by chronic angiotensin-converting enzyme inhibition in heart failure: Role of nitric oxide, prostanoids, oxidant stress, and bradykinin. *Circulation* **2000**, *102*, 351–356. [CrossRef]
18. Laurent, S.; Cockcroft, J.; Van Bortel, L.; Boutouyrie, P.; Giannattasio, C.; Hayoz, D.; Pannier, B.; Vlachopoulos, C.; Wilkinson, I.; Struijker-Boudier, H.; et al. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur. Heart J.* **2006**, *27*, 2588–2605. [CrossRef]
19. Mitchell, G.F.; Parise, H.; Benjamin, E.J.; Larson, M.G.; Keyes, M.J.; Vita, J.A.; Vasan, R.S.; Levy, D. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The Framingham Heart Study. *Hypertension* **2004**, *43*, 1239–1245. [CrossRef]

20. Cruz, D.N.; Antonelli, M.; Fumagalli, R.; Foltran, F.; Brienza, N.; Donati, A.; Malcangi, V.; Petrini, F.; Volta, G.; Bobbio Pallavicini, F.M.; et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: The EUPHAS randomized controlled trial. *JAMA* **2009**, *301*, 2445–2452. [CrossRef]
21. Lambden, S.; Creagh-Brown, B.C.; Hunt, J.; Summers, C.; Forni, L.G. Definitions and pathophysiology of vasoplegic shock. *Crit. Care* **2018**, *22*, 174. [CrossRef] [PubMed]
22. Vincent, J.L.; Moreno, R.; Takala, J.; Willatts, S. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* **1996**, *22*, 707–710. [CrossRef] [PubMed]
23. Knaus, W.A.; Draper, E.A.; Wagner, D.P.; Zimmerman, J.E. APACHE II: A severity of disease classification system. *Crit. Care Med.* **1985**, *13*, 818–829. [CrossRef] [PubMed]
24. Kellum, J.A.; Lameire, N.; Aspelin, P.; Barsoum, R.S.; Burdmann, E.A.; Goldstein, S.L.; Herzog, C.A.; Joannidis, M.; Kribben, A.; Levey, A.S.; et al. Kidney Disease: Improving Global Outcomes KDIGO Acute Kidney Injury Work Group KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
25. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A.; Acute Kidney Injury Network. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef]
26. Macedo, E.; Malhotra, R.; Bouchard, J.; Wynn, S.K.; Mehta, R.L. Oliguria is an early predictor of higher mortality in critically ill patients. *Kidney Int.* **2011**, *80*, 760–767. [CrossRef]
27. D'Orio, V.; Wahlen, C.; Naldi, M.; Fossion, A.; Juchmes, J.; Marcelle, R. Contribution of peripheral blood pooling to central hemodynamic disturbances during endotoxin insult in intact dogs. *Crit. Care Med.* **1989**, *17*, 1314–1319. [CrossRef]
28. Teule, G.J.; von Lingen, A.; Verwey von Vught, M.A.; Kester, A.D.; Mackaay, R.C.; Bezemer, P.D.; Heidenal, G.A.; Thijs, L.G. Role of peripheral pooling in porcine Escherichia coli sepsis. *Circ. Shock* **1984**, *12*, 115–123.
29. Trancă, S.; Petrișor, C.; Hagău, N.; Ciuce, C. Can APACHE II, SOFA, ISS, and RTS Severity Scores be used to Predict Septic Complications in Multiple Trauma Patients? *J. Crit. Care Med. (Targu Mures)* **2016**, *10*, 124–130. [CrossRef]
30. Kellum, J.A.; Sileanu, F.E.; Murugan, R.; Lucko, N.; Shaw, A.D.; Clermont, G. Classifying AKI by Urine Output versus Serum Creatinine Level. *J. Am. Soc. Nephrol.* **2015**, *26*, 2231–2238. [CrossRef]
31. Lopes, J.A.; Jorge, S.; Resina, C.; Santos, C.; Pereira, A.; Neves, J.; Antunes, F.; Prata, M.M. Acute renal failure in patients with sepsis. *Crit. Care* **2007**, *11*, 411. [CrossRef] [PubMed]
32. Fleischmann, C.; Thomas-Rueddel, D.O.; Hartmann, M.; Hartog, C.S.; Welte, T.; Heublein, S.; Dennler, U.; Reinhart, K. Hospital Incidence and Mortality Rates of Sepsis. An Analysis of Hospital Episode (DRG) Statistics in Germany from 2007 to 2013. *Dtsch. Arztebl. Int.* **2016**, *113*, 159–166. [CrossRef] [PubMed]
33. Bagshaw, S.M.; Uchino, S.; Bellomo, R.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; Gibney, N.; et al. Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 431–439. [CrossRef] [PubMed]
34. Bagshaw, S.M.; Mortis, G.; Doig, C.J.; Godinez-Luna, T.; Fick, G.H.; Laupland, K.B. One-year mortality in critically ill patients by severity of kidney dysfunction: A population-based assessment. *Am. J. Kidney Dis.* **2006**, *48*, 402–409. [CrossRef]

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Secretory Leukocyte Protease Inhibitor (SLPI)—A Novel Predictive Biomarker of Acute Kidney Injury after Cardiac Surgery: A Prospective Observational Study

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Abstract: Acute kidney injury (AKI) is one of the most frequent complications after cardiac surgery and is associated with poor outcomes. Biomarkers of AKI are crucial for the early diagnosis of this condition. Secretory leukocyte protease inhibitor (SLPI) is an alarm anti-protease that has been implicated in the pathogenesis of AKI but has not yet been studied as a diagnostic biomarker of AKI. Using two independent cohorts (development cohort (DC), $n = 60$; validation cohort (VC), $n = 148$), we investigated the performance of SLPI as a diagnostic marker of AKI after cardiac surgery. Serum and urinary levels of SLPI were quantified by ELISA. SLPI was significantly elevated in AKI patients compared with non-AKI patients (6 h, DC: 102.1 vs. 64.9 ng/mL, $p < 0.001$). The area under the receiver operating characteristic curve of serum SLPI 6 h after surgery was 0.87 ((0.76–0.97); DC). The addition of SLPI to standard clinical predictors significantly improved the predictive accuracy of AKI (24 h, VC: odds ratio (OR) = 3.91 (1.44–12.13)). In a subgroup, the increase in serum SLPI was evident before AKI was diagnosed on the basis of serum creatinine or urine output (24 h, VC: OR = 4.89 (1.54–19.92)). In this study, SLPI was identified as a novel candidate biomarker for the early diagnosis of AKI after cardiac surgery.

Keywords: acute kidney injury; cardiovascular surgery; ICU; complications; biomarkers

1. Introduction

Acute kidney injury (AKI) is one of the most common complications after major surgery, especially after cardiac surgery [1,2]. Despite substantial improvement in intraoperative management and perioperative care, the incidence of AKI in patients in the intensive care unit (ICU) remains high and ranges between 20% and 67% [3]. AKI necessitates a prolonged ICU stay and is an important prognostic factor of poor mid- to long-term outcomes: it is associated with increased postoperative infections and cardiovascular complications, as well as markedly increased morbidity and mortality rates, even years after surgery [4–8]. Although distinct consensus criteria for the early detection of AKI have been defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice

guidelines, AKI continues to be underdiagnosed [9]. To date, the treatment options for AKI are limited, and renal replacement therapy is the standard approach to treating severe cases of AKI. The early identification of patients at risk could enable the timely initiation of preventive measures to reduce the sequelae of AKI [10]. In this context, the currently established and routinely used AKI indicators, such as serum creatinine and urine output, have been repeatedly demonstrated to be insufficient for the early detection of AKI because changes in serum creatinine indicative of altered kidney function are evident only after more than 50% of the baseline renal function has been compromised [11]. Moreover, serum creatinine only serves as a surrogate parameter to estimate the excretory function of the kidney. Thus, serum creatinine does not provide information about the underlying renal pathology and is unable to discriminate between reversible and irreversible injuries [12]. For a better approximation of the extent of injury and the early diagnosis, differential diagnosis, and prognosis of AKI, the international KDIGO board has called for the identification of appropriate AKI markers, analogous to serum troponin or liver enzymes used to identify organ injury [13].

Accordingly, studies have investigated several new biomarkers of AKI, and urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) ([TIMP-2]·[IGFBP7]) have been deemed promising markers [14]. The assessment of whole-genome mRNA profiles in human kidney biopsies from post-transplant AKI revealed that the most upregulated mRNA (15-fold) was that of secretory leukocyte protease inhibitor (SLPI) [15]. Despite these promising findings, to date, observational studies have not been conducted to evaluate circulating concentrations of SLPI as a biomarker of AKI. Therefore, in a cardiac surgery setting, we tested the predictive value of SLPI as a novel AKI biomarker in two independent prospective observational studies: one development cohort and one validation cohort.

2. Materials and Methods

2.1. Study Design and Patients

The aim of the study was to investigate the association between serum SLPI levels and the incidence of postoperative AKI after cardiac surgery. The studies, registered at clinicaltrials.gov (NCT 02488876, April 2009), were approved by the institutional review board (Ethics committee, RWTH Aachen University, Aachen, Germany) and performed in adherence to the Declaration of Helsinki. All patients were scheduled for elective cardiac surgery involving aortic cross-clamping, cardioplegic myocardial arrest, and cardiopulmonary bypass. Exclusion criteria were emergency operations, pregnancy, lack of informed consent, an age of less than 18 years, and end-stage renal disease requiring dialysis.

First, an explorative development study was conducted between September 2015 and March 2016. Second, the results of the development study were used as the basis for a prospective observational validation study, which was conducted from January to June 2017.

Serum creatinine was measured daily. The serum creatinine level on the day before cardiac surgery was used as the reference value. Urine output was quantified hourly by Foley catheter drainage while the patient remained in the intensive care unit.

In both the development and validation studies, serum samples for enzyme-linked immunosorbent assays (ELISA) were drawn one day prior to surgery and immediately (0 h) and 24 h after surgery. In the development study, additional samples were drawn 6 and 12 h after surgery, and, in the validation study, an additional sample was collected 48 h after surgery (Figure 1B).

After blood collection, the samples were centrifuged (3000 rpm for 10 min), and the supernatants were transferred to cryotubes for storage at −80 °C until further analysis. Urine samples were collected preoperatively, immediately postoperatively, and 24 h after surgery and transferred to cryotubes for storage at −80 °C.

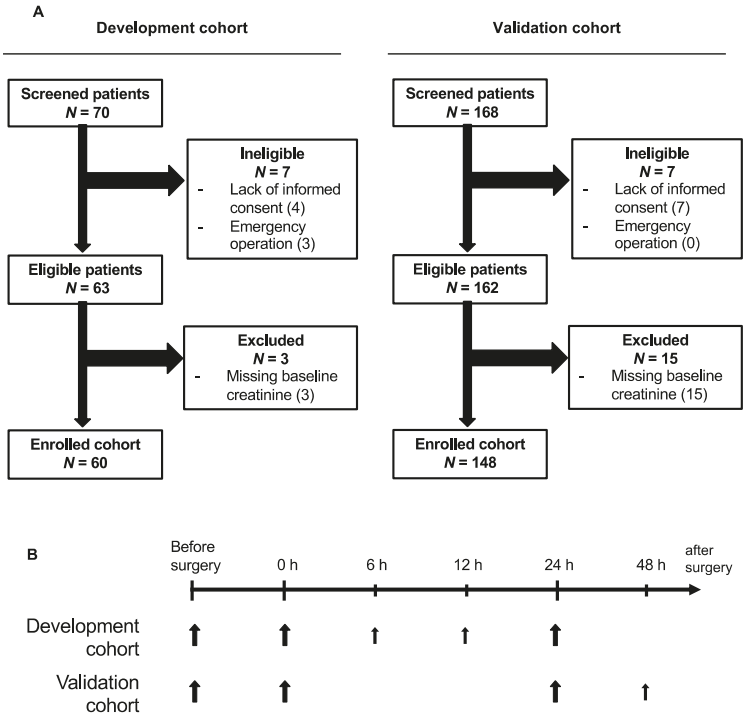

Figure 1. (**A**) Flowcharts of the two independent observational studies investigating SLPI as a biomarker of AKI after cardiac surgery. (**B**) The time points of sample collection for analysis. Larger arrows represent the collection of blood and urine, and smaller arrows represent the collection of blood only. SLPI, secretory leukocyte protease inhibitor; AKI, acute kidney injury.

2.2. Study Endpoints

The primary endpoint of both studies was the development of AKI within 72 h after cardiac surgery. AKI was diagnosed according to the KDIGO clinical practice guidelines by (1) an increase in serum creatinine of at least 0.3 mg/dL or a 50% increase from baseline and/or (2) a decline in urine output to below 0.5 mL/kg/h for at least 6 h [16].

The following patients' baseline characteristics are known to affect the risk of AKI and were thus determined: age, sex, body mass index (BMI), intake of heart medication, arterial hypertension, pulmonary hypertension, congestive heart disease, reduced left ventricular ejection fraction (LVEF) <35%, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, and previous cardiac surgery. On the basis of these data, we calculated the Cleveland Clinic Foundation Score—a clinical score used to estimate the risk of developing AKI after cardiac surgery [17]. We recorded the operational characteristics, including the type and duration of surgery, and the postoperative Sequential Organ Failure Score (SOFA) on the first day after surgery (POD1).

2.3. Biomarkers

Serum and urine levels of SLPI were measured by ELISA as previously described and according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA) [18]. For the urine samples taken from patients in the development study, we additionally quantified urine neutrophil gelatinase-associated lipocalin (NGAL)—a previously described biomarker of AKI—using a commercially available ELISA kit (R&D Systems, Minneapolis, MN, USA) [19,20]. Before analysis,

the serum samples were diluted 1:200 for SLPI ELISA, and urine samples were diluted 1:10 for SLPI ELISA and 1:100 for NGAL ELISA. In a subgroup of 25 patients (the first 25 patients of the validation cohort), we normalized SLPI to the creatinine concentration in the urine. The average coefficient of variation (CV) between duplicates was 9.7% (intra-assay CV) and the average inter-assay cooefficient was 11.9%.

2.4. Statistical Methods

Because SLPI serum levels ranged widely in the first study (development study), we performed an additional validation study. The sample size of the validation study was calculated on the basis of the development study. The median of the SLPI levels 24 h after surgery was used as a cut-off. We assumed a power of 90% and set the significance level to 0.05. From the difference in proportions of the "AKI events" in both groups (G1 (≤median SLPI) = 10.7% and G2 (>median SLPI) = 34.5%), we calculated a preferable sample size of 168 patients, assuming a drop-out rate of 25%. The sample size was calculated with PROC POWER, SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Categorical variables are described by absolute numbers and percentages, and continuous variables are reported as the median and interquartile range (IQR) with the first (Q1) and third (Q3) quartiles.

Differences in baseline characteristics between the two outcome groups were analyzed using univariable logistic regression. Correlations between SLPI and NGAL were calculated using Spearman's correlation.

The diagnostic accuracy of the biomarkers was calculated by the receiver operating characteristic (ROC) curve and the corresponding area under the curve (AUC). *p*-values were calculated for a hypothesis of AUC > 0.5. Optimal cut-offs were calculated using the Youden index, and 95% confidence intervals, sensitivities, and specificities are reported.

A univariable logistic regression model was used to investigate the performance of SLPI as a predictor of AKI. Given a nonlinear relationship between SLPI and the incidence of AKI, SLPI was considered a binary variable and categorized by the corresponding median to avoid biased estimates [21].

Using multivariable logistic regression models, we adjusted SLPI for the Cleveland Clinic Foundation Score (including sex, congestive heart disease, left ventricular ejection fraction, use of intra-aortic balloon-pump, chronic obstructive pulmonary disease, insulin-requiring diabetes, previous heart surgery, emergency surgery, type of surgery, and preoperative creatinine level) [17]. We applied Firths' bias reduction implemented in SAS-Macro %fl (SAS Institute Inc., Cary, NC, USA); the odds ratios (OR) with 95% confidence intervals (CI) and *P*-values are reported. To evaluate whether serum SLPI is able to predict AKI before an increase in serum creatinine is evident, we analyzed the time point at which a rise in serum creatinine was detected [22]. Then, in a subgroup analysis, we only considered the patients who received an AKI diagnosis after the time point of SLPI measurement. For example, when analyzing serum SLPI 24 h after surgery, all patients whose serum creatinine had already increased at 24 h after surgery or later were excluded.

In all cases, two-sided testing was used, and $p < 0.05$ was considered statistically significant. If not otherwise stated, statistical analyses were performed using SAS Software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS 25 (IBM SPSS Statistics for Windows, version 21.0. IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Characteristics and Outcomes of Patients

Of the 70 cardiac surgery patients initially screened for the development study, 60 patients were successfully enrolled. For the validation study, 148 of the 168 screened patients were enrolled (Figure 1A). The incidence of AKI during the first 72 h after cardiac surgery was 25% in the development cohort (DC; 14 of 60 patients) and 15% in the validation cohort (VC; 22 of 148 patients) (Table 1).

In both cohorts and for all cases, the diagnostic criterion "increased creatine" was met before oliguria occurred. Oliguria was detected in 21% of AKI cases in the DC and in 23% of AKI cases in the VC (Table 1). In most cases, AKI was diagnosed 48 h after surgery (DC, 50% of cases; VC, 41% of cases) (Table 1). In both cohorts, the overall proportion of AKI patients affected by persistent AKI (>48 h) was approximately 40% (Table 1).

Table 1. Incidence, diagnostic criteria, and time point of diagnosis of AKI by cohort. Categorical data are presented as the absolute number and percentage. Diagnosis of AKI was based on Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines ((1) an increase in serum creatinine of at least 0.3 mg/dL or an increase of 50% above baseline and/or (2) a decline in urine output to below 0.5 mL/kg/h for at least 6 h) [16]. Most patients diagnosed with AKI were affected by AKI stage 1 and were diagnosed 48 h after surgery. All patients suffering from AKI showed an increase in serum creatinine. Approximately 40% of AKI patients had persistent AKI lasting >48 h. AKI, acute kidney injury.

Acute Kidney Injury within 72 h after Cardiac Surgery	Development Cohort (n = 60)		Persistent AKI > 48 h	Validation Cohort (n = 148)		Persistent AKI > 48 h
AKI according to KDIGO diagnostic criteria	14	(25%)	6 (43%)	22	(15%)	9 (41%)
KDIGO Stage 1	8	(57%)		12	(54%)	
KDIGO Stage 2	5	(36%)		8	(36%)	
KDIGO Stage 3	1	(7%)		2	(9%)	
Diagnostic criteria met						
Increased creatinine	14	(100%)		22	(100%)	
Oliguria (<0.5 mL/kg/h for ≥6 h)	3	(21%)		5	(23%)	
Time point of diagnosis						
24 h after surgery	3	(21%)	1 (33%)	6	(27%)	2 (33%)
48 h after surgery	7	(50%)	3 (42%)	9	(41%)	6 (67%)
72 h after surgery	4	(29%)	2 (50%)	7	(32%)	1 (14%)

The majority of patients who developed AKI had significantly elevated baseline creatinine levels before surgery (DC: 0.93 mg/dL vs. 1.22 mg/dL, $p = 0.011$; VC: 0.99 mg/dL vs. 1.08 mg/dL, $p = 0.018$) (Table 2). In the development study, AKI was significantly associated with older age ($p = 0.047$), diabetes mellitus ($p = 0.012$), the intake of calcium channel blockers ($p = 0.037$), and an increased Cleveland Clinic Foundation Score ($p = 0.005$). In the VC, AKI was associated with a longer duration of cardiopulmonary bypass ($p = 0.046$, Table 2). No sex-based differences were observed.

3.2. AKI Was Associated with Higher Serum SLPI in Cardiac Surgery Patients

After cardiac surgery, serum SLPI significantly increased in both cohorts and peaked at 24 h after surgery (DC and VC: $p < 0.001$). Compared with patients not diagnosed with AKI, those diagnosed with AKI had significantly elevated SLPI serum levels 6, 12, 24, and 48 h after surgery (e.g., 24 h, DC: $p = 0.001$; 24 h, VC: $p = 0.008$; Table 3, Figure 2A,B). Serum SLPI did not differ significantly between transient (<48 h) and persistent (>48 h) AKI cases (Figure S1). Patients with high serum SLPI (higher the median value) 24 h after surgery had a significantly higher incidence of AKI (DC: 10% vs. 38%, $p = 0.03$; VC: 7% vs. 24%, $p = 0.01$; Figure 3). Similar to serum SLPI, urinary SLPI levels were significantly increased 24 h after cardiac surgery (Figure 2C,D). Compared with serum SLPI, urinary levels of SLPI were low overall (approximately 5–10 times lower). After surgery, urinary SLPI levels did not significantly differ between patients with and without AKI (Table 3, Figure 2C,D). When normalized to urinary creatinine, patients with AKI showed significantly higher SLPI levels 24 h after surgery (subgroup of VC, $n = 25$, $p = 0.01$; Figure 2F).

Table 2. Baseline and operative characteristics by cohort and AKI. Data are expressed as the median (Q1–Q3) or number (percentage). ACE, angiotensin-converting enzyme; AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; POD1, first postoperative day; Q1, Q3, first and third quartile, respectively; and SOFA, Sequential Organ Failure Score. The influence of baseline characteristics on AKI was analyzed by univariable logistic regression. Bold fonts indicate *p*-values < 0.05.

Characteristic	Development Cohort					Validation Cohort				
	No AKI (*n* = 46)		AKI (*n* = 14)		*p*-Value	No AKI (*n* = 126)		AKI (n = 22)		*p*-Value
Demographics										
Age (years)	67	(59–75)	69	(68–78)	**0.047**	67	(59–75)	69	(68–78)	0.171
Sex (female)	11	(24)	4	(29)	0.678	33	(26)	6	(27)	0.869
BMI (kg/m^2)	27.4	(25.0–29.9)	26.5	(23.8–33.2)	0.767	27.1	(24.8–30.3)	28.5	(22.9–30.4)	0.876
Medication, No (%)										
Beta blockers	40	(87)	9	(75)	0.292	91	(73)	17	(77)	0.733
ACE Inhibitors	35	(76)	8	(67)	0.478	69	(55)	12	(55)	0.943
Sartans	6	(13)	1	(8)	0.840	27	(22)	7	(32)	0.271
Calcium channel blockers	6	(13)	5	(42)	**0.037**	35	(28)	6	(27)	0.993
Diuretics	36	(78)	11	(92)	0.456	52	(42)	13	(59)	0.138
Statins	45	(98)	12	(100)	0.929	106	(85)	19	(86)	0.975
Acetylsalicylic acid	44	(96)	12	(100)	0.860	103	(82)	18	(82)	0.848
Comorbidities, No (%)										
Arterial hypertension	28	(61)	11	(85)	0.159	89	(71)	18	(82)	0.362
Pulmonary hypertension	3	(7)	1	(8)	0.741	6	(5)	2	(9)	0.328
Congestive heart disease	7	(15)	4	(29)	0.255	16	(13)	0	(0)	0.201
LVEF < 35%	10	(22)	2	(14)	0.651	6	(5)	2	(9)	0.328
Chronic kidney disease	3	(7)	2	(14)	0.345	9	(7)	4	(18)	0.090
COPD	3	(7)	2	(14)	0.345	15	(12)	3	(14)	0.707
Diabetes, insulin	3	(7)	5	(38)	**0.012**	13	(10)	3	(14)	0.545
Previous cardiac surgery	3	(7)	0	(0)	0.632	8	(6)	1	(5)	0.970
Serum creatinine at baseline (mg/dL)	0.93	(0.78–1.04)	1.22	(0.83–1.36)	**0.011**	0.99	(0.80–1.10)	1.08	(0.94–1.28)	**0.018**
Type of Surgery										
Isolated CABG	24	(52)	3	(21)	0.064	78	(62)	11	(50)	0.274
Isolated valvular surgery	8	(17)	4	(29)	0.344	16	(13)	4	(18)	0.425
Combined procedure	14	(30)	7	(50)	0.191	30	(24)	7	(32)	0.403
other						5	(4)	1	(5)	
Risk of AKI										
Cleveland Clinic Foundation Score	3	(2–3)	4	(3–5)	**0.005**	3	(2–4)	3	(2–4)	0.636
Duration of Surgery										
Aortic cross clamp	74.5	(57.5–99)	78.5	(47–105)	0.934	73	(55–89)	78	(60–101)	0.232
Cardiopulmonary bypass	115	(91–144)	118.5	(89.5–148.5)	0.769	109	(87–133)	139	(97–150)	**0.046**
SOFA on POD 1	10	(7.5–12)	9	(7–10)	0.674	8	(6–9)	9	(7–12)	**0.044**

Table 3. SLPI measured at different time points. Serum and urinary SLPI concentrations quantified by ELISA and compared between patients with and without AKI. Bold fonts indicate p-values < 0.05.

Serum SLPI										
SLPI (ng/mL)	**Development Cohort (n = 60)**					**Validation Cohort (n = 148)**				
	No AKI (n = 46)		**AKI (n = 14)**		**p-Value**	**No AKI (n = 226)**		**AKI (n = 22)**		**p-Value**
Pre-OP	67.3	(57.2–82.1)	87.6	(65.3–98.5)	**0.14**	40.1	(31.6 –48.5)	43.7	(36.6–52.4)	0.280
0 h after surgery	66.3	(52.8–81.15)	102.7	(83.2–128.2)	**0.06**	29.7	(22.4–39.9)	37.9	(25.4–45.3)	0.127
6 h after surgery	64.9	(53.9–84.7)	102.1	(93.2–131.5)	**<0.001**					
12 h after surgery	74.7	(52.0–88.1)	114.5	(95.0–134.5)	**<0.001**					
24 h after surgery	86.1	(69.0–113.5)	117.9	(105.6–145.2)	**0.001**	80.4	(64.7–111.7)	106.6	(83.0–135.3)	**0.008**
48 h after surgery						58.5	(58.5–90.0)	98.8	(76.0–110.4)	**0.000**
Urinary SLPI										
SLPI (ng/mL)	**Development Cohort (n = 60)**					**Validation Cohort (n = 148)**				
	No AKI (n = 46)		**AKI (n = 14)**		**p-Value**	**No AKI (n = 226)**		**AKI (n = 22)**		**p-Value**
Pre-OP	1.10	(0.40–2.09)	0.40	(0.17–0.96)	0.022	0.51	(0.15–1.53)	0.8	(0.20–1.36)	0.520
0 h after surgery	0.23	(0.07–1.09)	0.58	(0.31–2.02)	0.056	0.13	(0.025–0.35)	0.98	(0.98–1.40)	0.073
24 h after surgery	2.20	(0.74–5.05)	2.38	(0.33–9.23)	0.942	1.15	(0.71–1.92)	1.08	(0.90–1.62)	0.575

Patients with AKI showed significantly elevated serum SLPI after surgery. AKI, acute kidney injury; Pre-OP, before surgery; SLPI, secretory leukocyte protease inhibitor. Data are reported as median (Q1–Q3). p-values were analyzed using the Mann–Whitney U test.

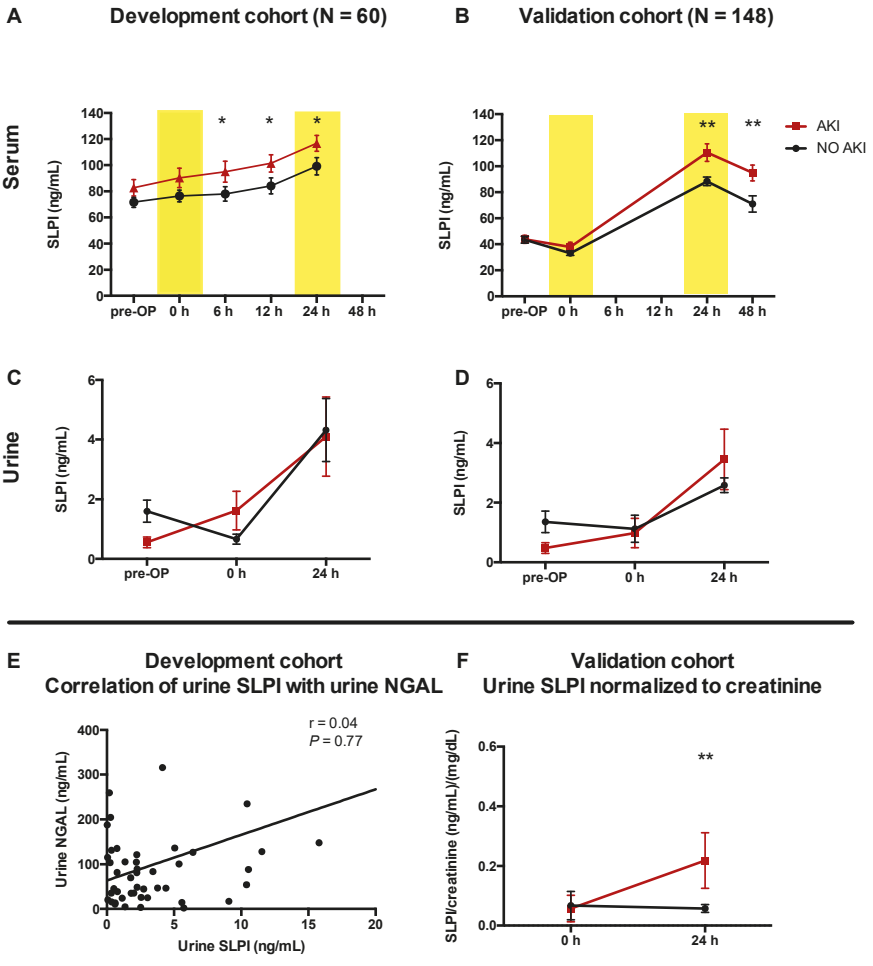

Figure 2. Higher serum SLPI levels were associated with a greater risk of AKI. (**A**,**B**) Perioperative kinetics of serum SLPI in patients without postoperative AKI compared with patients with AKI. (**C**,**D**) Perioperative kinetics of urinary SLPI. (**E**) Correlation between postoperative urinary SLPI and postoperative urinary NGAL 24 h after cardiac surgery. (**F**) Postoperative kinetics of urinary SLPI normalized to urinary creatinine. AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin; Pre-OP, before surgery; SLPI, secretory leukocyte protease inhibitor. Data are means ± SEM; *r*, Spearman's coefficient. (**A**,**B**) * $p < 0.05$, ** $p < 0.01$ versus other groups at the corresponding time point (difference between groups).

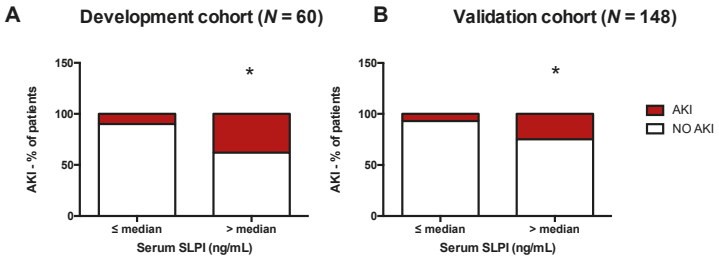

Figure 3. Percentage of patients with AKI within 72 h after cardiac surgery, stratified by median serum SLPI concentration 24 h after surgery (**A**) in the development cohort and (**B**) validation cohort. AKI, acute kidney injury; SLPI, secretory leukocyte protease inhibitor. * $p < 0.05$ analyzed by Fisher's exact test.

3.3. Accuracy of SLPI for Diagnosis of AKI

We assessed the predictive accuracy of SLPI for AKI by the ROC curve and the corresponding AUC. At 24 h after surgery, the area under the ROC curve of serum SLPI was 0.81 (95% CI 0.69–0.92) in the development cohort and 0.69 (95% CI 0.58–0.80) in the validation cohort (Figure 4). The additional earlier time points in the development cohort yielded AUCs of 0.87 (95% CI 0.76–0.97) 6 h after surgery and 0.85 (95% CI 0.74–0.95) 12 h after surgery. When only patients with a Cleveland Clinic Foundation Score ≥3 ("at risk for AKI") were selected, the diagnostic accuracy did not improve significantly (Figure S2). The AUCs of the absolute increase of SLPI from baseline before surgery (delta from pre-OP) were not superior to absolute SLPI (Figure S3). Compared with urinary NGAL, with an AUC of 0.52 (95% CI 0.31–0.73) 24 h after surgery, serum SLPI was more accurate in diagnosing AKI 24 h after surgery (Figure 4, Figure S4). However, urinary SLPI, even when normalized to urine creatinine, did not demonstrate significant results (AUC = 0.71, 95% CI 0.44–1.0). Table 4 lists the optimal cut-off concentrations calculated using the Youden index and the related sensitivities and specificities.

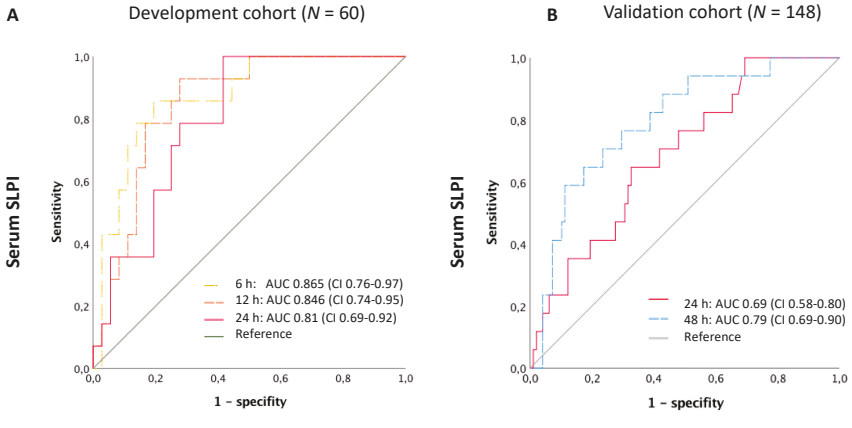

Figure 4. Receiver operating characteristic (ROC) curves of SLPI and NGAL for the diagnosis of AKI at different time points after surgery. (**A**) ROC of serum SLPI in the development study and (**B**) in the validation study. AKI, acute kidney injury; AUC, area under the curve; CI, 95% confidence interval; SLPI, secretory leukocyte protease inhibitor.

Table 4. Sensitivity and specificity of SLPI as a biomarker for AKI at optimal cut-off values.

Time Point after Surgery	Optimal Cut-off (ng/mL)	Sensitivity (%)	95% CI	Specificity (%)	95% CI	Likelihood Ratio	Youden Index
Development cohort, Serum SLPI							
6 h	>85.20	64.3	35.1–87.2	68.29	51.9–81.9	2.027	0.32
12 h	>92.72	66.7	34.9–90.1	73.17	57.1–85.8	2.485	0.39
24 h	>87.93	100.0	75.3–100.0	54.55	38.9–69.6	2.200	0.54
Validation cohort, Serum SLPI							
24 h	>101.8	70.0	45.7–88.1	67.6	57.8–76.4	2.162	0.38
48 h	>78.45	77.8	52.4–93.6	71.2	61.4–79.9	2.709	0.49

Optimal cut-off concentrations were calculated with the help of the Youden index; CI, confidence interval; Pre-OP, before surgery; SLPI, secretory leukocyte protease inhibitor.

3.4. SLPI as a Predictor of AKI in Univariate and Multivariate Analyses

As calculated in a univariate analysis, patients with higher postoperative serum SLPI (>median) had a significantly higher risk of AKI (e.g., validation cohort, 24 h, OR = 3.89, 95% CI 1.44–12.08, $p = 0.007$; 48 h, OR = 9.24, 95% CI 2.69–48.30, $p < 0.001$; Table 4).

Because the Cleveland Clinic Foundation Score is a clinical score for risk stratification of AKI after open cardiac surgery, this score was included in the multivariable analysis as the reference model (independent variable). The Cleveland Clinic Foundation Score includes the variables sex, congestive heart disease, left ventricular ejection fraction, use of intra-aortic balloon-pump, chronic obstructive pulmonary disease, insulin-requiring diabetes, previous heart surgery, emergency surgery, type of surgery, and preoperative serum creatinine. When adjusted for the Cleveland Clinic Foundation Score, serum SLPI remained a significant predictor of AKI at 6, 12, and 24 h after surgery in the development cohort and 24 and 48 h in the validation cohort (e.g., 6 h, DC: OR = 1.74; 95% CI 1.18–2.84, $p = 0.004$; 24 h, VC: OR = 3.91 95% CI, 1.44–12.13, $p = 0.007$; Table 5).

To determine whether SLPI can be regarded as a predictive biomarker, we performed a subgroup analysis in which we only considered AKI cases that were diagnosed after the respective SLPI measurement. Thus, for SLPI measured at 24 h, we only considered cases of AKI that were diagnosed at 48 or 72 h ($n = 11$ in the development and $n = 16$ in the validation study), and for SLPI measured at 48 h, we only considered cases of AKI that were diagnosed at 72 h after surgery. In addition to the early time points (6 and 12 h after surgery), in these univariable and multivariable analyses, SLPI was significantly predictive of AKI 24 h (multivariable: OR = 4.89; 95% CI, 1.54–19.92; $p = 0.006$) and 48 h (multivariable: OR = 15.24; 95% CI, 1.63–2025.31; $p = 0.013$) after surgery (Table 5).

Table 5. SLPI as a predictor of AKI. **(A)** Univariable logistic regression. Serum SLPI was a significant predictor of AKI 12, 24, and 48 h after surgery. Multivariable logistic regression adjusted for Cleveland Clinic Foundation Score (including the variables sex, congestive heart disease, left ventricular ejection fraction, use of intra-aortic balloon-pump, chronic obstructive pulmonary disease, insulin-requiring diabetes, previous heart surgery, emergency surgery, type of surgery, and preoperative serum creatinine). After adjustment for the Cleveland Clinic Foundation Score, serum SLPI remained a significant predictor of AKI. **(B)** Subgroup analysis of cases of AKI that were diagnosed after the respective SLPI measurement. For SLPI measured at 24 h, only the cases of AKI that were diagnosed at 48 or 72 h (n = 11 in the DC and n = 16 in the VC) were considered. For SLPI measured at 48 h, only the cases of AKI that were diagnosed at 72 h after surgery were considered. SLPI was categorized by the corresponding median; CI, confidence interval; OR, odds ratio; Pre-OP, before surgery; SLPI, secretory leukocyte protease inhibitor; bold fonts indicate p-values < 0.05.

(A) AKI, Time Point not Considered									
		Univariable Logistic Regression (Median)				**Multivariable Logistic Regression (Median)**			
Time Point after Surgery	**Median**	**OR**	**95% CI**		***p*-value**	**OR**	**adj. 95% CI**		***p*-value**
Development Cohort									
Pre-OP	71.3	1.37	0.42	4.57	0.601	1.12	0.30	4.16	0.868
0 h after surgery	77.2	2.06	0.63	7.28	0.230	1.69	0.46	6.61	0.431
6 h after surgery	69.6	2.19	0.67	7.82	0.197	**1.74**	1.18	2.84	**0.004**
12 h after surgery	79.9	**3.80**	1.03	17.09	**0.045**	**1.72**	1.15	2.83	**0.008**
24 h after surgery	95	**3.92**	1.10	17.31	**0.035**	**1.76**	1.16	2.98	**0.007**
Validation Cohort									
Pre-OP	41.00	1.46	0.58	3.75	0.417	1.47	0.59	3.76	0.412
0 h after surgery	13.00	1.029	0.41	2.59	0.945	1.01	0.38	2.66	0.19
24 h after surgery	88.3	**3.89**	1.44	12.08	**0.007**	**3.91**	1.44	12.13	**0.007**
48 h after surgery	65.3	**9.24**	2.69	48.30	**<0.001**	**9.45**	2.74	49.55	**<0.001**
(B) AKI, Time Point Considered									
		Univariable logistic regression (median)				**Multivariable Logistic Regression (Median)**			
Time Point	**Median**	**OR**	**95% CI**		***p*-value**	**OR**	**adj. 95% CI**		***p*-value**
Development Cohort									
SLPI measured at 24 h for AKI diagnosed later: 48 or 72 h after surgery (11 of 14 cases of AKI)	95	**4.45**	1.07	25.61	**0.039**	2.48	0.50	15.35	0.268
Validation Cohort									
SLPI measured at 24 h for AKI diagnosed later: 48 or 72 h after surgery (16 of 22 AKI cases)	88.3	**4.94**	1.55	20.15	**0.006**	**4.89**	1.54	19.92	**0.006**
SLPI measured at 48 h for AKI diagnosed later: 72 h after surgery (7 of 22 cases of AKI)	65.3	**15.4**	1.67	2042	**0.011**	**15.24**	1.63	2025.31	**0.013**

4. Discussion

SLPI is a 12 kDa (107 amino acids) non-glycosylated single-chain protein that is broadly expressed in myeloid and other epithelial cells [23–25]. SLPI functions as a non-redundant alarm anti-protease and is considered important in the defense against proteolytic attack from liberated granulocyte proteases [26]. Apart from its anti-protease activity, SLPI has antibacterial, antiviral, and anti-inflammatory properties and promotes wound healing [27].

Cardiac surgery patients with AKI, even those who achieve complete renal recovery, have a significantly increased risk of death and adverse long-term consequences compared with patients without AKI [8]. Over time, 10%–20% of patients with AKI develop chronic kidney disease [28,29]. The KDIGO clinical practice guideline recommends the early identification of patients at risk and suggests a bundle of preventive measures for the early treatment of kidney injury. Because serum creatinine and urine output show changes in renal function only after the occurrence of significant kidney injury, new biomarkers are needed to earlier identify patients who will later benefit from therapeutic measures [9]. In the 2006 Clinical Path Opportunities List, the Food and Drug Administration declared the identification of new biomarkers as a key area for improving clinical trials and medical therapies [30]. A major limitation in the identification of suitable biomarkers of AKI is the limited availability of human biopsies from kidneys with AKI; therefore, relevant tissue analyses have not yet been conducted in large-scale studies. In post-transplant kidney graft dysfunction, however, the retrieval of kidney biopsies is part of the routine diagnostic panel. The assessment of whole-genome mRNA profiles in eight injured kidney allografts with AKI revealed not only the upregulated expression of established biomarkers such as NGAL but also the significantly enhanced expression of *SLPI* mRNA [15]. The increase in *SLPI* gene expression is correlated with the protein levels of SLPI in the plasma and urine, which indicates a link between elevated SLPI in the urine and blood and the status of the kidney. In fact, immunohistochemical staining and in situ hybridization detected local SLPI protein expression in the kidney tubular epithelial cells, suggesting that the tubule epithelial cells are a source of elevated serum SLPI in patients suffering from post-transplant AKI [31]. Despite the striking baseline-adjusted increase in mRNA expression (15-fold change) that first implicated SLPI as a promising biomarker of AKI, to the best of our knowledge, SLPI has been exclusively tested in the post-transplant AKI setting and has not been examined in AKI after cardiac surgery.

In this prospective observational study, we investigated the possibility of using SLPI to diagnose and predict AKI in patients undergoing cardiac surgery. The incidence of AKI ranged between 15% (in the validation cohort) and 25% (in the development cohort), which is within the normal range of incidence of AKI observed after cardiac surgery [3]. Only a minority of patients met the KDIGO diagnostic criterion of oliguria lasting at least 6 h, which might be attributed to strict counteractive measures, including diuretics and fluid management, undertaken in the ICU setting.

The levels of serum and urinary SLPI considerably increased in the postoperative course and peaked 24 h after the surgical intervention. Compared with healthy blood donors with an average serum SLPI of 49 ng/mL, the serum concentrations of SLPI were approximately twice as high 24 h after cardiac surgery [32]. Contrasting the perioperative values of serum SLPI in the development and validation cohorts, we detected different baseline SLPI levels, whereas the relative changes were comparable. Whether these differences arose from different patient characteristics could not be reliably established.

Patients affected by AKI during the first 72 h after surgery had significantly higher serum SLPI 6, 12, 24, and 48 h after surgery compared with non-AKI patients. SLPI levels exceeding the median 24 h after surgery were associated with a markedly increased risk of AKI. Serum SLPI showed promising accuracy in the diagnosis of AKI, with an AUC of over 0.85 six hours after surgery in the development cohort. However, samples from later time points only yielded moderate results for the AUC and the corresponding sensitivity or specificity of cut-off values. Considering the optimal cut-off values calculated using the Youden index for the different time points, the overall cut-off value of serum SLPI to predict AKI might ranges from around 85 to 90 ng/mL. Compared with patient characteristics that

were prognostic for AKI, the addition of SLPI to the risk assessment models significantly improved the prediction of AKI. SLPI was found to detect AKI before a rise in serum creatinine or before decreased urine output became evident. These findings suggest that SLPI is a novel predictive marker of AKI, which may be of particular clinical significance after cardiac surgery but also in a broader intensive care setting associated with AKI.

To date, the functional role of SLPI in the pathogenesis of AKI after cardiac surgery is unknown and requires further examination in experimental studies. In animal models, SLPI has been shown to be an important protective mediator during ischemia–reperfusion injury in the liver and brain, as well as after cardiac transplantation [27,33–35]. In a renal ischemia–reperfusion injury mouse model, SLPI was suggested to contribute to tubular cell regeneration via Cyclin-D1 upregulation [36]. Cardiac surgery patients are exposed to a high risk of developing a systemic inflammatory response, which is a substantial factor in the pathogenesis of postoperative AKI [37,38]. After cardiac surgery, SLPI was significantly upregulated and might play a role as a counter-regulatory factor against the detrimental inflammatory response by modulating nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and promoting organ repair, such as proximal tubular cell regeneration [35,36,39–41]. The sufficient degradation of SLPI in the tubular cells of healthy individuals can be assumed [42,43]. The elevation of serum SLPI levels in acute kidney injury might be a multifactorial and multidirectional resulting from (1) SLPI release from injured kidney tissue, (2) impaired renal elimination, and (3) acute and chronic inflammatory conditions.

One strength of this study is the robust results obtained from two independent and heterogeneous cohorts with significant comorbidities related to AKI, including patients with chronic kidney disease. Compared with some other recently discovered biomarkers, SLPI seems to function accurately as an AKI marker in these unselected study cohorts, which might increase the generalizability of the received findings [44].

Some study limitations exist, and the presented findings need to be interpreted cautiously. Long-term data for the prediction of chronic kidney disease and long-term mortality were not captured in our database and therefore could not be analyzed. Another limitation to our trial is that, for the validation study, only postoperative samples taken 24 and 48 h after surgery were available; thus, the results obtained at 6 and 12 h in the development study could not be compared. However, the results obtained from the development study at 24 h after surgery were successfully confirmed in the validation cohort. Additionally, the appearance that serum SLPI is superior to urinary SLPI as a predictor of AKI should be approached carefully. If a tubular source of SLPI is assumed, then the concentration of SLPI in the urine should be robustly elevated, although we only detected elevated urinary SLPI levels when they were normalized to serum creatinine. As leukocytes are the best-established source of SLPI, elevated SLPI during AKI might, in part, result from a systemic inflammatory response. However, urine concentrations are subject to fluctuations caused by dilution effects (e.g., by diuretics). This might explain why we only observed a significant elevation of urinary SLPI after its normalization to creatinine.

Among the newly identified biomarkers of AKI, urine neutrophil gelatinase-associated lipocalin (NGAL) and [TIMP-2]·[IGFBP7] have provided promising results [14,19,45]. The combined measurement of [TIMP-2]·[IGFBP7] reflects the idea that biomarker panels might better depict the heterogeneous etiology of AKI than single markers. The combination of these identified markers with new biomarkers, such as SLPI, might further improve diagnostic accuracy [46–49].

5. Conclusions

In conclusion, we identified SLPI as a novel biomarker for the early detection of AKI after cardiac surgery. Our findings may lead to future perspectives of biomarker-based risk stratification and may identify patients who would benefit from the early initiation of preventive and treatment strategies.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/11/1931/s1, Figure S1. Comparison of serum SLPI in patients affected by transient AKI (<48 h) versus persistent AKI (>48 h).

Figure S2. Diagnostic accuracy of serum SLPI in patients "at risk" as identified by Cleveland Clinic Foundation Score. Figure S3. Association of absolute increase of serum SLPI from baseline (pre-OP, before surgery) with AKI. Figure S4. Receiver operating characteristic (ROC) curves of urine NGAL for the diagnosis of AKI. Figure S5. Association of perioperative serum SLPI with postoperative death and ICU length of stay.

Author Contributions: L.A., C.S., A.O., and G.M. (Gilbert Moeckel) substantially contributed to the design of the clinical studies; L.A., T.L., M.S., and J.V. acquired the clinical data and performed the experimental analyses; L.A., C.F., and C.S. performed the statistical analyses and contributed to the interpretation of presented findings; L.A. drafted the manuscript. C.S., D.E.L., and G.M. (Gernot Marx) substantially revised the manuscript. All authors read and approved the final manuscript.

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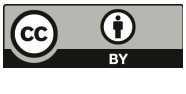
References

1. Kheterpal, S.; Tremper, K.K.; Heung, M.; Rosenberg, A.L.; Englesbe, M.; Shanks, A.M.; Campbell, D.A., Jr. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *Anesthesiology* **2009**, *110*, 505–515. [CrossRef] [PubMed]
2. Thiele, R.H.; Isbell, J.M.; Rosner, M.H. AKI associated with cardiac surgery. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 500–514. [CrossRef] [PubMed]
3. Grams, M.E.; Sang, Y.; Coresh, J.; Ballew, S.; Matsushita, K.; Molnar, M.Z.; Szabo, Z.; Kalantar-Zadeh, K.; Kovesdy, C.P. Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. *Am. J. Kidney Dis.* **2016**, *67*, 872–880. [CrossRef] [PubMed]
4. Thakar, C.V.; Yared, J.P.; Worley, S.; Cotman, K.; Paganini, E.P. Renal dysfunction and serious infections after open-heart surgery. *Kidney Int.* **2003**, *64*, 239–246. [CrossRef] [PubMed]
5. Go, A.S.; Chertow, G.M.; Fan, D.; McCulloch, C.E.; Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* **2004**, *351*, 1296–1305. [CrossRef] [PubMed]
6. Chertow, G.M.; Burdick, E.; Honour, M.; Bonventre, J.V.; Bates, D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–3370. [CrossRef] [PubMed]
7. Bihorac, A.; Yavas, S.; Subbiah, S.; Hobson, C.E.; Schold, J.D.; Gabrielli, A.; Layon, A.J.; Segal, M.S. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann. Surg.* **2009**, *249*, 851–858. [CrossRef]
8. Hobson, C.E.; Yavas, S.; Segal, M.S.; Schold, J.D.; Tribble, C.G.; Layon, A.J.; Bihorac, A. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* **2009**, *119*, 2444–2453. [CrossRef]
9. Meersch, M.; Volmering, S.; Zarbock, A. Prevention of acute kidney injury. *Best Pract. Res. Clin. Anaesthesiol.* **2017**, *31*, 361–370. [CrossRef]
10. Zarbock, A.; Kellum, J.A.; Schmidt, C.; Van Aken, H.; Wempe, C.; Pavenstadt, H.; Boanta, A.; Gerss, J.; Meersch, M. Effect of Early vs. Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* **2016**, *315*, 2190–2199. [CrossRef]
11. Moran, S.M.; Myers, B.D. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int.* **1985**, *27*, 928–937. [CrossRef] [PubMed]
12. Kellum, J.A.; Prowle, J.R. Paradigms of acute kidney injury in the intensive care setting. *Nat. Rev. Nephrol.* **2018**, *14*, 217–230. [CrossRef] [PubMed]
13. James, M.; Bouchard, J.; Ho, J.; Klarenbach, S.; LaFrance, J.P.; Rigatto, C.; Wald, R.; Zappitelli, M.; Pannu, N. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am. J. Kidney Dis.* **2013**, *61*, 673–685. [CrossRef] [PubMed]
14. Kashani, K.; Al-Khafaji, A.; Ardiles, T.; Artigas, A.; Bagshaw, S.M.; Bell, M.; Bihorac, A.; Birkhahn, R.; Cely, C.M.; Chawla, L.S.; et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit. Care* **2013**, *17*, R25. [CrossRef]

15. Wilflingseder, J.; Sunzenauer, J.; Toronyi, E.; Heinzel, A.; Kainz, A.; Mayer, B.; Perco, P.; Telkes, G.; Langer, R.M.; Oberbauer, R. Molecular pathogenesis of post-transplant acute kidney injury: Assessment of whole-genome mRNA and miRNA profiles. *PLoS ONE* **2014**, *9*, e104164. [CrossRef]
16. Palevsky, P.M.; Liu, K.D.; Brophy, P.D.; Chawla, L.S.; Parikh, C.R.; Thakar, C.V.; Tolwani, A.J.; Waikar, S.S.; Weisbord, S.D. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am. J. Kidney Dis.* **2013**, *61*, 649–672. [CrossRef]
17. Thakar, C.V.; Arrigain, S.; Worley, S.; Yared, J.P.; Paganini, E.P. A clinical score to predict acute renal failure after cardiac surgery. *J. Am. Soc. Nephrol.* **2005**, *16*, 162–168. [CrossRef]
18. Stoppe, C.; Rex, S.; Goetzenich, A.; Kraemer, S.; Emontzpohl, C.; Soppert, J.; Averdunk, L.; Sun, Y.; Rossaint, R.; Lue, H.; et al. Interaction of MIF family proteins in myocardial ischemia/reperfusion damage and their influence on clinical outcome of cardiac surgery patients. *Antioxid. Redox Signal.* **2015**, *23*, 865–879. [CrossRef]
19. Haase, M.; Bellomo, R.; Devarajan, P.; Schlattmann, P.; Haase-Fielitz, A.; NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **2009**, *54*, 1012–1024. [CrossRef]
20. Ho, J.; Tangri, N.; Komenda, P.; Kaushal, A.; Sood, M.; Brar, R.; Gill, K.; Walker, S.; MacDonald, K.; Hiebert, B.M.; et al. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. *Am. J. Kidney Dis.* **2015**, *66*, 993–1005. [CrossRef]
21. Altman, D.G.; McShane, L.M.; Sauerbrei, W.; Taube, S.E. Reporting recommendations for tumor marker prognostic studies (REMARK): Explanation and elaboration. *BMC Med.* **2012**, *10*, 51. [CrossRef] [PubMed]
22. Heinze, G.; Schemper, M. A solution to the problem of separation in logistic regression. *Stat. Med.* **2002**, *21*, 2409–2419. [CrossRef] [PubMed]
23. King, A.E.; Critchley, H.O.; Kelly, R.W. Presence of secretory leukocyte protease inhibitor in human endometrium and first trimester decidua suggests an antibacterial protective role. *Mol. Hum. Reprod.* **2000**, *6*, 191–196. [CrossRef] [PubMed]
24. Ohlsson, K.; Bjartell, A.; Lilja, H. Secretory leucocyte protease inhibitor in the male genital tract: PSA-induced proteolytic processing in human semen and tissue localization. *J. Androl.* **1995**, *16*, 64–74. [PubMed]
25. Bergenfeldt, M.; Nystrom, M.; Bohe, M.; Lindstrom, C.; Polling, A.; Ohlsson, K. Localization of immunoreactive secretory leukocyte protease inhibitor (SLPI) in intestinal mucosa. *J. Gastroenterol.* **1996**, *31*, 18–23. [CrossRef] [PubMed]
26. Thompson, R.C.; Ohlsson, K. Isolation, properties, and complete amino acid sequence of human secretory leukocyte protease inhibitor, a potent inhibitor of leukocyte elastase. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 6692–6696. [CrossRef]
27. Hannila, S.S. Secretory Leukocyte Protease Inhibitor (SLPI): Emerging Roles in CNS Trauma and Repair. *Neuroscientist* **2015**, *21*, 630–636. [CrossRef]
28. Basile, D.P.; Bonventre, J.V.; Mehta, R.; Nangaku, M.; Unwin, R.; Rosner, M.H.; Kellum, J.A.; Ronco, C.; Group, A.X.W. Progression after AKI: Understanding Maladaptive Repair Processes to Predict and Identify Therapeutic Treatments. *J. Am. Soc. Nephrol.* **2016**, *27*, 687–697. [CrossRef]
29. Coca, S.G.; Singanamala, S.; Parikh, C.R. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int.* **2012**, *81*, 442–448. [CrossRef]
30. Mahajan, R.; Gupta, K. Food and drug administration's critical path initiative and innovations in drug development paradigm: Challenges, progress, and controversies. *J. Pharm. Bioall. Sci.* **2010**, *2*, 307–313. [CrossRef]
31. Ohlsson, S.; Ljungkrantz, I.; Ohlsson, K.; Segelmark, M.; Wieslander, J. Novel distribution of the secretory leucocyte proteinase inhibitor in kidney. *Mediat. Inflamm.* **2001**, *10*, 347–350. [CrossRef] [PubMed]
32. Bergenfeldt, M.; Bjork, P.; Ohlsson, K. The elimination of secretory leukocyte protease inhibitor (SLPI) after intravenous injection in dog and man. *Scand. J. Clin. Lab. Investig.* **1990**, *50*, 729–737. [CrossRef] [PubMed]
33. Schneeberger, S.; Hautz, T.; Wahl, S.M.; Brandacher, G.; Sucher, R.; Steinmassl, O.; Steinmassl, P.; Wright, C.D.; Obrist, P.; Werner, E.R.; et al. The effect of secretory leukocyte protease inhibitor (SLPI) on ischemia/reperfusion injury in cardiac transplantation. *Am. J. Transplant.* **2008**, *8*, 773–782. [CrossRef] [PubMed]
34. Lentsch, A.B.; Yoshidome, H.; Warner, R.L.; Ward, P.A.; Edwards, M.J. Secretory leukocyte protease inhibitor in mice regulates local and remote organ inflammatory injury induced by hepatic ischemia/reperfusion. *Gastroenterology* **1999**, *117*, 953–961. [CrossRef]

35. Grobmyer, S.R.; Barie, P.S.; Nathan, C.F.; Fuortes, M.; Lin, E.; Lowry, S.F.; Wright, C.D.; Weyant, M.J.; Hydo, L.; Reeves, F.; et al. Secretory leukocyte protease inhibitor, an inhibitor of neutrophil activation, is elevated in serum in human sepsis and experimental endotoxemia. *Crit. Care Med.* **2000**, *28*, 1276–1282. [CrossRef]
36. Ochi, A.; Chen, D.; Schulte, W.; Leng, L.; Moeckel, N.; Piecychna, M.; Averdunk, L.; Stoppe, C.; Bucala, R.; Moeckel, G. MIF-2/D-DT enhances proximal tubular cell regeneration through SLPI- and ATF4-dependent mechanisms. *Am. J. Physiol.* **2017**, *313*, F767–F780. [CrossRef]
37. Billings, F.T.t.; Pretorius, M.; Schildcrout, J.S.; Mercaldo, N.D.; Byrne, J.G.; Ikizler, T.A.; Brown, N.J. Obesity and oxidative stress predict AKI after cardiac surgery. *J. Am. Soc. Nephrol.* **2012**, *23*, 1221–1228. [CrossRef]
38. Sureshbabu, A.; Ryter, S.W.; Choi, M.E. Oxidative stress and autophagy: Crucial modulators of kidney injury. *Redox Biol.* **2015**, *4*, 208–214. [CrossRef]
39. Lopez-Bermejo, A.; Ortega, F.J.; Castro, A.; Ricart, W.; Fernandez-Real, J.M. The alarm secretory leukocyte protease inhibitor increases with progressive metabolic dysfunction. *Clin. Chim. Acta* **2011**, *412*, 1122–1126. [CrossRef]
40. Taggart, C.C.; Cryan, S.A.; Weldon, S.; Gibbons, A.; Greene, C.M.; Kelly, E.; Low, T.B.; O'Neill, S.J.; McElvaney, N.G. Secretory leucoprotease inhibitor binds to NF-kappaB binding sites in monocytes and inhibits p65 binding. *J. Exp. Med.* **2005**, *202*, 1659–1668. [CrossRef]
41. Taggart, C.C.; Greene, C.M.; McElvaney, N.G.; O'Neill, S. Secretory leucoprotease inhibitor prevents lipopolysaccharide-induced IkappaBalpha degradation without affecting phosphorylation or ubiquitination. *J. Biol. Chem.* **2002**, *277*, 33648–33653. [CrossRef] [PubMed]
42. Nystrom, M.; Bergenfeldt, M.; Ohlsson, K. The elimination of secretory leukocyte protease inhibitor (SLPI) from the gastrointestinal tract in man. *Scand. J. Clin. Lab. Investig.* **1997**, *57*, 119–125. [CrossRef] [PubMed]
43. Strober, W.; Waldmann, T.A. The role of the kidney in the metabolism of plasma proteins. *Nephron* **1974**, *13*, 35–66. [CrossRef] [PubMed]
44. Smertka, M.; Chudek, J. Using NGAL as an early diagnostic test of acute kidney injury. *Ren. Fail.* **2012**, *34*, 130–133. [CrossRef] [PubMed]
45. Zhou, F.; Luo, Q.; Wang, L.; Han, L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: A meta-analysis. *Eur. J. Cardiothorac. Surg.* **2016**, *49*, 746–755. [CrossRef] [PubMed]
46. Hall, P.S.; Mitchell, E.D.; Smith, A.F.; Cairns, D.A.; Messenger, M.; Hutchinson, M.; Wright, J.; Vinall-Collier, K.; Corps, C.; Hamilton, P.; et al. The future for diagnostic tests of acute kidney injury in critical care: Evidence synthesis, care pathway analysis and research prioritisation. *Health Technol. Assess.* **2018**, *22*, 1–274. [CrossRef]
47. Nisula, S.; Yang, R.; Kaukonen, K.M.; Vaara, S.T.; Kuitunen, A.; Tenhunen, J.; Pettila, V.; Korhonen, A.M.; Group, F.S. The urine protein NGAL predicts renal replacement therapy, but not acute kidney injury or 90-day mortality in critically ill adult patients. *Anesth. Analg.* **2014**, *119*, 95–102. [CrossRef] [PubMed]
48. Bihorac, A.; Chawla, L.S.; Shaw, A.D.; Al-Khafaji, A.; Davison, D.L.; Demuth, G.E.; Fitzgerald, R.; Gong, M.N.; Graham, D.D.; Gunnerson, K.; et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *Am. J. Respir. Crit. Care Med.* **2014**, *189*, 932–939. [CrossRef]
49. Honore, P.M.; Nguyen, H.B.; Gong, M.; Chawla, L.S.; Bagshaw, S.M.; Artigas, A.; Shi, J.; Joannes-Boyau, O.; Vincent, J.L.; Kellum, J.A.; et al. Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 for Risk Stratification of Acute Kidney Injury in Patients With Sepsis. *Crit. Care Med.* **2016**, *44*, 1851–1860. [CrossRef]



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Use of Estimating Equations for Dosing Antimicrobials in Patients with Acute Kidney Injury Not Receiving Renal Replacement Therapy

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Abstract: Acute kidney injury (AKI) can potentially lead to the accumulation of antimicrobial drugs with significant renal clearance. Drug dosing adjustments are commonly made using the Cockcroft-Gault estimate of creatinine clearance (CLcr). The Modified Jelliffe equation is significantly better at estimating kidney function than the Cockcroft-Gault equation in the setting of AKI. The objective of this study is to assess the degree of antimicrobial dosing discordance using different glomerular filtration rate (GFR) estimating equations. This is a retrospective evaluation of antimicrobial dosing using different estimating equations for kidney function in AKI and comparison to Cockcroft-Gault estimation as a reference. Considering the Cockcroft-Gault estimate as the criterion standard, antimicrobials were appropriately adjusted at most 80.7% of the time. On average, kidney function changed by 30 mL/min over the course of an AKI episode. The median clearance at the peak serum creatinine was 27.4 (9.3–66.3) mL/min for Cockcroft Gault, 19.8 (9.8–47.0) mL/min/1.73 m^2 for MDRD and 20.5 (4.9–49.6) mL/min for the Modified Jelliffe equations. The discordance rate for antimicrobial dosing ranged from a minimum of 8.6% to a maximum of 16.4%. In the event of discordance, the dose administered was supra-therapeutic 100% of the time using the Modified Jelliffe equation. Use of estimating equations other than the Cockcroft Gault equation may significantly alter dosing of antimicrobials in AKI.

Keywords: acute kidney injury; Cockcroft Gault; Jelliffe; MDRD; drug dosing; antimicrobials

1. Introduction

Acute kidney injury (AKI) has been reported to occur in approximately 6% of hospitalized patients [1]. Among patients admitted with AKI, infection is present in approximately 18% [2]. AKI is particularly common among critically ill patients and has been associated with increased morbidity and significant in-hospital mortality [2,3]. A decline in kidney function can potentially lead to the accumulation of antimicrobial and other therapeutic agents, with resultant adverse effects [4]. An accurate assessment of kidney function is important in order to optimize drug administration in this population [5–7].

The most accurate way to determine glomerular filtration rate (GFR) in chronic kidney disease (CKD) is by formal measurement using an intravenous injection of inulin or a radioisotope and

subsequently collecting urine and serum samples at timed intervals [8,9]. However, the direct measurement of GFR is cumbersome, expensive and time consuming, and rarely performed in the acute hospital setting. These procedures are even more complicated in AKI. Pharmacists generally employ the Cockcroft-Gault (CG) equation to estimate kidney function, altering either or both the dose and frequency of drugs based on varying degrees of evidence in the setting of impaired kidney function and/or dialysis [10–16].

Several newer GFR estimating equations have been developed and used widely in epidemiological studies and clinical practice, including the Modification of Diet in Renal Disease (MDRD) study equation and the CKD-EPI equation. These equations were derived from varying populations who generally had stable kidney function. For example, the CG equation was derived from a hospitalized population including predominantly Caucasian men with stable serum creatinine concentrations (Scr) [17]. The MDRD study and CKD-EPI equations were largely derived from ambulatory populations with mild to moderate CKD and relatively stable Scr [12]. Additionally, acute changes in the Scr can invalidate conventional estimates of kidney function, where the estimates depend on the assumption that function is at steady state [18]. The Jelliffe equation was developed to estimate GFR in AKI, where kidney function is not in steady state [19]. Bouchard and colleagues demonstrated that the Jelliffe equation, modified by consideration of patient volume status, provided a more reliable and accurate assessment of kidney function when compared with timed urine collections in AKI [20]. While several studies have evaluated CG compared to MDRD estimates in patients with CKD, there is a paucity of data comparing whether alternative GFR estimating equations might alter dosing of drugs in AKI [11,21]. The objective of this study was to compare the theoretical influence of different estimating equations on drug dosing of antimicrobials in patients with AKI.

2. Experimental Section

The Program to Improve Care in Acute Renal Disease (PICARD) group included five academic medical centers in the United States. The study was approved by the ethics committees at each participating clinical site. A total of 618 subjects were enrolled over a 31-month period (February 1999 to August 2001), among who 398 required IHD or CRRT. We conducted a retrospective chart review of antimicrobial dosing for a subset of patients from one center in the PICARD data set. Complete descriptions of PICARD methods have been previously published [2,3].

AKI was defined differently depending on the baseline Scr. In patients with baseline Scr < 1.5 mg/dL, AKI was defined as an increase in Scr $\geq$ 0.5 mg/dL, whereas in those with baseline Scr $\geq$ 1.5 mg/dL and $\leq$ 5 mg/dL, as an increase in Scr $\geq$ 1 mg/dL. Patients with a baseline Scr > 5 mg/dL were not considered for study inclusion. Pertinent data elements from PICARD used for these analyses included age, sex, height, weight (to calculate body surface area), daily fluid balance, daily Scr and all dates on which patients received intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT).

For inclusion in this study, patients were required to have complete laboratory information and must have received antimicrobials during some dates of enrollment in the PICARD study. We excluded the time period during which patients were on IHD or CRRT, including the days before and after dialysis. Drug dispensation records were retrieved electronically and included antibiotic name, dose, frequency, route, start and stop dates.

2.1. Estimation of GFR Using Cockroft-Gault, MDRD, Jelliffe and Modified Jelliffe Equations

Estimations of CLcr or GFR using CG [17], abbreviated MDRD (age, race, gender and Scr) [10], MDRD adjusted for BSA, Jelliffe [19] and Modified Jelliffe equations [20] were calculated for each patient during each date of admission that they received an antimicrobial agent (Table 1). For the CG equation, total body weight was used if this weight was less than 130% of ideal body weight. If total body weight was greater than 130% of ideal body weight, an adjusted body weight was calculated by adding 40% of the difference between the total and ideal body weights to the ideal body weight.

Table 1. Equations used to estimate renal function.

Name	Equation
Cockcroft Gault	CLcr = ((140 – age) × weight (kg))/(72 × Scr (mg/dL)) Multiply by 0.85 if female
MDRD	GFR = 186 × (SCr (mg/dL))$^{-1.154}$ × (age (years))$^{-0.203}$ × (0.742 if patient is female) × (1.21 if patient is black)
MDRD adjusted for BSA	GFR = MDRD × BSA / 1.73 m^2
Jelliffe	(((Volume of distribution × (Scr on day 1 – Scr on day 2)) + creatinine production) × 100/1440/average Scr
Modified Jelliffe	Substitute Adjusted SCr into Jelliffe equation Adjusted SCr = SCr (measured) × Correction Factor Correction Factor = ((admit weight (kg) × 0.6) + Sum (Daily fluid balance))/admit weight × 0.6

CLcr = creatinine clearance, MDRD = modification of diet in renal disease, GFR = glomerular filtration rate, BSA = body surface area.

Clearances were calculated at the peak and nadir Scr values to describe the severity and resolution of the AKI. The CG equation was used as the reference estimate for the analysis, as the CG equation is the most frequently used equation by pharmacists for drug dosing [18]. Timed urine collections were performed as part of routine medical care for a small subset of patients and the duration ranged from 4 to 24 h.

2.2. Evaluation of the Discordance in Drug Dosing Among Estimating Equations

Institutional guidelines from the University of California, San Diego on drug dosing in patients with impaired kidney function were utilized to assess dose appropriateness. These guidelines suggest using the CG equation for drug dosing and are based on modified FDA recommendations. An antimicrobial episode was defined as each day that the patient received the antimicrobial or any time the antimicrobial was altered (e.g., change in antimicrobial dose or frequency). The rate of discordance in drug dosing was calculated as the difference in the number of correctly dosed antimicrobial episodes between the CG and the other estimating equations (Table 1) divided by the total number of antimicrobial episodes (Equation (1)).

$$\frac{\text{(\#Correct Episodes CG - \#Correct Episodes comparison)} \times 100}{\text{Total \#Episodes}} \quad (1)$$

We used antimicrobial episodes for calculating discordance since a single patient may receive numerous antimicrobials for varied durations of therapy. Additionally, the potential for error could be different depending on the antimicrobial and dosing range. A chi square test of independence with Bonferroni correction for multiple comparisons was used to assess if there was a difference in number of antimicrobial episodes dosed correctly between estimating equations for each antimicrobial (R 2.8.1). Two-tailed p-values < 0.05 were considered statistically significant.

3. Results

A total of 719 antimicrobial episodes from 32 unique patients were included in the analysis. The median age was 49.5 (range 31 to 89) years, 12.5% had CKD and the most common etiology of AKI was acute tubular necrosis (ATN). Demographic characteristics are summarized in Table 2.

Daily Scr values were used to estimate clearance for the entire cohort (Table 3). In order to show the spectrum of AKI, we calculated the median clearance at peak and nadir Scr and this ranged from 19.8 to 27.4 and 46.9 to 58.8 mL/min, respectively (Figures 1 and 2). During the course of AKI, there was a clinically meaningful change in kidney function of approximately 30 mL/min, which would indicate the need for re-evaluation of drug dosing.

Table 2. Demographics.

Variable	*n* (%) or Median (Range)
Age (years)	49.5 (31–89)
Gender	
Male	14 (44%)
Female	18 (56%)
Weight (kg)	73.9 (45–99)
Height (cm)	169 (152–191)
BSA (m^2)	1.81 (1.38–2.26)
APACHE III Score *	90 (38–151)
History of CKD	4 (12.5)
Etiology of AKI	
ATN	14 (44%)
Nephrotoxicity	2 (6%)
Multifactorial	11 (34%)
Hepatorenal	3 (10%)
Prerenal	2 (6%)

* APACHE III scores available for 30 patients.

Table 3. Clearance estimates.

Parameter	Timed Urine Collection	CG (mL/min)	MDRD (mL/min/1.73 m^2)	MDRD – Adj BSA (mL/min)	Jelliffe (mL/min)	Modified Jelliffe (mL/min)
CL peak Scr Median (range)	-	27.4 (9.3–66.3)	19.8 (9.8–47.0)	21.2 (9.9–60.4)	21.2 (5.2–56.4)	20.5 (4.9–49.6)
CL Nadir Sc rMedian (range)	-	58.8 (18.4–88.9)	46.9 (24.8–85.8)	50.8 (22.0–92.1)	52.8 (17.3–79.0)	47.2 (14.3–79.0)
Median CL (range)	22.8 (13.4–26.2)	34.4 (9.3–88.9)	28.6 (9.8–85.8)	29.3 (9.9–92.1)	30.3 (4.5–78.9)	26.7 (4.6–78.9)

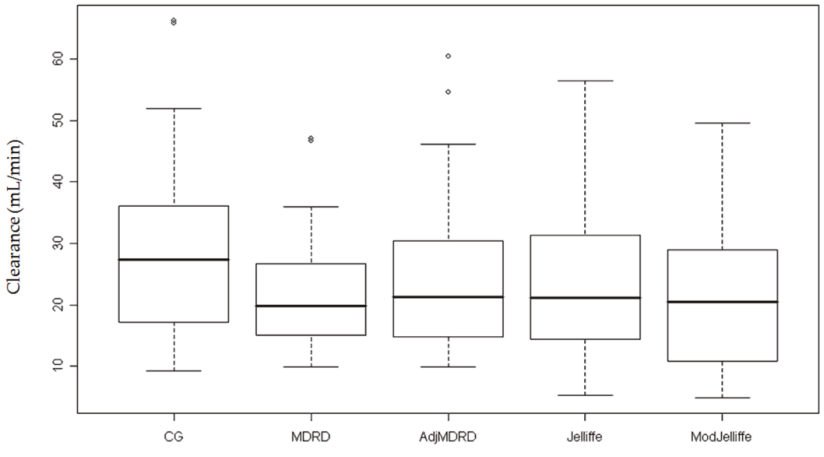

Figure 1. Clearance estimates at peak of kidney injury. This figure depicts the calculated median clearance using the peak serum creatinine value in each estimating equation. The circles represent outlier data points.

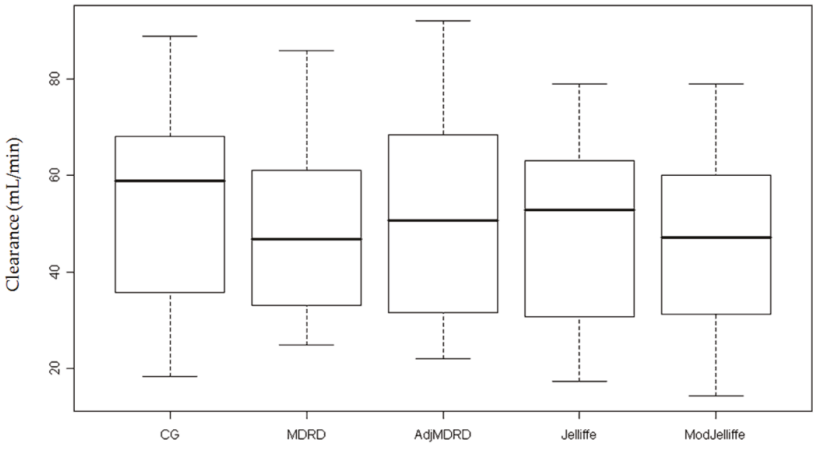

Figure 2. Clearance estimates at recovery of injury. This figure depicts the calculated median clearance at the time of injury recovery using the lowest serum creatinine value in each estimating equation.

3.1. Overall Impact on Drug Dosing Based on Individual Equations

Patients received at least one or more of the following antimicrobials whose disposition is influenced by kidney function: ampicillin, cefazolin, ceftazidime, ciprofloxacin, fluconazole, ganciclovir, metronidazole, piperacillin/tazobactam. Of the 719 dosing episodes, the appropriate dose of antimicrobials was administered at most 81% of the time (Table 4). Seventeen patients received a total of 139 episodes of inappropriate doses according to the CG equation, but after removing these inappropriate doses, 30 patients and 580 episodes remained. The discordance rate between the CG equation and the other estimation equations ranged from a minimum of 9% to a maximum of 16% (Table 4).

Table 4. Dose appropriateness for all drugs.

Estimating Equation	Number Dosed Correct (%) *n* = 719 episodes (32 patients)	Discordance Rate (%)	Number Dosed Correct (%) *n* = 580 episodes (30 patients)	Discordance Rate (%)
CG	580 (81)	-	580 (100)	-
MDRD	529 (74)	7	515 (89)	11
MDRD BSA	531 (74)	7	526 (91)	9
Jelliffe	531 (74)	7	530 (91)	9
Mod Jelliffe	488 (68)	12	485 (84)	16

3.2. Breakdown of Impact on Drug Dosing Based on Drug Administered

The most commonly prescribed drugs in our study population were ceftazidime, ciprofloxacin and fluconazole with 69%, 66% and 47% of patients receiving these medications. In the majority of cases, the discordance between estimating equations was statistically significant. The discordance rate for all episodes varied among the antimicrobial agents from 6 to 22% (Table 5).

Table 5. Dose appropriateness for specific antimicrobials.

Drug	# Patients Received (%)	# Correct CG (%)	# Correct Mod-Jelliffe (%)	Discordance Rate (%)	*p* Value
All drugs	-	580/719	488/719	13	<0.001
Ceftazidime	22 (69)	140/200 (70)	107/200 (54)	16	0.009
Ciprofloxacin	21 (66)	164/170 (96)	153/170 (90)	6	-
Fluconazole	15 (47)	104/129 (81)	91/129 (71)	10	-
Metronidazole	11 (34)	52/52 (100)	45/52 (87)	14	-
Cefazolin	7 (22)	31/36 (86)	23/36 (64)	22	-
Ganciclovir	7 (22)	59/92 (64)	41/92 (45)	20	-
Ampicillin	4 (13)	10/16 (63)	9/16 (56)	6	-
Piperacillin/ Tazobactam	4 (13)	16/16 (100)	15/16 (94)	6	-

The discordance in drug dosing between the CG and the Modified Jelliffe was highest for cefazolin (22%), ganciclovir (20%) and ceftazidime (16%). In patients who were not dosed correctly according to CG, we did not find any episodes of under-dosing. We analyzed the direction of error in dosing in the subset of episodes where the dose was correct based on the CG estimate of clearance (Table 6).

Table 6. Correct doses for Cockcroft Gault but overdosing for modified Jelliffe.

Antimicrobial	Number of Patients	Number of Dosing Episodes	Number of Overdosing Episodes	Median Daily Dose (Range)	Median Overdoseper Day (Range)
Acyclovir	2	4	0	2400 mg	0 mg
Ampicillin	3	10	1	3500 mg (3000–8000)	5000 mg
Cefazolin	7	31	7	3000 mg (2000–3000)	1000 mg
Ceftazidime	20	140	33	2000 mg (500–3000)	1000 mg (500–3000)
Ciprofloxacin	24	164	11	500 mg (400–1500)	400 mg (200–500)
Fluconazole	17	104	16	100 mg (50–400)	50 mg (50-100)
Ganciclovir	6	59	18	Oral: 3000 mg (1000–3000) IV: 100 mg (75–400)	Oral: 2000 mg (1000–2000) IV: 110 mg (45–200)
Metronidazole	11	52	7	1500 mg (1000–1500)	500 mg
Piperacillin/ Tazobactam	4	16	1	11,250 mg (6750–1,3500)	4500 mg

Depending on the frequency of antimicrobial administration, the percentage of over-dosing episodes was as high as 30%. Furthermore, in reviewing the doses administered, excess doses were clinically relevant for some antimicrobials (Table 6).

4. Discussion

In our study, we found that patients received an inappropriate dose of antimicrobials in approximately one in six dosing episodes. Almost half of the patients included in this study experienced a dosing error. The change in estimated clearance was clinically significant for the majority of patients, warranting a dosage adjustment of medications. The overall discordance rate between the CG equation and the other estimating equations was between 9% and 16%. Importantly, the difference in clearance between the estimating equations was approximately 8 mL/min or a 30% relative difference. This difference also crossed a cutoff value for our institutional guidelines for dosage adjustment (30 mL/min) resulting in antimicrobial dosing discordance. This presents a clinical challenge since physicians and pharmacists are faced with different kidney function estimates, which ultimately lead to variable doses of critical medications. We found that in cases of discordances between the CG and Modified Jelliffe equations, the dose of antimicrobial administered was supra-therapeutic when using the Modified Jelliffe estimate as the reference point.

Several factors can be attributed to the challenge of drug dosing in AKI. These include the delayed rise of Scr in response to injury, the accuracy of the various estimating equations in AKI, the lack of therapeutic drug monitoring for several antimicrobials, as well as the lack of published pharmacokinetic information on antimicrobial dosing in patients with AKI not receiving dialysis or hemofiltration.

Estimating kidney function in AKI remains controversial. Hoste and colleagues have demonstrated that in critically ill patients with normal Scr, urinary excretion of creatinine was markedly reduced [22]. They concluded that using Scr to predict kidney function was insensitive in the critically ill population and advocated for the use measured CLcr [22]. Clinicians often measure CLcr with urinary collections since patients may have an indwelling catheter and the collection can be completed by a nurse. However, urinary CLcrs have been shown to be inaccurate in the critically ill population. Robert and colleagues published results comparing the performance of 30 min urinary CLcr, 24 h urinary CLcr, and CG estimates to inulin clearance in 20 critically ill patients with stable Scr whose mean was 1.8 ± 1.5 mg/dL [16]. The 30 min collection performed similarly to the 24 h collection, but in a subset of patients, urinary CLcr over-predicted GFR by 30–300% [16]. Bragadottir and colleagues demonstrated that urinary CLcr had a low reproducibility compared to measured GFR [23]. Given the limitations of urinary collections in the critically ill population, estimating equations are attractive for routine bedside approximations of GFR. To date there are various studies comparing the ability of estimating equations to accurately predict measured CLcr or GFR in patients with stable renal function [8–17,24]. Analysis of these studies indicates that the most accurate equation varies according to the population studied [9,15]. Steady state equations such as CG will systematically over-estimate clearance and lead to over-dosing episodes in patients with AKI. Kirwan and colleagues compared the accuracy of the various steady state estimating equations to measured CLcr (4 h collection) in critically ill patients with AKI. They found that the accuracy of the various equations within 50% of measured CLcr to be 68, 78 and 81% for the CG, MDRD and CKD-EPI equations respectively [25]. The performance of these equations was not as good as in the setting of CKD. Poggio and colleagues examined the accuracy of the CG and MDRD equations in estimating GFR compared to measured GFR in hospitalized patients with kidney dysfunction [13]. They demonstrated that the MDRD and CG equations over-estimated GFR and the accuracy of the estimates within 50% of the measured GFR was 49% and 40%, respectively [13]. Bragadottir found that the MDRD, CKD-EPI and CG equations performed poorly when compared to measured GFR in critically ill patients with early AKI with biases of 7.39–11.58 mL/min [23]. This bias is consistent with other studies noting over-estimation of measured CLcr by approximately 6–17 mL/min [25,26]. These steady state equations are problematic for the estimation of kidney function in an intensive care setting or in AKI.

Non steady state equations such as Jelliffe will provide estimates of GFR that are closer to the true clearance [19]. Using data from PICARD, Bouchard and colleagues compared the accuracy of estimating GFR using CG, MDRD, Jelliffe and a modified Jelliffe equation to that of a 24-h measured urinary CLcr [20]. The authors found that among critically ill patients with AKI, traditional estimating equations (CG, MDRD) significantly overestimate kidney function compared to a modified Jelliffe equation adjusted for fluid balance [20].

One limitation of this study was the small sample size of 32 patients, as we could retrieve antimicrobial dosing data only on a small subset of patients from the PICARD database. In addition, the retrospective nature of the study is a limitation in capturing the dynamic nature of prescribing and pharmacist consulting on antimicrobial doses. This safety concern was unanticipated but provides strong rationale for electronic algorithms for drug dosage adjustments according to kidney function. Our retrospective study is limited in assessing the validity of the estimating equations for patients with AKI. We utilized the CG estimate as the criterion standard since this is the most commonly used equation for adjusting the doses of drugs [18]. We found discordance in kidney function estimates but we are limited in concluding which equation is most accurate and whether the use of the Modified Jelliffe equation would have resulted in appropriate antimicrobial concentrations.

Most clinicians feel that the therapeutic index is wide for many antimicrobials such as penicillins and cephalosporins. However, inappropriate dosing may contribute to the development of super-infections and increased costs.

Our study did not include antimicrobials in which therapeutic drug monitoring is available. If serum concentration monitoring is available, this guides dosage adjustments and little emphasis is placed on the renal estimating equation. The GFR estimating equations are used to calculate initial doses and subsequent dosing is based on serum concentrations.

Our study did not include patients on IHD or CRRT. In the setting of dialysis, a fixed clearance is prescribed. However, estimating CLcr from the prescribed effluent volumes may not be accurate since the clearance delivered is frequently less than that prescribed [27]. Dosing guidelines for many drugs in AKI are generally derived from experience in patients with CKD. This may not account for changes in drug metabolism, tubular function or drug transport in the setting of AKI [28–31]. Applying CLcr estimates from prescribed effluent volume, utilizing dosing guidelines derived from CKD and a lack of available therapeutic drug monitoring may create a potential for under-dosing antimicrobials in a critically ill population receiving IHD or CRRT [32].

The KDIGO position statement on drug dosing considerations indicates there is a lack of compelling evidence for the superiority of any one estimating equation for drug dosing [18]. The Acute Disease Quality Initiative (ADQI) recommends the use of short timed urine collections or the modified Jelliffe equation for estimating kidney function in persistent AKI [33]. Further research is needed on the quantification of kidney function in persistent AKI in the critically ill population.

5. Conclusions

Critically ill patients with AKI are at risk for significantly increased morbidity and mortality. It is essential that drugs be dosed as accurately as possible to minimize potential adverse effects and improve patient outcomes. The observations from our study indicate that there is discordance in drug dosing when using kidney function estimating equations. Prospective studies evaluating the Modified Jelliffe equation and other strategies for drug dosing in the setting of AKI should be undertaken.

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References

1. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef] [PubMed]
2. Chertow, G.M.; Burdick, E.; Honour, M.; Bonventre, J.V.; Bates, D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–3370. [CrossRef] [PubMed]
3. Mehta, R.L.; Pascual, M.T.; Soroko, S.; Savage, B.R.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Chertow, G.M.; Program to Improve Care in Acute Renal Disease. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int.* **2004**, *66*, 1613–1621. [CrossRef] [PubMed]
4. Peyriere, H.; Branger, B.; Bengler, C.; Vecina, F.; Pinzani, V.; Hillaire-Buys, D.; Blayac, J.P. Neurologic toxicity caused by zelitrex (valaciclovir) in 3 patients with renal failure. Is overdose associated with improvement of product bioavailability improvement? *Rev. Med. Int.* **2001**, *22*, 297–303.
5. Matzke, G.R.; McGory, R.W.; Halstenson, C.E.; Keane, W.F. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob. Agents Chemother.* **1984**, *25*, 433–437. [CrossRef] [PubMed]
6. Smith, C.R.; Moore, R.D.; Lietman, P.S. Studies of risk factors for aminoglycoside nephrotoxicity. *Am. J. Kidney Dis.* **1986**, *8*, 308–313. [CrossRef]

7. Matzke, G.R.; Frye, R.F. Drug administration in patients with renal insufficiency. Minimising renal and extrarenal toxicity. *Drug Saf.* **1997**, *16*, 205–231. [CrossRef] [PubMed]
8. Rosborough, T.K.; Shepherd, M.F.; Couch, P.L. Selecting an equation to estimate glomerular filtration rate for use in renal dosage adjustment of drugs in electronic patient record systems. *Pharmacotherapy* **2005**, *25*, 823–830. [CrossRef] [PubMed]
9. Goerdt, P.J.; Heim-Duthoy, K.L.; Macres, M.; Swan, S.K. Predictive performance of renal function estimate equations in renal allografts. *Br. J. Clin. Pharmacol.* **1997**, *44*, 261–265. [CrossRef] [PubMed]
10. Levey, A.S.; Bosch, J.P.; Lewis, J.B.; Greene, T.; Rogers, N.; Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Int. Med.* **1999**, *130*, 461–470. [CrossRef] [PubMed]
11. Wargo, K.A.; Eiland, E.H., 3rd; Hamm, W.; English, T.M.; Phillippe, H.M. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. *Ann. Pharmacother.* **2006**, *40*, 1248–1253. [CrossRef] [PubMed]
12. Lin, J.; Knight, E.L.; Hogan, M.L.; Singh, A.K. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J. Am. Soc. Nephrol.* **2003**, *14*, 2573–2580. [CrossRef] [PubMed]
13. Poggio, E.D.; Nef, P.C.; Wang, X.; Greene, T.; Van Lente, F.; Dennis, V.W.; Hall, P.M. Performance of the Cockcroft-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients. *Am. J. Kidney Dis.* **2005**, *46*, 242–252. [CrossRef] [PubMed]
14. le Riche, M.; Zemlin, A.E.; Erasmus, R.T.; Davids, M.R. An audit of 24-hour creatinine clearance measurements at Tygerberg Hospital and comparison with prediction equations. *S. Afr. Med. J.* **2007**, *97*, 968–970. [PubMed]
15. Kuan, Y.; Hossain, M.; Surman, J.; El Nahas, A.M.; Haylor, J. GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease. *Nephrol. Dial. Transplant.* **2005**, *20*, 2394–2401. [CrossRef] [PubMed]
16. Robert, S.; Zarowitz, B.J.; Peterson, E.L.; Dumler, F. Predictability of creatinine clearance estimates in critically ill patients. *Crit. Care Med.* **1993**, *21*, 1487–1495. [CrossRef] [PubMed]
17. Cockcroft, D.W.; Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* **1976**, *16*, 31–41. [CrossRef] [PubMed]
18. Matzke, G.R.; Aronoff, G.R.; Atkinson, A.J., Jr.; Bennett, W.M.; Decker, B.S.; Eckardt, K.U.; Golper, T.; Grabe, D.W.; Kasiske, B.; Keller, F.; et al. Drug dosing consideration in patients with acute and chronic kidney disease—A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* **2011**, *80*, 1122–1137. [CrossRef] [PubMed]
19. Jelliffe, R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *Am. J. Nephrol.* **2002**, *22*, 320–324. [CrossRef] [PubMed]
20. Bouchard, J.; Macedo, E.; Soroko, S.; Chertow, G.M.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Mehta, R.L.; Program to Improve Care in Acute Renal Disease. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. *Nephrol. Dial. Transplant.* **2010**, *25*, 102–107. [CrossRef] [PubMed]
21. Gill, J.; Malyuk, R.; Djurdjev, O.; Levin, A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group—A cautionary tale. *Nephrol. Dial. Transplant.* **2007**, *22*, 2894–2899. [CrossRef] [PubMed]
22. Hoste, E.A.; Damen, J.; Vanholder, R.C.; Lameire, N.H.; Delanghe, J.R.; Van den Hauwe, K.; Colardyn, F.A. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. *Nephrol. Dial. Transplant.* **2005**, *20*, 747–753. [CrossRef] [PubMed]
23. Bragadottir, G.; Redfors, B.; Ricksten, S.E. Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury—True GFR versus urinary creatinine clearance and estimating equations. *Crit. Care* **2013**, *17*, R108. [CrossRef] [PubMed]
24. Marx, G.M.; Blake, G.M.; Galani, E.; Steer, C.B.; Harper, S.E.; Adamson, K.L.; Bailey, D.L.; Harper, P.G. Evaluation of the Cockroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. *Ann. Oncol.* **2004**, *15*, 291–295. [CrossRef] [PubMed]
25. Kirwan, C.J.; Philips, B.J.; Macphee, I.A. Estimated glomerular filtration rate correlates poorly with four-hour creatinine clearance in critically ill patients with acute kidney injury. *Crit. Care Res. Pract.* **2013**, *2013*, 406075. [CrossRef] [PubMed]

26. Martin, J.H.; Fay, M.F.; Udy, A.; Roberts, J.; Kirkpatrick, C.; Ungerer, J.; Lipman, J. Pitfalls of using estimations of glomerular filtration rate in an intensive care population. *Int. Med. J.* **2011**, *41*, 537–543. [CrossRef] [PubMed]
27. Lyndon, W.D.; Wille, K.M.; Tolwani, A.J. Solute clearance in CRRT: Prescribed dose versus actual delivered dose. *Nephrol. Dial. Transplant.* **2012**, *27*, 952–956. [CrossRef] [PubMed]
28. Nolin, T.D.; Appiah, K.; Kendrick, S.A.; Le, P.; McMonagle, E.; Himmelfarb, J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J. Am. Soc. Nephrol.* **2006**, *17*, 2363–2367. [CrossRef] [PubMed]
29. Dixon, J.; Lane, K.; Macphee, I.; Philips, B. Xenobiotic metabolism: The effect of acute kidney injury on non-renal drug clearance and hepatic drug metabolism. *Int. J. Mol. Sci.* **2014**, *15*, 2538–2553. [CrossRef] [PubMed]
30. Vilay, A.M.; Churchwell, M.D.; Mueller, B.A. Clinical review: Drug metabolism and nonrenal clearance in acute kidney injury. *Crit. Care* **2008**, *12*, 235. [CrossRef] [PubMed]
31. Eyler, R.F.; Mueller, B.A.; Medscap. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat. Rev. Nephrol.* **2011**, *7*, 226–235. [CrossRef] [PubMed]
32. Goldstein, S.L.; Nolin, T.D. Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy. *Clin. Pharmacol. Ther.* **2014**, *96*, 159–161. [CrossRef] [PubMed]
33. Chawla, L.S.; Bellomo, R.; Bihorac, A.; Goldstein, S.L.; Siew, E.D.; Bagshaw, S.M.; Bittleman, D.; Cruz, D.; Endre, Z.; Fitzgerald, R.L.; et al. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat. Rev. Nephrol.* **2017**, *13*, 241–257. [CrossRef] [PubMed]

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Review

Meta-Analysis: Urinary Calprotectin for Discrimination of Intrinsic and Prerenal Acute Kidney Injury

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Abstract: Background: Urinary calprotectin is a novel biomarker that distinguishes between intrinsic or prerenal acute kidney injury (AKI) in different studies. However, these studies were based on different populations and different AKI criteria. We evaluated the diagnostic accuracy of urinary calprotectin and compared its diagnostic performance in different AKI criteria and study populations. **Method:** In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched PubMed, Embase, and the Cochrane database up to September 2018. The diagnostic performance of urinary calprotectin (sensitivity, specificity, predictive ratio, and cutoff point) was extracted and evaluated. **Result:** This study included six studies with a total of 502 patients. The pooled sensitivity and specificity were 0.90 and 0.93, respectively. The pooled positive likelihood ratio (LR) was 15.15, and the negative LR was 0.11. The symmetric summary receiver operating characteristic (symmetric SROC) with pooled diagnostic accuracy was 0.9667. The relative diagnostic odds ratio (RDOC) of the adult to pediatric population and RDOCs of different acute kidney injury criteria showed no significant difference in their diagnostic accuracy. **Conclusion:** Urinary calprotectin is a good diagnostic tool for the discrimination of intrinsic and prerenal AKI under careful inspection after exclusion of urinary tract infection and urogenital malignancies. Its performance is not affected by different AKI criteria and adult or pediatric populations.

Keywords: urine calprotectin; acute kidney injury; intrinsic renal injury

1. Introduction

Acute kidney injury (AKI) is a common and widespread problem with high mortality and morbidity. Despite understanding the pathogenesis of different etiologies, traditional diagnosis markers (including serum creatinine and urine output) are not a real-time, not a sensitive and specific renal marker for early diagnosis and interventions, not based on acute kidney etiology, and the differentiation of prerenal injury and intrinsic kidney injury is difficult. There are numerous causes of AKI, which are most

commonly classified as prerenal, intrinsic (intrarenal), or postrenal kidney injury. To date, many studies have revealed that neutrophil gelatinase-associated lipocalin (NGAL) has shown promising results in the early diagnosis of AKI [1–4], distinguishing between prerenal and intrinsic kidney injury ([5–7], and predicting the need for renal replacement therapy and prognosis. [8,9]. Urinary calprotectin is a heterodimer protein involved in the immune system [10] and plays a role in the AKI pathophysiology. Early studies have shown that the release of urinary calprotectin from neutrophil and renal tubular epithelial cells also produces calprotectin in response to injury [10–12]. Calprotectin has been demonstrated to be similar to NGAL as a diagnostic marker for early diagnosis and to make a different diagnosis of AKI etiology [5,13–17]. This biomarker, which can early detect acute kidney injury and distinguish between prerenal and intrinsic AKI, can facilitate intervention, reduce the time to initiate therapy, and reduce the number of unnecessary renal biopsies. Nevertheless, these studies used different AKI criteria and were based on different populations. Therefore, we conducted a systemic review and meta-analysis for evaluating the differential diagnostic accuracy of urinary calprotectin between prerenal and intrinsic kidney injury.

2. Methods

2.1. Literature Search

Our two investigators (J.-J.C., C.-H.C.) systematically and independently conducted a review of the published data in accordance with Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) guideline. A computerized search of the electronic databases of Pubmed, Embase, and the Cochrane database was performed to identify all relevant English-language studies up to September 2018 using the keywords and medical subject heading (MeSH) term: AKI, calprotectin, S100A8/A9 complex, and myeloid-related protein complex.

2.2. Study Selection

Two investigators independently determined the study eligibility based on an evaluation of the titles, abstracts, and subsequently, the full texts. Any difference in opinion regarding eligibility was resolved by consensus through discussion. Any article that was deemed potentially relevant was retrieved online for the full-text. Studies were included if they met the following criteria: full-length English original articles published and available, human studies, urinary calprotectin for distinguishing between intrinsic and pre-renal AKI, clear definition of AKI: (the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE), AKI Network (AKIN), Kidney Disease Improving Global Outcomes (KDIGO), or pediatric RIFLE criteria (pRIFLE)) and reported the definition/clinical criteria of intrinsic or prerenal AKI. Studies were excluded according to the following criteria: (1) focusing on chronic kidney disease, (2) duplicate cohort, (3) non-original studies (such as reviews, commentaries, letters), (4) studies with insufficient information, (5) studies that were not based on urinary calprotectin level, (6) studies with no reported intrinsic or prerenal AKI. Review articles or meta-analysis were not included in the analysis; however, their citations and references were searched for additional relevant studies. Full search strategies are available in Table S1.

2.3. Data Extraction

Two investigators (J.-J.C., C.-H.C.) independently extracted the relevant information from each study. Data elements related to the study level characteristics included first author, year of publication, study location, study design, definition of AKI, sample processing, method of storage, calprotectin measurement method, and test kit, see Table 1. As for patient characteristics, data included gender, age, diabetes, hypertension, urinary tract infection (UTI), creatinine on admission, creatinine prior to admission, C-reactive protein, urinary creatinine, urinary calprotectin, and urinary calprotectin to creatinine ratio and are summarized in Table 2. Items related to the diagnostic test performance were

also extracted, including cutoff points based on the Youden index, sensitivity, specificity, and the number of intrinsic and prerenal kidney injuries, see Table 3.

2.4. Outcome Measures

The diagnostic criteria of AKI were different in the six enrolled studies. Four of which (Heller, 2011; Seibert, 2013; Seibert, 2016; Basiratnia, 2017) used AKIN criteria [18]. One (Chang, 2015) used KDIGO AKI criteria [19]. One (Westhoff, 2016) used the pRIFLE criteria modified by Ackan-Arikan et al. [20]. Two of which (Westhoff, 2016; Basiratnia, 2017) were pediatric population studies.

The reference test for differentiating intrinsic or prerenal acute kidney diagnosis was based on clinical criteria as mentioned below (most studies used predefined criteria). The histologic diagnosis of hepato-renal syndrome or cardio-renal syndrome was considered the golden standard. The response to volume repletion (return of creatinine to baseline within 48 to 72 h) was considered an obligatory diagnostic criterion for prerenal kidney injury. Other findings for the diagnosis of prerenal kidney injury included compatible history (dehydration, fluid loss, heart failure, liver cirrhosis), compatible physical examination (low blood pressure, low jugular pulse, tachycardia, orthostatic blood pressure changes, poor skin turgor), and compatible urine analysis (no proteinuria, no hematuria). UTI was classified as an intrinsic kidney injury in three enrolled studies (Heller, 2011; Seibert, 2013; Seibert, 2016).

2.5. Risk of Bias

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and Review Manager version 5.3 to assess the quality of the included studies [21]. The QUADAS-2 score is based on four domains (patient selection, index test, reference standard, and flow and timing) to judge the risk of bias. Each study was reviewed independently by J.-J.C., C.-H.C., and rated as high, low, or of unclear risk for all four domains. The judgment principle of "applicability" was the same as the bias section, but there were no signaling questions. Disagreements between the two reviewers were solved by consensus through discussion. If the answer to all signaling questions in each domain is "yes", the domain is considered as low risk. If any signaling question is answered "no", the domain is considered as having a high risk of bias.

2.6. Statistical Analysis

True positive (TP), true negative (TN), false positive (FP), and false negative (FN) rates for each study were calculated according to the reported sensitivity, specificity, and patient number of prerenal and intrinsic AKI. Based on these data, the positive likelihood ratio (+LR), negative likelihood ratio (−LR), and diagnostic odds ratio (DOR) could be obtained for each study. The summary measures were calculated using a random effects model (DerSimonian and Laird method). To assess the diagnostic performance of urinary calprotectin in predicting intrinsic AKI in AKI patients, a symmetric summary receiver operating characteristic (symmetric SROC) curve was constructed based on TP and FP rates. The threshold effect was detected using the Spearman correlation coefficient between the logit of sensitivity and logit of '1−specificity', where a non-significant threshold effect was warranted before performing further subgroup analysis or meta-regression [22]. The degree of heterogeneity among studies was evaluated using the I^2 index, with <25%, 25%–50%, and >50% indicating mild, moderate, and high heterogeneity, respectively. Likelihood ratios indicate that the accuracy of a particular test would be more accurate for patients with a disease than for subjects without disease. Two variables (adult vs. pediatric; AKI criteria) were performed as moderators in the meta-regression analyses to explore possible sources of heterogeneity. A sensitivity analysis was done to exclude patients with a UTI. All analyses were conducted by Meta-DiSc (version 1.4) software [23]. A two-sided p value of <0.05 was considered statistically significant.

Table 1. The characteristics of the six included studies.

Study/year	Location	Design	AKI Criteria	Population	Sample Time	Storage	Assay	Test Kit
Basiratnia/2017 [24]	Iran	PC	AKIN	Pediatric	Immediately at diagnosis of AKI	−20 °C, no centrifugation	ELISA	PhiCal® Calprotectin, catalogue number K 6928; Immundiagnostik AG, Bensheim, Germany
Chang/2015 [17]	Taiwan	PC	KDIGO	Adult CCU	Immediately at admission	−80 °C, centrifugation	ELISA	R&D Systems, DLCN20, McKinley Place NE Minneapolis; MPLS, USA and Phi Cal® Calprotectin, K 6935; and Immundiagnostik AG, Bensheim, Germany
Heller/2011 [13]	Germany	PC	AKIN	Adult	Within 3 days	−20 °C, no centrifugation	ELISA	PhiCal® Calprotectin, catalog number K 6935; Immundiagnostik AG, Bensheim, Germany
Seibert/2013 [5]	Germany	PC	AKIN	Adult	NR	−20 °C, no centrifugation	ELISA	PhiCal® Calprotectin, catalog number K 6935; Immundiagnostik AG, Bensheim, Germany
Seibert/2017 [14]	Germany	PC	AKIN	Adult transplant	At admission or on clinics	−20 °C, no centrifugation	ELISA	PhiCal® Calprotectin, catalogue number K 6928; Immundiagnostik AG, Bensheim, Germany
Westhoff/2016 [15]	Germany	PC	pRIFLE	Pediatric	Immediately at diagnosis or after admission with AKI.	−80 °C, centrifugation	ELISA	PhiCal® Calprotectin; Immundiagnostik AG, Bensheim, Germany

Abbreviation: AKI (acute kidney injury), AKIN (Acute Kidney Injury Network), CCU (coronary care unit), ELISA (enzyme linked immunosorbent assay), KDIGO (Kidney Disease Global Outcomes), NR (not reported), pRIFLE (pediatric Risk, Injury, Failure, Loss of kidney function and End stage kidney disease), PC (prospective cohort).

Table 2. Patient characteristics based on available data.

Variable	Adult			Pediatric		
	Prerenal (n = 116)	**Intrinsic (n = 258)**	p	**Prerenal (n = 44)**	**Intrinsic (n = 84)**	p
Male (%)	73.3	49.2	<0.001	54.6	40.5	<0.001
Age (years)	68 (66, 68)	68 (58, 71)	0.007	7.5 (2.6, 7.5)	6.0 (0.6, 6.0)	<0.001
Hypertension (%)	80.2	82.6	<0.001	NA	NA	NA
Diabetes (%)	28.5	30.6	<0.001	NA	NA	NA
Urinary tract infection (%)	0	41.1	<0.001	NA	NA	NA
Creatinine on admission or diagnosis (mg/dL)	3.1 (2.6, 4.4)	3.4 (3.1, 4.1)	0.054	1.1 (0.9, 1.1)	1.8 (1.8, 1.9)	<0.001
Creatinine at baseline (mg/dL)	1.4 (1.4, 1.7)	1.4 (1.4, 1.9)	0.023	NA	NA	NA
CRP (mg/dL)	5.2 (3.5, 5.3)	5.1 (0.7, 6.7)	0.412	NA	NA	NA
Urine creatinine (g/L)	0.7 (0.7, 0.8)	0.6 (0.5, 0.6)	<0.001	NA	NA	NA
Urinary calprotectin (ng/mL)	54 (28, 385)	1955 (1955, 2405)	<0.001	29 (19, 29)	1240 (427, 1240)	<0.001
Urinary calprotectin (ng/mL)/Cr (g/L) ratio	57 (52, 310)	2775 (2775, 3698)	<0.001	NA	NA	NA

CRP, C-reactive protein; NA, not applicable; Cr, creatinine; continuous variable was presented as median and interquartile range.

Table 3. Summary of diagnostic performance of the six included studies.

Study/Year	Sample Size	Event (Prerenal/Intrinsic)	Cufoff (ng/mL)	Sensitivity	Specificity	PPV	NPV
Basiratnia 2017	75	30/45	230	96.7	96.7	97.7	96.7
Chang 2015	74	31/43	314.6	88.4	96	NR	NR
Heller 2011	86	34/52	300	92.3	97.1	98	89.2
Seibert 2013	62	24/38	600	97.4	95.8	97.4	95.8
Seibert 2017	152	27/125	134.5	90.4	74.1	NR	NR
Westhoff 2016	53	14/39	76	77	93	97	60

PPV, positive predicted value; NPV, negative predicted value; NR, not reported.

3. Results

3.1. Literature Search

The initial search retrieved 83 records. After excluding duplicated articles and removing irrelevant articles, the remaining 30 articles were screened based on the title and abstract. Ten potentially relevant articles were identified and full-text articles were downloaded and accessed for eligibility. Of these 10 articles, one of which [16] was suspected of using a duplicate cohort to another study [15], two of which reported no data of intrinsic and prerenal AKI, and one of which had no data on urinary calprotectin. Finally, six studies were included in this meta-analytic study, see Figure 1.

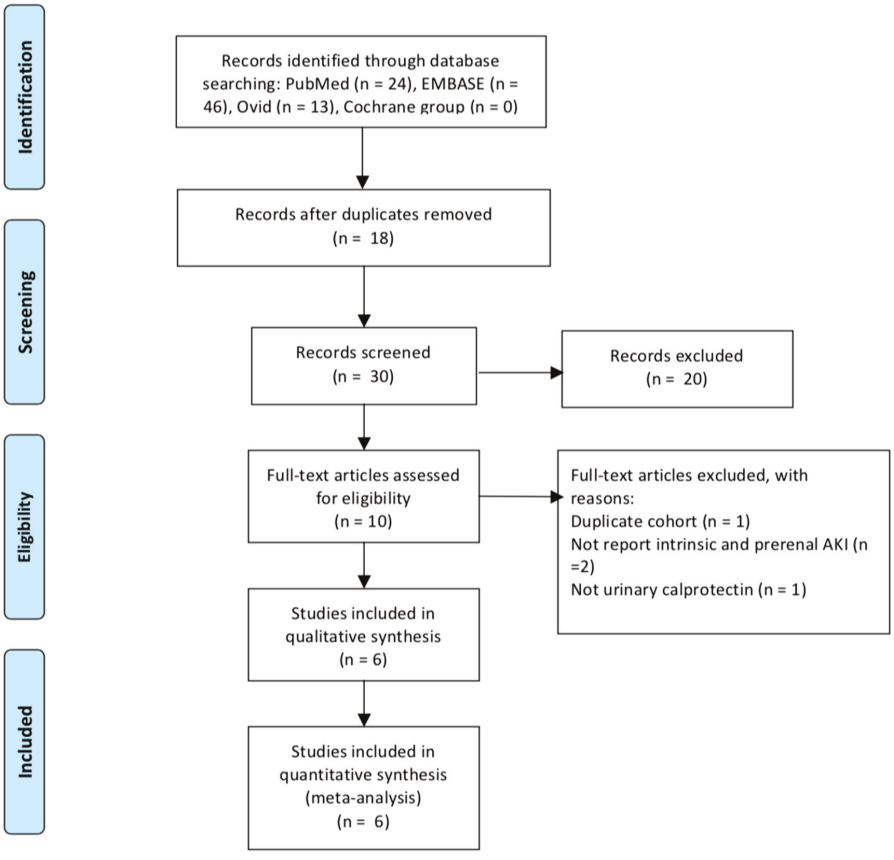

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

3.2. Risk of Bias

With the QUADAS-2 tool, some study characteristics that might increase the risk of bias were identified. Domain 1 of QUADAS-2 focused on patient selection. Four of the included studies were based on an adult population and two on a pediatric population. One of the studies (Seibert, 2016) selected a population that was not a consecutive or random sample of patients but rather focused on post-kidney-transplant adults. Another study (Chang, 2015) selected a narrow spectrum population in the coronary care unit (CCU). Domain three addresses aspects of the reference standard. Inconsistent standard criteria of AKI (KDIGO, AKIN, or pRIFLE) and a lack of pathological evidence of intrinsic kidney injury were found in all studies. In addition, most studies used the clinical observation

of a rapid decrease in serum creatinine with convergence to the baseline within 72 h after fluid repletion to diagnose prerenal AKI, except for one study (Basiratnia, 2017) that used 48 h as a time interval. Because there was one study (Seibert, 2016) with an adult kidney transplant population and two others (Basiratnia, 2017, Westhoff 2016) with pediatric populations, the answer regarding the applicability of the patient selection of these three studies was considered to be unclear. We summarized the risk of bias data for all the included studies in Figure 2.

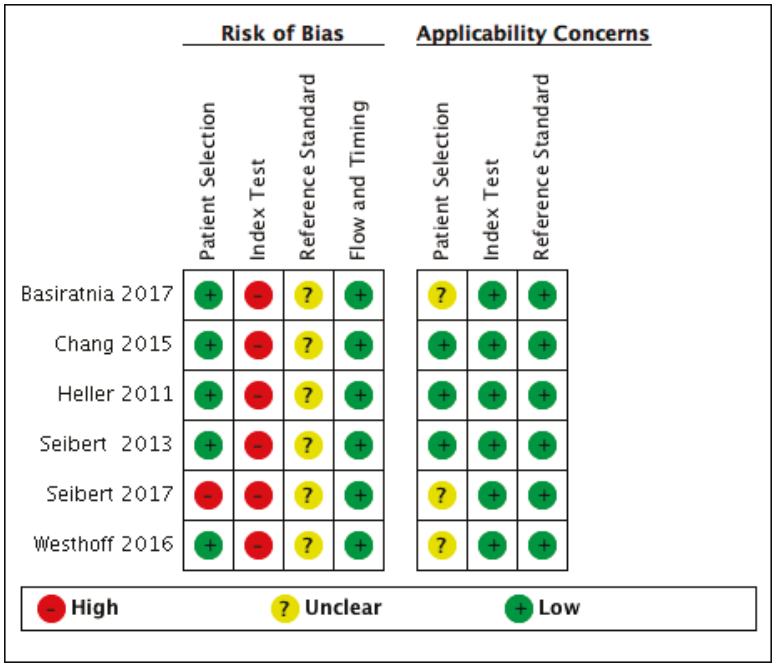

Figure 2. Summary of risk of bias and applicability concerns.

3.3. Study Characteristics

The characteristics of the six included studies are summarized in Table 1. Four of the studies were performed in Germany, one in Taiwan, and one in Iran. Sample sizes ranged from 53 to 152 patients. Two studies were conducted on pediatric populations, one on an adult kidney transplant population, and three on adult populations. Two studies excluded patients with UTI, two provided data for the entire cohort and data of excluded UTI patients, and three provided data of urinary calprotectin and normalization by urine creatinine. The optimal cutoffs were determined by the Youden index in three studies. These six studies adopted clinical diagnostic criteria for prerenal or intrinsic kidney injury, including rapid decreasing serum creatinine (Cr) (<72 h) after fluid repletion as prerenal AKI, physical examination finding, and urine examination. The detailed information of the reference test is described earlier in this article.

3.4. Patient's Characteristics

A total of 502 patients were included in these six studies. All studies were single-center trials. Study populations included adult and children populations, kidney transplant populations, and CCU patients. The mean age of the four adult AKI studies was 68 years, and there were more males with prerenal acute kidney than males with an intrinsic kidney injury ($p < 0.001$). The prevalence of hypertension, diabetes mellitus, and UTI was higher in the intrinsic kidney group. The level of serum

creatinine on admission or AKI diagnosis was not significantly different ($p = 0.054$). The C-reactive protein level was also not significantly different ($p = 0.412$). Not surprisingly, the urinary calprotectin and urinary calprotectin to creatinine ration were higher in patients with an intrinsic kidney injury. Two pediatric AKI studies had a mean age of 7.5 and 6.0 years in the prerenal and intrinsic kidney injury groups, respectively. The level of serum creatinine on admission or AKI diagnosis was significantly higher in the pediatric intrinsic kidney injury group ($p < 0.001$). Detailed information is summarized in Table 2.

3.5. Urinary Calprotectin for Discriminating Prerenal and Intrinsic Acute Kidney Injuries

The diagnostic values, cutoffs, and key results are summarized in Table 3. The pooled sensitivity and specificity were 0.90 (95% CI: 0.87–0.93) and 0.93 (95% CI: 0.88–0.96), respectively. The pooled positive LR was 15.15 (95% CI: 4.45–51.55), and the negative LR was 0.11 (95% CI: 0.06–0.20), as shown in Figure 3. The symmetric SROC with pooled diagnostic accuracy was 0.9667, see Figure 4. The heterogeneity of the aforementioned four pooled indices was moderate to high (I^2 ranged from 55% to 68.9%).

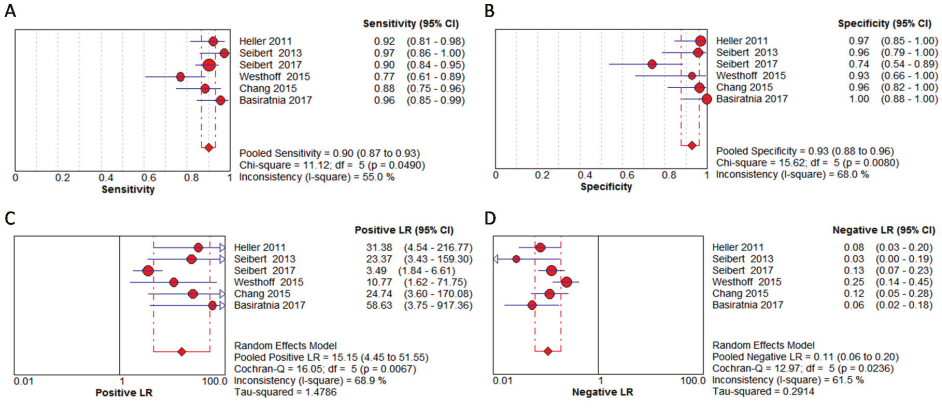

Figure 3. Diagnostic performance of urinary calprotectin on discriminating between intrinsic acute kidney injuries and prerenal acute kidney injury.

By using normalization according to urine creatinine, the data of three studies were pooled. The pooled sensitivity and specificity were 0.93 (95% CI: 0.87–0.97) and 0.95 (95% CI: 0.88–0.98), respectively. The pooled positive LR was 14.75 (95% CI: 5.54–39.3), and the negative LR was 0.08 (95% CI: 0.04–0.18), see Supplementary Information, Figure S1. The SROC with pooled diagnostic accuracy was 0.9840, see the Supplementary Information, Figure S2.

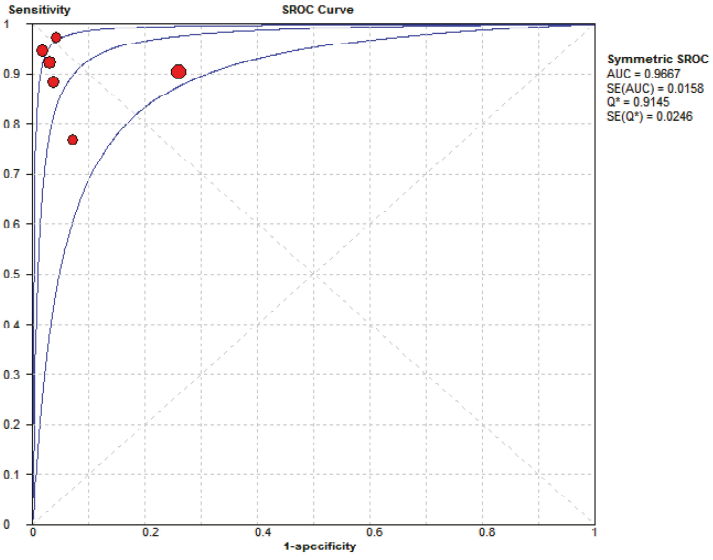

Figure 4. Symmetric summary receiver operating characteristic (symmetric SROC) according to the cutoffs of the six studies. Abbreviation: SROC, summary receiving operating characteristics; AUC, area under the curve; SE, standard error.

3.6. Subgroup Analysis

Due to the moderate to high heterogeneity, several study characteristics (population age and criteria of AKI) were used to explore the sources of heterogeneity. The analysis of the diagnosis threshold was performed with Spearman rank correlation ($\rho = -0.429$; $p = 0.397$), indicating no threshold effect and allowing for further subgroup analysis. The relative diagnostic odds ratio (RDOC) of the adult population relative to the pediatric population was 2.48 (95% CI: 0.01–737.91), indicating no significant difference in the diagnostic accuracy between adult and pediatric cohorts. The RDOCs of AKIN and KDIGO (both relative to RIFLE) were 25.13 (95% CI: 0.04–15927.64) and 5.38 (95% CI: 0.01–4757.39), respectively, indicating no significant difference in the diagnostic accuracy under different criteria of AKI (data not shown).

3.7. Sensitivity Analyses

There were three studies that provided data after excluding patients with a UTI. The pooled sensitivity and specificity of these two studies were 0.92 (95% CI: 0.85–0.96) and 0.98 (95% CI: 0.92–1.00), respectively. The pooled positive LR was 31.95 (95% CI: 9.40–108.54), and the negative LR was 0.10 (95% CI: 0.05–0.17), see the Supplementary Information, Figure S3. The symmetric SROC with pooled diagnostic accuracy was 0.9995, see the Supplementary Information, Figure S4.

4. Discussion

Calprotectin is a heterodimer protein (S100A8/S100A9) that plays a role in the innate immune system, acute kidney pathophysiology, and kidney repair processes as described below. Our findings can be summarized in the following points: (1) Urinary calprotectin is a good marker for differentiation of intrinsic and prerenal AKI; (2) the diagnostic performance of urinary calprotectin is not significantly different in different acute kidney diagnostic criteria and in adult or pediatric populations.

The urinary calprotectin is higher in intrinsic kidney injury than prerenal kidney injury. It may be reasonable to conclude that urinary calprotectin is a good diagnostic test in the discrimination of an intrinsic kidney injury with a pooled diagnostic accuracy of symmetric SROC of 0.9667.

It has been noted in earlier studies that calprotectin is released from the immune system cells (neutrophils and to lesser degree monocytes) and renal collecting duct epithelial cells [10,11,25,26]. It has also been demonstrated that renal tubular epithelial cells produce calprotectin in response to unilateral ureteral obstruction [11]. Calprotectin also increases expression after ischemia-reperfusion injury and plays a role in M2 macrophage-mediated renal repair [12]. It acts as a danger-associated molecular pattern protein that activates toll-like receptor 4 (TLR4). The available immunostainings of the clinical studies suggest that inflammatory infiltration rather than the tubular epithelial cells is the major source of urinary calprotectin in AKI [13,27]. Therefore, different etiologies of an intrinsic kidney injury which involved calprotectin, neutrophils infiltration, and TLR4 are expected to have higher urinary calprotectin. For example, in the leading causes of intrinsic kidney injury, renal epithelial tubular damage and inflammatory renal disease (including glomerulonephritis, tubular-interstitial nephritis and vasculitis, pyelonephritis) can lead to higher levels of urinary calprotectin. In contrast, in prerenal AKI, there is a functional deficit leading to low levels of urinary calprotectin. Elevated urinary calprotectin has been described in different diseases such as urinary bladder malignancies [28]. Gastroenterologists also used fecal calprotectin to distinguish between function disorder (irritable bowel syndrome) and inflammatory bowel diseases [29,30].

Heller (2011) has indicated that a UTI has a higher urinary calprotectin level than other intrinsic kidney injury causes. Pyuria is a potential confounder because it increases the calprotectin level in the urine, independent of renal function. Three above-mentioned studies (Heller, 2011; Seibert, 2013; Seibert, 2016) enrolled a UTI population as having intrinsic kidney injury. Three of the six enrolled studies (Heller, 2011; Chang 2015; Basiratnia, 2017) reported population or subgroup data showing an accuracy after exclusion of UTI and the symmetric SROC of pooled diagnostic accuracy was 0.9995. This might suggest that the diagnostic value of calprotectin is better if UTI can be excluded before examination.

Our research also supports the notion that the diagnostic accuracy of urinary calprotectin does not differ from different AKI criteria. The current AKI criteria are based on serum creatinine and urine output. It is widely noted that serum creatinine is not only a delayed but also a functional marker, rather than a damage marker to kidney injury. The novel biomarker was elevated earlier than serum Cr, and in a previous human renal ischemia-reperfusion study [26], calprotectin even increased earlier than NGAL (2 h and 8 h after injury, respectively). This may be an explanation for why we found that the accuracy of urinary calprotectin is not interfered by different AKI criteria.

Calprotectin has several characteristics that make it a promising novel marker and even a troponin for nephrologists [31]. First, as mentioned above, it rises earlier than NGAL. Second, according to Azimi [31], calprotectin combined with serum endocan may further differentiate pure tubular injury from glomerular-tubular injury. In addition, calprotectin has been reported to be associated with mortality and can predict the progression of kidney disease. In an AKI pediatric population, Westhoff et al. concluded that urinary calprotectin can predict the 30-day mortality and the need for renal replacement therapy [16]. Another kidney transplantation adult population study conducted by Tepel et al. revealed that urinary calprotectin levels on day 1 after operation predicted allograft injury and renal function decline after 1 month, 6 months, and 12 months after surgery [32].

The first limitation concerns the moderate to high heterogeneity of enrolled studies due to different study populations, even in adult patients (cardiac care unit and kidney transplant populations). As with other similar AKI biomarker systemic studies [33], different acute kidney definitions are also sources of heterogeneity. The second limitation is that our enrolled studies are all published online, the data may represent an optimistic estimate. In addition, few studies have addressed the role of calprotectin so far and only six articles were enrolled in our studies. Furthermore, to date, there is no clinical golden standard for the diagnosis of intrinsic AKI, and current studies are all based on history, clinical, and physical examination criteria. This may result in the misclassification of kidney injury etiology. Urogenital malignancies and UTI may increase urinary calprotectin concentrations independent of

acute kidney injury. The careful inspection for urogenital malignancies and UTI is warranted before clinical application.

5. Conclusion

In conclusion, early diagnosis of acute kidney injury is of great significance to clinical practice and guides further therapy. Our study demonstrated that urinary calprotectin is a good diagnostic marker for discriminating intrinsic and prerenal AKI in adult or pediatric populations, and its performance was not interfered by different AKI criteria. Further large, multicenter trials may be needed to clarify and identify the possible role of urinary calprotectin in different populations. More efforts on developing biomarkers to guide therapy or treatment protocol and more rapid and accurate etiology diagnosis for AKI are still needed before before the troponin of nephrologist coming true.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/1/74/s1, Table S1: Primary reasons for exclusion of excluded studies, Figure S1. Diagnostic performance of the three studies providing data on urinary calprotectin with normalization to urine creatinine, Figure S2. Symmetric SROC according to the cutoffs of the three studies with urinary calprotectin with normalization to urine creatinine, Figure S3. Diagnostic performance of urinary calprotectin with three studies excluding patients with urinary tract infection, Figure S4. Symmetric SROC according to the cutoffs of the three studies excluding patients with urinary tract infection.

Author Contributions: J.-J.C. and C.-H.C. methodology; P.-C.F., G.K., S.-W.C., Y.-T.C., formal analysis; J.-J.C. and C.-H.C., data extraction; J.-J.C., writing—Original draft preparation; G.K., C.-C.L. and P.-C.F., writing—Review and editing; C.-H.C., project administration.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AKI	acute kidney injury
Cr	creatinine
CCU	coronary care unit
CRP	C-reactive protein
ELISA	Enzyme linked immunosorbent assay
KDIGO	Kidney Disease Global outcomes
NGAL	Neutrophil gelatinase-associated lipocalin
NR	Not report
pRIFLE	Pediatric Risk, Injury, Failure, Loss of kidney function and End stage kidney disease
PC	Prospective cohort

References

1. Haase, M.; Devarajan, P.; Haase-Fielitz, A.; Bellomo, R.; Cruz, D.N.; Wagener, G.; Krawczeski, C.D.; Koyner, J.L.; Murray, P.; Zappitelli, M.; et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: A multicenter pooled analysis of prospective studies. *J. Am. Coll. Cardiol.* **2011**, *57*, 1752–1761. [CrossRef] [PubMed]
2. Siew, E.D.; Ware, L.B.; Gebretsadik, T.; Shintani, A.; Moons, K.G.; Wickersham, N.; Bossert, F.; Ikizler, T.A. Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. *J. Am. Soc. Nephrol.* **2009**, *20*, 1823–1832. [CrossRef] [PubMed]
3. Koyner, J.L.; Vaidya, V.S.; Bennett, M.R.; Ma, Q.; Worcester, E.; Akhter, S.A.; Raman, J.; Jeevanandam, V.; O'Connor, M.F.; Devarajan, P.; et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2010**, *5*, 2154–2165. [CrossRef] [PubMed]
4. Zelt, J.G.E.; Mielniczuk, L.M.; Liu, P.P.; Dupuis, J.Y.; Chih, S.; Akbari, A.; Sun, L.Y. Utility of Novel Cardiorenal Biomarkers in the Prediction and Early Detection of Congestive Kidney Injury Following Cardiac Surgery. *J. Clin. Med.* **2018**, *7*, 540. [CrossRef] [PubMed]

5. Seibert, F.S.; Pagonas, N.; Arndt, R.; Heller, F.; Dragun, D.; Persson, P.; Schmidt-Ott, K.; Zidek, W.; Westhoff, T.H. Calprotectin and neutrophil gelatinase-associated lipocalin in the differentiation of pre-renal and intrinsic acute kidney injury. *Acta Physiol. (Oxf.)* **2013**, *207*, 700–708. [CrossRef]
6. Singer, E.; Elger, A.; Elitok, S.; Kettritz, R.; Nickolas, T.L.; Barasch, J.; Luft, F.C.; Schmidt-Ott, K.M. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int.* **2011**, *80*, 405–414. [CrossRef] [PubMed]
7. Au, V.; Feit, J.; Barasch, J.; Sladen, R.N.; Wagener, G. Urinary neutrophil gelatinase-associated lipocalin (NGAL) distinguishes sustained from transient acute kidney injury after general surgery. *Kidney Int. Rep.* **2016**, *1*, 3–9. [CrossRef] [PubMed]
8. Zhang, A.; Cai, Y.; Wang, P.F.; Qu, J.N.; Luo, Z.C.; Chen, X.D.; Huang, B.; Liu, Y.; Huang, W.Q.; Wu, J.; et al. Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: A systematic review and meta-analysis. *Crit. Care* **2016**, *20*, 41. [CrossRef] [PubMed]
9. Wu, V.C.; Shiao, C.C.; Chi, N.H.; Wang, C.H.; Chueh, S.J.; Liou, H.H.; Spapen, H.D.; Honore, P.M.; Chu, T.S. Outcome Prediction of Acute Kidney Injury Biomarkers at Initiation of Dialysis in Critical Units. *J. Clin. Med.* **2018**, *7*, 202. [CrossRef]
10. Striz, I.; Trebichavsky, I. Calprotectin—A pleiotropic molecule in acute and chronic inflammation. *Physiol. Res.* **2004**, *53*, 245–253.
11. Fujiu, K.; Manabe, I.; Nagai, R. Renal collecting duct epithelial cells regulate inflammation in tubulointerstitial damage in mice. *J. Clin. Investig.* **2011**, *121*, 3425–3441. [CrossRef] [PubMed]
12. Dessing, M.C.; Tammaro, A.; Pulskens, W.P.; Teske, G.J.; Butter, L.M.; Claessen, N.; van Eijk, M.; van der Poll, T.; Vogl, T.; Roth, J.; et al. The calcium-binding protein complex S100A8/A9 has a crucial role in controlling macrophage-mediated renal repair following ischemia/reperfusion. *Kidney Int.* **2015**, *87*, 85–94. [CrossRef] [PubMed]
13. Heller, F.; Frischmann, S.; Grunbaum, M.; Zidek, W.; Westhoff, T.H. Urinary calprotectin and the distinction between prerenal and intrinsic acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 2347–2355. [CrossRef] [PubMed]
14. Seibert, F.S.; Rosenberger, C.; Mathia, S.; Arndt, R.; Arns, W.; Andrea, H.; Pagonas, N.; Bauer, F.; Zidek, W.; Westhoff, T.H. Urinary Calprotectin Differentiates Between Prerenal and Intrinsic Acute Renal Allograft Failure. *Transplantation* **2017**, *101*, 387–394. [CrossRef]
15. Westhoff, J.H.; Fichtner, A.; Waldherr, S.; Pagonas, N.; Seibert, F.S.; Babel, N.; Tonshoff, B.; Bauer, F.; Westhoff, T.H. Urinary biomarkers for the differentiation of prerenal and intrinsic pediatric acute kidney injury. *Pediatr. Nephrol.* **2016**, *31*, 2353–2363. [CrossRef] [PubMed]
16. Westhoff, J.H.; Seibert, F.S.; Waldherr, S.; Bauer, F.; Tonshoff, B.; Fichtner, A.; Westhoff, T.H. Urinary calprotectin, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin for the prediction of adverse outcome in pediatric acute kidney injury. *Eur. J. Pediatr.* **2017**, *176*, 745–755. [CrossRef] [PubMed]
17. Chang, C.H.; Yang, C.H.; Yang, H.Y.; Chen, T.H.; Lin, C.Y.; Chang, S.W.; Chen, Y.T.; Hung, C.C.; Fang, J.T.; Yang, C.W.; et al. Urinary Biomarkers Improve the Diagnosis of Intrinsic Acute Kidney Injury in Coronary Care Units. *Medicine (Baltimore)* **2015**, *94*, e1703. [CrossRef]
18. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A.; Acute Kidney Injury, N. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef]
19. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* **2012**, *2*, 19–36. [CrossRef]
20. Akcan-Arikan, A.; Zappitelli, M.; Loftis, L.L.; Washburn, K.K.; Jefferson, L.S.; Goldstein, S.L. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int.* **2007**, *71*, 1028–1035. [CrossRef]
21. Whiting, P.F.; Rutjes, A.W.; Westwood, M.E.; Mallett, S.; Deeks, J.J.; Reitsma, J.B.; Leeflang, M.M.; Sterne, J.A.; Bossuyt, P.M.; QUADAS-2 Group. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* **2011**, *155*, 529–536. [CrossRef] [PubMed]
22. Arends, L.R.; Hamza, T.H.; van Houwelingen, J.C.; Heijenbrok-Kal, M.H.; Hunink, M.G.; Stijnen, T. Bivariate random effects meta-analysis of ROC curves. *Med. Decis. Making* **2008**, *28*, 621–638. [CrossRef] [PubMed]

23. Zamora, J.; Abraira, V.; Muriel, A.; Khan, K.; Coomarasamy, A. Meta-DiSc: A software for meta-analysis of test accuracy data. *BMC Med. Res. Methodol.* **2006**, *6*, 31. [CrossRef] [PubMed]
24. Basiratnia, M.; Kosimov, M.; Farhadi, P.; Azimi, A.; Hooman, N. Urinary calprotectin as marker to distinguish functional and structural acute kidney injury in pediatric population. *Iran. J. Pediatr.* **2017**, *27*, e9727. [CrossRef]
25. Vogl, T.; Tenbrock, K.; Ludwig, S.; Leukert, N.; Ehrhardt, C.; van Zoelen, M.A.; Nacken, W.; Foell, D.; van der Poll, T.; Sorg, C.; et al. Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat. Med.* **2007**, *13*, 1042–1049. [CrossRef] [PubMed]
26. Ebbing, J.; Seibert, F.S.; Pagonas, N.; Bauer, F.; Miller, K.; Kempkensteffen, C.; Gunzel, K.; Bachmann, A.; Seifert, H.H.; Rentsch, C.A.; et al. Dynamics of Urinary Calprotectin after Renal Ischaemia. *PLoS One* **2016**, *11*, e0146395. [CrossRef] [PubMed]
27. Schrezenmeier, E.V.; Barasch, J.; Budde, K.; Westhoff, T.; Schmidt-Ott, K.M. Biomarkers in acute kidney injury—pathophysiological basis and clinical performance. *Acta Physiol. (Oxf.)* **2017**, *219*, 554–572. [CrossRef]
28. Ebbing, J.; Mathia, S.; Seibert, F.S.; Pagonas, N.; Bauer, F.; Erber, B.; Gunzel, K.; Kilic, E.; Kempkensteffen, C.; Miller, K.; et al. Urinary calprotectin: A new diagnostic marker in urothelial carcinoma of the bladder. *World J. Urol.* **2014**, *32*, 1485–1492. [CrossRef]
29. Langhorst, J.; Elsenbruch, S.; Koelzer, J.; Rueffer, A.; Michalsen, A.; Dobos, G.J. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: Performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am. J. Gastroenterol.* **2008**, *103*, 162–169. [CrossRef]
30. Gisbert, J.P.; McNicholl, A.G. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. *Dig. Liver Dis.* **2009**, *41*, 56–66. [CrossRef]
31. Azimi, A. Could "calprotectin" and "endocan" serve as "Troponin of Nephrologists"? *Med. Hypotheses* **2017**, *99*, 29–34. [CrossRef] [PubMed]
32. Tepel, M.; Borst, C.; Bistrup, C.; Marcussen, N.; Pagonas, N.; Seibert, F.S.; Arndt, R.; Zidek, W.; Westhoff, T.H. Urinary calprotectin and posttransplant renal allograft injury. *PLoS One* **2014**, *9*, e113006. [CrossRef] [PubMed]
33. Ho, J.; Tangri, N.; Komenda, P.; Kaushal, A.; Sood, M.; Brar, R.; Gill, K.; Walker, S.; MacDonald, K.; Hiebert, B.M.; et al. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. *Am. J. Kidney Dis.* **2015**, *66*, 993–1005. [CrossRef] [PubMed]

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Norepinephrine Administration Is Associated with Higher Mortality in Dialysis Requiring Acute Kidney Injury Patients with Septic Shock

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Abstract: (1) Background: Norepinephrine (NE) is the first-line vasoactive agent used in septic shock patients; however, the effect of norepinephrine on dialysis-required septic acute kidney injury (AKI-D) patients is uncertain. (2) Methods: To evaluate the impact of NE on 90-day mortality and renal recovery in septic AKI-D patients, we enrolled patients in intensive care units from 30 hospitals in Taiwan. (3) Results: 372 patients were enrolled and were divided into norepinephrine users and non-users. After adjustment by Inverse probability of treatment weighted (IPTW), there was no significant difference of baseline comorbidities between the two groups. NE users had significantly higher 90-day mortality rate and using NE is a strong predictor of 90-day mortality in the multivariate Cox regression (HR = 1.497, $p = 0.027$) after adjustment. The generalized additive model disclosed norepinephrine alone exerted a dose–dependent effect on 90-day mortality, while other vasoactive agents were not. (4) Conclusion: Using norepinephrine in septic AKI-D patients is associated with higher 90-day mortality and the effect is dose-dependent. Further study to explore the potential mechanism is needed.

Keywords: critical care; vasoactive agents; norepinephrine; sepsis; acute kidney injury; dialysis

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction due to dysregulated host response to infection in accordance to recent Sepsis-3 consensus [1]; it is the leading cause of acute kidney injury (AKI) in critically ill patients in intensive care units (ICU) [2,3]. Using sepsis-3 criteria, analysis of data from a large cohort from 409 hospitals in the USA from 2004–2009 revealed that more than 40% of patients with sepsis also had AKI [4]. Septic AKI is associated with high mortality [3,5,6], extended hospitalization [5], and costly long-term treatment [7].

Septic shock, which is a condition of systemic vasodilatation and arterial hypotension, is now evidenced by a serum lactate level >2 mmol/L and vasopressor requirement to maintain a mean arterial pressure (MAP) of at least 65 mm Hg in the absence of hypovolemia [4]. The use of vasopressors is necessary, especially when fluid resuscitation fails to restore arterial blood pressure; they are still the cornerstone of hypotension management in patients with septic AKI for maintaining adequate organ perfusion [8,9]. Although norepinephrine (NE) is still recommended as the first-line vasoactive agent used in these patients [10], little is known about the impact of NE and other vasoactive agents on the progression of septic AKI.

However, in AKI patients with septic shock, the different effects of NE, and other vasoactive agents has not been surveyed. In this study, we compare the impact of NE and other vasoactive agents on mortality and dialysis dependency in acute kidney injury patients who require dialysis (AKI-D).

2. Material and Methods

2.1. Study Design and Population

The nephrologists and intensivists in Taiwan have appealed for the development of a consortium to unite strength in the field of critical nephrology in Taiwan. The Consortium for Acute Kidney Injury and Renal Diseases (CAKs) and a division focusing on AKI (CAKs-AKI) were launched in the beginning of 2014. This study group has established a multicenter database since 2002 to improve the quality of care and the prognosis of AKI in critically ill patients and then set up a national registry program of AKI to prospectively enroll a large number of dialysis-requiring AKI (AKI-D) patients. This nationwide epidemiology and prognosis of AKI (NEP-AKI-D) requiring dialysis study is the first flagship study of CAKs-AKI, which aims to explore the epidemiology, risk factors, modality, dose, and frequency of renal replacement therapy (RRT), as well as prognoses of the patients with AKI-D, by using the established anonymous nationwide AKI database launched in the beginning of 2014. Up to January of 2016, 30 hospitals have joined this consortium. These hospitals are distributed widely through the four geographical regions (north, middle, south, and east) of Taiwan, and have a 1:1 ratio of medical centers to regional hospitals in each region [11]. In the included hospitals, adult patients fulfilling the diagnosis of septic shock according to the sepsis-3 criteria [1] at initialized RRT in the ICU were prospectively enrolled in the study and followed until hospital discharge from the six seasonally sampled months (October 2014, along with January, April, July, October 2015, and January 2016). Patients who had ever received dialysis treatment or arteriovenous creation before the index hospitalization were excluded. The use of vasoactive agents was assessed, and septic shock patients were separated into NE (NE) users and other inotropic users (NE nonusers). The outcomes of interest were 90-day mortality and recovery from dialysis-dependency after hospital discharge.

2.2. Data Collection and Variable Definitions

Sepsis is defined in Sepsis-3 as life-threatening organ dysfunction, which is known as an acute change in total SOFA score $\geq$2 points, caused by a dysregulated host response to infection. And septic

shock is defined by a serum lactate level >2 mmol/L and persistent hypotension after fluid resuscitation; it also requires vasopressors to maintain MAP >65 mmHg [1,4].

Other organ failure is classified as the following [12,13]: (1) respiratory failure: requiring ventilator support; (2) central nervous system failure: Glasgow Coma Score <9; (3) cardiac failure: signs of low cardiac output with a central venous pressure >12 mmHg; and (4) liver dysfunction: total bilirubin >2.0 mg/dL and international normalized ratio (INR) >1.4 [12].

Disease severity was assessed by using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [14], the Sequential Organ Failure Assessment (SOFA) score [15], and inotropic equivalent (IE) score [16]. We also recorded ICU procedure, infection site, the use of vasoactive agents, and laboratory data at the time of dialysis initiation. We defined "baseline serum creatinine (SCr)" as the latest SCr value during outpatient department (OPD) follow-up for patients who had not visited an OPD within 6 months before index admission. The etiologies of AKI, which included sepsis and other etiologies in the meantime, were documented as well. RRT in this study was performed via a double-lumen catheter. The modality of RRT was chosen according to clinical judgment of the consulting nephrologist and the in-charge intensivist. (Supplemental methods) Because the type and dosage of catecholamines preferred by physicians can vary, this study compared the dosage of catecholamines according to inotropic equivalents (IE, μg/kg/min = dopamine + dobutamine + 100 × epinephrine + 100 × NE + 100 × isoproterenol + 15 × milrinone) in order to compare the severity of heart failure, [16] which was composed of most common used vasoactive agents nowadays. This score had been used in other studies [16,17] for evaluating the severity of cardiovascular dysfunction and it is a valid surrogate outcome measure in pediatric sepsis by testing its association with important short-term outcomes [17–20]. In this study, the vasoactive agents we recorded included dopamine, dobutamine, norepinephrine, epinephrine, isoproterenol, and milrinone. The "other vasoactive agents" were identified as vasoactive agents, except norepinephrine, which was included in the IE score. We evaluated the disease severity before dialysis.

2.3. Statistical Analyses

Continuous variables between groups were compared using the Student t test. The chi-square test was applied for categorical variables with Yates' correction where applicable. The inverse probability of treatment weighting (IPTW) using the propensity score was applied to correct the bias of the two groups in basic characteristics and outcomes [21]. Applying these weights has the effect of creating a pseudo-population with a covariate distribution of the individual treatment groups similar to that of the overall study population. Covariate balance was assessed by examining the magnitude of any residual differences between the treatment groups after applying the weight [22]. Accumulated hazard ratio was modeled by Cox regression models and adjusted for the covariates for the outcomes of interest (Table 1). The significance levels for entry (SLE) and for stay (SLS) were set to 0.15 for being conservative. Then, with the aid of substantive knowledge, the best candidate final logistic regression model was identified manually by dropping the covariates with p value > 0.05 one at a time until all regression coefficients were significantly different from 0 [13,23].

Table 1. Comparison of baseline characteristic and outcomes of septic shock patients with norepinephrine (NE) or other vasoactive agents at dialysis initiation.

Variables	Before IPTW			After IPTW		
	NE Non-User (n = 57)	NE User (n = 315)	p * Value	NE Non-User (n = 57)	NE User (n = 315)	p * Value
Age (year)	65.79 ± 15.22	64.77 ± 15.72	0.637	66.56 ± 14.53	64.66 ± 15.95	0.587
Gender (male)	36 (63.16%)	224 (71.11%)	0.272	21 (31.11%)	91 (29.82%)	0.797
DM	29 (50.88%)	155 (49.21%)	0.886	29 (47.73%)	155 (50.00%)	0.772
CAD	17 (29.82%)	65 (20.63%)	0.163	17 (22.22%)	65 (22.59%)	0.946
CVA	5 (8.77%)	33 (10.48%)	0.816	5 (11.11%)	33 (16.27%)	0.293
CHF						
I	13 (22.81%)	3 (5.26%)	<0.001	13 (31.11%)	3 (41.99%)	0.551
II	12 (21.05%)	153 (48.57%)		12 (28.89%)	153 (22.66%)	
III	12 (21.05%)	68 (21.59%)		12 (26.67%)	68 (16.92%)	
IV	17 (29.82%)	59 (18.73%)		17 (11.11%)	59 (10.57%)	
BUN (mg/dL)	57.59 ± 47.42	50.19 ± 40.14	0.225	51.01 ± 49.62	50.19 ± 39.48	0.700
Lactate(mmol/L)	10.65 ± 9.03	8.77 ± 6.98	0.160	9.14 ± 8	9.62 ± 7.36	0.734
Baseline Cr (mg/dL)	1.62 ± 1.16	1.36 ± 1.02	0.074	1.65 ± 1.18	1.37 ± 1.03	0.254
eGFR (mL/min/1.73 m^2)	57.03 ± 35.28	69.63 ± 46.76	0.048	57.34 ± 36.15	68.12 ± 44.9	0.319
Etiology of AKI						
Shock	29 (50.88%)	242 (76.83%)	<0.001	29 (60.00%)	242 (68.37%)	0.306
CRS	34 (59.65%)	82 (26.03%)	<0.001	34 (35.56%)	82 (33.13%)	0.663
Drug	2 (3.51%)	21 (6.67%)	0.551	2 (8.89%)	21 (5.72%)	0.363
Rhabdomyolysis	4 (7.02%)	43 (13.65%)	0.198	4 (4.44%)	43 (13.86%)	0.054
Pigmentation	0 (0.00%)	14 (4.44%)	0.140	0 (0.00%)	14 (6.02%)	0.092
Hepatorenal	4 (7.02%)	23 (7.30%)	0.999	4 (8.89%)	23 (6.93%)	0.648
Contrast	4 (7.02%)	24 (7.62%)	0.999	4 (11.11%)	24 (10.54%)	0.956
Others	4 (7.02%)	33 (10.48%)	0.630	4 (4.44%)	33 (9.04%)	0.299
Infection site						
Respiratory	22 (38.60%)	157 (49.84%)	0.149	22 (46.67%)	157 (46.08%)	0.999
GU	19 (33.33%)	77 (24.44%)	0.188	19 (20.00%)	77 (22.36%)	0.738
Bacteremia	12 (21.05%)	96 (30.48%)	0.204	12 (26.67%)	96 (28.61%)	0.903
Abdomen	3 (5.26%)	53 (16.83%)	0.026	3 (6.67%)	53 (14.16%)	0.157
Others	6 (10.53%)	39 (12.38%)	0.827	6 (8.89%)	39 (12.95%)	0.435
Disease severity score						
Total IE Score	13.97 ± 14.11	31.99 ± 25.36	<0.001	24.23 ± 23.62	29.17 ± 24.21	0.261
SIRS	2.7 ± 0.89	2.92 ± 0.83	0.080	2.87 ± 0.95	2.87 ± 0.81	0.822
SOFA	14.02 ± 2.66	15.6 ± 2.96	<0.001	15.42 ± 2.69	15.28 ± 2.99	0.663
qSOFA	2.3 ± 0.46	2.37 ± 0.48	0.311	2.25 ± 0.45	2.35 ± 0.48	0.300
APACHEII	25.79 ± 7.57	27.27 ± 6.46	0.289	26.51 ± 6.74	27.21 ± 6.49	0.851
Outcome						
ICU day	28.65 ± 38.07	17.22 ± 17.88	0.014	30.94 ± 37.27	17.58 ± 18.32	0.204
Length of hospital dialysis	26.07 ± 36.97	12.68 ± 19.19	<0.001	18.67 ± 27.78	12.85 ± 19.47	0.012
Hospital Mortality	41 (71.93%)	252 (80.00%)	0.217	41 (75.56%)	252 (81.02%)	0.330
90-day outcome			0.142			0.753
Mortality	42 (73.68%)	260 (82.54%)		42 (76.09%)	260 (83.13%)	
Recovery from dialysis	13 (22.81%)	52 (16.51%)		13 (21.74%)	52 (15.66%)	
Dialysis-dependent	2 (3.51%)	3 (0.95%)		2 (2.17%)	3 (1.20%)	

Abbreviations: AKI: acute kidney injury; APACHEII: acute physiology and chronic health evaluation; BUN: blood urea nitrogen; CAD: coronary artery disease; CHF: congestive heart failure; Cr: creatinine; CRS: cardiorenal syndrome; CVA: cerebrovascular accident; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; GU: genitourinary; IABP: intra-aortic balloon pump; ICU: intensive care unit; IE: inotropic equivalent; IHD: intermittent dialysis; IPTW: inverse probability of treatment weighting; qSOFA: quick sequential organ failure assessment; SOFA: sequential organ failure assessment; SIRS: systemic inflammatory response syndrome. * All statistics were two-tailed, and significance was accepted for $p < 0.05$.

Forest plot was constructed for odds ratio of NE use (vs. other vasoactive agents) on 90-day mortality according to prior comorbidities and clinical conditions. The generalized additive model was used to analyze the dose-response relationship between vasoactive agents and the 90-day mortality [24,25]. Because of the high mortality rate in sepsis patients after AKI-D, competing risk regression was also performed to show the risks for dialysis dependence using the Fine and Gray model considering the subdistribution hazard [26,27].

We used R software version 3.2.2 (Free Software Foundation, Inc., Vienna, Austria) for the time-varying Cox model and Stata/MP version 14 (Stata Corporation, College Station, TX, USA) for the competing risk analysis. Two-sided p values < 0.05 were considered statistically significant.

2.4. Ethics Approval and Consent to Participate

Approval of this prospective multi-center study follows the regulations of the National Research Program for Biopharmaceuticals (NRPB)-Institutional Review Board (IRB). All clinical trial consortiums have to fill in the application forms on the official website of the NRPB-IRB. Written t informed consent was obtained from all participants before inclusion. (Approval No. NRPB2014050014).

3. Results

3.1. Baseline Characteristics of the Study Cohort

A total of 372 AKI-D patients fulfilled the criteria of septic shock at initialization of dialysis and 315 patients were NE users. The characteristics of patients are listed in Table 1. The mean SOFA score was 15.42 ± 2.69 in the non-user group and 15.28 ± 2.99 in the user group. The APACHE II score was 26.51 ± 6.74 in the user group and 27.21 ± 6.49 in the non-user group. The mean age was 65.8 ± 15.2 years in the non-NE user group and 64.8 ± 15.7 years in the NE user group. After adjustment by IPTW (Table 1), there was no significant difference of baseline comorbidities between the two groups. The biochemical data and ICU procedure were similar. There was the sum of 263 (70.7%) patients who received surgery during admission. Regarding disease severity, there was no significant difference in APACHEII score (25.79 ± 7.57 in NE non-user and 27.27 ± 6.46 in NE user, p = 0.289) between the two groups initially, and other scoring systems including IE score and SOFA (15.42 ± 2.69 in NE non-user and 15.28 ± 2.99 in NE user, p = 0.663) were similar after adjustment. We record the etiology of acute kidney injury included with/without cardiorenal syndrome, drug, rhabdomyolysis, pigmentation (pigment nephropathy), hepatorenal syndrome, and contrast. And there was no significant difference in the etiologies of AKI between two groups. Besides, no significant difference was noted in major infection site which included respiratory tract, genitourinary tract, blood stream, or abdomen between NE user and non-user. Oliguria (81.9%) is the leading cause for RRT, followed by fluid overloaded (67.8%). The indications for RRT were similar except for oliguria (p = 0.009). Regarding the RRT modality, NE users tended to receive CVVH, and SLEDD (p = 0.034). The detail of these baseline characteristics is in the Supplementary Table S1.

3.2. 90-Day Mortality in Septic-Shock-Related AKI-D

A total of 302 (81.2%) patients died within 90 days of hospital discharge (Table 1) and 260 (92.54%) patients were NE users and 42 (73.68%) were NE non-users. The median ICU stay for NE users was similar to that of NE non-users (p = 0.204). The number of dialysis days of the NE non-user groups was larger than that of the NE user group (user vs. non-user = 12.9 ± 19.5 vs. 18.7 ± 27.8 days, p = 0.012).

Table 2 showed the independent risk predictors for 90-day mortality analyzed by multivariate Cox proportional hazards model incorporated with IPTW. After adjustment by age, sex, comorbidities, kidney function, APACHE II score, indication for dialysis, and dialysis modalities, the use of NE was an independent risk for 90-day mortality (hazard ratio = 1.504, p = 0.026).

Table 2. Cox regression for 90-day m4.ortality in septic shock patients with NE or other vasoactive agents at dialysis initiation *.

Variables	HR	Lower 95% CI	95% CI	*p*
NE user (yes)	1.497	1.046	2.141	0.027
Hepatorenal syndrome (yes)	1.992	1.320	3.007	0.001
Cr (mg/dL)	0.840	0.776	0.910	<0.001
BUN (mg/dL)	1.008	1.004	1.012	<0.001
APACHEII Score	1.042	1.030	1.836	<0.001

Concordance = 0.645; R square = 0.152; APACHEII: acute physiology and chronic health evaluation; BUN: blood urea nitrogen; CHF: congestive heart failure; CI: confidence interval; Cr.: creatinine; HR: hazard ratio; NE: norepinephrine; NYHA: New York heart association; * Cox proportional hazard model adjusted with IPTW.

We further analyzed the outcomes of the use of NE; subgroup analysis using forest plots was performed to calculate IPTW adjusted HRs (HRs) of 90-day mortality. The detrimental effects of NE were consistent across the subgroups stratified by respiratory tract infection, congestive heart failure, diabetes mellitus, BUN with more than 64 mg/dL, and patients who did not have cerebrovascular disease (Figure 1).

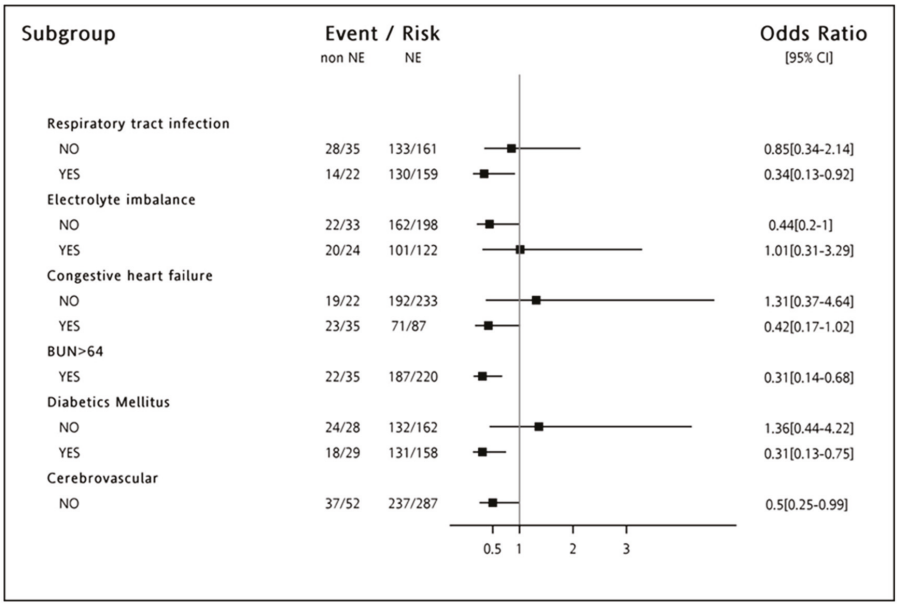

Figure 1. Odds ratio of Norepinephrine user on the development of 90 days mortality. Odds ratio of Norepinephrine users (vs. other vasoactive agents) on the development of 90-day mortality, according to demographics in septic shock patients at dialysis initiation. Patients those who had respiratory tract infection, congestive heart failure, diabetes mellitus, BUN with more than 64 mg/dL, and did not have cerebrovascular disease tended to have a higher 90-day mortality while norepinephrine (NE) was prescribed.

3.3. The Dose-Response Relationship between NE and 90-Day Mortality

The quantity of NE was plotted against the log odds of predicting 90-day mortality by using generalized additive mode (GAM) after adjusting the risk factors in the final model (Figure 2). We separated the use of vasoactive agents into 3 groups by measurement of IE score which included vasoactive agents mentioned above (Figure 2A), NE alone (Figure 2B), and vasoactive agents other

than NE (Figure 2C). The dose of total vasoactive agents and those without NE did not show a dose-dependent effect relating to 90 day-mortality. However, NE equivalence showed a positive relationship to 90-day mortality. In terms of the risks of 90-day mortality, the GAM plot disclosed with NE alone exerted a significant disadvantage when compared to other vasoactive agents; it was dose-dependent (Figure 2).

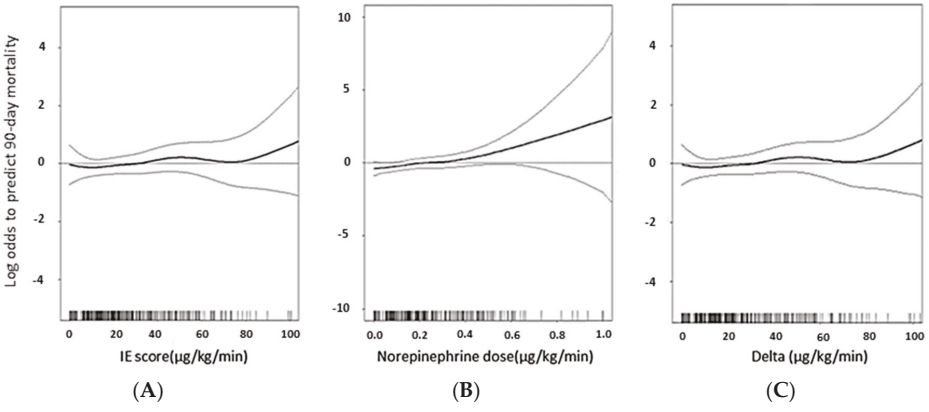

Figure 2. Generalized additive mode (GAM) plot of the probability of 90-day mortality regarding the dose equivalent of inotropes. The model incorporates subject-specific (longitudinal) random effects, expressed as the logarithm of the odd (logit). The probability of mortality was constructed with the equivalent dose of (**A**) inotropes (**B**) NE (**C**) inotropic dose deduct NE dose and was centered to have an average of zero over the range of the data as constructed with the GAM. IE: inotropic equivalent.

3.4. Dialysis Dependency in Septic Shock Patients with or without NE

In the evaluation of the relation between the use of NE and dialysis dependency, we conducted a competing-risk regression model which took mortality as a competing risk (Figure 3). It revealed that the use of NE was not associated with the cumulative proportions of weaning from dialysis (p = 0.651).

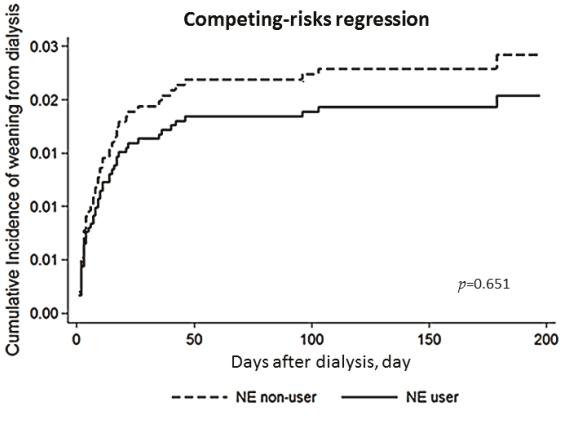

Figure 3. Cox proportional plot depict cumulative proportions of renal recovery between NE user and non-user groups. There was no significant difference (p = 0.651) in weaning from dialysis between NE user group and non-user group when taking mortality as a competing risk. BUN: blood urea nitrogen; GAM: generalized additive model; NE: norepinephrine.

4. Discussion

4.1. Main Finding

In this multi-center, observational study of AKI-D patients with septic shock at initialization of dialysis, we found that 81.2% of patients died within 90 days of hospital discharge. Our report first showed the high mortality of AKI-D patients with septic shock according to Sepsis-3 criteria. The use of NE was associated with a higher 90-day mortality rate than other vasoactive agents and that the detrimental effect is dose-dependence. We applied inverse probability of treatment weighting (IPTW), to minimize the effect of confounding in observational study [28]. And importantly, the risk of NE on 90-day mortality is constant after adjusting for the bias of baseline characteristics by using inverse probability of treatment weighting.

4.2. The Use of NE in AKI-D Patients with Septic Shock

In the general population, the use of NE is the first-line choice of vasoactive agents to restore organ perfusion and maintain the blood pressure in septic shock patients [29]. The influence of the use of NE on AKI-D patients with septic shock is still warranted.

Chou et al [30]. conducted a retrospective study which prescribed a high-dose of vasopressor used before the initiation of continuous renal replacement therapy (CRRT). A high dose of NE is associated with higher mortality by way of the catecholamine effect on the cardiovascular system [31]. In a multi-center, double-blind, randomized, controlled trial, vasopressin reduce progression to mortality in early stage AKI patients when compared to NE [32].

Thus, differences between vasopressin and nor epinephrine-treated patient outcomes may be due to the beneficial effects of vasopressin or, alternatively, due to reduction in the detrimental effects of norepinephrine. This result is also consistent with the primary subgroup analysis of the VASST study in which vasopressin treatment was associated with decreased mortality in patients who had less severe shock and not in patients who had more severe shock [33].

In a recent prospective cohort study [34], Passos et al. tried to establish a scoring system to predict 7-day mortality in septic patients requiring CRRT. The use of norepinephrine was recognized as one of the predictors in the study based on the magnitude of regression coefficients in the multivariate analysis. One multi-center, prospective, observational study which enrolled 897 patients with community-acquiring sepsis from seventeen Portuguese ICUs evaluated the impact of vasopressor on mortality. The study reported that the use of NE, either used as single agents or in combination, was associated with worse outcome due to increased cardiovascular events when compared to dopamine in community-acquired sepsis patients during ICU stay [35].

Adequate fluid resuscitation is recommended and it is closely associated with blood pressure maintenance with the ultimate aim of maintaining tissue perfusion and oxygenation [36]. However, insufficiency of fluid resuscitation insufficiency may occur in oliguric septic AKI-D patients because clinician are often anxious to aggressive hydration related fluid overload. One retrospective study enrolled dialysis patients who had sepsis revealed severely under resuscitated and it might contribute to the patients' mortality [37]. To maintain the hemodynamic status, even in dialysis patients, clinicians should add sufficient fluid supplement before adding more vasoactive agents [37]. In addition to fluid resuscitation, antimicrobials therapy should be initiated as soon as possible when the diagnosis of sepsis and septic shock is established [10].

In our study we found worse outcomes when using NE in AKI-D patients with septic shock when compared to other vasoactive agents, even after adjustment for the disease severity. Besides, the disease severity was more severe in our study population in accordance with SOFA score and APACHEII score which might lead to higher mortality rate in our study. In previous study, the highest SOFA scores, higher than 11, were associated with a mortality rate greater than 80% [38]. The mean SOFA score was 15.6–2.96 in the NE user group and 14.02–2.66 in the NE non-user group in our study. Besides, almost 80% patients were from a medical center that assembled very ill patients in

our country. Septic shock patients who were not candidates for NE could differ from patients who were candidates, and it will be noted as an indication bias in this observational study. However, the disease severity score, the dose of inotropic equivalent, and even the level of serum lactate, in terms of the severity of septic shock, were similar between the two groups. Therefore, the indication bias, if any, will be trivial in this observational study. NE was known as a more potent vasopressor than dopamine and had favorable outcome on mortality in earlier studies [39]. However, one current large randomized trial—the SOAP II trial, demonstrated that there was no significant difference-in 28-day mortality between the use of NE and dopamine in patients with shock. The result was similar in septic shock and hypovolemic shock, except in cardiogenic shock when the researchers conducted subgroup analysis [40]. Recently, the NE as Initial Therapy in Septic Shock (VANISH) trial [41] reported that AKI occurred in about 45% of patients, and AKI requiring RRT developed in 30% of patients. Although the clinical use of inotropic agents is common in patients with septic AKI requiring dialysis, little was known about which inotropic agent is preferable in these patients. In light of our study, the use of NE in septic AKI requiring dialysis was associated with higher 90-day mortality, and the detrimental effect was dose-dependent. Further study is warranted to reconsider the early use of NE in AKI-D patients with septic shock.

4.3. NE and Renal Recovery

In general, the infusion of NE deceases the renal blood flow [42] and renal vasoconstriction, which may lead to reversible AKI [43]. In light of our study, the vasopressin and septic shock trial (VASST) did not show any difference in the incidence of AKI or need for RRT with the use of vasopressin or NE [33].

However, in acute endotoxemic status, the infusion of NE appears to improve renal blood flow, and had favorable effects on renal function in septic patients. One recent animal study [44] tried to evaluate the NE effects on the kidney in septic AKI ovine, and it found that medullary hypoxia and ischemia were exacerbated after NE infusion. In our study, we showed that the use of NE could not be the crucial factor for recovery from dialysis.

4.4. Study Limitation

This is the first study evaluating NE in critical AKI-D patients with septic shock according to the sepsis-3 criteria from a nationwide cohort. We followed up patients with septic AKI on dialysis to 90 days after hospital discharge, and further evaluated the recovery from AKI promptly. However, our study still had some limitations. First, our study did not evaluate the catecholamine-sparing effect of NE, in addition to the different patient population; and we did not evaluate the vascular response to NE under critical dialysis. Secondly, the indication for the use of NE or other vasoactive agents is not standardized. However, due to the difficulty in the randomness of enrolling patients with septic shock, an observational study could provide valuable information. Third, there could be a selection bias in choosing vasoactive agents due to current guidelines showed that norepinephrine is the first choice for septic shock and low dose dopamine for prophylactic use is no longer recommended. Last but not the least, we did not record pre-dialysis data of hemodynamic status, such as central venous pressure or volume of fluid resuscitation completely. Therefore, we could not evaluate the impact of fluid status when dialysis-required septic AKI developed and the association with the vasoactive agent usage to mortality.

5. Conclusions

The use of NE in septic AKI patients at the initialization of dialysis is associated with a higher 90-day mortality after we adjusted for severity by IPTW compared to other vasoactive agents, and the detrimental effect was dose-dependent. Therefore, consideration of early treatment to block septic AKI vicious cycle to stabilize the hemodynamic status should nonetheless precede increased doses of

norepinephrine at dialysis initiation. Further study to explore the potential and possible mechanism is needed.

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References

1. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 801–810. [CrossRef] [PubMed]
2. Hoste, E.A.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef] [PubMed]
3. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef] [PubMed]

4. Rhee, C.; Dantes, R.; Epstein, L.; Murphy, D.J.; Seymour, C.W.; Iwashyna, T.J.; Kadri, S.S.; Angus, D.C.; Danner, R.L.; Fiore, A.E.; et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs. Claims Data, 2009-2014. *JAMA* **2017**, *318*, 1241–1249. [CrossRef] [PubMed]
5. Bagshaw, S.M.; George, C.; Bellomo, R. Committee ADM: Early acute kidney injury and sepsis: A multicentre evaluation. *Crit. Care* **2008**, *12*, R47. [CrossRef] [PubMed]
6. Thakar, C.V.; Christianson, A.; Freyberg, R.; Almenoff, P.; Render, M.L. Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study. *Crit. Care Med.* **2009**, *37*, 2552–2558. [CrossRef] [PubMed]
7. Bagshaw, S.M.; Uchino, S.; Bellomo, R.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; Gibney, N.; et al. Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 431–439. [CrossRef] [PubMed]
8. Chawla, L.S.; Busse, L.; Brasha-Mitchell, E.; Davison, D.; Honiq, J.; Alotaibi, Z.; Seneff, M.G. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): A pilot study. *Crit. Care* **2014**, *18*, 534. [CrossRef] [PubMed]
9. Myburgh, J.A.; Higgins, A.; Jovanovska, A.; Lipman, J.; Ramakrishnan, N.; Santamaria, J. Investigators CATS: A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med.* **2008**, *34*, 2226–2234. [CrossRef] [PubMed]
10. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit. Care Med.* **2017**, *45*, 486–552. [CrossRef] [PubMed]
11. Shiao, C.C.; Wu, P.C.; Wu, V.C.; Lin, J.H.; Pan, H.C.; Yang, Y.F.; Lai, T.S.; Huang, T.M.; Wu, C.H.; Yang, W.S.; et al. Nationwide epidemiology and prognosis of dialysis-requiring acute kidney injury (NEP-AKI-D) study: Design and methods. *Nephrology (Carlton)* **2016**, *21*, 758–764. [CrossRef] [PubMed]
12. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.W.; Lin, Y.F.; Shiao, C.C.; Chen, Y.M.; Chen, Y.S.; Tsai, P.R.; Hu, F.C.; et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive Care Med.* **2008**, *34*, 101–108. [CrossRef] [PubMed]
13. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.S.; Chen, Y.W.; Chen, Y.M.; Hu, F.C.; Lin, Y.H.; Tsai, P.R.; Wu, K.D. Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: Effect on postoperative outcomes. *J. Am. Coll. Surg.* **2007**, *205*, 266–276. [CrossRef] [PubMed]
14. Knaus, W.A.; Draper, E.A.; Wagner, D.P.; Zimmerman, J.E. APACHE II: A severity of disease classification system. *Crit. Care Med.* **1985**, *13*, 818–829. [CrossRef] [PubMed]
15. Vincent, J.L.; Moreno, R.; Takala, J.; Willatts, S.; De Mendonca, A.; Bruining, H.; Reinhart, C.K.; Suter, P.M.; Thijs, L.G. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* **1996**, *22*, 707–710. [CrossRef] [PubMed]
16. Chen, Y.S.; Ko, W.J.; Lin, F.Y.; Huang, S.C.; Chou, T.F.; Chou, N.K.; Hsu, R.B.; Wang, S.S.; Chu, S.H. Preliminary result of an algorithm to select proper ventricular assist devices for high-risk patients with extracorporeal membrane oxygenation support. *J. Heart Lung Transplant.* **2001**, *20*, 850–857. [CrossRef]
17. Gaies, M.G.; Jeffries, H.E.; Niebler, R.A.; Pasquali, S.K.; Donohue, J.E.; Yu, S.; Gall, C.; Rice, T.B.; Thiagarajan, R.R. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: An analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. *Pediatr. Crit. Care Med.* **2014**, *15*, 529–537. [CrossRef] [PubMed]
18. Gaies, M.G.; Gurney, J.G.; Yen, A.H.; Napoli, M.L.; Gajarski, R.J.; Ohye, R.G.; Charpie, J.R.; Hirsch, J.C. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr. Crit. Care Med.* **2010**, *11*, 234–238. [CrossRef] [PubMed]
19. Kumar, M.; Sharma, R.; Sethi, S.K.; Bazaz, S.; Sharma, P.; Bhan, A.; Kher, V. Vasoactive Inotrope Score as a tool for clinical care in children post cardiac surgery. *Indian J. Crit. Care Med.* **2014**, *18*, 653–658. [PubMed]
20. McIntosh, A.M.; Tong, S.; Deakyne, S.J.; Davidson, J.A.; Scott, H.F. Validation of the Vasoactive-Inotropic Score in Pediatric Sepsis. *Pediatr. Crit. Care Med.* **2017**, *18*, 750–757. [CrossRef] [PubMed]
21. Wu, V.C.; Hu, Y.H.; Wu, C.H.; Kao, C.C.; Wang, C.Y.; Yang, W.S.; Lee, H.H.; Chang, Y.S.; Lin, Y.H.; Wang, S.M.; et al. Administrative data on diagnosis and mineralocorticoid receptor antagonist prescription identified patients with primary aldosteronism in Taiwan. *J. Clin. Epidemiol.* **2014**, *67*, 1139–1149. [CrossRef] [PubMed]

22. Roy, J.; Lum, K.J.; Daniels, M.J. A Bayesian nonparametric approach to marginal structural models for point treatments and a continuous or survival outcome. *Biostatistics* **2017**, *18*, 32–47. [CrossRef] [PubMed]
23. Wu, V.C.; Young, G.H.; Huang, P.H.; Lo, S.C.; Wang, K.C.; Sun, C.Y.; Liang, C.J.; Huang, T.M.; Chen, J.H.; Chang, F.C.; et al. In acute kidney injury, indoxyl sulfate impairs human endothelial progenitor cells: Modulation by statin. *Angiogenesis* **2013**, *16*, 609–624. [CrossRef] [PubMed]
24. Wu, V.C.; Huang, T.M.; Shiao, C.C.; Lai, C.F.; Tsai, P.R.; Wang, W.J.; Huang, H.Y.; Wang, K.C.; Ko, W.J.; Wu, K.D.; et al. The hemodynamic effects during sustained low-efficiency dialysis versus continuous veno-venous hemofiltration for uremic patients with brain hemorrhage: A crossover study. *J. Neurosurg.* **2013**, *119*, 1288–1295. [CrossRef] [PubMed]
25. Wu, C.H.; Yang, Y.W.; Hung, S.C.; Tsai, Y.C.; Hu, Y.H.; Lin, Y.H.; Chu, T.S.; Wu, K.D.; Wu, V.C. Effect of Treatment on Body Fluid in Patients with Unilateral Aldosterone Producing Adenoma: Adrenalectomy versus Spironolactone. *Sci. Rep.* **2015**, *5*, 15297. [CrossRef] [PubMed]
26. Wu, V.C.; Chang, C.H.; Wang, C.Y.; Lin, Y.H.; Kao, T.W.; Lin, P.C.; Chu, T.S.; Chang, Y.S.; Chen, L.; Wu, K.D.; et al. Risk of Fracture in Primary Aldosteronism: A Population-Based Cohort Study. *J. Bone Miner. Res.* **2017**, *32*, 743–752. [CrossRef] [PubMed]
27. Wu, V.C.; Chueh, S.J.; Chen, L.; Chang, C.H.; Hu, Y.H.; Lin, Y.H.; Wu, K.D.; Yang, W.S.; Group, T.S. Risk of new-onset diabetes mellitus in primary aldosteronism: A population study over 5 years. *J. Hypertens.* **2017**, *35*, 1698–1708. [CrossRef] [PubMed]
28. Austin, P.C. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat. Med.* **2016**, *35*, 5642–5655. [CrossRef] [PubMed]
29. Dellinger, R.P.; Levy, M.M.; Rhodes, A.; Annane, D.; Gerlach, H.; Opal, S.M.; Sevransky, J.E.; Sprung, C.L.; Douglas, I.S.; Jaeschke, R.; et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* **2013**, *39*, 165–228. [CrossRef] [PubMed]
30. Chou, C.Y.; Yeh, H.C.; Chen, W.; Liu, J.H.; Lin, H.H.; Liu, Y.L.; Yang, Y.F.; Wang, S.M.; Huang, C.C. Norepinephrine and hospital mortality in critically ill patients undergoing continuous renal replacement therapy. *Artif. Organs* **2011**, *35*, E11–E17. [CrossRef] [PubMed]
31. Levy, B.; Dusang, B.; Annane, D.; Gibot, S.; Bollaert, P.E. College Interregional des Reanimateurs du N-E: Cardiovascular response to dopamine and early prediction of outcome in septic shock: A prospective multiple-center study. *Crit. Care Med.* **2005**, *33*, 2172–2177. [CrossRef] [PubMed]
32. Gordon, A.C.; Russell, J.A.; Walley, K.R.; Singer, J.; Ayers, D.; Storms, M.M.; Holmes, C.L.; Hebert, P.C.; Cooper, D.J.; Mehta, S.; et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med.* **2010**, *36*, 83–91. [CrossRef] [PubMed]
33. Russell, J.A.; Walley, K.R.; Singer, J.; Gordon, A.C.; Hebert, P.C.; Cooper, D.J.; Holmes, C.L.; Mehta, S.; Granton, J.T.; Storms, M.M.; et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N. Engl. J. Med.* **2008**, *358*, 877–887. [CrossRef] [PubMed]
34. da Hora Passos, R.; Ramos, J.G.; Mendonca, E.J.; Miranda, E.A.; Dutra, F.R.; Coelho, M.F.; Pedroza, A.C.; Correia, L.C.; Batista, P.B.; Macedo, E.; et al. A clinical score to predict mortality in septic acute kidney injury patients requiring continuous renal replacement therapy: The HELENICC score. *BMC Anesthesiol.* **2017**, *17*, 21. [CrossRef] [PubMed]
35. Povoa, P.R.; Carneiro, A.H.; Ribeiro, O.S.; Pereira, A.C. Portuguese Community-Acquired Sepsis Study G: Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Crit. Care Med.* **2009**, *37*, 410–416. [CrossRef] [PubMed]
36. Vincent, J.L.; Gerlach, H. Fluid resuscitation in severe sepsis and septic shock: An evidence-based review. *Crit. Care Med.* **2004**, *32* (Suppl. 11), S451–S454. [CrossRef] [PubMed]
37. Abou Dagher, G.; Harmouche, E.; Jabbour, E.; Bachir, R.; Zebian, D.; Bou Chebl, R. Sepsis in hemodialysis patients. *BMC Emerg. Med.* **2015**, *15*, 30. [CrossRef] [PubMed]
38. Ferreira, F.L.; Bota, D.P.; Bross, A.; Melot, C.; Vincent, J.L. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* **2001**, *286*, 1754–1758. [CrossRef] [PubMed]
39. Martin, C.; Viviand, X.; Leone, M.; Thirion, X. Effect of norepinephrine on the outcome of septic shock. *Crit. Care Med.* **2000**, *28*, 2758–2765. [CrossRef] [PubMed]
40. De Backer, D.; Biston, P.; Devriendt, J.; Madl, C.; Chochrad, D.; Aldecoa, C.; Brasseur, A.; Defrance, P.; Gottignies, P.; Vincent, J.L.; et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N. Engl. J. Med.* **2010**, *362*, 779–789. [CrossRef] [PubMed]

41. Gordon, A.C.; Mason, A.J.; Thirunavukkarasu, N.; Perkins, G.D.; Cecconi, M.; Cepkova, M.; Pogson, D.G.; Aya, H.D.; Anjum, A.; Frazier, G.J.; et al. Effect of Early Vasopressin vs. Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA* **2016**, *316*, 509–518. [CrossRef] [PubMed]
42. Richer, M.; Robert, S.; Lebel, M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. *Crit. Care Med.* **1996**, *24*, 1150–1156. [CrossRef] [PubMed]
43. Cronin, R.E.; Erickson, A.M.; de Torrente, A.; McDonald, K.M.; Schrier, R.W. Norepinephrine-induced acute renal failure: A reversible ischemic model of acute renal failure. *Kidney Int.* **1978**, *14*, 187–190. [CrossRef] [PubMed]
44. Lankadeva, Y.R.; Kosaka, J.; Evans, R.G.; Bailey, S.R.; Bellomo, R.; May, C.N. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int.* **2016**, *90*, 100–108. [CrossRef] [PubMed]

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Safety Lapses Prior to Initiation of Hemodialysis for Acute Kidney Injury in Hospitalized Patients: A Patient Safety Initiative

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Abstract: Background: Safety lapses in hospitalized patients with acute kidney injury (AKI) may lead to hemodialysis (HD) being required before renal recovery might have otherwise occurred. We sought to identify safety lapses that, if prevented, could reduce the need for unnecessary HD after AKI; **Methods:** We conducted a retrospective observational study that included consecutive patients treated with HD for AKI at a large, tertiary academic center between 1 September 2015 and 31 August 2016. Exposures of interest were pre-specified iatrogenic processes that could contribute to the need for HD after AKI, such as nephrotoxic medication or potassium supplement administration. Other outcomes included time from AKI diagnosis to initial management steps, including Nephrology referral; **Results:** After screening 344 charts, 80 patients were included for full chart review, and 264 were excluded because they required HD within 72 h of admission, were deemed to have progression to end-stage kidney disease (ESKD), or required other renal replacement therapy (RRT) modalities in critical care settings such as continuous renal replacement therapy (CRRT) or sustained low efficiency dialysis (SLED). Multiple safety lapses were identified. Sixteen patients (20%) received an angiotensin converting enzyme inhibitor or angiotensin receptor blocker after AKI onset. Of 35 patients with an eventual diagnosis of pre-renal AKI due to hypovolemia, only 29 (83%) received a fluid bolus within 24 h. For 28 patients with hyperkalemia as an indication for starting HD, six (21%) had received a medication associated with hyperkalemia and 13 (46%) did not have a low potassium diet ordered. Nephrology consultation occurred after a median (IQR) time after AKI onset of 3.0 (1.0–5.7) days; **Conclusions:** Although the majority of patients had multiple indications for the initiation of HD for AKI, we identified many safety lapses related to the diagnosis and management of patients with AKI. We cannot conclude that HD initiation was avoidable, but, improving safety lapses may delay the need for HD initiation, thereby allowing more time for renal recovery. Thus, development of automated processes not only to identify AKI at an early stage but also to guide appropriate AKI management may improve renal recovery rates.

Keywords: acute kidney injury; patient safety; hemodialysis

1. Introduction

Acute kidney injury (AKI) is a frequent and serious complication of hospitalization, affecting up to 20% of hospitalized patients, and conferring a four-fold increased risk of in-hospital mortality [1]. In-hospital mortality increases with increasing severity of AKI, with the highest mortality observed

in patients that require renal replacement therapy (RRT) [2,3]. Systematic reviews have shown that AKI is associated with long term consequences including increased mortality, chronic kidney disease (CKD), and progression to end-stage kidney disease (ESKD) [4,5]. Although the use of RRT for AKI is life-sustaining when urgently indicated, it is costly [6,7] and may be harmful for renal recovery [8].

Currently, there are no effective pharmacological interventions for AKI, [9] and management is aimed at limiting further kidney injury and reducing the likelihood that acute indications for RRT will develop prior to renal recovery [8]. The progression of AKI may be limited by timely diagnostic workup if worsening renal injury (and the consequent need for RRT) is prevented by limiting the use of nephrotoxic medications [10], and iodinated contrast dye [11], although there is debate in the literature surrounding the association between intravenous iodinated contrast and AKI in hospitalized patients [12]. Limiting excess dietary or intravenous potassium may increase the likelihood of recovery prior to hyperkalemia becoming an indication for RRT, however there is a paucity of data in this area. Nonetheless, there is some evidence that safety lapses in the care of hospitalized patients with AKI are frequent [13].

Early identification of AKI in hospitalized patients using electronic alerts has the potential to reduce the likelihood of AKI progression and need for RRT [14–16], however, this has not been supported by the literature up to now. A large single-center randomized controlled trial assessing automated electronic clinician notifications did not reduce death or need for RRT [17]. In addition, a recent systematic review of six studies of electronic alerts for AKI found no improvement in survival or need for RRT, with variable impact on processes of care [18]. The lack of efficacy of these early alerts may relate to AKI being a syndrome of many causes that require different interventions. Another issue is that alerts may not trigger significant changes in care processes, such as medication review with cessation of nephrotoxic medications, or IV fluid administration [19]. Consequently, to improve outcomes and reduce the need for unnecessary RRT, it may be first necessary to identify the processes that are most likely to lead to iatrogenic harm.

As such, we undertook a study to characterize safety lapses that might have contributed to the need for potentially avoidable hemodialysis (HD) for AKI patients at our center. Given that patients who initiate forms of RRT for AKI other than HD (e.g., continuous renal replacement therapy (CRRT) or slow low-efficiency dialysis (SLED)/prolonged intermittent RRT (PIRRT)) typically do so in the intensive care unit (ICU) setting due to hemodynamic instability, we sought to focus on more stable patients initiating HD for AKI with respect to their preceding exposure to nephrotoxic oral medications and incorrect dietary orders (while still including patients if their HD for AKI was ultimately initiated in the ICU setting).

2. Experimental Section

2.1. Study Design and Setting

We conducted a retrospective chart review of patients who started treatment with HD for AKI while hospitalized at The Ottawa Hospital (TOH) between 1 September 2015 and 31 August 2016. TOH is a tertiary care academic medical center with 1061 inpatient beds that services a population of approximately 1.2 million people across Eastern Ontario, Canada [20]. TOH has over 50,000 patient admissions annually at three campuses (Ottawa General Hospital; Ottawa Civic Hospital and University of Ottawa Heart Institute) [20]. At the time of this study, TOH did not have computer physician order entry (CPOE) for medications or investigations other than imaging studies.

Prior to the start of the study, approval for waived patient consent was obtained from TOH research ethics board.

2.2. Patient Population, Inclusion and Exclusion Criteria

Patients were identified retrospectively for screening using consecutive nephrology billing codes that had been submitted for new, inpatient hemodialysis starts.

Inclusion criteria were: hospitalized patients; aged 18 years or older; with AKI (as defined below); who required initiation of RRT in the form of intermittent HD. We excluded patients who: required HD within 72 h of admission (as such cases were considered to be more likely reflective of severe AKI at the outset of hospitalization in which RRT was less likely to be avoidable); patients with ESKD; RRT started for a reason other than AKI (e.g., intoxication, hypothermia); or if RRT was started using a modality other than HD (i.e., CRRT or SLED). For patients re-admitted to hospital requiring HD on re-admission, we gathered data from both admissions to capture the initial AKI that did not resolve.

2.3. Data Sources and Data Collection

Data was collected through a retrospective chart review of electronic medical records. Electronic medical records included relevant investigations (labs and imaging), as well as consultation notes, scanned progress notes, physician orders and medication administration records.

Two investigators (AD, KZ) independently screened charts then reviewed the electronic charts of included patients and collected data on their baseline demographics, co-morbidities and iatrogenic processes. All charts were reviewed by both investigators and disagreements between the two primary chart reviewers on aspects of data collection were resolved by a third investigator (E.C.) for consistency of data collection.

Data was extracted from the inpatient chart, and recorded on data collection forms before being entered into an Excel database. The onset of AKI was determined as the first instance that patients fulfilled the serum creatinine (SCr)-based Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI, which corresponds to a rise in SCr of $\geq$1.5 times baseline over 7 days or an increase in SCr by at least 26.5 μmol/L [21] within 48 h. Baseline SCr was calculated using the lowest available outpatient SCr within 12 months [22]. When none was available, the first SCr following hospitalization was used [22].

2.4. Outcomes and Analysis

Our outcomes of interest were the frequency with which specific iatrogenic processes may have contributed to the need for RRT in our population (described below). Other outcomes included time from AKI diagnosis to initial management steps, including Nephrology referral (which occurred at some point for all included patients as it is a necessary pre-requisite to receiving HD at our institution).

To identify delays in AKI identification and initial management, the timing of Nephrology consultation and HD initiation relative to the onset of AKI was reported as the median number of days with interquartile ranges. The possible causes of AKI were determined from admission notes, Nephrology consultations, and progress notes. Renal investigations post-AKI, including urine studies and imaging, were recorded. IV fluid administration within 24 h of AKI onset when AKI was recorded to be 'pre-renal' from hypovolemia, was recorded. We did not differentiate between a bolus or infusion of IV crystalloid as ordering practices varied between prescribing physicians depending on clinical context. The number and type of iodinated contrast imaging studies after AKI were recorded. The indications for first HD were obtained from Nephrology consult and progress notes.

Iatrogenic events and processes relating to AKI and hyperkalemia were recorded. This included the administration of certain medications after the onset of AKI including non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor antagonists (ARBs) and potassium-sparing diuretics or aldosterone inhibitors. The administration of oral K^+ supplements, and IV solutions containing at least 10 mmol/L of potassium after the onset of AKI and when serum potassium was $\geq$5.0 mmol/L was also recorded. Ordered diets were recorded, including failure to order 'renal' or low potassium diet after onset of AKI who were ultimately dialyzed with hyperkalemia (defined as potassium $\geq$ 5.5 mmol/L). The frequency of iatrogenic events was calculated.

The collected data was also analyzed qualitatively and selected cases that were felt by the investigators to be representative of particular patient safety lapses in this population are reported in a narrative synthesis.

3. Results

3.1. Patient Demographics and AKI Information

We reviewed 344 charts and excluded 264 patients for a total of 80 consecutive patients, over a one-year period, treated with at least one HD session for AKI while hospitalized. The process is outlined in Figure 1.

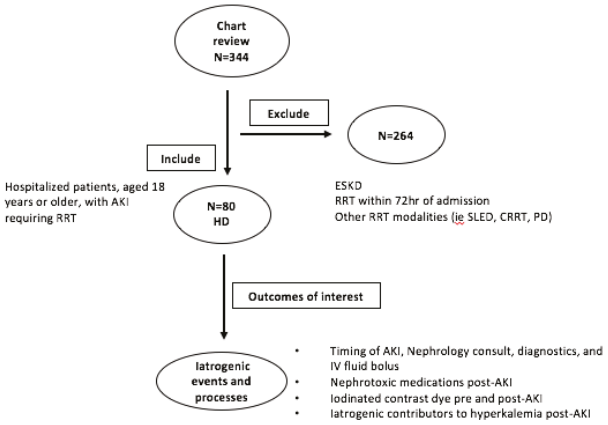

Figure 1. Summary of study design for this retrospective chart review. A total of 344 electronic inpatient records were reviewed, and 80 consecutive hospitalized patients meeting inclusion criteria were included. Data was collected for qualitative assessment of iatrogenic events and processes that may have contributed to the need for RRT (in the form of HD) for AKI. AKI, acute kidney injury; RRT, renal replacement therapy; HD, intermittent hemodialysis; ESKD, end-stage kidney disease; SLED, slow low efficiency dialysis; PD, peritoneal dialysis.

Table 1 summarizes baseline patient characteristics. The mean age of patients was 65 years old and over half were documented to have CKD. The average baseline serum creatinine (SCr) was 1.9 mg/dL (138 µmol/L). All patients were initiated on HD for AKI at the Ottawa Hospital (TOH), but 19 patients (23.7%) were initially admitted to other hospitals and transferred to TOH for specialty or intensive care. In-hospital mortality was 26% (21 patients) and the median length of stay in hospital was 28.0 days [IQR 16.3–53.5]. Overall, 64 patients (80%) were initially admitted to a medical service and 16 (20%) to a surgical service. Thirty patients (38%) required critical care (in an intensive care unit (ICU), cardiac care unit, or cardiac surgery ICU) by the time of HD initiation. The most common admission diagnosis was sepsis (in 25 patients (31%)) but cardiac causes were listed for 27 patients (34%) (classified as acute coronary syndrome in 13 patients (16%) and CHF in 14 patients (18%) overall).

Supplementary Figure S1 details the etiology of AKI for included patients, as determined by documentation in each patient's chart from admitting services and Nephrology consultants. More than one etiology was implicated in 51 patients (64%).

Timing of AKI recognition, work-up, and management is reported in Table 2. As summarized in Table 2, half of our patients met criteria for AKI at the time of admission. Of those who developed AKI in hospital, the median time to AKI was 4.5 days. The time from AKI to Nephrology consultation and HD initiation was 3 days and 6 days, respectively. With respect to diagnostic work up for AKI, urinalysis with microscopy and urine electrolytes were assessed for 61 patients (76%) and 45 patients (56%), respectively. The median time between AKI and obtaining urine electrolytes was 3 days. Fifty-three (66%) patients underwent renal ultrasonography or another form of abdominal imaging that could rule out hydronephrosis. Lastly, of the 35 patients with pre-renal AKI secondary

to hypovolemia, 29 (83%) received an IV fluid administration of crystalloid or colloid within 24 h of AKI onset.

Table 1. Baseline patient characteristics (n = 80).

Mean age in years (SD)	65.5 (+/− 15.4)
Male sex, n (%)	50 (62)
Mean baseline serum creatinine in mg/dL (SD)	1.6 (+/− 0.9)
Co-morbidities, n (%)	
Hypertension	54 (68)
Diabetes mellitus	47 (59)
Chronic kidney disease	43 (54)
Congestive heart failure	33 (41)
Peripheral vascular disease	13 (16)
Home medications, n (%)	
Thiazide diuretic or furosemide	(54)
ACEi or ARB	(50)
Metformin	(23)
Spironolactone	(15)
Admission diagnoses *	
Sepsis	26 (33)
Congestive heart failure	17 (21)
Acute coronary syndrome	14 (18)
Acute kidney injury	15 (19)
Malignancy	8 (10)
Hospitalization and outcomes	
Admitted upon hospital transfer, n (%)	(23.7)
Median hospital length of stay, days (IQR)	28.0 (16.3–53.5)
In-hospital mortality, n (%)	(26.2)

* Patients could have more than one diagnosis recorded as the reason for admission. SD, standard deviation; IQR, interquartile range; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 2. Diagnosis and management of Acute Kidney Injury, n = 80 *.

AKI present at admission, n (%)	40 (50.0)
Median time from admission to AKI, days (IQR)	4.5 (2.0–11.2)
Median time from AKI to Nephrology consult, days (IQR)	3.0 (1.0–5.7)
Median time from AKI to first hemodialysis, days (IQR)	6.0 (4.0–11.0)
Tests and initial management, n (%)	
IV fluid administration within 24 h for pre-renal AKI, n = 35	29 (83)
Urinalysis and routine microscopy	61 (76)
Renal ultrasound	53 (66)
Urine electrolytes	45 (56)

* Unless otherwise specified. AKI, acute kidney injury; IQR, interquartile range

3.2. Nephrotoxins, Medications, Hyperkalemia and Indications for Dialysis

Table 3 summarizes the frequency of selected medications and exposure to contrast dye after the onset of AKI and prior to HD. Either an ACEi or ARB was given post-AKI in 16 patients (20%) and 11 patients (14%) were given spironolactone. Three patients (4%) received both ACEi or ARB

plus spironolactone after AKI. One patient (1%) received NSAIDs post-AKI. In the post-AKI period, 15 patients (19%) and 9 patients (11%) received either intravenous or intra-arterial contrast, respectively.

Figure 2 illustrates the frequency of the presence of indications for initiation of HD at the time it was started. Volume overload was the most common indication, present in 69 patients (86%). Uremia was cited as an indication in 40 patients (50%). Hyperkalemia (with a serum potassium $\geq$ 5.5 mmol/L in all such cases) was documented as an indication for HD in 28 patients (35%). Most patients had multiple indications for HD initiation, and hyperkalemia was only an isolated indication for 2 patients (3%). For the 28 patients dialyzed with hyperkalemia as an indication for initiation of HD, all had serum potassium $\geq$ 5.5 mmol/L and 6 (21%) had serum potassium $\geq$ 6.0 mmol/L at HD initiation.

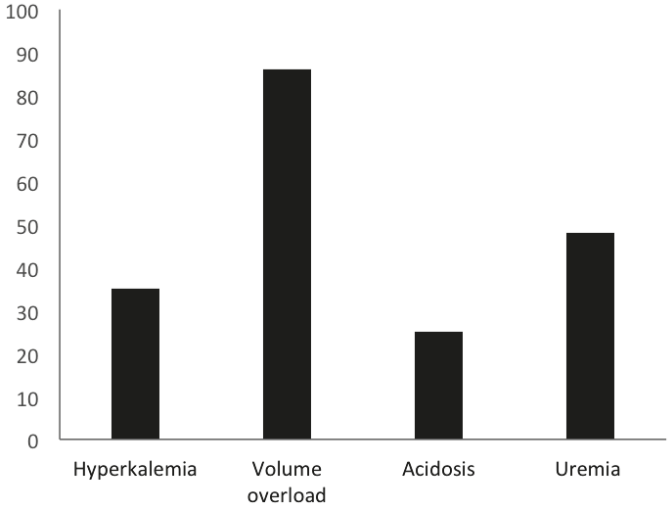

Figure 2. Indications for initiation of hemodialysis (n = 80). Legend: Percentage of patients with a particular indication for initiation of hemodialysis. Fifty-one patients (64%) had two or more indications present.

Table 3. Selected iatrogenic medications and contrast exposure after Acute Kidney Injury.

Medications, *n* (%)	
ACEi or ARB	16 (20)
Spironolactone	11 (14)
NSAIDs	1 (1)
Aminoglycoside antibiotic	1 (1)
Contrast exposure, *n* (%)	24 (30)
Intravenous	15 (19)
Intra-arterial	9 (11)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drug.

Table 4 highlights iatrogenic contributors to hyperkalemia. Of the 28 patients dialyzed with hyperkalemia, 13 (46%) were not given a low potassium diet and 3 (11%) were receiving either an ACEi, ARB or spironolactone; one (4%) received potassium supplements in addition to spironolactone. Further, of the 6 patients with serum potassium $\geq$ 6.0 mmol/L at HD initiation, 3 were not provided with low potassium diets, and 2 received potassium supplements or potassium sparing diuretics.

Table 4. Iatrogenic contributors to hyperkalemia after Acute Kidney Injury.

Occurrence of hyperkalemia (n = 80), n (%)	
During admission, after AKI	33 (41)
As an indication for dialysis	28 (35)
Safety lapses in patients with hyperkalemia as a subsequent indication for hemodialysis (n = 28), n (%)	
Low potassium diet not ordered	13 (46)
Oral potassium supplements given while serum potassium $\geq$ 5.0 mmol/L	2 (7)
ACEi, ARB and/or spironolactone given while serum potassium $\geq$ 5.0 mmol/L	6 (21)

AKI, acute kidney injury; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

3.3. Summary of Representative Cases

Table 5 summarizes four cases that highlight safety lapses that may have contributed to the need to initiate HD after the onset of AKI.

Table 5. Selected cases that highlight safety lapses in patients requiring hemodialysis after Acute Kidney Injury.

Admission Diagnoses	Indication(s) for HD	Summary of Events after AKI and Prior to Initiation of HD
Lymphoma, AKI	Hyperkalemia, Volume overload	• Diuresis then IV contrast for CT scan; worsening AKI • Spironolactone and potassium supplements continued despite serum potassium 5.5 mmol/L.
Sepsis, NSTEMI and AKI	Volume overload	• Long-acting CCB, BB and nitropatch continued despite relative hypotension; CT with IV contrast • Given 9 L of IV crystalloid for refractory hypotension while oligoanuric with subsequent development of pulmonary edema.
NSTEMI, then AKI *	Volume overload Hyperkalemia	• CKD with baseline Cr 200 • Discharged 24 h after coronary angiogram with Cr 210, K 5.6. Was continued on ARB and started on NSAID at discharge. • Re-admitted 48 h later with oliguric AKI, serum potassium up to 6.3 mmol/L, volume overload.
Anemia, AKI	Respiratory failure	• Late Nephrology referral (9 days post-admission with AKI non-responsive to IV fluids • Urinalysis at admission showed microscopic hematuria, proteinuria with hypoalbuminemia. • GN work up initiated by Nephrology, including renal biopsy. • Transfer to ICU for respiratory failure; initiated HD, and started plasmapheresis, cyclophosphamide, steroids for microscopic polyangiitis.

AKI, acute kidney injury; CT, computed tomography; IV, intravenous; CCB, Calcium channel blocker; BB, beta-blocker; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; GN, glomerulonephritis; HD, intermittent hemodialysis. * This case was excluded from our study cohort because this patient was initiated on hemodialysis within 48 h of admission. It has been included in this table to highlight a patient safety issue around this patient's discharge post-angiogram that was still detected on chart review.

4. Discussion

Our study of 80 consecutive inpatients who required hemodialysis for AKI after at least 72 h of hospitalization revealed that safety lapses occur frequently and may have contributed to the need for

initiation of HD in some instances. This is consistent with previous studies that have demonstrated safety lapses occur frequently in patients who die in hospital with a primary admission diagnosis of AKI [13] and in end-stage kidney disease patients admitted to surgical services [23].

Our results suggest deficiencies in diagnostic testing to determine the etiology of acute kidney injury. In particular, it was notable that only 61 patients (76%) had urinalysis testing after AKI while the KDIGO Clinical Practice Guidelines for AKI [21] suggest that urinalysis testing is necessary to ensure a complete diagnostic work-up for AKI. Another safety lapse we discovered was the frequent failure to order low potassium diets in patients with AKI who ultimately started dialysis with elevated serum potassium levels. Low potassium diets were ordered in less than half of such patients. Although there is no published data in the literature on low potassium diets and RRT initiation in patients with AKI, we feel this is a low risk intervention that has the potential to delay HD in the AKI population. As well, supplemental potassium or medications known to increase the serum potassium level were continued in many such patients. This suggests that our institution might improve care through an automated trigger to review these particular medications after the onset of AKI and/or elevated serum potassium. For potassium supplements, automatic substitution to a *prn* order restricted according to serum potassium values could also be useful.

Another issue that our study identified is that Nephrology consultation was often delayed, with a median time from AKI to consultation of three days. Studies of hospitalized patients with AKI, including a recent systematic review and meta-analysis [24], have shown that delayed Nephrology consultation for AKI is associated with increased in-hospital mortality in both non-critically ill [25] and critically ill patients [24,26,27], increased risk of requiring RRT [25], and increased dialysis dependence rates upon hospital discharge [26]. One particular study found that for hospital-acquired AKI (using the same KDIGO definition [21] as our study), nephrology assessment within 18 h was associated with significantly fewer patients progressing to a 2.5-fold increase in SCr level from admission [28]. We also found that, for patients who had urine electrolyte testing performed, it was done a median of three days after the AKI onset. Although the clinical utility of urine electrolyte testing for AKI is itself debatable, it does suggest a substantial time lapse between the onset of AKI and investigations related to AKI and that AKI may be under-recognized. Further evidence that AKI is under-recognized is that only 29 of the 35 patients (83%) with a pre-renal element to their AKI received IV fluids as a bolus or infusion within 24 h of AKI. Overall, our findings suggest that an automated trigger for nephrology assessment (and initial diagnostic testing, including serial SCr measurements, urinalysis, microscopy, ultrasound, and initial management strategies including medication review and volume status) might be one avenue to reducing the likelihood of AKI patients progressing to require RRT initiation at our institution. We recognize that this could add substantial burden to the existing inpatient Nephrology service and may require a dedicated team to address assessments.

The main strength of our study is that it involved a comprehensive case-by-case review to capture clearly defined, pre-specified, safety lapses. However, there are many important limitations. The study was not comprehensive and did not evaluate a myriad of other possible medication or treatment-related safety lapses that could have a bearing on AKI progression to HD initiation. As well, our study was not able to determine the clinical significance of any safety lapses with respect to whether they impacted the subsequent requirement for HD as we did not assess a comparator group of AKI patients who did not progress to require HD. Furthermore, many 'iatrogenic' processes are likely unavoidable. For example, although it was not possible to quantify, on the basis of our case-by-case analysis, the vast majority of contrast imaging was clearly indicated in the overall context of patients' clinical management despite its potential nephrotoxicity. As briefly discussed earlier, there is also controversy in the literature regarding the association between IV iodinated contrast dye and AKI [12]. A final limitation relates to generalizability: some of the lapses in safety might be less likely to occur in institutions utilizing CPOE. Furthermore, our experience might not be generalizable to the community hospital setting where specialist consultations or subspecialty admitting services are less likely to be available.

Despite its limitations, this study clearly highlights several care processes to target for improvement. The development of an automated trigger to ensure discontinuation of medications that are either nephrotoxic and/or promote hyperkalemia could be beneficial. As well, an automated review of diet orders (to ensure a low potassium diet, when indicated) and automated triggers for nephrology referral soon after AKI onset could increase the frequency with which renal recovery occurs prior to hemodialysis being required.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/10/317/s1. Supplemental Figure S1: Etiology of Acute Kidney Injury (n = 80).

Author Contributions: A.D. and K.Z. performed data acquisition. E.G.C. and A.D. undertook statistical analysis and manuscript creation. All authors revised the manuscript. E.G.C. conceived and supervised the project. S.H., P.A.B., M.M.S. and G.M. provided critical intellectual input. All authors have read and approved the manuscript.

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Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Wang, H.E.; Muntner, P.; Chertow, G.M.; Warnock, D.G. Acute Kidney Injury and Mortality in Hospitalized Patients. *Am. J. Nephrol.* **2012**, *35*, 349–355. [CrossRef] [PubMed]
2. Uchino, S.; Bellomo, R.; Goldsmith, D.; Bates, S.; Ronco, C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit. Care Med.* **2006**, *34*, 1913–1917. [CrossRef] [PubMed]
3. Metnitz, P.G.H.; Krenn, C.G.; Steltzer, H.; Lang, T.; Ploder, J.; Lenz, K.; Gall, J.-R.L.; Druml, W. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit. Care Med.* **2002**, *30*, 2051–2058. [CrossRef] [PubMed]
4. Coca, S.G.; Yusuf, B.; Shlipak, M.G.; Garg, A.X.; Parikh, C.R. Long-Term Risk of Mortality and Other Adverse Outcomes After Acute Kidney Injury: A Systematic Review and Meta-analysis. *Am. J. Kidney Dis.* **2009**, *53*, 961–973. [CrossRef] [PubMed]
5. Coca, S.G.; Singanamala, S.; Parikh, C.R. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int.* **2012**, *81*, 442–448. [CrossRef] [PubMed]
6. Chertow, G.M.; Burdick, E.; Honour, M.; Bonventre, J.V.; Bates, D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–3370. [CrossRef] [PubMed]
7. Kerr, M.; Bedford, M.; Matthews, B.; O'Donoghue, D. The economic impact of acute kidney injury in England. *Nephrol. Dial. Transplant.* **2014**, *29*, 1362–1368. [CrossRef] [PubMed]
8. Clark, E.G.; Bagshaw, S.M. Unnecessary Renal Replacement Therapy for Acute Kidney Injury is Harmful for Renal Recovery. *Semin. Dial.* **2015**, *28*, 6–11. [CrossRef] [PubMed]
9. Jo, S.K.; Rosner, M.H.; Okusa, M.D. Pharmacologic Treatment of Acute Kidney Injury: Why Drugs Haven't Worked and What Is on the Horizon. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 356–365. [CrossRef] [PubMed]
10. Perazella, M.A. Renal vulnerability to drug toxicity. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1275–1283. [CrossRef] [PubMed]
11. Ozkok, S.; Ozkok, A. Contrast-induced acute kidney injury: A review of practical points. *World J. Nephrol.* **2017**, *6*, 86–99. [CrossRef] [PubMed]
12. Aycock, R.D.; Westafer, L.M.; Boxen, J.L.; Majlesi, N.; Schoenfeld, E.M.; Bannuru, R.R. Acute kidney injury after computed tomography: A meta-analysis. *Ann. Emerg. Med.* **2018**, *71*, 44–53. [CrossRef] [PubMed]
13. Stewart, J.; Findlay, G.; Smith, N.; Kelly, K.; Mason, M. *Adding Insult to Injury: A Review of the Care of Patients Who Died in Hospital with a Primary Diagnosis of Acute Kidney Injury (Acute Renal Failure)*; National Confidential Enquiry into Patient Outcome and Death: London, UK, 2009.
14. Handler, S.M.; Kane-Gill, S.L.; Kellum, J.A. Optimal and early detection of acute kidney injury requires effective clinical decision support systems. *Nephrol. Dial. Transplant.* **2014**, *29*, 1802–1803. [CrossRef] [PubMed]
15. Kirkendall, E.S.; Spires, W.L.; Mottes, T.A.; Schaffzin, J.K.; Barclay, C.; Goldstein, S.L. Development and perfmance of acute kidney injury triggers to identuify pediatric patients at risk for nephrotoxic medication-associated harm. *Appl. Clin. Inform.* **2014**, *5*, 313–333. [PubMed]

16. Porter, C.J.; Jurrlink, I.; Bisset, L.H.; Bavakunji, R.; Mehta, R.L.; Devonald, M.A. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. *Nephrol. Dial. Transplant.* **2014**, *29*, 1888–1893. [CrossRef] [PubMed]
17. Wilson, F.P.; Shashaty, M.; Testani, J. Automated, electronic alerts for acute kidney injury: A single-blind, parallel-group, randomised controlled trial. *Lancet* **2015**, *385*, 1966–1974. [CrossRef]
18. Lachance, P.; Villeneuve, P.-M.; Rewa, O.G.; Wilson, F.P.; Selby, N.M.; Featherstone, R.M.; Bagshaw, S.M. Association between e-alert implementation for detection of acute kidney injury and outcomes: A systematic review. *Nephrol. Dial. Transplant.* **2017**, *32*, 265–272. [CrossRef] [PubMed]
19. Laing, C. On the alert for outcome improvement in acute kidney injury. *Lancet* **2015**, *385*, 1924–1926. [CrossRef]
20. About Our Hospital. Available online: http://www.ottawahospital.on.ca/en/about-us (accessed on 20 November 2017).
21. Kidney Disease Improving Global Outcomes (KDIGO); Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Nephron Clin. Pract.* **2012**, *120*, c179–c184.
22. Ricci, Z.; Cruz, D.N.; Ronco, C. Classification and staging of acute kidney injury: Beyond the RIFLE and AKIN criteria. *Nat. Rev. Nephrol.* **2011**, *7*, 201–208. [CrossRef] [PubMed]
23. Harel, Z.; Wald, R.; Liu, J.J.; Bell, C.M. Lapses in safety in end-stage renal disease patients admitted to surgical services. *Hemodial. Int.* **2012**, *16*, 286–293. [CrossRef] [PubMed]
24. Soares, D.M.; Pessanha, J.F.; Sharma, A.; Brocca, A.; Ronco, C. Delayed Nephrology Consultation and High Mortality on Acute Kidney Injury: A. Meta-Analysis. *Blood Purif.* **2017**, *43*, 57–67. [CrossRef] [PubMed]
25. Meier, P.; Bonfils, R.M.; Vogt, B.; Burnand, B.; Burnier, M. Referral Patterns and Outcomes in Noncritically Ill Patients with Hospital-Acquired Acute Kidney Injury. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 2215–2225. [CrossRef] [PubMed]
26. E Silva, V.T.C.; Liaño, F.; Muriel, A.; Díez, R.; de Castro, I.; Yu, L. Nephrology Referral and Outcomes in Critically Ill Acute KIdney Injury Patients. *PLoS ONE* **2013**, *8*, e70482.
27. Ponce, D.; Zorzenon, C.D.P.F.; Santos, N.Y.D.; Balbi, A.L. Early nephrology consultation can have an impact on outcome of acute kidney injury patients. *Nephrol. Dial. Transplant.* **2011**, *26*, 3202–3206. [CrossRef] [PubMed]
28. Balasubramanian, G.; Al-Aly, Z.; Moiz, A.; Rauchman, M.; Zhang, Z.; Gopalakrishnan, R.; Balasubramanian, S.; El-Achkar, T.M. Early nephrologist involvement in hospital-acquired acute kidney injury: A pilot study. *Am. J. Kidney Dis.* **2011**, *57*, 228–234. [CrossRef] [PubMed]

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Does the Implementation of a Quality Improvement Care Bundle Reduce the Incidence of Acute Kidney Injury in Patients Undergoing Emergency Laparotomy?

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Abstract: Purpose: Previous work has demonstrated a survival improvement following the introduction of an enhanced recovery protocol in patients undergoing emergency laparotomy (the emergency laparotomy pathway quality improvement care (ELPQuiC) bundle). Implementation of this bundle increased the use of intra-operative goal directed fluid therapy and ICU admission, both evidence-based strategies recommended to improve kidney outcomes. The aim of this study was to determine if the observed mortality benefit could be explained by a difference in the incidence of AKI pre- and post-implementation of the protocol. Method: The primary outcome was the incidence of AKI in the pre- and post-ELPQuiC bundle patient population in four acute trusts in the United Kingdom. Secondary outcomes included the KDIGO stage specific incidence of AKI. Serum creatinine values were obtained retrospectively at baseline, in the post-operative period and the maximum recorded creatinine between day 1 and day 30 were obtained. Results: A total of 303 patients pre-ELPQuiC bundle and 426 patients post-ELPQuiC bundle implementation were identified across the four centres. The overall AKI incidence was 18.4% in the pre-bundle group versus 19.8% in the post bundle group $p = 0.653$. No significant differences were observed between the groups. Conclusions: Despite this multi-centre cohort study demonstrating an overall survival benefit, implementation of the quality improvement care bundle did not affect the incidence of AKI.

Keywords: post-operative complications; acute kidney injury; enhanced recovery; goal directed therapy; emergency surgery; laparotomy

1. Introduction

Enhanced recovery pathways are now integral in many surgical pathways in order to optimize patient care, with the aim of reducing both post-operative morbidity and mortality [1]. The application of standardized pathways has been shown to reduce both post-operative complications and length of stay in elective surgery [2]. The adoption of care bundles in order to improve outcomes has been applied to both scheduled non-emergent surgery and also to emergency surgery. Recently published data reported a significant case mix-adjusted risk of death reduction from 15.6% to 9.6% at 30 days following the implementation of the emergency laparotomy pathway quality improvement care (ELPQuiC) bundle [3]. This pathway is comprised of the following steps:

1. All emergency surgical admissions risk assessed using the M(EWS) score [4]. Those with M(EWS) ≥4 reviewed by critical care outreach team.
2. Broad spectrum antibiotics given to all patients with suspicion of peritoneal soiling or with sepsis.
3. Once the decision is made for a laparotomy then next available theatre slot is used (or within 6 h) with senior clinical input (consultant anaesthetist and surgeon).
4. Resuscitation commenced using goal-directed techniques and continued for a minimum of six hours post-operatively.
5. All patients admitted to critical care when possible after surgery or held in a post anaesthetic care unit for at least six hours.

The need for such an integrated approach was highlighted in the UK when the Emergency Laparotomy Network group published data on 1800 patients showing a 30 day mortality of 14.9%, which rose to 24.4% in patients aged 80 and over [5]. This high mortality was also demonstrated in other countries with differing healthcare systems [6,7]. Following the evidence of such high mortality, standards of care were developed in the UK which recommended defined pathways with evidence-based interventions for all high risk and emergency surgical patients [8]. The use of a care-bundle concept is not new in critical care with several successful examples in current practice, such as the Surviving Sepsis Campaign with substantial morbidity and mortality improvements observed through the global implementation of this care bundle [9].

The observed mortality and morbidity in high risk groups of patients admitted to intensive care, including patients undergoing emergency surgery, remains significant with acute kidney injury (AKI) being a major factor complicating critical illness. AKI is associated with a mortality rate of up to 60% [10]. The relevance of AKI in emergency surgery is reflected in the results from the AKI EPI study where AKI complicated 51% of elective surgical patients admitted to ICU, and increased further to 56% in those undergoing emergency surgery [11]. This is further compounded in elderly patients with higher rates of AKI and worse mortality [12]. Furthermore, the long term sequelae after an episode of AKI are substantial, with a single episode of AKI independently associated with an increase in 10-year mortality [13]. Currently available treatment strategies have the potential to improve patient outcome and provide considerable health savings if implemented early [14]. The implementation of the ELPQuiC bundle was associated with significant increase in the use of goal directed fluid therapy and admission to ICU across the participating sites. These interventions form part of the KDIGO (Kidney Disease Improving Global Outcomes) clinical practice guidelines for the management of AKI, which recommend maintenance of perfusion pressure, functional haemodynamic monitoring and ICU admission [15]. It is unclear whether the adoption of such a goal directed approach in high risk patients may result in a reduction in AKI or indeed whether the development of AKI in this group is specifically associated with worse outcomes [16]. Given the observed risk-adjusted mortality improvement seen in the ELPQuiC study, we examined the data to see if this effect could be explained by a reduction in AKI translating into a survival benefit.

2. Methods

Development and components of the care bundle are described elsewhere [3,17]. The ELPQUiC study was conducted in 4 acute hospital trusts in the United Kingdom, with an intervention period from December 2012 to July 2013 after a baseline monitoring period. A multi-centre cohort subgroup analysis was performed with data gathered from the original ELPQuiC study. Colleagues in the ELPQuiC collaborator group accessed the relevant components of their ELPQuiC raw data. Where needed, additional biochemical data was obtained from the hospital's electronic pathology system. All data was reviewed by a second investigator.

AKI was defined as described by the KDIGO serum creatinine thresholds only. Urine output thresholds were not used, as data for this was not complete. We defined the reference or baseline creatinine as the lowest preoperative serum creatinine from the 12 months prior to admission. Serum creatinine values at baseline, immediately post-operatively (within the first 24 h but usually within hours of surgery completion), on day 30 and the maximum recorded creatinine between day 1 and day 30 were taken. P-POSSUM (Physiological and Operative Severity Score for the enumeration of Mortality and morbidity) and 30-day mortality data were also collected [18]. CKD stage was identified via the MDRD (Modification of Diet in Renal Disease study) equation with age, gender and baseline creatinine [19].

The primary outcome was the incidence of AKI in the pre- and post-ELPQuiC bundle patient population. Secondary outcomes included the KDIGO stage specific incidence of AKI.

As this project was an assessment of current practice and implementation of best-practice guidelines, it was confirmed by the National Research Ethics service that formal ethical approval was not required [3].

Statistical Analysis

For discrete data, we used Pearson's chi-squared test, Fisher's exact test, Wilcoxon rank sum test and the Mantel-Haenszel odds ratio (stratifying for centre), along with the φ-coefficient or Goodman-Kruskal γ statistic where appropriate. In addition, we used four-fold plots to provide a visual representation of the odds ratios, which align the vertical and horizontal quadrants with an odds ratio equal to 1. This also permits the use of confidence rings that provide a visual indication for the test of no association; they will only overlap if and only if the observed counts are consistent with the null hypothesis. Furthermore, the width of the confidence rings provides a visual guide to the precision of the data. All analyses were carried using the open source statistical package R (Foundation for Statistical Computing, Vienna, Austria) [20], along with ggplot2 [21], Forest plot [22] and vcd packages [23].

3. Results

Table 1 shows the baseline demographics and outcomes obtained from the four centres. A total of 292 patients pre-ELPQuiC bundle and 424 patients post-ELPQuiC were identified across the four centres with no significant differences observed between the groups. Ten patients from the initial ELPQuiC study were excluded due to incomplete data on renal function. There was no significant difference in P-POSSUM scores pre- or post-ELPQuiC implementation: the pre-ELPQuiC median was 9.0% (IQR 2.9–27.0%) versus the post-ELPQuiC median of 8.6% (IQR 3.5–31.4%) (Wilcoxon rank sum test $p = 0.5842$; Figure 1). However, although the baseline CKD rates in the pooled post-ELPQuiC group were significantly higher than in the pre-ELPQuiC group, $p = 0.01961$, the Goodman and Kruskal γ statistic of 0.036 suggests this is a very weak association. Moreover, this is for all CKD, if one considers only CKD stages 3 to 5 (the highest risk of AKI) then there is no difference ($p = 0.19$).

Table 1. Demographics and outcomes of patients before and after inplementation of the emergency laparotomy pathway quality improvement care bundle.

	Site 1		Site 2		Site 3		Site 4		All Patients	
	Before ELPQuiC (*n* = 51)	**After ELPQuiC (*n* = 109)**	**Before ELPQuiC (*n* = 144)**	**After ELPQuiC (*n* = 144)**	**Before ELPQuiC (*n* = 44)**	**After ELPQuiC (*n* = 97)**	**Before ELPQuiC (*n* = 60)**	**After ELPQuiC (*n* = 77)**	**Before ELPQuiC (*n* = 299)**	**After ELPQuiC (*n* = 427)**
Age (years) *	66.6 (16.6)	65.3 (17.7)	65.1 (16.6)	63.7 (17.5)	65.7 (13.9)	69.3 (14.0)	66.2 (15.0)	66.0 (15.5)	65.6 (15.8)	65.8 (16.5)
Sex										
F	38 (75)	56 (51.4)	73 (50.7)	79 (54.9)	19 (43)	49 (51)	31 (52)	41 (53)	161 (53.8)	225 (52.7)
M	13 (25)	53 (48.6)	71 (49.3)	65 (45.1)	25 (57)	48 (49)	29 (48)	36 (47)	138 (46.2)	202 (47.3)
Outcomes at 30 days										
alive	42 (82)	96 (88.1)	123 (85.4)	126 (87.5)	39 (89)	89 (92)	53 (88)	71 (92)	257 (86.0)	382 (89.5)
dead	9 (18)	13 (11.9)	21 (14.6)	18 (12.5)	5 (11)	8 (8)	7 (12)	6 (8)	42 (14.0)	45 (10.5)
Died in hospital										
no	41 (80)	96 (88.1)	122 (84.7)	125 (86.8)	37 (84)	89 (92)	52 (87)	70 (91)	252 (84.3)	380 (89.0)
yes	10 (20)	13 (11.9)	22 (15.3)	19 (13.2)	7 (16)	8 (8)	8 (13)	7 (9)	47 (15.7)	47(11.0)
ASA fitness grade										
I	5 (10)	14 (12.8)	12 (8.3)	16 (11.1)	4 (9)	8 (8)	6 (10)	7 (9)	27 (9.0)	45 (10.5)
II	10 (20)	36 (33.0)	48 (33.3)	52 (36.1)	9 (21)	32 (33)	28 (47)	27 (35)	95 (31.8)	147 (34.4)
III	19 (37)	40 (36.7)	46 (31.9)	44 (30.6)	18 (41)	40 (41)	20 (33)	32 (42)	103 (34.5)	156 (36.5)
IV	16 (31)	18 (16.5)	31 (21.5)	26 (18.1)	12 (27)	12 (12)	5 (8)	10 (13)	64 (21.4)	66 (15.5)
V	1 (2)	1 (0.9)	7 (4.9)	6 (4.2)	1 (2)	5 (5)	1 (2)	1 (1)	10 (3.3)	13 (3.0)
Length of hospital stay (days) †	11 (7–24)	11 (7–21)	12 (7–23)	10 (6–18)	12 (8–21)	12 (8–19)	10 (7–21)	13 (6–32)	11 (7–23)	11 (6–21)
P-POSSUM risk score *	0.226 (0.282)	0.251 (0.298)	0.193 (0.234)	0.267 (0.307)	0.200 (0.207)	0.179 (0.241)	0.179 (0.237)	0.159 (0.212)	0.197 (0.239)	0.223 (0.278)
p ‡	0.730		0.140		0.764		0.755		0.395	

Values in parentheses are percentages unless indicated otherwise; * values are mean (s.d.) and † median (i.q.r.) for survivors. ELPQuiC, emergency laparotomy pathway quality improvement care; ASA, American Society of Anesthesiologists; P-POSSUM, Portsmouth modification of Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; ‡, test for proportions.

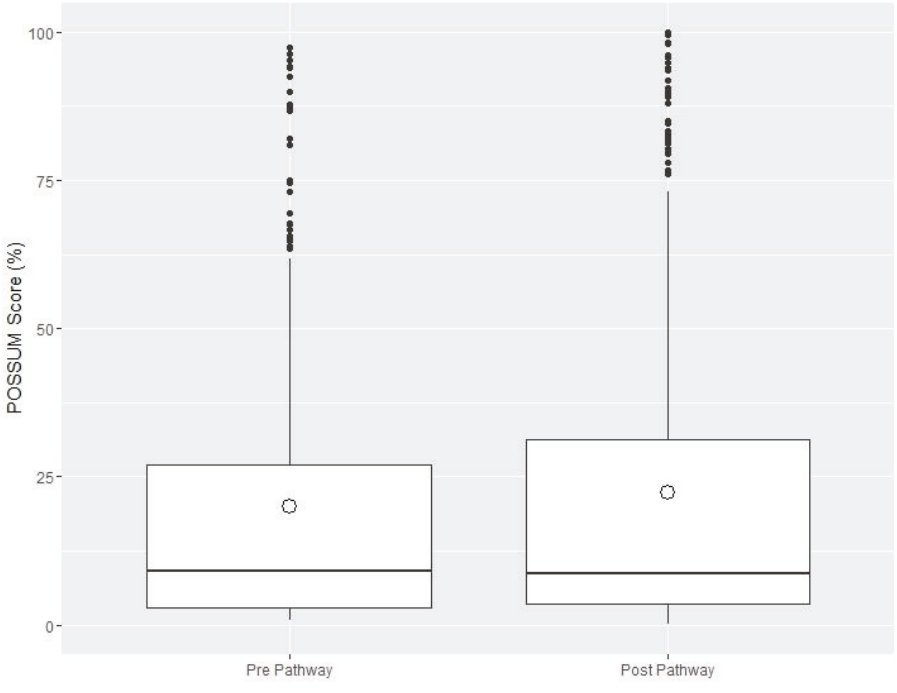

Figure 1. Cumulative P-POSSUM scores pre- and post-ELPQuiC implementation—circle represents the mean value.

3.1. Day 1 AKI

For our primary outcome; incidence of AKI between pre- and post-ELPQuiC implementation on day 1 post-op, the Mantel-Haenszel odds ratio (95% CI) for the four centres was 0.93 (0.72, 1.61). Using four-fold plots, crude numbers for day 1 incidence of AKI for each centre demonstrate that the odds ratios do not significantly differ from 1, but that the precision of the data is low (Figures 1 and 2). Additionally, the cumulative rates of AKI for day 1 post-surgery were 18.4% versus 19.8% (pre- and post-pathway, respectively), with the data for each centre and combined data for all 4 centres showing no statistical significance (Centre 1; $p = 0.460$, Centre 2; $p = 0.346$, Centre 3; $p = 0.319$, Centre 4; $p = 0.817$, pooled $p = 0.686$).

There was no significant association between the incidence of KDIGO defined AKI and the use of the pathway on the first post-operative day for each individual centre or when the data was merged.

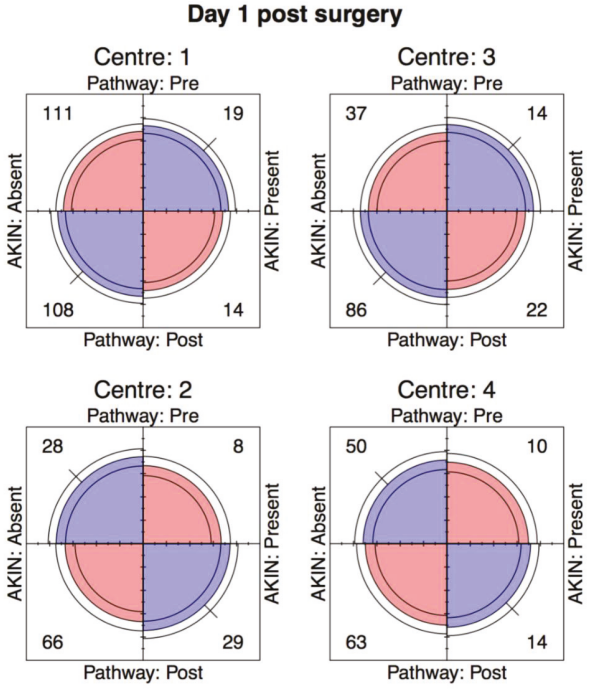

Figure 2. Four-fold Plot. Incidence of AKI day 1 post-op.

3.2. Maximum AKI Day 1–30

Using the maximum creatinine level and associated AKI incidence between days 1 and 30 post-surgery, the Mantel-Haenszel odds ratio (95% CI) for the 4 centres was 0.87 (0.61, 1.24) (Figure 3). There was no significant association between the incidence of AKI and the use of the pathway (Centre 1; $p = 0.137$, Centre 2; $p = 0.501$, Centre 3; $p = 0.388$, Centre 4; $p = 0.680$) or when the data was pooled ($p = 0.740$) (Figure 4B). For the maximum creatinine levels (when assessed using KDIGO criteria) there was no significant association demonstrated for each individual centre or when the data was merged.

3.3. Day 30 AKI

On day 30 after surgery, the Mantel-Haenszel odds ratio (95% CI) for the 4 centres was 0.56 (0.31, 1.00) (Figure 3). Using four-fold plots, crude numbers demonstrate that the day 30 incidence of AKI does not significantly differ from day 1, but the precision of the data is very low and varied across the centres (Figure 4).

There was no significant association between the incidence of AKI and the implementation of ELPQuiC at day 30 post-operatively for each individual centre (Centre 1 $p = 1.00$, Centre 2 $p = 1.00$, Centre 3 $p = 0.077$, Centre 4 $p = 0.241$). However, a small and weak association was observed when the data was pooled (Figure 4C) $p = 0.069$, phi-coefficient 0.09).

In a comparison of KDIGO AKI subgroups, again no significant difference was found on either day 1 ($p = 0.5321$) or day 30 ($p = 0.1516$) using crude data.

However, when correcting for rates of AKI for pre-existing CKD the Mantel-Haenzel Chi Squared test confirmed that the incidence of AKI relating to ELPQuiC implementation is not statistically associated with pre-existing CKD (Day 1 AKI $p = 0.771$, Max day 1–30 AKI $p = 0.929$, Day 30 AKI $p = 0.087$).

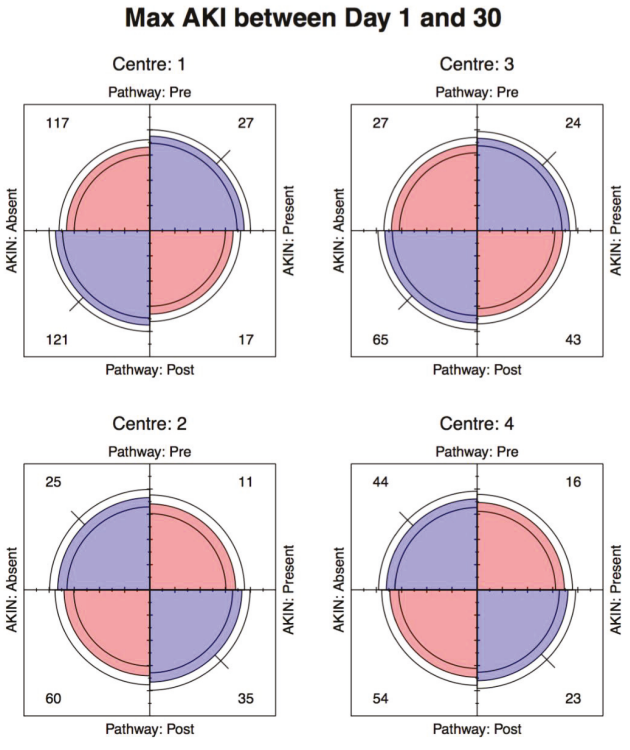

Figure 3. Four-fold Pl–t. Incidence of maximum AKI obtained between day 1 and day 30 post-op.

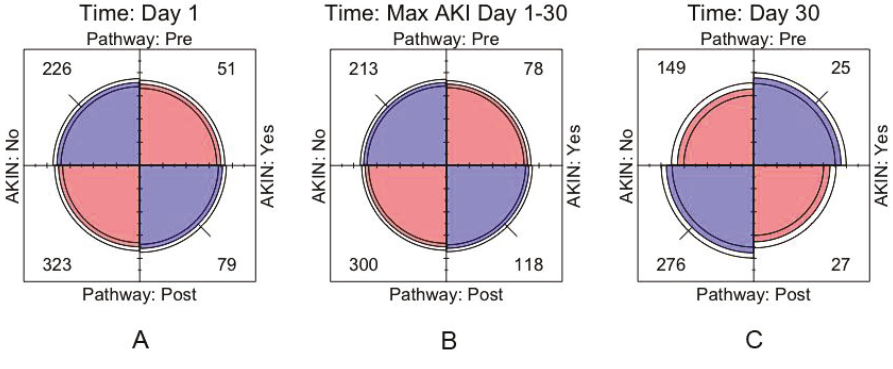

Figure 4. Cumulative AKI incidence (**A**) Day 1, (**B**) Max (day1-day30) and (**C**) Day 30 post-op pre and post-ELPQuiC implementation:

3.4. Mortality

Mortality incidence at 30 days was reported by the original ELPQuiC study and there was no significant association between the incidence of unadjusted 30-day mortality and the implementation of ELPQuiC for each individual centre (Figures 5 and 6, respectively) or when the data was pooled ($p = 0.08$) (Figure 7), this is in keeping with the original ELPQuiC paper [3], which then identified the risk-adjusted survival benefit.

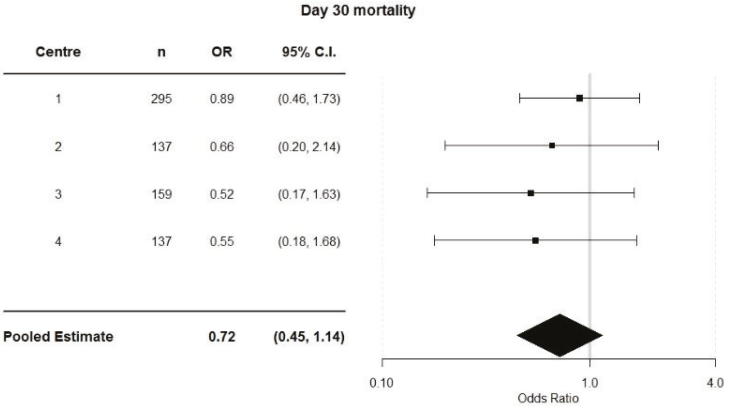

Figure 5. Incidence of 30-day mortality.

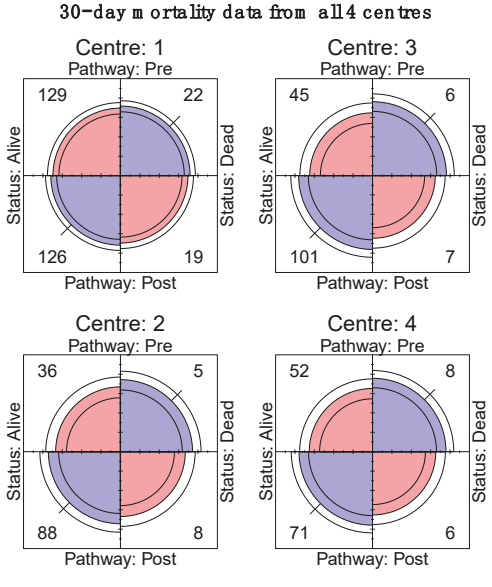

Figure 6. Centre specific 30-day mortality data.

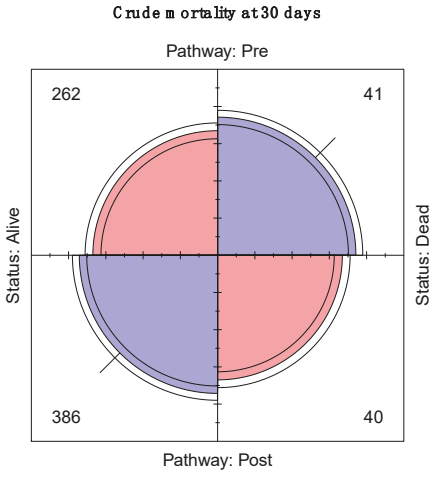

Figure 7. Cumulative 30-day mortality data.

4. Discussion

Our results suggest that the implementation of a quality improvement care bundle, although conferring a survival benefit, does not affect the incidence of AKI in the immediate post-operative period or in the 30 days after surgery. This is true for both the individual institutions and the cumulative data from all four centres. Therefore, it is reasonable to conclude that the survival benefit seen in the original study is not related to a reduction in AKI, as defined by changes in serum creatinine. This is in keeping with studies on goal-directed therapy in surgery, where a benefit in terms of renal outcomes tends to be observed mainly where vasopressors are employed together with goal directed fluid therapy. The effects of goal-directed fluid therapy have been examined in major gastrointestinal surgery. The OPTIMISE trial randomised 734 high risk patients across 17 UK centres who were undergoing major gastrointestinal surgery to receive usual care or goal-directed fluid therapy and inotropy (dopexamine) to achieve stroke volume targets. Observer blinding was used. Primary outcomes included moderate or major complications and mortality. These outcomes occurred in 36.6% of patients in the intervention group and 43.4% in the usual care group giving a relative risk of 0.84 (95% CI 0.71–1.01; $p = 0.07$), which failed to reach statistical significance. Secondary outcomes, including infection, length of stay, mortality at 30 and 180 days, and morbidity at day 7 were also no different between the cohorts [24]. However, meta-analyses and systematic reviews have suggested some benefits of peri-operative goal directed therapy. A 2014 Cochrane review by Grocott et al. of 31 studies with 5292 patients showed reductions in renal failure, respiratory failure and wound infections in intervention groups. Fewer patients suffered complications in the intervention groups and on average their hospital length of stay was 1.16 days shorter. Mortality and total time in critical care was no different. However, the review was limited by a single large study that exerted a sizeable influence on the overall data pool and this must be considered when interpreting the results. It was noted that there seemed to be no harm associated with the use of goal-directed therapy; and therefore, with some putative benefits it may be a reasonable peri-operative strategy [25].

In the ELPQuiC study, commencement, dosing or timing of vasopressor use was not protocolised in either group. This may be of relevance given that vasopressin, for example, has achieved popularity as the vasopressor of choice in terms of limiting the degree of AKI, notably most recently in the VANISH trial for sepsis associated AKI [26]. It is unknown whether unit preferences for vasopressors affected the incidence of AKI in this study or affected the observed mortality benefit. Interestingly the incidence of overall AKI at day one post-surgery is about 50% of that reported in AKI-EPI, although this probably reflects the fact that all comers were admitted to ICU or held in a post-anaesthesia recovery area for an

extended period, where the incidence of AKI would be expected to be less. Furthermore, given that 25% of patients had AKI at day 1 this almost certainly implies that the AKI was present prior to surgery given the creatinine kinetics following AKI. This gives further support to the importance of caring for these patients in a critical care setting where renal function and fluid balance can be closely monitored. The use of vasopressors may limit intra-operative hypotension (a risk factor for AKI), the extent and duration of which relate to the severity of the renal insult. Sun et al. conducted a retrospective analysis of 5127 patients undergoing elective non-cardiac surgery to delineate the relationship of intra-operative hypotension with renal outcomes. Mean arterial pressures of less than 60 mmHg for more than 20 min or less than 55 mmHg for more than 10 min were associated with increased risk of acute kidney injury [27]. This is unsurprising given the findings in both animal and human studies, which have demonstrated that renal blood flow becomes pressure-dependent when mean arterial pressure falls below the level at which the kidneys can autoregulate. Outside this window, renal blood flow declines with reductions in mean arterial pressure. Renal perfusion is also dependent on an adequate cardiac output in addition to a sufficient mean arterial pressure [28,29]. We did not stratify according to the presence of intra-operative hypotension, or additional risk factors for AKI, including use of nephrotoxic drugs, sepsis or volume depletion in the pre-operative period. These risk factors may be particularly relevant to the population undergoing emergency laparotomy. Moreover, we have defined AKI solely by serum creatinine, which is relevant in that several studies that have demonstrated a reduction in AKI post operatively with the use of a care bundle, principally observed an increase in urine output and hence a reduction in AKI using this criteria [30,31]. Given the heterogeneity in terms of AKI, it is unlikely that such an approach would influence AKI rates, but this provides further support for the observed mortality benefit being a product of global improvement in care rather than one aspect.

Consensus in terms of the nomenclature of AKI [32,33], has allowed a considerable body of evidence to accumulate regarding the epidemiology and pathophysiology of this syndrome. However, the methods of assessing renal function remain limited. For this study, creatinine was used as the renal biomarker, which has significant limitations outside steady state conditions [34]. Utilising more specific renal biomarkers may unmask "sub clinical AKI" and improved renal recovery with the implementation of a quality improvement care bundle, which may yet explain the survival improvement, particularly if sustained. Moreover, given the data on long term morbidity and mortality following an episode of AKI, any possibility of significantly reducing AKI after emergency laparotomy would be expected to see improved long term benefits.

Since the ELPQuIC project was published, the National Emergency Laparotomy Audit data has documented outcome data on almost 24,000 cases [35]. The 30 day mortality across all English and Welsh hospitals appears to have decreased from the 14.9% previously described in the US and UK [3,6] to 9.5%, according to the fourth NELA report on 2017 data. It is likely that the increased focus on patients undergoing emergency surgery and the quality improvement approach used in the ELPQuIC study and the larger EPOCH and Emergency Laparotomy Collaborative studies [36] are helping to improve outcomes in this high risk group of patients.

Limitations of this study include the lack of urinary output data for AKI classification and assessment of fluid balance. Using serum creatinine alone in such a heterogenous group may lead to inaccuracies in GFR estimation given changes in creatinine metabolism as well as the effects of administered drugs, although it seems unlikely that this was different in the two groups. Data was also lacking on the rates and duration of any renal replacement therapy (RRT) provided to those patients with an AKI 3. However, in the initial post-operative period the rate of RRT in one of the four centres was 22% amongst those patients classified as having AKI 3. Given a larger number of study participants it is possible that the strength of the association for ELPQuiC implementation and a reduction of AKI by day 30 would improve, however, the aim of this subgroup analysis was not to consider the power to detect AKI but rather, the reason for the identified risk-adjusted survival benefit.

5. Conclusions

This multi-centre cohort subgroup analysis suggests that the implementation of a quality improvement care bundle did not affect the incidence of AKI. This is in contrast to the survival benefit demonstrated using a care bundle and provides the stimulus to clarify the factors that may yet improve AKI in this high-risk patient group.

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Abbreviations

AKI	Acute kidney injury
ELPQuiC	Emergency laparotomy pathway quality improvement care bundle

References

1. Gustafsson, U.O.; Scott, M.J.; Schwenk, W.; Demartines, N.; Roulin, D.; Francis, N.; McNaught, C.E.; Macfie, J.; Liberman, A.S.; Soop, M.; et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. *World J. Surg.* **2013**, *37*, 259–284. [CrossRef] [PubMed]
2. Nicholson, A.; Lowe, M.C.; Parker, J.; Lewis, S.R.; Alderson, P.; Smith, A.F. Systematic review and meta-analysis of enhanced recoveryprogrammes in surgical patients. *Br. J. Surg.* **2014**, *101*, 172–188. [CrossRef] [PubMed]
3. Huddart, S.; Peden, C.J.; Swart, M.; McCormick, B.; Dickinson, M.; Mohammed, M.A.; Quiney, N.; Group, E.L.C. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. *Br. J. Surg.* **2015**, *102*, 57–66. [CrossRef]
4. Subbe, C.P.; Kruger, M.; Rutherford, P.; Gemmel, L. Validation of a modified Early Warning Score in medical admissions. *QJM* **2001**, *94*, 521–526. [CrossRef] [PubMed]
5. NELA Project Team. *The First Patient Report of the National Emergency Laparotomy Audit*; RCoA: London, UK, 2015.
6. Al-Temimi, M.H.; Griffee, M.; Enniss, T.M.; Preston, R.; Vargo, D.; Overton, S.; Kimball, E.; Barton, R.; Nirula, R. When is death inevitable after emergency laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *J. Am. Coll. Surg.* **2012**, *215*, 503–511. [CrossRef]
7. Vester-Andersen, M.; Lundstrøm, L.H.; Møller, M.H.; Waldau, T.; Rosenberg, J.; Møller, A.M. Mortality and postoperative care pathways after emergency gastrointestinal surgery in 2904 patients: A population-based cohort study. *Br. J. Anaesth.* **2014**, *112*, 860–870. [CrossRef]
8. The Royal College of Surgeons of England. *The Higher Risk General Surgical Patient: Towards Improved Care for a Forgotten Group*; RCSENG: London, UK, 2011.
9. Chang, C.H.; Fan, P.C.; Chang, M.Y.; Tian, Y.C.; Hung, C.C.; Fang, J.T.; Yang, C.W.; Chen, Y.C. Acute kidney injury enhances outcome prediction ability of sequential organ failure assessment score in critically ill patients. *PLoS ONE* **2014**, *9*, e109649. [CrossRef] [PubMed]

10. Hoste, E.A.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef] [PubMed]
11. Howes, T.E.; Cook, T.M.; Corrigan, L.J.; Dalton, S.J.; Richards, S.K.; Peden, C.J. Postoperative morbidity survey, mortality and length of stay following emergency laparotomy. *Anaesthesia* **2015**, *70*, 1020–1027. [CrossRef]
12. Linder, A.; Fjell, C.; Levin, A.; Walley, K.R.; Russell, J.A.; Boyd, J.H. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. *Am. J. Respir. Crit. Care Med.* **2014**, *189*, 1075–1081. [CrossRef] [PubMed]
13. Doyle, J.F.; Forni, L.G. Acute kidney injury: Short-term and long-term effects. *Crit. Care* **2016**, *20*, 188. [CrossRef]
14. Khwaja, A. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Nephron Clin. Pract.* **2012**, *120*, 179–184. [CrossRef] [PubMed]
15. O'Connor, M.E.; Kirwan, C.J.; Pearse, R.M.; Prowle, J.R. Incidence and associations of acute kidney injury after major abdominal surgery. *Intensive Care Med.* **2016**, *42*, 521–530. [CrossRef]
16. Quiney, N.H.S.; Peden, C.; Dickinson, M. Use of a care bundle to reduce mortality following emergency laparotomy. *Br. J. Hosp. Med.* **2015**, *76*, 358–362. [CrossRef]
17. Prytherch, D.R.; Whiteley, M.S.; Higgins, B.; Weaver, P.C.; Prout, W.G.; Powell, S.J. POSSUM and Portsmouth POSSUM for predicting mortality. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. *Br. J. Surg.* **1998**, *85*, 1217–1220. [CrossRef] [PubMed]
18. Levey, A.S.; Coresh, J.; Greene, T.; Stevens, L.A.; Zhang, Y.L.; Hendriksen, S.; Kusek, J.W.; Van Lente, F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann. Intern. Med.* **2006**, *145*, 247–254. [CrossRef] [PubMed]
19. The R Development Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2015.
20. Wickham, H. *Ggplot2: Elegant Graphics for Data Analysis*; Springer: New York, NY, USA, 2009.
21. Gordon, M.L.T. Advanced Forest Plot Using 'grid' Graphics. Available online: https://cran.r-project.org/web/packages/forestplot/forestplot.pdf (accessed on 20 August 2019).
22. Meyer, D.Z.A.; Hornik, A. Vcd: Visualizing Categorical Data. Available online: https://cran.r-project.org/web/packages/vcd/vcd.pdf (accessed on 20 August 2019).
23. Pearse, R.M.; Harrison, D.A.; MacDonald, N.; Gillies, M.A.; Blunt, M.; Ackland, G.; Grocott, M.P.; Ahern, A.; Griggs, K.; Scott, R.; et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. *JAMA* **2014**, *311*, 2181–2190. [CrossRef] [PubMed]
24. Grocott, M.P.; Dushianthan, A.; Hamilton, M.A.; Mythen, M.G.; Harrison, D.; Rowan, K. Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: A Cochrane Systematic Review. *Br. J. Anaesth.* **2013**, *111*, 535–548. [CrossRef]
25. Russell, J.A.; Walley, K.R.; Singer, J.; Gordon, A.C.; Hébert, P.C.; Cooper, D.J.; Holmes, C.L.; Mehta, S.; Granton, J.T.; Storms, M.M.; et al. Investigators TV: Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. *N. Eng. J. Med.* **2008**, *358*, 877–887. [CrossRef]
26. Sun, L.Y.; Wijeysundera, D.N.; Tait, G.A.; Beattie, W.S. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* **2015**, *123*, 515–523. [CrossRef]
27. Rhee, C.J.; Kibler, K.K.; Easley, R.B.; Andropoulos, D.B.; Czosnyka, M.; Smielewski, P.; Brady, K.M. Renovascular reactivity measured by near-infrared spectroscopy. *J. Appl. Physiol.* **2012**, *113*, 307–314. [CrossRef] [PubMed]
28. Bayliss, W.M. On the local reactions of the arterial wall to changes of internal pressure. *J. Physiol.* **1902**, *28*, 220–231. [CrossRef] [PubMed]
29. Meersch, M.; Schmidt, C.; Hoffmeier, A.; Van Aken, H.; Wempe, C.; Gerss, J.; Zarbock, A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med.* **2017**, *43*, 1551–1561. [CrossRef] [PubMed]

30. Gocze, I.; Jauch, D.; Gotz, M.; Kennedy, P.; Jung, B.; Zeman, F.; Gnewuch, C.; Graf, B.M.; Gnann, W.; Banas, B.; et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. *Ann. Surg.* **2017**, *267*, 1013–1020. [CrossRef]
31. Eknoyan, G.; Lameire, N.; Eckardt, K.; Kasiske, B.; Wheeler, D.; Levin, A.; Stevens, P.E.; Bilous, R.W.; Lamb, E.J.; Coresh, J.; et al. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int.* **2013**, *3*, 5–14.
32. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2007**, *11*, 411.
33. Ye, M.; Dai, Q.; Zheng, J.; Jiang, X.; Wang, H.; Lou, S.; Yu, K. The significance of post-operative creatinine in predicting prognosis in cardiac surgery patients. *Cell Biochem. Biophys.* **2014**, *70*, 587–591. [CrossRef]
34. Pearse, R. *Enhanced Peri-Operative Care for High-risk patients (EPOCH) Trial: A stepped Wedge Cluster Randomised Trial of a Quality Improvement Intervention for Patients Undergoing Emergency Laparotomy*; Queen Mary University of London: London, UK, 2014.
35. Dellinger, R.P.; Levy, M.M.; Rhodes, A.; Annane, D.; Gerlach, H.; Opal, S.M.; Sevransky, J.E.; Sprung, C.L.; Douglas, I.S.; Jaeschke, R.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. *Crit. Care Med.* **2013**, *41*, 580–637.
36. Aggarwal, G.; Peden, C.J.; Mohammed, M.A.; Pullyblank, A.; Williams, B.; Stephens, T.; Kellett, S.; Kirkby-Bott, J.; Quiney, N.; Emergency Laparotomy, C. Evaluation of the Collaborative Use of an Evidence-Based Care Bundle in Emergency Laparotomy. *JAMA Surg.* **2019**, *154*, e190145. [CrossRef]

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Acute Kidney Injury and In-Hospital Mortality: A Retrospective Analysis of a Nationwide Administrative Database of Elderly Subjects in Italy

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Abstract: Background: The aim of this study was to investigate the association between acute kidney injury (AKI) and in-hospital mortality (IHM) in a large nationwide cohort of elderly subjects in Italy. Methods: We analyzed the hospitalization data of all patients aged ≥65 years, who were discharged with a diagnosis of AKI, which was identified by the presence of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and extracted from the Italian Health Ministry database (January 2000 to December 2015). Data regarding age, gender, dialysis treatment, and comorbidity, including the development of sepsis, were also collected. Results: We evaluated 760,664 hospitalizations, the mean age was 80.5 ± 7.8 years, males represented 52.2% of the population, and 9% underwent dialysis treatment. IHM was 27.7% (210,661 admissions): Deceased patients were more likely to be older, undergoing dialysis treatment, and to be sicker than the survivors. The population was classified on the basis of tertiles of comorbidity score (the first group 7.48 ± 1.99, the second 13.67 ± 2,04, and third 22.12 ± 4.13). IHM was higher in the third tertile, whilst dialysis-dependent AKI was highest in the first. Dialysis-dependent AKI was associated with an odds ratios (OR) of 2.721; 95% confidence interval (CI) 2.676–2.766; $p < 0.001$, development of sepsis was associated with an OR of 1.990; 95% CI 1.948–2.033; $p < 0.001$, the second tertile of comorbidity was associated with an OR of 1.750; 95% CI 1.726–1.774; $p < 0.001$, and the third tertile of comorbidity was associated with an OR of 2.522; 95% CI 2.486–2.559; $p < 0.001$. Conclusions: In elderly subjects with AKI discharge codes, IHM is a frequent complication affecting more than a quarter of the investigated population. The increasing burden of comorbidity, dialysis-dependent AKI, and sepsis are the major risk factors.

Keywords: acute kidney injury; in-hospital mortality; comorbidity; International Classification of Diseases; 9th Revision; Clinical Modification (ICD-9-CM)

1. Introduction

Comorbidity is a risk factor for in-hospital mortality (IHM) and appears to be high in admitted elderly patients [1]. In elderly subjects, admissions due to acute medical complications, determinants of health status decline, and prediction of negative outcomes could be based on comorbidities [2]. Mortality has been associated with the development of acute kidney injury (AKI) [3]. In western society, multi-morbidity is frequently and increasingly reported, causing increased complexity in elderly subjects with different burdens of organ dysfunction [4–6]. The presence of comorbidities could increase the risk of AKI, and in previous studies, our group, utilizing administrative databases, evaluated

the relationship between renal dysfunction, comorbidities, and IHM in individuals hospitalized with myocardial infarction, pulmonary embolism, stroke, and severe chronic obstructive pulmonary disease [7–10]. Even a small increase in serum creatinine during admission has been significantly associated with mortality, hospital length-of-stay (LOS), and costs, after adjustment for age, gender, severity of illness, and chronic kidney disease in a sample of 19,982 adults [11]. It has been recently reported that in a large USA database, AKI increased hospitalization costs and LOS, especially if dialysis was required [12]. More than 50% of elderly adults have three or more chronic diseases and poor general conditions are associated with many adverse consequences. A comorbidity index is able to summarize all the coexistent illnesses in a single numeric score, allowing comparisons between different groups—the index suggests the severity of the patient's conditions [13]. In clinical practice, the Elixhauser Index is a well-known score able to summarize comorbidity into an index providing a single parameter [14]; however, because it was conceived in 1998, our group decided to modify and adapt it for our hospitalized patients [1]. Management of a specific disease in the presence of comorbidity is complex [15], and recognition of the high risk related to AKI in an aging population may help to avoid further morbidity and mortality. Elderly subjects are often treated similarly to the general population regardless of the comorbidity; this practice is unrealistic due to the fact that survival in sexagenarians is significantly different to survival in nonagenarians [16,17]. The risk factors for AKI in older adults are multiple comorbidities and polypharmacy [18,19], and AKI is a common complication in hospitalized older individuals [20]. The aim of this retrospective study was to evaluate the relationship between AKI, comorbidities, dialysis treatment, and IHM in a large sample of Italian elderly subjects.

2. Experimental Section

2.1. Patient Selection and Eligibility

The total number of hospitalizations due to AKI between 1 January 2000, and 31 December 2015, recorded in the Italian National Hospital database, provided by the Ministry of Health (SDO Database, Ministry of Health, General Directorate for Health Planning) were considered in this analysis. All hospitalizations of patients in public and private Italian hospitals are recorded in the National database of Hospital Discharge Records (HDR). Gender, age, date of hospital admission and discharge, department of admission and discharge, vital status at discharge (in-hospital death vs. discharged alive), main diagnosis, up to five co-morbidities, and up to six procedures/interventions, based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), are recorded in the HDR file. Because of the national disposition-by-law in terms of privacy, patients' names and all other potential identifiers were removed by the Ministry of Health from the database for this analysis. The only identifier, allowing us to search the database for possible recurrence of hospital admissions of the same patient, was a consecutive number for each patient. Administrative database codes usually make reference to acute renal failure, but in clinical settings, the term AKI has largely replaced that term. AKI was identified using as first or second discharge diagnosis ICD-9-CM code 584.xx. Finally, diagnosis of sepsis and diabetes were taken into consideration, and LOS was calculated.

2.2. Data Analysis

The outcome of this analysis was IHM being a hard clinical outcome indicator; therefore, fatal cases (death during hospitalization) were compared with non-fatal ones (patient discharged alive). The comorbidity score was evaluated using ICD-9-CM, and a novel score recently proposed by our group was calculated for considering the comorbidity burden [1]. The conditions of age, gender, presence of chronic kidney disease, neurological disorders, lymphoma, solid tumor with metastasis, ischemic heart disease, congestive heart disease, coagulopathy, fluid and electrolyte disorders, liver disease, weight loss, and metastatic cancer were taken into account for score calculation. The original score was corrected, removing the diagnosis of previous AKI, therefore points assigned to renal

diseases were considered only if chronic kidney disease was recorded during admission. The points for each condition ranged from 0 to 16, and the total score calculated could vary between 0 and 89. When the score was >40, the risk of IHM was >60%. The score, developed using administrative data, was calculated automatically. The points assigned to different conditions in order to calculate the risk score of IHM are reported in Table 1 [1]. Finally, data of IHM related to these patients were extracted from the general database.

Table 1. Points assigned to different conditions in order to calculate the score for risk of in-hospital mortality (IHM).

Items	Score
Age 0–60 (years)	0
Age 61–70 (years)	3
Age 71–80 (years)	7
Age 81–90 (years)	11
Age 91+ (years)	16
Chronic kidney disease	1
Male gender	2
Neurological disorders	3
Lymphoma	4
Solid tumor without metastasis	4
Ischemic heart disease	5
Congestive heart failure	5
Coagulopathy	8
Fluid and electrolyte disorders	8
Liver disease	10
Cachexia	11
Metastatic cancer	12

2.3. Statistical Analysis

Absolute numbers, percentages, and means ± SD were used to present data. A descriptive analysis of the whole population was performed, followed by a comparison of survivors and deceased during admission. The population was divided in tertiles based on the comorbidity score, and the three groups were compared according to all the parameters investigated. The analysis of the variables was done by using the Chi-Squared test, Student *t*-tests, Mann–Whitney *U* test, and ANOVA as appropriate. Moreover, in order to assess the independent parameters associated with IHM, the latter was considered as a dependent variable in a logistic regression analysis and demography; tertiles of the comorbidity score, dialysis treatment, and sepsis were considered as independent ones. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were reported. All *p*-values were 2-tailed, and p-value < 0.5 was considered significant. SPSS 13.0 for Windows (SPSS IN., Chicago, IL, USA, 2004) was used for statistical analysis.

2.4. Ethical Issues

This retrospective study was conducted in agreement with the declaration of Helsinki of 1975, revised in 2013. Subject identifiers were deleted before the analysis of the database in order to maintain data anonymity and confidentiality. None of the patients could be identified, either in this paper or

in the database. The study was conducted in agreement with the existent Italian disposition-by-law (G.U. n.76, 31/03/2008), and due to the study design ethics committee approval was not necessary.

3. Results

We analyzed 760,664 records, of which 52.2% were males. The mean age of the population was 80.5 ± 7.8 years, and mean LOS was 13.72 ± 15.49 days. The mean comorbidity score was 14.57 ± 6.21. The distribution of the score in the population is shown in Figure 1.

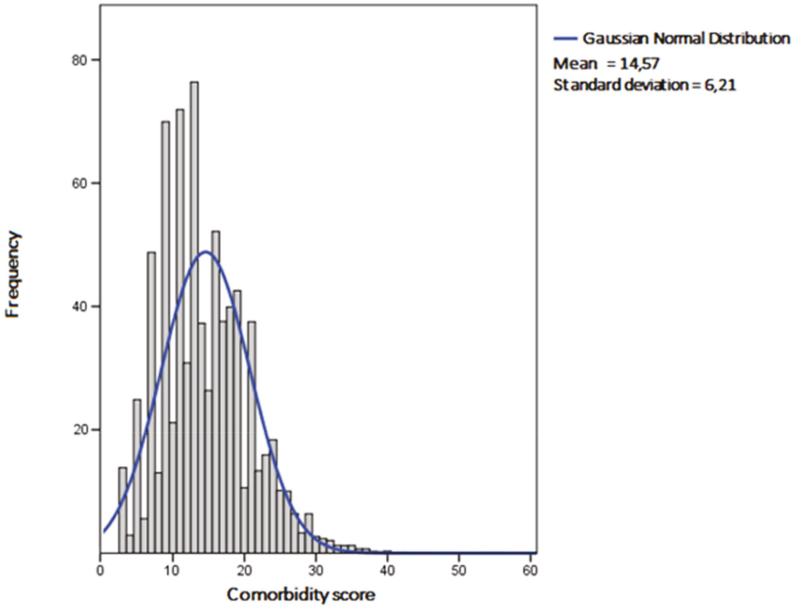

Figure 1. Distribution of the comorbidity score values in the population investigated.

The main characteristics of the investigated population are reported in Table 2.

Table 2. Characteristics of the considered population with acute kidney injury.

Total Number of Records	**760,664**
Men, (n (%))	397,174 (52.2)
Women, (n (%))	363,490 (47.8)
Age (years)	80.5 ± 7.8
Comorbidity score	14.57 ± 6.21
Dialysis-dependent acute kidney injury (AKI), (n (%))	68,653 (9)
Diabetes, (n (%))	115,238 (15.6)
Sepsis, (n (%))	39,144 (5.1)
Length-of-stay (LOS) (days)	13.72 ± 15.49
Deceased subjects, (n (%))	210,661 (27.7)

Heart failure was diagnosed in 146,359 (19.2%), fluid and electrolyte disorders in 126,702 (16.7%), chronic kidney disease in 115,238 (15.1%), cancer in 71,624 (9.4%,), ischemic heart diseases in 34,943 (4.6%), liver diseases in 34,015 (4.5%), metastatic cancer in 30,425 (4%), neurological disorders in 17,912

(2.4%), lymphoma in 16,443 (2.2%), cachexia in 15,363 (2%), and coagulopathy in 8266 (1.1%). Diabetics were 15.6% (n = 118,299) and patients with diagnosis of sepsis 5.1% (n = 39,144). Nine percent of the population underwent dialysis treatment, and overall IHM was 27.7% (210,661 hospitalizations). The frequency of survivors and deceased patients during the study period is reported in Figure 2.

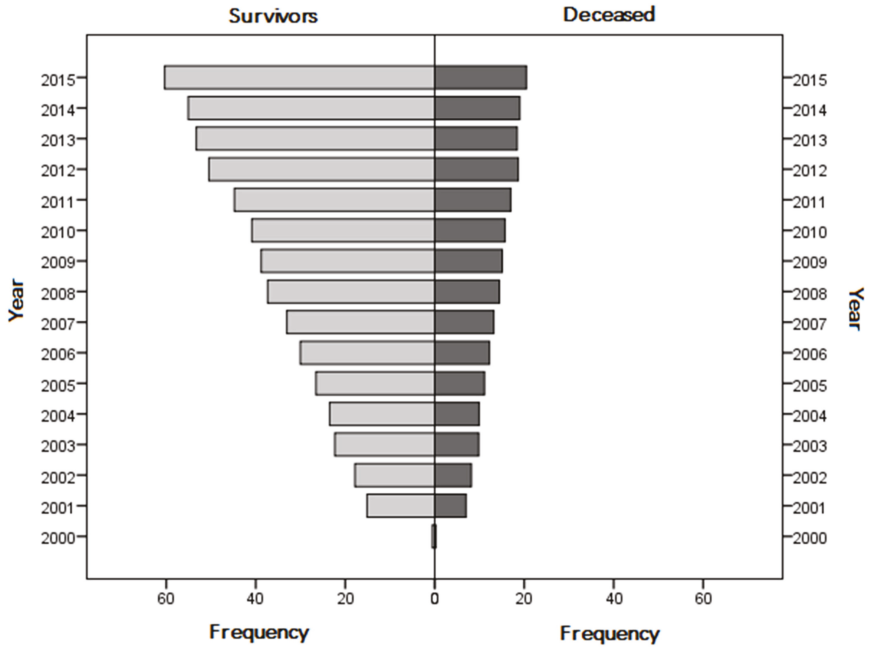

Figure 2. Prevalence of survivors and in-hospital mortality during the study period.

Deceased patients were older and the prevalence of women was higher. Moreover, deceased subjects had higher rates of sepsis diagnosis, were more likely to be on dialysis treatment, and were sicker than survivors; however, diabetes was more frequent in survivors (Table 3).

Table 3. Comparison of survivors and deceased individuals with acute kidney injury.

Parameters	Survivors	Deceased	*p*
	n = 550,003	n = 210,661	
Men, (n (%))	288,120 (52.4)	109,054 (51.8)	<0.001
Women, (n (%))	261,883 (47.6)	101,607 (48.2)	
Age (years)	80 ± 7.72	81.9 ± 7.9	<0.001
Comorbidity score	14.04 ± 6.02	15.96 ± 6.48	<0.001
Dialysis-dependent AKI, (n (%))	37,598 (6.8)	31,055 (14.7)	<0.001
Diabetes, (n (%))	95,433 (17.4)	22,866 (10.9)	<0.001
Sepsis, (n (%))	23,230 (4.2)	15,914 (7.6)	<0.001

The comorbidity score of the population was classified on the basis of tertiles: in the first tertile, the score was lower than 11; in the second, it was between 11 and 17; and in the third, it was higher than 17. Comparison between the three groups is reported in Table 4.

Table 4. Comparison of subjects divided into tertiles.

Parameters	First Tertile (Score < 11)	Second Tertile (11 ≤ Score ≤ 17)	Third Tertile (Score > 17)	*p*
Number of subjects	200,131 (26.3%)	332,533 (43.7%)	228,000 (30%)	
Length-of-stay (days)	15.6 ± 19	13.59 ± 14.5	12.28 ± 13.1	<0.001
Comorbidity score	7.48 ± 1.99	13.67 ± 2,04	22.12 ± 4.13	<0.001
Males, (n (%))	119,798 (59.9%)	144,464 (43.4%)	132,912 (58.3%)	<0.001
Females, (n (%))	80,333 (40.1%)	188,069 (56.6%)	95,088 (41.7%)	
Deceased, (n (%))	38,740 (19.4%)	92,987 (28%)	78,934 (34.6%)	<0.001
Dialysis-dependent AKI, (n (%))	26,901 (13.4%)	29,054 (8.7%)	12,698 (5.6%)	<0.001
Sepsis, (n (%))	12,652 (6.3%)	17,944 (5.4%)	8,548 (3.7%)	<0.001
Chronic kidney disease (n (%))	32,217 (16.1%)	49,308 (14.8%)	33,713 (14.8%)	<0.001
Neurological disorders (n (%))	2609 (1.3%)	8661 (2.6%)	6642 (2.9%)	<0.001
Lymphoma (n (%))	2856 (1.4%)	9145 (2.8%)	4442 (1.9%)	<0.001
Solid tumor without metastasis (n (%))	5888 (2.9%)	29,907 (9%)	35,829 (15.7%)	<0.001
Ischemic heart disease (n (%))	2042 (1%)	14,001 (4.2%)	18,900 (8.3%)	<0.001
Congestive heart failure (n (%))	7109 (3.6%)	67,211 (20.2%)	72,039 (31.6%)	<0.001
Coagulopathy (n (%))	0	2780 (0.8%)	5486 (2.4%)	<0.001
Fluid and electrolyte disorders (n (%))	0	33,322 (10%)	93,380 (41%)	<0.001
Liver disease (n (%))	0	8578 (2.6%)	25,437 (11.2%)	<0.001
Cachexia (n (%))	0	441 (0.1%)	14,922 (6.5%)	<0.001
Metastatic cancer (n (%))	0	2009 (0.6%)	28,416 (12.5%)	<0.001

IHM was independently associated with dialysis-dependent AKI (OR 2.721; 95% CI 2.676–2.766; $p < 0.001$), development of sepsis (OR 1.990; 95% CI 1.948–2.033; $p < 0.001$), the second tertile of comorbidity (OR 1.750; 95% CI 1.726–1.774; $p < 0.001$), and the third tertile of comorbidity (OR 2.522; 95% CI 2.486–2.559; $p < 0.001$) (Figure 3, the first tertile was used as the reference).

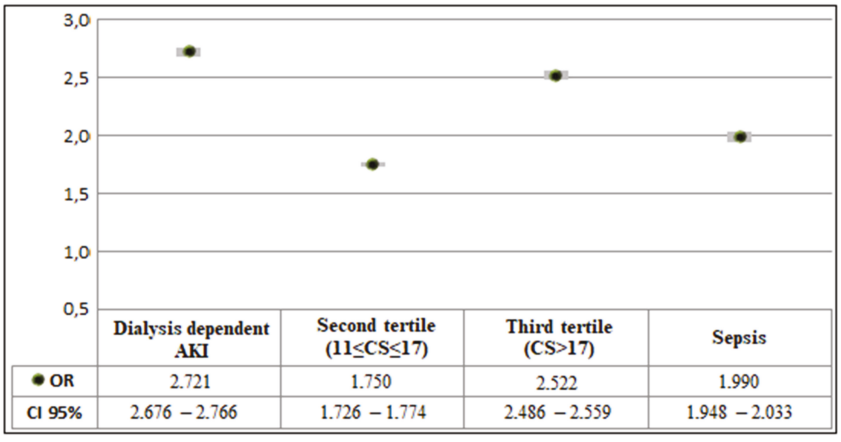

Figure 3. Multivariate analysis results relating the association between in-hospital mortality, comorbidity, and dialysis treatment in individuals with acute kidney injury. CS: Comorbidity Score (in all cases $p < 0.001$; Hosmer and Lemeshow test $p < 0.001$).

4. Discussion

To the best of our knowledge, this is the first national Italian study testing the impact of comorbidity on IHM in elderly subjects admitted with AKI. The score tested had an approximately normal distribution, and the population showed a gradual increase in the number of admissions and IHM during the study period. The mean score in the whole population was 14.57, and the mean score in deceased subjects was 15.96. However, when the tertiles were analyzed, in the highest tertile, we detected a mean score value of 22.12, and more than one-third of subjects belonging to this group died during hospitalization. Univariate analysis showed that the group of patients in the third tertile had a higher comorbidity burden due to a higher prevalence of cancer and cardiovascular morbidity, the two major causes of death in western societies. Such a burden of comorbidity was not related to sepsis or to dialysis-dependent AKI. Our data suggest that physicians did not think that dialyzing AKI patients with a high comorbidity burden could be beneficial. Probably, as a result of this finding, LOS in patients with a high comorbidity score was lower. Previously, we reported that the score used in this study and sepsis diagnosis were able to predict IHM in patients hospitalized for infectious diseases [21]. In this study, sepsis had a lower prevalence in the third tertile of the comorbidity burden; however, as well as increasing comorbidity, it was independently associated with IHM. In this study, a diagnosis of sepsis was made more frequently in the group of patients with a lower comorbidity burden, and in the same group, dialysis-dependent AKI had a higher prevalence, suggesting that there was a relationship between the two findings, i.e., subjects with sepsis developed dialysis-dependent AKI. Diabetes, a well-known risk factor for mortality, was recorded in 15.6% of cases, and appeared to be more frequent in survivors. However, this finding could be ascribed to a bias associated with our study design. Conditions pre-existing at the time of admission, such as diabetes, are poorly coded if the hospitalization procedure is complicated and if the patient dies [22]. In studies analyzing administrative databases, diabetes usually appears to be protective. The comparison of survivors and deceased patients could not show the real difference in the comorbidity burden, but the analysis of tertiles of the comorbidity burden and logistic regression analysis suggested that the three factors related to IHM were increasing comorbidity score due to cardiovascular and liver disease, cachexia and cancer, diagnosis of sepsis, and advanced renal damage requiring dialysis treatment. Increasing the tertiles of comorbidity score had an impact on mortality similar to dialysis-dependent AKI and sepsis.

We run the Hosmer–Lemeshow test in order to evaluate the goodness of fit of our logistic regression, and we could detect that our data were not fitting well into the model. The Hosmer–Lemeshow test calculates if the observed event rates match the expected event rates in population subgroups. By this analysis, data are grouped by ordering the predicted probabilities and forming the number of groups. The small p-value indicates mean that the fit of the model is poor, however, large p-values don't necessarily mean that the model is a good fit. Changing the number of subgroups by very small amounts may result in wild changes in p-values. Therefore, we do not think that Hosmer–Lemeshow calculated by our data could be of any significance, due to the fact that, we analyzed a very large population at a national level.

The real-world epidemiology of AKI in western societies is still a matter of debate. The different figures reported in the medical literature are due to the different clinical settings in which studies have been carried out. Several comorbidities have been reported in the list of risk factors for AKI, including diabetes mellitus, cardiovascular disease, chronic liver disease, cancer, and complex surgery [23]; moreover, in individuals with AKI, mortality appears to be related to the stage of the syndrome [24,25]. AKI is a complex condition related to different etiologies and pathophysiological mechanisms; it is commonly diagnosed in hospitalized patients, and leads to increased morbidity, mortality, and health care costs [26]. Different biomarkers have been investigated in order to predict AKI outcomes [27,28], however, we think that consideration of the clinical history of patients developing AKI could improve risk stratification.

Similar to our study, Hsu et al. [29] evaluated dialysis-requiring AKI cases using ICD-9-CM codes. Over a decade (2000–2009), incidence of dialysis-requiring AKI increased, and the risk factors

for its development were older age, male sex, black race, and sepsis, as well as acute heart failure, and invasive procedures; mortality was associated with dialysis-requiring AKI and showed an increased frequency [29].

We detected an increasing number of hospitalizations with AKI during the study period. Similar findings were reported by a study analyzing administrative databases between 1988 and 2002. During this period, the incidence of AKI increased from 61 to 288 per 100,000; the incidence of AKI requiring dialysis rose from 4 to 27 per 100,000. On the contrary, IHM decreased from 40.4% to 20.3% in patients with AKI and from 41.3% to 28.1% in those with AKI that required dialysis [30]. The increasing number of admissions and deaths during the study period would be ascribed to two different factors, the first one could be related to a better way of coding by physicians, the second one, could be related to the aging of the population and the change in the organization of Italian health system.

Similar to our study, Liangos et al. [31] defined the epidemiology of AKI using the United States national administrative ICD-9-CM database. AKI was frequent in older, male, black individuals and was associated with chronic kidney disease, congestive heart failure, chronic lung disease, sepsis, and cardiac surgery. In our study, diagnosis of chronic kidney disease was higher in the lowest tertile of the comorbidity score, the same group with a higher prevalence of dialysis-dependent AKI. We cannot exclude the possibility that this group included elderly patients with a low comorbidity burden with decreasing renal function who needed dialysis treatment. Moreover, AKI can be a post-surgical complication, but even in these cases, comorbidity appears to be crucial in determining patients' prognosis, as shown by Thakar et al. [32] in their study on open-heart surgery. Female gender, congestive heart failure with low ejection fraction, preoperative use of an intra-aortic balloon pump, chronic obstructive pulmonary disease, diabetes, previous surgery, and serum creatinine were associated with mortality and AKI. As in our study, the authors classified subjects in different risk categories of increasing severity [32].

Several studies stratified populations with AKI using different scores, but these indexes were mainly developed in intensive care settings. On the contrary, we tried to stratify our population using a simple score based on administrative data and derived from internal medicine admitted patients. The use of the APACHE II score, especially when modified by the presence or absence of oliguria, should help in predicting the outcome when evaluating interventions for patients with AKI [33]. In 2000, Fiaccadori et al. [34] tested the predictive ability of three general prognostic models: version II of the Acute Physiology and Chronic Health Evaluation (APACHE II), version II of the Simplified Acute Physiology Score, and version II of the Mortality Probability Model at 24 h in a prospective, single-center cohort of patients with AKI in a nephrology setting. They concluded that the APACHE II score was slightly better in predicting mortality. Again, the score used in this study was simple, taking into consideration a small amount of demographic data; in fact, the score included only age and gender; we did not consider race. In Italy, the great majority of hospitalized patients were Caucasian. In 2006, Xue et al. [35] determined the incidence and mortality of AKI in Medicare beneficiaries. They found that older age, male sex, and black race were associated with development of AKI. IHM was 15.2% if AKI was the principal diagnosis at the time of discharge, and 32.6% in discharges with AKI as a secondary diagnosis [35].

Even small acute changes in serum creatinine levels in hospitalized patients increased short-term mortality [36]. In our study, we included elderly patients with AKI without considering different hospital settings. AKI is encountered in 5%–10% of hospitalized patients and up to 60% in individuals admitted to the intensive care unit [37]. In 1996, the epidemiology of AKI was evaluated in 13 tertiary-care Spanish hospitals, covering a population of 4.2 million persons. During a nine-month period, the incidence of AKI was 209 cases per million. Mortality was calculated to be 45%; however, negative outcome in many cases was attributed to underlying diseases, reducing the mortality caused by AKI to 26.7%. Dialysis-dependent AKI was recorded in 36% of individuals [37]. Our mortality was similar, but the percentage of dialysis-dependent AKI was much lower, suggesting that a different selection of the population was investigated. Our data are in agreement with results reported by

Chertow et al. [38] who showed that dialysis-dependent AKI and sepsis were independently associated with IHM.

Limitations

We are aware of several limitations of our study: (i) The design was retrospective, based on administrative data, and we could not assess complications due to AKI such as fluid overload, electrolyte abnormalities, and coagulopathy. It has been reported that complications related to AKI such as fluid overload could be associated with a risk of death [39]. However, our results suggest that conditions diagnosed well before the detection of AKI could be associated with IHM; (ii) we did not provide reasons for admission, specific cause of death, intensive care level, including aggressive therapy and/or device use, neither did we identify AKI on the basis of international Kidney Disease Improving Global Outcomes (KDIGO) guidelines [40]; (iii) we could not evaluate the impact of clinical or biochemical parameters due to the fact that they were not available. There are evident disadvantages in studies based on administrative databases, such as a lack of specific clinical information, the effects of administrative use (i.e., reimbursement), possible misclassification of outcomes, and difficulties in controlling confounding factors [41]. Moreover, as previously stated, race and clinical settings (i.e., surgical and intensive care settings) were not considered; (iv) patients could be wrongly coded, and subjects that are nowadays coded with AKI may have suffered a less severe renal insult than previously. This could be because awareness of AKI has improved; (v) we did not differentiate patients on the basis of the cause of AKI and the treatment setting, we only considered dialysis treatment. On the other hand, only advanced stages of AKI undergo renal replacement therapy. Furthermore, we could not distinguish if AKI happened before or during admission. In 2006, Waikar et al. [42] calculated the performance of ICD-9-CM for acute renal failure and found that the sensitivity was 35.4%, specificity 97.7%, positive predictive value 47.9%, and negative predictive value 96.1% [42]. The validity of AKI codes in administrative databases was analyzed in 2011 in Canada: sensitivity was poor, the median value was 29% (in the range 1%–81%), and median of the positive predictive value was 67% (in the range 15%–96%) [43]. In 2013, Tomlinson et al. [44] calculated a positive predictive value for patients with AKI of 95%. In 2014, Grams et al. [45] validated administrative codes for AKI against the KDIGO AKI definition. They calculated a sensitivity of 17.2% if the comparison was the evaluation of serum creatinine criteria, and 11.7% if the comparison was serum creatinine and urine output-based criteria, whilst specificity was >98% in both cases. Sensitivity was significantly higher when they considered a more recent time period and individuals aged ≥65 years. AKI diagnosed by administrative data was related to more severe disease and higher in-hospital mortality [45]. All these data seem to reinforce our results.

Our study also has some strengths: (i) The high number of records derived from a national administrative database, recording all real diagnoses of AKI; (ii) the long period considered; (iii) the choice of IHM as hard outcome indicator.

5. Conclusions

Nowadays, multi-morbidity is receiving greater attention [15], and our findings confirm that comorbidity stratification is crucial to understanding the reasons for IHM of hospitalized elderly patients with AKI. The results of this study emphasize that in elderly subjects, IHM is associated with a degree of renal impairment (especially if the damage needs dialysis treatment), sepsis development, and an increasing burden of comorbidity. Increasing comorbidity score, ascribed to cardiovascular and liver disease, cachexia and cancer, diagnosis of sepsis and advanced renal damage requiring dialysis treatment should be taken into account when evaluating the risk of IHM in hospitalized elderly subjects with AKI.

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F.F. and C.S.; writing—review and editing, R.M.; supervision, A.S. and M.G.; project administration, M.G.; funding acquisition, R.M.

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References

1. Fabbian, F.; De Giorgi, A.; Maietti, E.; Gallerani, M.; Pala, M.; Cappadona, R.; Manfredini, R.; Fedeli, U. A modified Elixhauser score for predicting in-hospital mortality in internal medicine admissions. *Eur. J. Intern. Med.* **2017**, *40*, 37–42. [CrossRef] [PubMed]
2. Clegg, A.; Young, J.; Iliffe, S.; Rikkert, M.O.; Rockwood, K. Frailty in elderly people. *Lancet* **2013**, *381*, 752–762. [CrossRef]
3. Hounkpatin, H.O.; Fraser, S.D.S.; Glidewell, L.; Blakeman, T.; Lewington, A.; Roderick, P.J. Predicting risk of recurrent acute kidney injury: A systematic review. *Nephron* **2019**, *142*, 83–90. [CrossRef] [PubMed]
4. Xu, X.; Mishra, G.D.; Jones, M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. *Ageing Res. Rev.* **2017**, *37*, 53–68. [CrossRef] [PubMed]
5. Klompstra, L.; Ekdahl, A.W.; Krevers, B.; Milberg, A.; Eckerblad, J. Factors related to health-related quality of life in older people with multimorbidity and high health care consumption over a two-year period. *BMC Geriatr.* **2019**, *19*, 187. [CrossRef] [PubMed]
6. Millá-Perseguer, M.; Guadalajara-Olmeda, N.; Vivas-Consuelo, D.; Usó-Talamantes, R. Measurement of health-related quality by multimorbidity groups in primary health care. *Health Qual. Life Outcomes* **2019**, *17*, 8. [CrossRef] [PubMed]
7. Fabbian, F.; Pala, M.; De Giorgi, A.; Manfredini, F.; Mallozzi Menegatti, A.; Salmi, R.; Portaluppi, F.; Gallerani, M.; Manfredini, R. In-hospital mortality in patients with renal dysfunction admitted for myocardial infarction: The Emilia-Romagna region of Italy database of hospital admissions. *Int. Urol. Nephrol.* **2013**, *45*, 769–775. [CrossRef] [PubMed]
8. Fabbian, F.; Gallerani, M.; Pala, M.; De Giorgi, A.; Salmi, R.; Manfredini, F.; Portaluppi, F.; Dentali, F.; Ageno, W.; Mikhailidis, D.P.; et al. In-hospital mortality for pulmonary embolism: Relationship with chronic kidney disease and end-stage renal disease. The hospital admission and discharge database of the Emilia Romagna region of Italy. *Intern. Emerg. Med.* **2013**, *8*, 735–740.
9. Fabbian, F.; Gallerani, M.; Pala, M.; De Giorgi, A.; Salmi, R.; Dentali, F.; Ageno, W.; Manfredini, R. Association between in-hospital mortality and renal dysfunction in 186 219 patients hospitalized for acute stroke in the Emilia-Romagna region of Italy. *Angiology* **2014**, *65*, 906–910. [CrossRef]
10. Fabbian, F.; De Giorgi, A.; Manfredini, F.; Lamberti, N.; Forcellini, S.; Storari, A.; Gallerani, M.; Caramori, G.; Manfredini, R. Impact of renal dysfunction on in-hospital mortality of patients with severe chronic obstructive pulmonary disease: A single-center Italian study. *Int. Urol. Nephrol.* **2016**, *48*, 1121–1127. [CrossRef]
11. Chertow, G.M.; Burdick, E.; Honour, M.; Bonventre, J.V.; Bates, D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–7330. [CrossRef] [PubMed]
12. Silver, S.A.; Long, J.; Zheng, Y.; Chertow, G.M. Cost of Acute Kidney Injury in Hospitalized Patients. *J. Hosp. Med.* **2017**, *12*, 70–76. [CrossRef] [PubMed]
13. Gijsen, R.; Hoeymans, N.; Schellevis, F.G.; Ruwaard, D.; Satariano, W.A.; van den Bos, G.A. Causes and consequences of comorbidity: A review. *J. Clin. Epidemiol.* **2001**, *54*, 661–674. [CrossRef]
14. Elixhauser, A.; Steiner, C.; Harris, D.R.; Coffey, R.M. Comorbidity measures for use with administrative data. *Med. Care* **1998**, *36*, 8–27. [CrossRef] [PubMed]
15. Barnett, K.; Mercer, S.W.; Norbury, M.; Watt, G.; Wyke, S.; Guthrie, B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **2012**, *380*, 37–43. [CrossRef]
16. Randall, G.K.; Martin, P.; Bishop, A.J.; Poon, L.W.; Johnson, M.A. Age differences and changes in resources essential to aging well: A comparison of sexagenarians, octogenarians, and centenarians. *Curr. Gerontol. Geriatr. Res.* **2011**, *2011*, 357896. [CrossRef] [PubMed]

17. Santoni, G.; Angleman, S.; Welmer, A.K.; Mangialasche, F.; Marengoni, A.; Fratiglioni, L. Age-related variation in health status after age 60. *PLoS ONE* **2015**, *10*, e0120077.
18. Ge, S.; Nie, S.; Liu, Z.; Chen, C.; Zha, Y.; Qian, J.; Liu, B.; Teng, S.; Xu, A.; Bin, W.; et al. Epidemiology and outcomes of acute kidney injury in elderly Chinese patients: A subgroup analysis from the EACH study. *BMC Nephrol.* **2016**, *17*, 136. [CrossRef]
19. Chao, C.T.; Tsai, H.B.; Wu, C.Y.; Lin, Y.F.; Hsu, N.C.; Chen, J.S.; Hung, K.Y. Cumulative cardiovascular polypharmacy is associated with the risk of acute kidney injury in elderly patients. *Medicine* **2015**, *94*, e1251. [CrossRef]
20. Gong, Y.; Zhang, F.; Ding, F.; Gu, Y. Elderly patients with acute kidney injury (AKI): Clinical features and risk factors for mortality. *Arch. Gerontol. Geriatr.* **2012**, *54*, e47–e51. [CrossRef]
21. Fabbian, F.; De Giorgi, A.; Boari, B.; Misurati, E.; Gallerani, M.; Cappadona, R.; Cultrera, R.; Manfredini, R.; Rodrìguez Borrego, M.A.; Lopez-Soto, P.J. Infections and internal medicine patients: Could a comorbidity score predict in-hospital mortality? *Medicine* **2018**, *97*, e12818. [CrossRef] [PubMed]
22. Grimes, D.A. Epidemiologic research using administrative databases—Garbage in, garbage out. *Obstet. Gynecol.* **2010**, *116*, 1018–1019. [CrossRef] [PubMed]
23. Lameire, N.H.; Bagga, A.; Cruz, D.; De Maeseneer, J.; Endre, Z.; Kellum, J.A.; Liu, K.D.; Mehta, R.L.; Pannu, N.; Van Biesen, W.; et al. Acute kidney injury: An increasing global concern. *Lancet* **2013**, *382*, 170–179. [CrossRef]
24. Moore, P.K.; Hsu, R.K.; Liu, K.D. Management of acute kidney injury: Core curriculum 2018. *Am. J. Kidney Dis.* **2018**, *72*, 136–148. [CrossRef] [PubMed]
25. Joannidis, M.; Metnitz, B.; Bauer, P.; Schusterschitz, N.; Moreno, R.; Druml, W.; Metnitz, P.G. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* **2009**, *35*, 1692–1702. [CrossRef] [PubMed]
26. Gameiro, J.; Fonseca, J.A.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef] [PubMed]
27. Wu, V.-C.; Shiao, C.-C.; Chi, N.-H.; Wang, C.-H.; Chueh, S.-C.J.; Liou, H.-H.; Spapen, H.D.; Honore, P.M.; Chu, T.-S. Outcome Prediction of Acute Kidney Injury Biomarkers at Initiation of Dialysis in Critical Units. *J. Clin. Med.* **2018**, *7*, 202. [CrossRef]
28. Douvris, A.; Zeid, K.; Hiremath, S.; Brown, P.A.; Sood, M.M.; Abou Arkoub, R.; Malhi, G.; Clark, E.G. Safety Lapses Prior to Initiation of Hemodialysis for Acute Kidney Injury in Hospitalized Patients: A Patient Safety Initiative. *J. Clin. Med.* **2018**, *7*, 317. [CrossRef]
29. Hsu, R.K.; McCulloch, C.E.; Dudley, R.A.; Lo, L.J.; Hsu, C.Y. Temporal changes in incidence of dialysis-requiring AKI. *J. Am. Soc. Nephrol.* **2013**, *24*, 37–42. [CrossRef]
30. Waikar, S.S.; Curhan, G.C.; Wald, R.; McCarthy, E.P.; Chertow, G.M. Declining mortality in patients with acute renal failure, 1988 to 2002. *J. Am. Soc. Nephrol.* **2006**, *17*, 1143–1150. [CrossRef]
31. Liangos, O.; Wald, R.; O'Bell, J.W.; Price, L.; Pereira, B.J.; Jaber, B.L. Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. *Clin. J. Am. Soc. Nephrol.* **2006**, *1*, 43–51. [CrossRef] [PubMed]
32. Thakar, C.V.; Arrigain, S.; Worley, S.; Yared, J.P.; Paganini, E.P. A clinical score to predict acute renal failure after cardiac surgery. *J. Am. Soc. Nephrol.* **2005**, *16*, 162–168. [CrossRef] [PubMed]
33. Parker, R.A.; Himmelfarb, J.; Tolkoff-Rubin, N.; Chandran, P.; Wingard, R.L.; Hakim, R.M. Prognosis of patients with acute renal failure requiring dialysis: Results of a multicenter study. *Am. J. Kidney Dis.* **1998**, *32*, 432–443. [CrossRef]
34. Fiaccadori, E.; Maggiore, U.; Lombardi, M.; Leonardi, S.; Rotelli, C.; Borghetti, A. Predicting patient outcome from acute renal failure comparing three general severity of illness scoring systems. *Kidney Int.* **2000**, *58*, 283–292. [CrossRef] [PubMed]
35. Xue, J.L.; Daniels, F.; Star, R.A.; Kimmel, P.L.; Eggers, P.W.; Molitoris, B.A.; Himmelfarb, J.; Collins, A.J. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J. Am. Soc. Nephrol.* **2006**, *17*, 1135–1142. [CrossRef]
36. Coca, S.G.; Peixoto, A.J.; Garg, A.X.; Krumholz, H.M.; Parikh, C.R. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **2007**, *50*, 712–720. [CrossRef]

37. Liaño, F.; Pascual, J. Epidemiology of acute renal failure: A prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. *Kidney Int.* **1996**, *50*, 811–818. [CrossRef]
38. Chertow, G.M.; Soroko, S.H.; Paganini, E.P.; Cho, K.C.; Himmelfarb, J.; Ikizler, T.A.; Mehta, R.L. Mortality after acute renal failure: Models for prognostic stratification and risk adjustment. *Kidney Int.* **2006**, *70*, 1120–1126. [CrossRef]
39. Bouchard, J.; Soroko, S.B.; Chertow, G.M.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Mehta, R.L. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* **2009**, *76*, 422–427. [CrossRef]
40. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO. clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
41. Mazzali, C.; Duca, P. Use of administrative data in healthcare research. *Intern. Emerg. Med.* **2015**, *10*, 517–524. [CrossRef] [PubMed]
42. Waikar, S.S.; Wald, R.; Chertow, G.M.; Curhan, G.C.; Winkelmayer, W.C.; Liangos, O.; Sosa, M.A.; Jaber, B.L. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure. *J. Am. Soc. Nephrol.* **2006**, *17*, 1688–1694. [CrossRef] [PubMed]
43. Vlasschaert, M.E.; Bejaimal, S.A.; Hackam, D.G.; Quinn, R.; Cuerden, M.S.; Oliver, M.J.; Iansavichus, A.; Sultan, N.; Mills, A.; Garg, A.X. Validity of administrative database coding for kidney disease: A systematic review. *Am. J. Kidney Dis.* **2011**, *57*, 29–43. [CrossRef] [PubMed]
44. Tomlinson, L.A.; Riding, A.M.; Payne, R.A.; Abel, G.A.; Tomson, C.R.; Wilkinson, I.B.; Roland, M.O.; Chaudhry, A.N. The accuracy of diagnostic coding for acute kidney injury in England—A single centre study. *BMC Nephrol.* **2013**, *14*, 58. [CrossRef] [PubMed]
45. Grams, M.E.; Waikar, S.S.; MacMahon, B.; Whelton, S.; Ballew, S.H.; Coresh, J. Performance and limitations of administrative data in the identification of AKI. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 682–689. [CrossRef]

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Review

Acute Kidney Injury Definition and Diagnosis: A Narrative Review

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Abstract: Acute kidney injury (AKI) is a complex syndrome characterized by a decrease in renal function and associated with numerous etiologies and pathophysiological mechanisms. It is a common diagnosis in hospitalized patients, with increasing incidence in recent decades, and associated with poorer short- and long-term outcomes and increased health care costs. Considering its impact on patient prognosis, research has focused on methods to assess patients at risk of developing AKI and diagnose subclinical AKI, as well as prevention and treatment strategies, for which an understanding of the epidemiology of AKI is crucial. In this review, we discuss the evolving definition and classification of AKI, and novel diagnostic methods.

Keywords: acute kidney injury; definition; incidence; classification

1. Introduction

Acute kidney injury (AKI) is a complex syndrome characterized by a decrease in renal function, associated with numerous etiologies and pathophysiological mechanisms [1,2]. It is a common diagnosis in hospitalized patients, associated with poorer short- and long-term outcomes and increased health care costs [3].

The incidence of AKI has increased in recent years [2,3]. However, there is significant variability in the reported incidence of AKI, which is associated with the different characteristics of the populations studied, cause of AKI, and diagnostic criteria used [1–4]. Additionally, the lack of studies assessing AKI in community settings and comparing critically ill and non-critical patients hampers the characterization of the epidemiology of AKI [2–4].

The importance of recognizing AKI applies to pediatric and adult patients, as well as ambulatory, hospitalized, and critically ill patients in multiple clinical settings, due to its prognostic impact [4–6]. The incidence of AKI is lowest in ambulatory patients and higher in critically ill and patients which need dialysis [4–8]. In literature reviews, AKI is most commonly reported in surgical and critical settings, where patients are systematically monitored by assessing hourly urinary output and daily creatinine. Despite the lack of extensive data, this syndrome has undeniable importance also in internal medicine wards, where cardiorenal syndrome plays a substantial role [1–3,9]. Indeed, AKI occurs in up to 40% of acute decompensated heart failure hospitalizations, which differs according to the criteria used to define AKI [10]. This is known as cardiorenal syndrome type 1 and is an important prognostic factor [10]. Importantly, with the increase in patients with heart failure, the prevalence of this syndrome is also estimated to rise in the near future [9,10]. Mortality rates have declined in critically ill patients, although an increase has been reported in patients with dialysis-requiring AKI [5–11].

AKI is more common in older patients and those with predisposing factors, who present with a higher rate of comorbidities and higher probability of developing severe disease [12]. Sepsis is

the leading cause of AKI in critically ill patients, accounting for 50% of cases [13,14]. Furthermore, the differences in patient characteristics, setting, pathophysiology, and outcomes distinguish septic AKI as a separate clinical entity from non-septic AKI [14]. Indeed, septic AKI patients are more likely to require mechanically assisted ventilation and vasoactive drugs, and have longer hospital stays, a higher likelihood of dialysis-requiring AKI, and higher in-hospital mortality rates. Moreover, they have an increased probability of renal function recovery [15,16].

Surgery is another important cause of AKI that accounts for up to 40% of in-hospital AKI cases [17,18]. The highest rates of AKI are found after cardiac (18.7%), general (13.2%), and thoracic (12.0%) surgeries, representing the impact of surgical settings on the incidence variability [19,20].

Recently, the Acute Disease Quality Initiative Workgroup proposed the term acute kidney disease (AKD) to reflect the continuing pathological processes and adverse events developing after AKI [20]. AKD is defined by presenting Kidney Disease Improving Global Outcomes (KDIGO) stage 1 criteria for longer than 7 days after an AKI initiating event [20]. This definition includes the post-AKI period in which critical interventions potentially alter the progression of kidney disease, therefore recognizing a population at risk of chronic kidney disease (CKD) development, cardiovascular events, and mortality [20].

Considering the impact of AKI on patient prognosis, research has focused on methods to assess patients at risk for developing AKI and diagnose subclinical AKI, as well as prevention and treatment strategies, for which it is crucial to have an understanding of the epidemiology of AKI. In this review, we discuss the evolving definition and classification of AKI, and its novel diagnostic methods.

2. Definitions and Classification

Over the last century, the definition of AKI has evolved significantly [21]. In fact, the diagnosis of AKI has changed from a clinical and biochemical level to a molecular level, with the most recent advances in tubular damage biomarkers increasing the accuracy of the diagnosis [21]. The use of standard classifications to define and stratify AKI has helped to increase the recognition of this disease in clinical practice and epidemiological research, which has led to defining the incidence of AKI in different settings and assessing its association with adverse outcomes [20,21]. This highlighted the importance of prevention, early diagnosis, and prompt treatment of AKI.

2.1. Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) Classification

The RIFLE classification was first published in 2004, resulting from the Acute Dialysis Quality Initiative (ADQI) group conference, which aimed to determine a consensual AKI definition [22]. This classification defines AKI based on variations in serum creatinine (SCr) or estimated glomerular filtration rate (eGFR) and/or urine output (UO), and contemplates three severity levels (risk, injury, and failure) and two outcomes (loss of kidney function and end-stage kidney disease) in AKI [22]. The criteria to use are those that lead to the most negative classification, meaning the maximum RIFLE. The deterioration of renal function from baseline must occur within 7 days and persist for more than 24 h. When baseline SCr is unknown and there is no history of chronic kidney disease, the Modification of Diet in Renal Disease (MDRD) equation should be used to calculate the baseline SCr [23].

The RIFLE classification has been used for determining the incidence of AKI, stratifying AKI severity in multiple settings, and establishing the association between AKI severity and mortality [3,8,24,25]. Despite some limitations, this classification was vital in standardizing the criteria of AKI and confirming AKI severity as an outcome predictor [26].

2.2. Acute Kidney Injury Network (AKIN) Classification

In 2007, the AKIN classification was proposed and published by the AKIN working group [27]. There was cumulative evidence demonstrating that small increases in SCr were associated with poor outcomes and that there was variation between hospitals regarding the start of renal replacement therapy, leading to the importance of revising the RIFLE classification [28–30].

The AKIN classification depends only on SCr and not on eGFR changes, and does not require baseline SCr, but needs at least two values of SCr obtained within a period of 48 h, thus defining AKI as an increase in SCr of at least 0.3 mg/dL or a percentage increase in SCr equal to or higher than 50%, or by a decrease in UO lower than 0.5 mL/kg/h for more than 6 h. The diagnosis of AKI is only to be considered after achieving an adequate hydration status and excluding urinary obstruction. This classification also excluded the two outcome classes [27].

Both the AKIN and RIFLE classifications led to the identification and stratification of AKI in hospitalized patients, which was independently associated with outcome [31–34]. The AKIN classification, despite improving diagnostic sensitivity and specificity, shows no evidence of better prognostic acuity [34–39].

2.3. Kidney Disease Improving Global Outcomes (KDIGO) Classification

Recently, the KDIGO work group has developed a classification by merging the RIFLE and AKIN classifications to provide simplified and integrated criteria that could be applied in clinical practice and research (Table 1) [40].

Table 1. Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) [22], Acute Kidney Injury Network (AKIN) [27], and Kidney Disease Improving Global Outcomes (KDIGO) [40] classifications.

Class/Stage	SCr/GFR			UO		
	RIFLE	AKIN	KDIGO	RIFLE	AKIN	KDIGO
Risk/1 *	↑ SCr X 1.5 or ↓ GFR > 25%	↑ SCr ≥ 26.5 µmol/L (≥0.3 mg/dL or ↑ SCr ≥ 150 to 200% (1.5 to 2X)	↑ SCr ≥ 26.5 µmol/L (≥0.3 mg/dL) or ↑ SCr ≥ 150 to 200% (1.5 to 2X)	<0.5 mL/kg/h (>6 h)	<0.5 mL/kg/h (>6 h)	<0.5 mL/kg/h (>6 h)
Injury/2 *	↑ SCr X 2 or ↓ GFR > 50%	↑ SCr > 200 to 300% (>2 to 3X)	↑ SCr > 200 to 300% (>2 to 3X)	<0.5 mL/kg/h (>12 h)	<0.5 mL/kg/h (>12 h)	<0.5 mL/kg/h (>12 h)
Failure/3*	↑ SCr X 3 or ↓ GFR >75% or if baseline SCr ≥ 353.6 µmol/L (≥4 mg/dL) ↑ SCr > 44.2 µmol/L (>0.5 mg/dL)	↑ SCr >300% (>3X) or if baseline SCr ≥ 353.6 µmol/L (≥4 mg/dL) ↑ SCr ≥ 44.2 µmol/L (≥0.5 mg/dL) or initiation of renal replacement therapy	↑ SCr > 300% (>3X) or ↑ SCr to ≥353.6 µmol/L (≥4 mg/dL) or initiation of renal replacement therapy	<0.3 mL/kg/h (>24 h) or anuria (>12 h)	<0.3 mL /kg/h (24 h) or anuria (12 h)	<0.3 mL/kg/h (24 h) or anuria (12 h) or GFR < 35 mL/min/1.73 m^2 in patients younger than 18 years

SCr: serum creatinine; GFR: glomerular filtration rate; UO: urine output; RIFLE: Risk, Injury, Failure, Loss of kidney function (dialysis dependence for at least 4 weeks), End-stage kidney disease (dialysis dependence for at least 3 months); AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes. * Risk class (RIFLE) corresponds to stage 1 (AKIN and KDIGO), Injury class (RIFLE) corresponds to stage 2 (AKIN and KDIGO), and Failure class (RIFLE) corresponds to stage 3 (AKIN and KDIGO), ↑ increase, ↓ decrease.

Accordingly, AKI is defined as an increase in SCr of at least 0.3 mg/dL within 48 h, or an increase in SCr to more than 1.5 times of baseline level, which is known or presumed to have occurred within the prior 7 days, or a UO decrease to less than 0.5 mL/kg/h for 6 h. AKI stratification according to KDIGO follows the stages of the AKIN criteria, except for a simplification of stage 3 [40].

2.4. RIFLE vs. AKIN vs. KDIGO

The KDIGO classification, theoretically, offers superior diagnostic and prognostic accuracy than the former classifications. Recent studies have conducted evaluations of these classifications to assess differences, advantages, and limitations in their incidence determination and prognostic ability in different settings (Table 2).

Table 2. Incidence of AKI and patient outcomes according to AKI definitions.

Study	Design	Setting	Criteria	AKI Definition	N	AKI Incidence	Mortality
Nisula et al. (2013) [41]	Prospective, multi-centre	ICU	SCr, UO	AKIN, KDIGO	2901	AKIN 39.3% KDIGO 39.3%	AKIN 26% KDIGO 26%
Roy et al. (2013) [42]	Prospective	Hospitalized, HF	SCr	RIFLE, AKIN, KDIGO	637	RIFLE 25.6%, AKIN 27.9%, KDIGO 36.7%	RIFLE AUROC 0.76 AKIN AUROC 0.72 KDIGO AUROC 0.74 $p = 0.02$
Bastin et al. (2013) [43]	Retrospective	Cardiac surgery	SCr	RIFLE, AKIN, KDIGO	1881	RIFLE 24.9%, AKIN 25.9%, KDIGO 25.9%	RIFLE AUROC 0.78, AKIN AUROC 0.86, $p < 0.001$
Zeng et al. (2014) [44]	Retrospective	Hospitalized	SCr	RIFLE, AKIN, KDIGO	31,970	RIFLE 16.1%, AKIN 16.6%, KDIGO 18.3%	RIFLE OR 2.9, AKIN OR 2.6, KDIGO OR 2.8
Levi et al. (2013) [45]	Prospective	ICU	SCr, UO	RIFLE, AKIN, KDIGO	190	RIFLE 62.6%, AKIN 63.2%, KDIGO 63.2%	RIFLE OR 0.56, AKIN OR 0.58, KDIGO OR 0.58
Rodrigues et al. (2013) [46]	Prospective	AMI	SCr	RIFLE, KDIGO	1050	RIFLE 14.8% KDIGO 36.6%	RIFLE HR 3.51 (early) 1.84 (late) KDIGO HR 3.99 (early) 2.43 (late)
Luo et al. (2014) [47]	Prospective	ICU	SCr, UO	RIFLE, AKIN, KDIGO	3107	RIFLE 46.9%, AKIN 38.4%, KDIGO 51% $p = 0.001$	RIFLE AUROC 0.738 AKIN AUROC 0.746 KDIGO AUROC 0.757 KDIGO vs. RIFLE $p = 0.12$ KDIGO vs. AKIN $p < 0.001$
Fuji et al. (2014) [48]	Retrospective	Hospitalized	SCr	RIFLE, AKIN, KDIGO	49,518	RIFLE 11.0%, AKIN 4.8%, KDIGO 11.8%	RIFLE AUROC 0.77 AKIN AUROC 0.69 KDIGO AUROC 0.78 $p = 0.02$
Neves et al. (2014) [49]	Prospective	Hospitalized	SCr, UO	RIFLE, AKIN, KDIGO	1045	RIFLE 6.2%, AKIN 5.5%, KDIGO 5.5%	N/A
Li et al. (2014) [50]	Retrospective	Hospitalized	SCr	RIFLE, AKIN, KDIGO	1005	RIFLE 32.1%, AKIN 34.7%, KDIGO 38.9%	RIFLE OR 2.56 AKIN OR 2.68 KDIGO OR 4.00 $p < 0.05$
Pereira et al. (2017) [51]	Retrospective	ICU, Sepsis	SCr, UO	RIFLE, AKIN, KDIGO	457	RIFLE 84.2%, AKIN 72.8%, KDIGO 87.5%	RIFLE AUROC 0.652 AKIN AUROC 0.686 KDIGO AUROC 0.658 $p < 0.001$

Table 2. *Cont.*

Study	Design	Setting	Criteria	AKI Definition	N	AKI Incidence	Mortality
Koeze et al. (2017) [52]	Retrospective	ICU	SCr, UO	RIFLE, AKIN, KDIGO	1376	RIFLE 28% (SCr) 35% (SCr + UO) AKIN 12% (SCr) 38% (SCr + UO) KDIGO 11% (SCr) 38% (SCr + UO)	RIFLE 84.2%, AKIN 72.8%, KDIGO 87.5%
Tsai et al. (2017) [53]	Retrospective	ECMO	SCr, UO	RIFLE, AKIN, KDIGO	167	RIFLE 75.4%, AKIN 84.4%, KDIGO 85%	RIFLE AUROC 0.826 AKIN AUROC 0.774 KDIGO AUROC 0.840 $p < 0.001$
Wu et al. (2016) [54]	Retrospective	ICU, Surgical	SCr, UO	AKIN, KDIGO	826	AKIN 31% KDIGO 30%	AKIN 21.8% (1), 20.2% (2), 27.8% (3) KDIGO 16.9% (1), 17.5% (2), 34.1% (3)
Zhou et al. (2016) [55]	Retrospective	ICU	SCr, UO, Cys-C	RIFLE, AKIN, KDIGO	1036	RIFLE 26.4%, AKIN 34.1%, KDIGO 37.8%, Cys-C 36.1%	RIFLE 57.9%, AKIN 54.4%, KDIGO 51.8%, Cys-C 52.1%
Pan et al. (2016) [56]	Retrospective	ICU, Cirrhosis	SCr, UO	RIFLE, AKIN, KDIGO	242	RIFLE, AKIN, KDIGO	RIFLE AUROC 0.774 AKIN AUROC 0.741 KDIGO AUROC 0.781 $p < 0.001$

ICU: Intensive care unit, SCr: Serum creatinine, UO: Urinary output, HF: Heart failure, AMI: acute myocardial infarction, Cys-C: Cystatin C, N/A not applicable, AUROC: area under the receiving operating characteristic curve, HR: hazard ratio, OR: odds ratio.

The Finnaki study demonstrated similar incidence in AKI defined by AKIN and KDIGO in a cohort of 2901 critically patients [41]. Roy et al. also found that the incidence of AKI was similar using the RIFLE, AKIN, and KDIGO criteria in a prospective study of 637 hospitalized patients with acute heart failure, although there were discrete differences in the predictive ability of the 30-day outcomes between RIFLE and KDIGO (area under the receiving operating characteristic curve (AUROC) of 0.76 and 0.74, respectively) [42]. In a retrospective study of 1881 cardiac surgery patients, the RIFLE, AKIN, and KDIGO criteria reported a similar incidence of AKI, although AKIN performed significantly better than RIFLE (AUROC = 0.86 versus 0.78, $p < 0.001$) [43]. Another retrospective cohort study of 31970 hospitalizations reported similar AKI incidence and prognosis using RIFLE, AKIN, and KDIGO [44]. Levi et al. compared the classifications in a study of 190 critical care patients and reported similar incidences [45]. In a prospective study of 1045 hospitalized patients on internal medicine wards conducted by Neves et al., the incidence of AKI was also similar using AKIN and KDIGO criteria, but higher with the RIFLE classification due to the incidence of pre-renal AKI [46].

The KDIGO classification was superior to RIFLE in diagnosing AKI (36.6% versus 14.8%) and predicting early and late mortality (adjusted hazard ratio (HR) for 30-day death of 3.51 by RIFLE and 3.99 by KDIGO; adjusted hazard ratio for 1-year mortality of 1.84 by RIFLE and 2.43 by KDIGO) in a cohort of 1050 patients with acute myocardial infarction [47].

The KDIGO criteria demonstrated a higher incidence of AKI than both RIFLE (51% versus 46.9%, $p = 0.001$) and AKIN (51% versus 38.4%, $p < 0.001$) criteria in a prospective cohort of 3107 critically ill patients [47]. Furthermore, evaluating in-hospital mortality, KDIGO was more predictive than RIFLE ($p < 0.001$), but not AKIN ($p = 0.12$) [48].

AKI was identified in more patients using the RIFLE and KDIGO criteria than AKIN (11% versus 4.8%) in a retrospective analysis of 49518 hospitalizations [49]. In this study, the KDIGO criteria had superior prognostic ability (AUROC: KDIGO 0.78, RIFLE 0.77, AKIN 0.69) [49]. Li et al. also demonstrated the superior performance of KDIGO in diagnosis and outcome prediction compared to RIFLE and AKIN in a retrospective study of 1005 patients with type 1 cardiorenal syndrome (AUROC: KDIGO 4.00, AKIN 2.68, RIFLE 2.56) [50].

We performed a single-center study of 457 critically ill septic patients and demonstrated that RIFLE and KDIGO criteria identified more AKI cases than did AKIN criteria (RIFLE 84.2% vs. KDIGO 87.5% vs. AKIN 72.8%, $p < 0.001$), although there were no differences in AKI incidence comparing RIFLE and KDIGO classifications, and the prediction of in-hospital mortality was similar between the three classifications [51]. Additionally, in this cohort of septic patients, AKI defined only by UO criteria was a better predictor of in-hospital mortality than was AKI defined either by SCr itself or by both SCr and UO (adjusted odds ratio (OR) = 2.7 (95% CI 1.7–4.5), $p < 0.001$), demonstrating the diagnostic and prognostic importance of UO in patients with septic AKI [51].

In a cohort of 1376 critically ill patients by Koeze et al., the AKIN (15%) and KDIGO (14%) criteria identified more AKI patients than the RIFLE criteria (10%). Moreover, by adding UO criteria, patients were detected earlier than when using only SCr criteria (median time of detection using UO 13 h and SCr 24 h) [52].

The KDIGO classification was also superior to AKIN and RIFLE in predicting in-hospital mortality (AUROC: KDIGO 0.840, AKIN 0.836, RIFLE 0.826, $p < 0.001$) in a study of 167 patients on extracorporeal membrane oxygenation (ECMO) support [53].

Wu et al. performed a retrospective analysis of 826 critically ill surgical patients and demonstrated that KDIGO was a better predictor of in-hospital mortality after surgery than AKIN (AUROC: KDIGO 0.678, AKIN 0.670, $p < 0.001$) [54].

In a retrospective multi-center cohort of 1036 critically ill patients, the KDIGO criteria identified more AKI patients than RIFLE and AKIN (37.8%, 26.4%, and 34.1%, respectively) [55]. The KDIGO criteria was also a better predictor of mortality (AUROC: KDIGO 0.7013, AKIN 0.6934, RIFLE 0.7016, $p < 0.001$) [55]. Additionally, this study incorporated the Cystatin-C (Cys-C) criteria, which demonstrated good concordance with the RIFLE, AKIN, and KDIGO criteria, and had better

predictive ability of mortality than the three definitions (AUROC 0.7023), validating Cys-C as an important biomarker of AKI [55,56].

In a prospective study of 242 critically ill cirrhotic patients, the incidence of AKI was higher with the KDIGO criteria (67%) than with AKIN (65%) or RIFLE (63%), and KDIGO was a better predictor of in-hospital mortality (AUROC: KDIGO 0.781, AKIN 0.741, RIFLE 0.744, $p < 0.001$) [57].

The KDIGO classification appears to perform better in diagnosis and prognosis determination than AKIN and RIFLE. Nonetheless, future prospective studies with larger populations are still required to better assess the sensitivity and prognostic performance of these definitions.

2.5. Limitations

Despite the importance of these classifications in defining the epidemiology of AKI, it is increasingly recognized that novel biomarkers have to be researched to improve the definition of AKI and its application in predicting outcomes.

The fact that these classifications rely on SCr, eGFR, and UO, which are insensitive and unspecific markers of AKI and do not account for its duration or cause, is a significant caveat [58]. The value of SCr is influenced by factors altering its production (age, gender, diet, muscle mass), elimination (previous renal dysfunction), secretion (medications) and, importantly, concentration according to fluid balance variations. Baseline SCr is frequently unknown and its assessment is complex, with several studies pointing to the use of minimum preadmission SCr or estimated SCr using the Modification of Diet in Renal Disease formula. Furthermore, UO is difficult to assess without a urinary catheter and can be significantly altered by hypovolemic status and diuretics, and UO adjustment to actual versus ideal body weight affects AKI incidence reports [58–64].

2.6. Future Biomarkers

Recently, potential biomarkers of AKI have been identified. Ideally, novel biomarkers should be specific, identify the cause, identify patients at risk, provide an early diagnosis, stratify the severity of the injury, and predict outcomes.

With the enhanced understanding of the pathophysiology of AKI, novel biomarkers were identified, including proteins filtered by the glomerulus, enzymes released by tubular cells after injury, and inflammatory mediators [65]. These include Cys-C, neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin 18 (IL-18), liver-type fatty acid-binding protein (L-FABP), calprotectin, urine angiotensinogen (AGT), urine microRNAs, insulin-like growth factor-binding protein 7 (IGFBP7), and tissue inhibitor of metalloproteinases-2 (TIMP-2), which have been evaluated in multiple settings, primarily on critically ill and surgical patients [66–77].

NGAL was one of the primarily studied biomarkers, which has demonstrated significant prediction of AKI in critically ill, cardiac surgery, sepsis, trauma, and contrast nephropathy patients [65,66,72]. Most recently, the use of IGFBP7 and TIMP-2 has been promising in the critical care setting, demonstrating greater accuracy and stability than former biomarkers [77–82]. However, further studies in different clinical settings are still required.

Most of these biomarkers can be detected in both serum and urine, and have been significantly associated with early AKI prediction. The association of these novel biomarkers with the need for dialysis, renal recovery, progression to CKD, and mortality has also been reported, although further studies are still warranted [65,77].

With recent advances in the understanding of AKI pathogenesis, the role of intrarenal and systemic inflammation leading to multi-organ dysfunction has been emphasized [82,83]. A new marker of systemic inflammation has become available, the neutrophil-lymphocyte ratio (NLR), which has been identified as an AKI prediction tool in multiple settings, being a simple, effective, and low-cost marker [84–86].

Despite the current progress in the development of new biomarkers, important drawbacks have limited their widespread applicability in clinical practice. For instance, they have not been able to reliably distinguish pre-renal and renal AKI; moreover, several patient characteristics and comorbidities, such as age, gender, diabetes mellitus, and chronic inflammation, are associated with range variations that limit their validity. The increased cost associated with testing and the need for multiple assessments to increase accuracy limits the cost-effectiveness. Furthermore, evidence of improvement of outcomes associated with using these biomarkers is still lacking [65,77].

Indeed, AKI is a complex syndrome and perhaps the use of a panel of several biomarkers covering different phases of the syndrome could provide a better understanding of its etiology and pathophysiology, and identify targets for future treatments [87].

Additionally, the use of automated electronic alerts (e-alerts) has received much attention in the past few years [88,89]. These consist of algorithms configured from patients' electronic medical records and clinical information to notify of early or imminent AKI, prompting an earlier clinical evaluation and application of prevention and treatment strategies, potentially improving clinical outcomes [89–92]. Indeed, a UK consensus conference has encouraged the use of these e-alerts for early detection of AKI [93]. Nevertheless, e-alerts are heterogeneous, do not include clear decision-making strategies, and have not been associated with decreased mortality or renal replacement technique (RRT) use [94]. Further development of these alerts is required to assess their impact on clinical outcomes and recommendation of use in clinical practice. We believe that it is essential to incorporate these scientific advances in daily clinical practice in the near future.

3. Conclusions

AKI is a complex syndrome with significant impact on patient outcomes; thus, its prevention, early detection, and prompt treatment are important to minimize the associated morbidity and mortality.

Research has led to an improvement in our understanding of AKI, raising our awareness of its incidence and prognostic impact. The KDIGO classification unified previous definitions and improved the recognition of AKI in clinical practice. The search for the perfect biomarker of AKI is still ongoing. Future studies should focus on early diagnostic measures, outcome predictors, and new treatments.

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References

1. Hoste, E.A.J.; Kellum, J.A.; Selby, N.M.; Zarbock, A.; Palevsky, P.M.; Bagshaw, S.M.; Goldstein, S.L.; Cerdá, J.; Chawla, L.S. Global epidemiology and outcomes of acute kidney injury. *Nat. Rev. Nephrol.* **2018**, *14*, 607–625. [CrossRef] [PubMed]
2. Susantitaphong, P.; Cruz, D.N.; Cerda, J.; Abulfaraj, M.; Alqahtani, F.; Koulouridis, I.; Jaber, B.L. Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: A meta-analysis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1482–1493. [CrossRef] [PubMed]
3. Chertow, G.; Burdick, E.; Honour, M.; Bonventre, J.; Bates, D. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–3370. [CrossRef] [PubMed]
4. Lameire, N.; van Biesen, W.; Vanholder, R. The changing epidemiology of acute renal failure. *Nat. Clin. Nephrol.* **2006**, *2*, 364–377. [CrossRef] [PubMed]
5. Bagshaw, S.M.; George, C.; Bellomo, R.; ANZICS Database Management Committee. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. *Crit. Care* **2007**, *11*, R68. [CrossRef] [PubMed]
6. Bellomo, R. The epidemiology of acute renal failure: 1975 versus 2005. *Curr. Opin. Crit. Care.* **2006**, *12*, 557–560. [CrossRef] [PubMed]

7. Feest, T.G.; Round, A.; Hamad, S. Incidence of severe acute renal failure in adults: Results of a community-based study. *BMJ* **1993**, *306*, 481–483. [CrossRef] [PubMed]
8. Liano, F.; Pascual, J. Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int.* **1996**, *50*, 811–818. [CrossRef] [PubMed]
9. Amin, A.P.; Salisbury, A.C.; McCullough, P.A.; Gosch, K.; Spertus, J.A.; Venkitachalam, L.; Stolker, J.M.; Parikh, C.R.; Masoudi, F.A.; Jones, P.G.; et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch. Intern. Med.* **2012**, *172*, 246–253. [CrossRef] [PubMed]
10. Ronco, C.; McCullough, P.; Anker, S.D.; Anand, I.; Aspromonte, N.; Bagshaw, S.M.; Bellomo, R.; Berl, T.; Bobek, I.; Cruz, D.N.; et al. Cardio-renal syndromes: Report from the consensus conference of the acute dialysis quality initiative. *Eur. Heart J.* **2010**, *31*, 703–711. [CrossRef] [PubMed]
11. Hsu, R.K.; McCulloch, C.E.; Dudley, R.A.; Lo, L.J.; Hsu, C.Y. Temporal changes in incidence of dialysis-requiring AKI. *J. Am. Soc. Nephrol.* **2013**, *24*, 37–42. [CrossRef] [PubMed]
12. Singbartl, K.; Kellum, J.A. AKI in the ICU: Definition, epidemiology, risk stratification, and outcomes. *Kidney Int.* **2012**, *81*, 819–825. [CrossRef] [PubMed]
13. Uchino, U.S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef] [PubMed]
14. Bellomo, R.; Kellum, J.A.; Ronco, C.; Wald, R.; Martensson, J.; Maiden, M.; Bagshaw, S.M.; Glassford, N.J.; Lankadeva, Y.; Vaara, S.T.; et al. Acute kidney injury in sepsis. *Intensive Care Med.* **2017**, *43*, 816–828. [CrossRef] [PubMed]
15. Bagshaw, S.M.; George, C.; Bellomo, R.; ANZICS Database Management Committee. Early acute kidney injury and sepsis: A multicentre evaluation. *Crit. Care* **2008**, *12*, R47. [CrossRef] [PubMed]
16. Lopes, J.A.; Jorge, S.; Resina, C.; Santos, C.; Pereira, A.; Neves, J.; Antunes, F.; Prata, M.M. Acute kidney injury in patients with sepsis: A contemporary analysis. *Int. J. Infect. Dis.* **2009**, *13*, 176–181. [CrossRef] [PubMed]
17. Thakar, C.V. Perioperative acute kidney injury. *Adv. Chronic Kidney Dis.* **2013**, *20*, 67–75. [CrossRef] [PubMed]
18. Grams, M.E.; Sang, Y.; Coresh, J.; Ballew, S.; Matsushita, K.; Molnar, M.Z.; Szabo, Z.; Kalantar-Zadeh, K.; Kovesdy, C.P. Acute kidney injury after major surgery: A retrospective analysis of veteran's health administration data. *Am. J. Kidney Dis.* **2016**, *67*, 872–880. [CrossRef] [PubMed]
19. Gameiro, J.; Fonseca, J.A.; Neves, M.; Jorge, S.; Lopes, J.A. Acute kidney injury in major abdominal surgery: Incidence, risk factors, pathogenesis and outcomes. *Ann. Intensive Care* **2018**, *8*, 22. [CrossRef] [PubMed]
20. Chawla, L.S.; Bellomo, R.; Bihorac, A.; Goldstein, S.L.; Siew, E.D.; Bagshaw, S.M.; Bittleman, D.; Cruz, D.; Endre, Z.; Fitzgerald, R.L.; et al. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 workgroup. *Nat. Rev. Nephrol.* **2017**, *13*, 241–257. [CrossRef] [PubMed]
21. Husain-Syed, F.; Ronco, C. The odyssey of risk stratification in acute kidney injury. *Nat. Rev. Nephrol.* **2018**. [CrossRef] [PubMed]
22. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. *Crit. Care* **2004**, *8*, R204–R212. [CrossRef] [PubMed]
23. Manjunath, G.; Sarnak, M.J.; Levey, A.S. Prediction equations to estimate glomerular filtration rate: An update. *Curr. Opin. Nephrol. Hypertens.* **2001**, *10*, 785–792. [CrossRef] [PubMed]
24. Brivet, F.G.; Kleinknecht, D.J.; Loirat, P.; Landais, P.J. Acute renal failure in intensive care units—Causes, outcome, and prognostic factors of hospital mortality: A prospective, multicenter study. *Crit. Care Med.* **1996**, *24*, 192–198. [CrossRef] [PubMed]
25. Silvester, W.; Bellomo, R.; Cole, L. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. *Crit. Care Med.* **2001**, *29*, 1910–1915. [CrossRef] [PubMed]
26. Lopes, J.A.; Jorge, S. The RIFLE and AKIN classifications for acute kidney injury: A critical and comprehensive review. *Clin. Kidney J.* **2013**, *6*, 8–14. [CrossRef] [PubMed]
27. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef] [PubMed]

28. Uchino, S.; Bellomo, R.; Goldsmith, D.; Bates, S.; Ronco, C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit. Care Med.* **2006**, *34*, 1913–1917. [CrossRef] [PubMed]
29. Hoste, E.A.; Clermont, G.; Kersten, A.; Venkataraman, R.; Angus, D.C.; De Bacquer, D.; Kellum, J.A. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit. Care* **2006**, *10*, R73. [CrossRef] [PubMed]
30. Lassnigg, A.; Schmidlin, D.; Mouhieddine, M.; Bachmann, L.M.; Druml, W.; Bauer, P.; Hiesmayr, M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J. Am. Soc. Nephrol.* **2004**, *15*, 1597–1605. [CrossRef] [PubMed]
31. Lopes, J.A.; Fernandes, P.; Jorge, S.; Gonçalves, S.; Alvarez, A.; Costae, S.Z.; França, C.; Prata, M.M. Acute kidney injury in intensive care unit patients: A comparison between the RIFLE and the Acute Kidney Injury Network classifications. *Crit. Care* **2008**, *12*, R110. [CrossRef] [PubMed]
32. Barrantes, F.; Feng, Y.; Ivanov, O.; Yalamanchili, H.B.; Patel, J.; Buenafe, X.; Cheng, V.; Dijeh, S.; Amoateng-Adjepong, Y.; Manthous, C.A. Acute kidney injury predicts outcomes of non-critically ill patients. *Mayo Clin. Proc.* **2009**, *84*, 410–416. [CrossRef]
33. Barrantes, F.; Tian, J.; Vazquez, R.; Amoateng-Adjepong, Y.; Manthous, C.A. Acute kidney injury criteria predict outcomes of critically ill patients. *Crit. Care Med.* **2008**, *36*, 1397–1403. [CrossRef] [PubMed]
34. Bagshaw, S.M.; George, C.; Bellomo, R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol. Dial. Transplant.* **2008**, *23*, 1569–1574. [CrossRef] [PubMed]
35. Lassnigg, A.; Schmid, E.R.; Hiesmayr, M.; Falk, C.; Druml, W.; Bauer, P.; Schmidlin, D. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: Do we have to revise current definitions of acute renal failure? *Crit. Care Med.* **2008**, *36*, 1129–1137. [CrossRef] [PubMed]
36. Joannidis, M.; Metnitz, B.; Bauer, P.; Schusterschitz, N.; Moreno, R.; Druml, W.; Metnitz, P.G. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* **2009**, *35*, 1692–1702. [CrossRef] [PubMed]
37. Ostermann, M.; Chang, R.W. Challenges of defining acute kidney injury. *QJM* **2011**, *104*, 237–243. [CrossRef] [PubMed]
38. Englberger, L.; Suri, R.M.; Li, Z.; Casey, E.T.; Daly, R.C.; Dearani, J.A.; Schaff, H.V. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. *Crit. Care* **2011**, *15*, R16. [CrossRef] [PubMed]
39. Robert, A.M.; Kramer, R.S.; Dacey, L.J.; Charlesworth, D.C.; Leavitt, B.J.; Helm, R.E.; Hernandez, F.; Sardella, G.L.; Frumiento, C.; Likosky, D.S.; et al. Cardiac surgery associated acute kidney injury: A comparison of two consensus criteria. *Ann. Thorac. Surg.* **2010**, *90*, 1939–1943. [CrossRef] [PubMed]
40. Khwaja, A. KDIGO clinical practice guideline for acute kidney injury. *Nephron Clin. Pract.* **2012**, *120*, c179–c184. [CrossRef] [PubMed]
41. Nisula, S.; Kaukonen, K.M.; Vaara, S.T.; Korhonen, A.M.; Poukkanen, M.; Karlsson, S.; Haapio, M.; Inkinen, O.; Parviainen, I.; Suojaranta-Ylinen, R.; et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: The FINNAKI study. *Intensive Care Med.* **2013**, *39*, 420–428. [CrossRef] [PubMed]
42. Roy, A.K.; Mc Gorrian, C.; Treacy, C.; Kavanaugh, E.; Brennan, A.; Mahon, N.G.; Murray, P.T. A comparison of traditional and novel definitions (RIFLE, AKIN, and KDIGO) of acute kidney injury for the prediction of outcomes in acute decompensated heart failure. *Cardiorenal Med.* **2013**, *3*, 26–37. [CrossRef] [PubMed]
43. Bastin, A.J.; Ostermann, M.; Slack, A.J.; Diller, G.P.; Finney, S.J.; Evans, T.W. Acute kidney injury after cardiac surgery according to risk/injury/failure/loss/end-stage, acute kidney injury network, and kidney disease: Improving global outcomes classifications. *J. Crit. Care* **2013**, *28*, 389–396. [CrossRef] [PubMed]
44. Zeng, X.; McMahon, G.M.; Brunelli, S.M.; Bates, D.W.; Waikar, S.S. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 12–20. [CrossRef] [PubMed]
45. Levi, T.M.; de Souza, S.P.; de Magalhães, J.G.; de Carvalho, M.S.; Cunha, A.L.; Dantas, J.G.; Cruz, M.G.; Guimarães, Y.L.; Cruz, C.M. Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients. *Rev. Bras. Ter. Intensiva* **2013**, *25*, 290–296. [CrossRef] [PubMed]
46. Neves, M.; Fidalgo, P.; Gonçalves, C.; Leitão, S.; Santos, R.M.; Carvalho, A.; Costa, J.M. Acute kidney injury in an internal medicine ward in a Portuguese quaternary hospital. *Eur. J. Intern. Med.* **2014**, *25*, 169–172. [CrossRef] [PubMed]

47. Rodrigues, F.B.; Bruetto, R.G.; Torres, U.S.; Otaviano, A.P.; Zanetta, D.M.; Burdmann, E.A. Incidence and mortality of acute kidney injury after myocardial infarction: A comparison between KDIGO and RIFLE criteria. *PLoS ONE* **2013**, *8*, e69998. [CrossRef] [PubMed]
48. Luo, X.; Jiang, L.; Du, B.; Wen, Y.; Wang, M.; Xi, X. A comparison of different diagnostic criteria in acute kidney injury in critically ill patients. *Crit. Care* **2014**, *18*, R144. [CrossRef] [PubMed]
49. Fujii, T.; Uchino, S.; Takinami, M.; Bellomo, R. Validation of the kidney disease improving global outcomes criteria for AKI and comparison of three criteria in hospitalized patients. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 848–854. [CrossRef] [PubMed]
50. Li, Z.; Cai, L.; Liang, X.; Du, Z.; Chen, Y.; An, S.; Tan, N.; Xu, L.; Li, R.; Li, L.; et al. Identification and predicting short-term prognosis of early cardiorenal syndrome type 1: KDIGO is superior to RIFLE or AKIN. *PLoS ONE* **2014**, *9*, e114369. [CrossRef] [PubMed]
51. Pereira, M.; Rodrigues, N.; Godinho, I.; Gameiro, J.; Neves, M.; Gouveia, J.; Costa, E.; Silva, Z.; Lopes, J.A. Acute kidney injury in patients with severe sepsis or septic shock: A comparison between the "Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease" (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. *Clin. Kidney J.* **2017**, *10*, 332–340. [PubMed]
52. Koeze, J.; Keus, F.; Dieperink, W.; van der Horst, I.C.C.; Zijlstra, J.G.; van Meurs, M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol.* **2017**, *18*, 70. [CrossRef] [PubMed]
53. Tsai, T.Y.; Chien, H.; Tsai, F.C.; Pan, H.C.; Yang, H.Y.; Lee, S.Y.; Hsu, H.H.; Fang, J.T.; Yang, C.W.; Chen, Y.C. Comparison of RIFLE, AKIN, and KDIGO classifications for assessing prognosis of patients on extracorporeal membrane oxygenation. *J. Formos. Med. Assoc.* **2017**, *116*, 844–851. [CrossRef] [PubMed]
54. Wu, H.C.; Lee, L.C.; Wang, W.J. Incidence and mortality of postoperative acute kidney injury in non-dialysis patients: Comparison between the AKIN and KDIGO criteria. *Ren. Fail.* **2016**, *38*, 330–339. [CrossRef] [PubMed]
55. Zhou, J.; Liu, Y.; Tang, Y.; Liu, F.; Zhang, L.; Zeng, X.; Feng, Y.; Tao, Y.; Yang, L.; Fu, P. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. *Int. Urol. Nephrol.* **2016**, *48*, 125–132. [CrossRef] [PubMed]
56. Zhang, Z.; Lu, B.; Sheng, X.; Jin, N. Cystatin C in prediction of acute kidney injury: A systemic review and meta-analysis. *Am. J. Kidney Dis.* **2011**, *58*, 356–365. [CrossRef] [PubMed]
57. Pan, H.C.; Chien, Y.S.; Jenq, C.C.; Tsai, M.H.; Fan, P.C.; Chang, C.H. Acute kidney injury classification for critically Ill cirrhotic patients: A comparison of the KDIGO, AKIN, and RIFLE classifications. *Sci. Rep.* **2016**, *6*, 23022. [CrossRef] [PubMed]
58. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef] [PubMed]
59. Thongprayoon, C.; Cheungpasitporn, W.; Kittanamongkolchai, W.; Srivali, N.; Ungprasert, P.; Kashani, K. Optimum methodology for estimating baseline serum creatinine for the acute kidney injury classification. *Nephrology (Carlton)* **2015**, *20*, 881–886. [CrossRef] [PubMed]
60. Thongprayoon, C.; Cheungpasitporn, W.; Harrison, A.M.; Kittanamongkolchai, W.; Ungprasert, P.; Srivali, N.; Akhoundi, A.; Kashani, K.B. The comparison of the commonly used surrogates for baseline renal function in acute kidney injury diagnosis and staging. *BMC Nephrol.* **2016**, *17*, 6. [CrossRef] [PubMed]
61. Waikar, S.S.; Betensky, R.A.; Emerson, S.C.; Bonventre, J.V. Imperfect gold standards for kidney injury biomarker evaluation. *J. Am. Soc. Nephrol.* **2012**, *23*, 13–21. [CrossRef] [PubMed]
62. Macedo, E.; Malhotra, R.; Claure-Del Granado, R.; Fedullo, P.; Mehta, R.L. Defining urine output criterion for acute kidney injury in critically ill patients. *Nephrol. Dial. Transplant.* **2011**, *26*, 509–515. [CrossRef] [PubMed]
63. Macedo, E.; Bouchard, J.; Soroko, S.H.; Chertow, G.M.; Himmelfarb, J.; Ikizler, T.A.; Paganini, E.P.; Mehta, R.L. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit. Care* **2010**, *14*, R82. [CrossRef] [PubMed]
64. Thongprayoon, C.; Cheungpasitporn, W.; Akhoundi, A.; Ahmed, A.H.; Kashani, K.B. Actual versus ideal body weight for acute kidney injury diagnosis and classification in critically ill patients. *BMC Nephrol.* **2014**, *15*, 176. [CrossRef] [PubMed]

65. Ostermann, M.; Philips, B.J.; Forni, L.G. Clinical review: Biomarkers of acute kidney injury: Where are we now? *Crit. Care* **2012**, *16*, 233. [CrossRef] [PubMed]
66. Schinstock, C.A.; Semret, M.H.; Wagner, S.J.; Borland, T.M.; Bryant, S.C.; Kashani, K.B.; Larson, T.S.; Lieske, J.C. Urinalysis is more specific and urinary neutrophil gelatinase-associated lipocalin is more sensitive for early detection of acute kidney injury. *Nephrol. Dial. Transplant.* **2013**, *28*, 1175–1185. [CrossRef] [PubMed]
67. Han, W.K.; Bailly, V.; Abichandani, R.; Thadhani, R.; Bonventre, J.V. Kidney Injury Molecule-1 (KIM-1): A novel biomarker for human renal proximal tubule injury. *Kidney Int.* **2002**, *62*, 237–244. [CrossRef] [PubMed]
68. Parikh, C.R.; Mishra, J.; Thiessen-Philbrook, H.; Dursun, B.; Ma, Q.; Kelly, C.; Dent, C.; Devarajan, P.; Edelstein, C.L. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Kidney Int.* **2006**, *70*, 199–203. [CrossRef] [PubMed]
69. Di Somma, S.; Magrini, L.; De Berardinis, B.; Marino, R.; Ferri, E.; Moscatelli, P.; Ballarino, P.; Carpinteri, G.; Noto, P.; Gliozzo, B.; et al. Additive value of blood neutrophil gelatinase associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department. *Crit. Care* **2013**, *17*, R29–R13. [CrossRef] [PubMed]
70. Bennett, M.; Dent, C.L.; Ma, Q.; Dastrala, S.; Grenier, F.; Workman, R.; Syed, H.; Ali, S.; Barasch, J.; Devarajan, P. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: A prospective study. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 665–673. [CrossRef] [PubMed]
71. Hall, I.E.; Yarlagadda, S.G.; Coca, S.G.; Wang, Z.; Doshi, M.; Devarajan, P.; Han, W.K.; Marcus, R.J.; Parikh, C.R. IL-18 and urinary NGAL predict dialysis and graft recovery after kidney transplantation. *J. Am. Soc. Nephrol.* **2010**, *21*, 189–197. [CrossRef] [PubMed]
72. Jia, H.M.; Huang, L.F.; Zheng, Y.; Li, W.X. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: A meta-analysis. *Crit. Care* **2017**, *21*, 77. [CrossRef] [PubMed]
73. Bargnoux, A.S.; Piéroni, L.; Cristol, J.P. Analytical study of a new turbidimetric assay for urinary neutrophil gelatinase-associated lipocalin (NGAL) determination. *Clin. Chem. Lab. Med.* **2013**, *51*, e293–e296. [CrossRef] [PubMed]
74. Westhoff, J.H.; Tönshoff, B.; Waldherr, S.; Pöschl, J.; Teufel, U.; Westhoff, T.H.; Fichtner, A. Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) insulin-like growth factor-binding protein 7 (IGFBP7) predicts adverse outcome in pediatric acute kidney injury. *PLoS ONE* **2015**, *10*, e0143628. [CrossRef] [PubMed]
75. Lima, C.; Macedo, E. Urinary biochemistry in the diagnosis of acute kidney injury. *Dis. Markers* **2018**. [CrossRef] [PubMed]
76. Vanmassenhove, J.; Vanholder, R.; Nagler, E.; van Biesen, W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: An in-depth review of the literature. *Nephrol. Dial. Transplant.* **2013**, *28*, 254–273. [CrossRef] [PubMed]
77. Kashani, K.; Cheungpasitporn, W.; Ronco, C. Biomarkers of acute kidney injury: The pathway from discovery to clinical adoption. *Clin. Chem. Lab. Med.* **2017**, *55*, 1074–1089. [CrossRef] [PubMed]
78. Fan, W.; Ankawi, G.; Zhang, J.; Digvijay, K.; Giavarina, D.; Yin, Y.; Ronco, C. Current understanding and future directions in the application of TIMP-2 and IGFBP7 in AKI clinical practice. *Clin. Chem. Lab. Med.* **2018**. [CrossRef]
79. Koyner, J.L.; Garg, A.X.; Coca, S.G.; Sint, K.; Thiessen-Philbrook, H.; Patel, U.D.; Shlipak, M.G.; Parikh, C.R. TRIBE-AKI Consortium. Biomarkers predict progression of acute kidney injury after cardiac surgery. *J. Am. Soc. Nephrol.* **2012**, *16*, 905–914. [CrossRef] [PubMed]
80. Bell, M.; Granath, F.; Martensson, J.; Lofberg, E.; Ekbom, A.; Martling, C.R. Cystatin C is correlated with mortality in patients with and without acute kidney injury. *Nephrol. Dial. Transplant.* **2009**, *16*, 3096–3102. [CrossRef] [PubMed]
81. Srisawat, N.; Murugan, R.; Lee, M.; Kong, L.; Carter, M.; Angus, D.C.; Kellum, J.A. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney Int.* **2011**, *16*, 545–552. [CrossRef] [PubMed]
82. Rabb, H.; Griffin, M.D.; McKay, D.B.; Swaminathan, S.; Pickkers, P.; Rosner, M.H.; Kellum, J.A.; Ronco, C. Inflammation in AKI: Current understanding, key questions, and knowledge gaps. *J. Am. Soc. Nephrol.* **2016**, *27*, 371–379. [CrossRef] [PubMed]

83. Gomez, H.; Ince, C.; De Backer, D.; Pickkers, P.; Payen, D.; Hotchkiss, J.; Kellum, J.A. A unified theory of sepsis-induced acute kidney injury: Inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. *Shock* **2014**, *41*, 3–11. [CrossRef] [PubMed]
84. Yilmaz, H.; Cakmak, M.; Inan, O.; Darcin, T.; Akcay, A. Can neutrophil-lymphocyte ratio be independent risk factor for predicting acute kidney injury in patients with severe sepsis? *Ren. Fail.* **2015**, *37*, 225–229. [CrossRef] [PubMed]
85. Kim, W.H.; Park, J.Y.; Ok, S.H.; Shin, I.W.; Sohn, J.T. Association Between the neutrophil/lymphocyte ratio and acute kidney injury after cardiovascular surgery: A retrospective observational study. *Medicine (Baltimore)* **2015**, *94*, e1867. [CrossRef] [PubMed]
86. Abu Alfeilat, M.; Slotki, I.; Shavit, L. Single emergency room measurement of neutrophil/lymphocyte ratio for early detection of acute kidney injury (AKI). *Intern. Emerg. Med.* **2017**. [CrossRef] [PubMed]
87. Marx, D.; Metzger, J.; Pejchinovski, M.; Gil, R.B.; Frantzi, M.; Latosinska, A.; Belczacka, I.; Heinzmann, S.S.; Husi, H.; Zoidakis, J.; et al. Proteomics and Metabolomics for AKI Diagnosis. *Semin. Nephrol.* **2018**, *38*, 63–87. [CrossRef] [PubMed]
88. Hobson, C.E.; Darmon, M.; Mohan, S.; Hudson, D.; Goldstein, S.L.; Ronco, C.; Kellum, J.A.; Bagshaw, S.M. Applications for detection of acute kidney injury using electronic medical records and clinical information systems: Workgroup statements from the 15(th) ADQI Consensus Conference. *Can. J. Kidney Health Dis.* **2016**, *3*, 9.
89. Selby, N.M.; Crowley, L.; Fluck, R.J.; McIntyre, C.W.; Monaghan, J.; Lawson, N.; Kolhe, N.V. Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 533–540. [CrossRef] [PubMed]
90. Cheungpasitporn, W.; Kashani, K. Electronic data systems and acute kidney injury. *Contrib. Nephrol.* **2016**, *187*, 73–83. [PubMed]
91. Sutherland, S.M.; Goldstein, S.L.; Bagshaw, S.M. Leveraging big data and electronic health records to enhance novel approaches to acute kidney injury research and care. *Blood Purif.* **2017**, *44*, 68–76. [CrossRef] [PubMed]
92. Prendecki, M.; Blacker, E.; Sadeghi-Alavijeh, O.; Edwards, R.; Montgomery, H.; Gillis, S.; Harber, M. Improving outcomes in patients with acute kidney injury: The impact of hospital based automated AKI alerts. *Postgrad. Med. J.* **2016**, *92*, 9–13. [CrossRef] [PubMed]
93. Feehally, J.; Gilmore, I.; Barasi, S.; Bosomworth, M.; Christie, B.; Davies, A.; Dhesi, J.; Dowdle, R.; Gibbins, C.; Gonzalez, I.; et al. Royal College of Physicians of Edinburgh UK Consensus Conference on Management of acute kidney injury: The role of fluids, e-alerts and biomarkers. *J. R. Coll. Physicians Edinb.* **2013**, *43*, 37–38. [CrossRef] [PubMed]
94. Lachance, P.; Villeneuve, P.M.; Rewa, O.G.; Wilson, F.P.; Selby, N.M.; Featherstone, R.M.; Bagshaw, S.M. Association between e-alert implementation for detection of acute kidney injury and outcomes: A systematic review. *Nephrol. Dial. Transplant.* **2017**, *32*, 265–272. [CrossRef] [PubMed]

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Factors Associated with Early Mortality in Critically Ill Patients Following the Initiation of Continuous Renal Replacement Therapy

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Abstract: Continuous renal replacement therapy (CRRT) is an important modality to support critically ill patients, and the need for CRRT treatment has been increasing. However, CRRT management is costly, and the associated resources are limited. Thus, it remains challenging to identify patients that are likely to have a poor outcome, despite active treatment with CRRT. We sought to elucidate the factors associated with early mortality after CRRT initiation. We analyzed 240 patients who initiated CRRT at an academic medical center between September 2016 and January 2018. We compared baseline characteristics between patients who died within seven days of initiating CRRT (early mortality), and those that survived more than seven days beyond the initiation of CRRT. Of the patients assessed, 130 (54.2%) died within seven days of CRRT initiation. Multivariate logistic regression models revealed that low mean arterial pressure, low arterial pH, and high Sequential Organ Failure Assessment score before CRRT initiation were significantly associated with increased early mortality in patients requiring CRRT. In conclusion, the mortality within seven days following CRRT initiation was very high in this study. We identified several factors that are associated with early mortality in patients undergoing CRRT, which may be useful in predicting early outcomes, despite active treatment with CRRT.

Keywords: continuous renal replacement therapy; early mortality; clinical illness

1. Introduction

Acute kidney injury (AKI) is a major complication in critically ill patients, and it is associated with high mortality [1–3]. Continuous renal replacement therapy (CRRT) is a widely chosen treatment option in AKI patients requiring renal replacement therapy (RRT), particularly for hemodynamically unstable patients with considerable fluid accumulation [4–6]. Although CRRT is commonly considered as an initial option for critically ill patients who need RRT, the cost of CRRT treatment is higher than that of intermittent RRT, and CRRT-associated resources are limited [7,8].

Despite advances in CRRT techniques over the last several years, the mortality rate of patients undergoing CRRT remains high [9–12]. Many studies have investigated the benefit of CRRT treatment with regard to clinical outcomes and assessed potential prognostic factors for mortality [13–15]. Several factors, including sepsis, high acute physiology, and chronic health evaluation (APACHE) II score and/or sequential organ failure assessment (SOFA) score, poor urine output before CRRT initiation, comatose state, need for mechanical ventilation, fluid overload status, and type of CRRT solution are associated with increased mortality rate [16–22]. However, some patients die within one week of CRRT initiation, causing physicians to often doubt the benefits of such an invasive procedure on patient survival and/or renal preservation. Unfortunately, there are few studies to determine which factors are associated with increased early mortality in critically ill patients undergoing CRRT.

Considering the high cost and the limited resources available, identification of patients who would be more likely to have a poor outcome despite active treatment with CRRT is necessary to make an informed decision for patients requiring RRT. Thus, the aim of this study was to investigate the factors that are associated with increased early mortality, which we defined as death in the 7 days following CRRT initiation.

2. Methods

2.1. Study Population

This was a retrospective observational study of patients aged 18 years or older who initiated CRRT at a tertiary academic medical center between September 2016 and January 2018. Patients who were younger than 18 years, who were undergoing chronic dialysis due to end-stage renal disease, or who had a less than 3 month life expectancy due to malignancy were excluded. Ultimately, 240 patients were enrolled and assessed to determine the factors that were associated with early mortality in critically ill patients undergoing CRRT. We defined 'early mortality' as mortality within seven days of CRRT initiation. In addition, we defined 'very early mortality' as mortality within 24 h of CRRT initiation. This study was approved by the Institutional Review Board of Ewha Womans University, College of Medicine, and informed consent was waived because it was a retrospective cohort study.

2.2. Data Collection

Baseline characteristics were age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate, comorbidities, Charlson Comorbidity Index (CCI) [23], SOFA score, and laboratory diagnostic data collected at the start of CRRT. Moreover, estimated glomerular filtration rate (eGFR) was calculated using the IDMS-traceable Modification of Diet in Renal Disease equation [24]. The presence of systemic inflammatory response syndrome (SIRS) [25]. APACHE II score and one-hour urine output immediately before CRRT initiation was also investigated. As a parameter for acute lung injury (ALI), patients with $PaO_2/FiO_2 \leq 300$ mmHg were evaluated. Data from patients collected until 28 days after CRRT initiation was used, and their survival or all-cause mortality was examined during this period.

2.3. CRRT Protocol

The decision to initiate the CRRT and the CRRT settings of target clearance, blood flow, dialysate, and replacement fluid rates, and anticoagulation administration were determined through discussion and consultation with nephrologists. The criteria for CRRT initiation were medically intractable or persistent electrolyte imbalance and/or metabolic acidosis, and decreased urine output with volume overload and/or progressive azotemia. Hemodynamic instability was also an important indication. Generally, vascular access for CRRT was via a femoral venous catheter, and the predilution method of continuous venovenous hemodiafiltration was usually performed. Blood flow was gradually increased from an initial rate of 100 to 150 mL/min according to the hemodynamic status of the patient. Although the target clearance was 35–40 mL/kg/h in most patients, this target was increased

to 60 mL/kg/h or higher in patients with severe sepsis or septic shock if possible [26]. Additionally, the anticoagulant administered was selected by nephrologists, and they were dependent on bleeding tendency or contraindications to conventional heparin. After CRRT initiation, attending physicians and experienced nurses monitored the body weight, urine output, laboratory results, actual delivered dose, and the hemodynamic status of the patients, and discussed the results with nephrologists to maintain the adequacy of CRRT.

2.4. Statistical Analysis

Continuous variables are expressed as the mean and standard deviation (SD), and categorical variables as number and percentage. Chi-square tests for categorical variables and Student's t-test for continuous variables were used to compare baseline data between the two groups. We also performed univariate and multivariate logistic regression analyses to determine the factors associated with early or very early mortality. All statistical analyses were performed using SPSS version 23 software (SPSS, Chicago, IL, USA), and all *p*-values were two-tailed, with a predetermined alpha level <0.05 being considered statistically significant.

3. Results

3.1. Baseline Characteristics

Baseline demographic and clinical characteristics of these study patients are described in Table 1. For the 240 patients assessed, the mean age was 65.8 ± 14.7 years, and 150 patients (62.5%) were male. Mean SBP, DBP, and MAP were 112.5, 64.1, and 80.2 mmHg, respectively. In addition, there were 45 patients (18.8%) who had MAPs of less than 65 mmHg. Of the patients, 128 (53.3%) had hypertension, 89 (37.1%) were diagnosed with diabetes mellitus (DM), and the mean CCI was 6.6 ± 2.3. The mean volume of 1-hour urine outputs before CRRT was 27.2 ± 56.8 mL, and the mean APACHE II and SOFA scores were 26.1 ± 6.8 and 11.6 ± 3.9, respectively.

Table 1. Baseline characteristics of study patients.

Variables	Total	7-Day Mortality	7-Day Survivors	*p* Value
	(*n* = 240, 100%)	(*n* = 130, 54.2%)	(*n* = 110, 45.8%)	
Age (year)	65.8 ± 14.7	65.9 ± 14.2	65.7 ± 15.3	0.928
Male sex, *n* (%)	150 (62.5)	78 (60.0)	72 (65.5)	0.231
BMI (kg/m^2)	23.1 ± 4.3	23.0 ± 4.7	23.1 ± 3.7	0.850
SBP (mmHg)	112.5 ± 23.9	107.3 ± 22.6	118.6 ± 24.2	<0.001
DBP (mmHg)	64.1 ± 15.2	61.9 ± 14.1	66.8 ± 16.1	0.013
MAP (mmHg)	80.2 ± 16.0	77.0 ± 15.1	84.0 ± 16.3	0.001
MAP < 65 mmHg, *n* (%)	45 (18.8)	32 (24.6)	13 (11.8)	0.008
Heart rate (per min)	107.2 ± 24.0	110.7 ± 22.5	103.1 ± 25.2	0.015
Comorbidity disease				
Hypertension, *n* (%)	128 (53.3)	65 (50.0)	47 (42.7)	0.160
Diabetes mellitus, *n* (%)	89 (37.1)	43 (33.1)	46 (41.8)	0.103
CHF, *n* (%)	15 (6.3)	9 (6.9)	6 (5.5)	0.423
COPD, *n* (%)	4 (1.7)	2 (1.8)	2 (1.5)	0.624
Age CCI	6.60 ± 2.31	6.50 ± 2.42	6.72 ± 2.18	0.468
SIRS, *n* (%)	199 (82.9)	114 (87.7)	85 (77.3)	0.025
Sepsis, *n* (%)	75 (31.3)	42 (32.3)	33 (30.0)	0.404
Amount of 1-h UO (mL)	27.2 ± 56.8	26.6 ± 60.1	27.8 ± 52.9	0.879
APACHE II score	26.1 ± 6.8	28.9 ± 6.2	22.9 ± 6.0	<0.001
SOFA score	11.58 ± 3.87	12.70 ± 3.53	10.27 ± 3.86	<0.001

Data are presented as mean ± standard deviation or number (%). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; CHF, congestive heart failure; COPD, chronic obstructive heart failure; CCI, Charlson comorbidity index; SIRS, systemic inflammatory response syndrome; UO, urine output.

When we divided these patients into two groups (early mortality vs. 7-day survival past CRRT initiation), 138 (54.2%) died within seven days following the start of CRRT, and 110 (45.8%) survived more than seven days following CRRT initiation. There were no significant differences in age, sex distribution, BMI, the prevalence of underlying diseases, CCI, or 1-h urine volume output at baseline between the two groups. The proportion of patients diagnosed with sepsis was also not significantly different between the two groups.

However, SBP, DBP, and MAP were significantly lower in the patients that exhibited early mortality following CRRT initiation compared to 7-day survivors. Additionally, heart rate and APACHE II and SOFA scores were significantly higher in the early mortality group compared to those of 7-day survivors. Finally, we observed that a higher proportion of patients suffered from SIRS in the early mortality group compared to the 7-day survivor group.

Table 2 shows laboratory data of the patients at baseline. The mean white blood cell count was 13,100/μL; the mean hemoglobin was 9.4 ± 2.1 g/dL; and serum sodium, potassium, and bilirubin levels were 138.9 ± 7.3, 4.5 ± 1.0, and 2.8 ± 4.9 mEq/L, respectively. Additionally, the mean aspartate transaminase (AST) and alanine transaminase (ALT) levels were 401.8 ± 1157.2 and 158.8 ± 575.5 IU/L, respectively, and the mean eGFR was 22.7 ± 17.1 ml/min/1.73 m^2. The mean arterial pH was 7.29 ± 0.13, and the base excess was −7.74 ± 7.10 mmol/L. When these data were compared between the early mortality and the 7-day survivor groups, serum phosphate level was significantly higher, while arterial pH was significantly lower in the early mortality group compared to the survivor group. Moreover, there was a higher proportion of patients with pH < 7.35 in the early mortality group than in the survivor group, and base excess was lower (base excess = −8.88) in the early mortality group compared to the survivor group (base excess = −6.43). Meanwhile, there was no difference in the proportion of patients with $PaO_2/FiO_2 \leq 300$ mmHg between groups. The baseline characteristics and laboratory findings of patients with very early mortality were additionally described in Supplementary Materials (Tables S1 and S2).

Table 2. Baseline laboratory data of study patients.

Variables	Total	7-Day Mortality	7-Day Survivors	*p* Value
	(*n* = 240, 100%)	(*n* = 130, 54.2%)	(*n* = 110, 45.8%)	
WBC (103/μL)	13.1 ± 12.3	14.1 ± 15.5	11.9 ± 7.1	0.147
Hemoglobin (g/dL)	9.4 ± 2.1	9.5 ± 2.3	9.4 ± 1.9	0.892
Platelet (103/μL)	127.8 ± 86.5	127.9 ± 89.1	127.6 ± 83.8	0.980
Sodium (mEq/L)	138.9 ± 7.3	139.6 ± 7.9	138.1 ± 6.4	0.119
Potassium (mEq/L)	4.5 ± 1.0	4.6 ± 1.0	4.5 ± 0.9	0.289
Calcium (mg/dL)	7.8 ± 1.3	7.7 ± 1.2	7.8 ± 1.4	0.669
Phosphate (mg/dL)	5.5 ± 2.9	5.9 ± 3.2	5.0 ± 2.5	0.021
Bilirubin, total (mg/dL)	2.8 ± 4.9	2.9 ± 4.9	2.6 ± 4.8	0.568
AST (IU/L)	401.8 ± 1157.2	416.8 ± 1012.7	384.5 ± 1308.8	0.831
ALT (IU/L)	185.8 ± 575.5	199.1 ± 473.4	170.6 ± 675.7	0.706
eGFR (ml/min/1.73 m^2)	22.7 ± 17.1	23.7 ± 16.2	21.4 ± 18.1	0.300
pH	7.29 ± 0.13	7.25 ± 0.12	7.33 ± 0.12	<0.001
pH < 0.35, *n* (%)	164 (68.3)	107 (82.3)	57 (51.8)	<0.001
BE (mmol/L)	−7.75 ± 7.10	−8.88 ± 6.64	−6.43 ± 7.43	0.008
PaO_2/FiO_2 < 300	188 (78.3)	106 (81.5)	82 (74.5)	0.125

Data are presented as mean ± standard deviation or number (%). Abbreviations: WBC, whole blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; BE, base excess.

3.2. Factors Associated with Early Mortality

In this study, 162 patients (67.5%) died in the 28 days following CRRT initiation, and most of those deaths occurred in the early period following CRRT initiation (Figure 1). Specifically, 130 patients (80.2%) died within seven days following CRRT initiation, with 54 of those patients dying within 24 h following CRRT initiation.

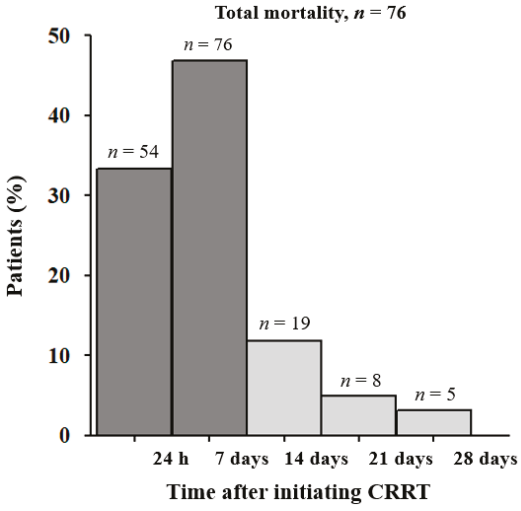

Figure 1. Mortality rate according to time after continuous renal replacement therapy (CRRT) initiation.

By univariate logistic regression analysis, patients with MAP < 65 mmHg and SIRS had an odds ratio (OR) of 2.436 (95% CI; 1.206–4.922, $p = 0.013$) and OR of 2.096 (95% CI; 1.054–4.168, $p = 0.035$) for an increased risk of early mortality, compared to patients with MAP > 65 mmHg, and an absence of SIRS. Moreover, a 1-SD increase of serum phosphate was significantly associated with an increased risk of early mortality (OR = 1.393, 95% CI (1.044–1.858), $p = 0.024$), and a 1-SD increase in SOFA score was also significantly associated with an increased incidence of early mortality (OR = 1.992, 95% CI (1.488–2.668), $p < 0.001$). Finally, the patients with pH < 7.35 also had a higher risk of early mortality compared to those with pH > 7.35 (OR = 4.326, 95% CI (2.409–7.768), $p < 0.001$). Importantly, after adjustment for demographic factors and other factors found to associate by univariate analysis with early mortality, increased SOFA score, low MAP (<65 mmHg), and low arterial pH (<7.35) all remained significantly associated with an increased risk of early mortality (SOFA score; OR = 1.758, 95% CI (1.282–2.412), $p < 0.001$, low MAP; OR = 2.771, 95% CI (1.213–6.327), $p = 0.016$, and low pH; OR = 3.067, 95% CI (1.593–5.903), $p = 0.001$) (Table 3). With consideration for overlapping parts between MAP, SIRS, and SOFA scores, additional multivariate regression analyses were performed by adjusting one of these three parameters to add to the other variables. As a result, SIRS showed a loss of significance, even in the analysis, without adjustment with MAP and SOFA scores.

We also performed multivariate logistic regression analyses to assess factors associated with very early mortality, to determine the similarities and differences between those factors related to the increased early mortality. We found that an increased serum sodium level, phosphate level, SOFA score, and low MAP (<65 mmHg) were all significantly associated with increased very early mortality, even after multivariate adjustment, as described previously (Table 4). Therefore, low MAP and increased SOFA scores are associated with an increased risk of both early and very early mortality.

Table 3. Logistic regression analysis for early mortality *.

Factors	Univariate		Multivariate	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age (per 1-SD increase)	1.012 (0.785−1.305)	0.928	1.079 (0.803−1.450)	0.614
Male (versus Female)	0.792 (0.467−1.341)	0.385	0.877 (0.477−1.610)	0.671
BMI (per 1-SD increase)	0.976 (0.757−1.259)	0.976	0.929 (0.695−1.240)	0.616
MAP < 65 mmHg (versus MAP ≥ 65 mmHg)	2.436 (1.206−4.922)	0.013	2.771 (1.213−6.327)	0.016
SIRS (versus no SIRS)	2.096 (1.054−4.168)	0.035	1.602 (0.717−3.583)	0.251
Sepsis (versus no sepsis)	0.898 (0.519−1.555)	0.898	-	-
Phosphate (per 1-SD increase)	1.393 (1.044−1.858)	0.024	1.197 (0.869−1.649)	0.270
pH < 7.35 (versus pH ≥ 7.35)	4.326 (2.409−7.768)	<0.001	3.067 (1.593−5.903)	0.001
SOFA score (per 1-SD increase)	1.992 (1.488−2.668)	<0.001	1.758 (1.282−2.412)	<0.001

* The early mortality was defined by the death within seven days after CRRT initiation. Abbreviations: OR, odds ratio; CI, confidential interval; SD, standard deviation; BMI, body mass index; MAP, mean arterial blood pressure; SIRS, systemic inflammatory response syndrome

Table 4. Logistic regression analysis for very early mortality *.

Factors	Univariate		Multivariate	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Age (per 1-SD increase)	1.069 (0.785−1.456)	0.672	1.363 (0.909−2.043)	0.134
Male (versus female)	0.632 (0.337−1.151)	0.131	0.707 (0.327−1.532)	0.380
BMI (per 1-SD increase)	1.038 (0.768−1.402)	0.810	0.956 (0.657−1.391)	0.816
Diabetes mellitus (versus non-diabetes)	0.354 (0.172−0.730)	0.005	0.456 (0.189−1.101)	0.081
MAP < 65 mmHg (versus MAP ≥ 65 mmHg)	4.295 (2.144−8.607)	<0.001	8.498 (3.379−21.375)	<0.001
SIRS (versus no SIRS)	2.352 (0.874−6.326)	0.090	-	-
Sepsis (versus no sepsis)	1.103 (0.570−2.136)	0.770	-	-
Sodium (per 1-SD increase)	1.458 (1.202−1.769)	<0.001	1.588 (1.241−2.031)	<0.001
Phosphate (per 1-SD increase)	1.632 (1.207−2.207)	0.001	1.669 (1.149−2.424)	0.007
pH < 7.35 (versus pH ≥ 7.35)	4.828 (1.965−11.863)	0.001	2.395 (0.860−6.675)	0.095
SOFA score (per 1-SD increase)	1.895 (1.329−2.702)	<0.001	1.691 (1.049−2.725)	0.031

* Very early mortality was defined by death within 24 h after CRRT initiation. Abbreviations: OR, odds ratio; CI, confidential interval; SD, standard deviation; BMI, body mass index; MAP, mean arterial blood pressure; SIRS, systemic inflammatory response syndrome

4. Discussion

This study demonstrated that early mortality within seven days following CRRT initiation was high in critically ill patients undergoing CRRT (54.2%). Moreover, MAP < 65 mmHg, arterial pH < 7.35, and high SOFA score at CRRT initiation significantly associated with increased risk of early mortality in these patients.

When we stratified the mortality rate of critically ill patients undergoing CRRT initiation, 80.2% of the total 162 patients that died during the 28-day follow-up period died within seven days following CRRT initiation, and 33.3% (54/162 patients) died within 24 h following CRRT initiation. A smaller percentage of patients, 19.8% (32/162 patients), died between eight and 28 days following CRRT initiation. Thus, we assessed which factors were associated with early or very early mortality in this group.

There are many studies assessing prognostic factors for the mortality risk of CRRT to predict and prevent poor clinical outcomes [13–22]. However, most of these studies assessed mortality beyond 28 days post-initiation of CRRT. Only a few studies have been conducted to investigate early mortality among critically ill patients undergoing CRRT [27,28]. In contrast, clinicians are often challenged to determine the benefit of CRRT, and it is difficult to identify patients that are more likely to demonstrate poor clinical outcomes, despite active treatment with CRRT to make the best decision for patients requiring RRT.

In this study, MAP < 65 mmHg, arterial pH < 7.35, and high SOFA score at CRRT initiation were risk factors for early mortality. Additionally, MAP < 65 mmHg, increased serum sodium, and phosphate levels, and high SOFA score at CRRT initiation, were significantly associated with an

increased rate of very early mortality. Above these factors can be found in the other studies which were performed for the 28-, 60-, or 90-day mortality, which means that such factors may be more likely to be issued for early mortality.

CRRT treatment is primarily considered for patients in critical condition, who are hemodynamically unstable, and/or who suffer from increased intracranial pressure due to acute brain injury [29,30]; thus, the mortality rate of patients requiring CRRT is generally high. The mortality rate within hours or days following CRRT initiation is particularly high, mainly due to the poor condition of the patients at the initiation of CRRT. Specifically, Passos et al. [31] demonstrated a 7-day mortality of 45.0% (84/186 patients), and Prasad et al. [27] reported that 16.0% (17/106 patients) died within 24 h after the start of CRRT. In this study, 22.5% (54/240 patients) died within 24 h, and 54.2% (130/240 patients) died within seven days following CRRT initiation. Moreover, 80.2% of the total number of patients that died within the 28-day period (130/162 patients) died within 7 days following CRRT initiation. To our knowledge, this is the first study comparing the mortality rate at different time periods following CRRT initiation, and these results suggest that a majority of patients undergoing CRRT die within seven days following initiation. However, a prospective cohort study with a larger population should be performed to confirm these results.

AKI, combined with cardiovascular instability, fluid overload, cerebral edema, and high fluid requirement, generally indicates a need for CRRT [32,33]. In addition, the need to eliminate inflammatory mediators, remove fluid, or eliminate other endogenous toxic solutes have been presented as non-renal reasons to initiate CRRT [34]. In our study, several factors were found to be associated with early or very early mortality in patients undergoing CRRT. MAP is a hemodynamic parameter, and maintaining MAP $\geq$ 65 mmHg is recommended in the management of patients with septic shock, a condition for which CRRT is a common treatment [35]. In addition, a SOFA score represents a severity parameter and it is a widely accepted prognostic factor for critically ill patients [36,37]. Several studies report a significant association between a high SOFA score at CRRT initiation, and increased mortality [38–40]. Arterial pH is one of the variables that is considered in the APACHE II score, which was designed to measure the disease severity and the risk of death in critically ill patients, and several studies have demonstrated that arterial pH is associated with increased mortality in patients undergoing CRRT [41–43]. In addition, previous studies have reported that hypernatremia and hyperphosphatemia are common in critically ill patients, and they were associated with increased morbidity and mortality [44–47]. The factors identified in this study could be predictable through previous studies; however, this study has significance because it reaffirms the clinical importance of these factors by assessing the association with early death showing high mortality rate. The results presented here do not indicate the futility of CRRT treatment for patients with lower MAP, lower pH, higher serum sodium or phosphate, or high SOFA score. However, these results could be useful in predicting the prognosis of critically ill patients after CRRT initiation.

There are some limitations to our study. First, this was a single center study with a relatively small sample size, so we cannot rule out selection bias, and these results may not be generalizable to other populations. Therefore, a future multiple-center study with a larger sample size is warranted to verify factors that are associated with early mortality in critically ill patients undergoing CRRT. Second, because of the inherent limitations of a retrospective study, other potential factors associated with early death in critically ill patients, such as causes of CRRT initiation or primary diagnosis at admission may not have been assessed. Third, we investigated mortality events based on arbitrarily stratified time periods, such as within 24 h, 7 days, or 28 days following CRRT initiation, and defined 'early mortality' or 'very early mortality' discretionally. However, several studies for mortality of the patients undergoing CRRT have used 28-days mortality as the end-point and there have been also some studies for 24-hour and 7-day mortality, so that these timeframes are not without precedent. Moreover, in this study, we found that the highest mortality following CRRT occurred in the early timeframe following CRRT initiation. Lastly, this observational study does not allow us to conclude a causal relationship,

and it only demonstrates the associations between clinical factors and early or very early mortality in patients undergoing CRRT treatment.

5. Conclusions

In conclusion, we found that the early mortality rate within seven days following CRRT initiation was very high in this cohort of critically ill patients undergoing CRRT. Moreover, low MAP, low arterial pH, and high SOFA score at CRRT initiation were associated with early mortality in these patients. Although these factors may not be used as determinants in deciding whether or not CRRT should be initiated in critically ill patients, they may be useful in predicting early or very early mortality despite active treatment with CRRT.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/10/334/s1, Table S1: Baseline characteristics of study subjects, Table S2: Laboratory data of study subjects at baseline.

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References

1. Liangos, O.; Wald, R.; O'Bell, J.W.; Price, L.; Pereira, B.J.; Jaber, B.L. Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. *Clin. J. Am. Soc. Nephrol.* **2006**, *1*, 43–51. [CrossRef] [PubMed]
2. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef] [PubMed]
3. Bagshaw, S.M.; Laupland, K.B.; Doig, C.J.; Mortis, G.; Fick, G.H.; Mucenski, M.; Godinez-Luna, T.; Svenson, L.W.; Rosenal, T. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: A population-based study. *Crit. Care* **2005**, *9*, R700. [CrossRef] [PubMed]
4. Truche, A.S.; Darmon, M.; Bailly, S.; Clec'h, C.; Dupuis, C.; Misset, B.; Azoulay, E.; Schwebel, C.; Bouadma, L.; Kallel, H.; et al. Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: Impact on mortality and renal recovery. *Intensiv. Care Med.* **2016**, *42*, 1408–1417. [CrossRef] [PubMed]
5. Davenport, A.; Will, E.J.; Davidson, A.M. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit. Care Med.* **1993**, *21*, 328–338. [CrossRef] [PubMed]
6. Kruczynski, K.; Irvine-Bird, K.; Toffelmire, E.B.; Morton, A.R. A comparison of continuous arteriovenous hemofiltration and intermittent hemodialysis in acute renal failure patients in the intensive care unit. *ASAIO* **1993**, *39*, M778–M781.
7. Srisawat, N.; Lawsin, L.; Uchino, S.; Bellomo, R.; Kellum, J.A. Cost of acute renal replacement therapy in the intensive care unit: Results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit. Care* **2010**, *14*, R46. [CrossRef] [PubMed]
8. Farese, S.; Jakob, S.M.; Kalicki, R.; Frey, F.J.; Uehlinger, D.E. Treatment of acute renal failure in the intensive care unit: Lower costs by intermittent dialysis than continuous venovenous hemodiafiltration. *Artif. Organs* **2009**, *33*, 634–640. [CrossRef] [PubMed]
9. Brivet, F.G.; Kleinknecht, D.J.; Loirat, P.; Landais, P.J. Acute renal failure in intensive care units—Causes, outcome, and prognostic factors of hospital mortality: A prospective, multicenter study. *Crit. Care Med.* **1996**, *24*, 192–198. [CrossRef] [PubMed]
10. Metnitz, P.G.; Krenn, C.G.; Steltzer, H.; Lang, T.; Ploder, J.; Lenz, K.; Le Gall, J.R.; Druml, W. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit. Care Med.* **2002**, *30*, 2051–2058. [CrossRef] [PubMed]

11. Cho, K.C.; Himmelfarb, J.; Paganini, E.; Ikizler, T.A.; Soroko, S.H.; Mehta, R.L.; Chertow, G.M. Survival by dialysis modality in critically ill patients with acute kidney injury. *J. Am. Soc. Nephrol.* **2006**, *17*, 3132–3138. [CrossRef] [PubMed]
12. Uchino, S.; Bellomo, R.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; Gibney, N.; Tolwani, A.; et al. Continuous renal replacement therapy: A worldwide practice survey. *Intensiv. Care Med.* **2007**, *33*, 1563–1570. [CrossRef] [PubMed]
13. Sasaki, S.; Gando, S.; Kobayashi, S.; Nanzaki, S.; Ushitani, T.; Morimoto, Y.; Demmotsu, O. Predictors of mortality in patients treated with continuous hemodiafiltration for acute renal failure in an intensive care setting. *ASAIO* **2001**, *47*, 86–91. [CrossRef]
14. Wald, R.; Deshpande, R.; Bell, C.M.; Bargman, J.M. Survival to discharge among patients treated with continuous renal replacement therapy. *Hemod. Int.* **2006**, *10*, 82–87. [CrossRef] [PubMed]
15. Oh, H.J.; Park, J.T.; Kim, J.K.; Yoo, D.E.; Kim, S.J.; Han, S.H.; Kang, S.W.; Choi, K.H.; Yoo, T.H. Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy. *Nephrol. Dial. Transplant.* **2011**, *27*, 589–594. [CrossRef] [PubMed]
16. Kellum, J.A.; Angus, D.C.; Johnson, J.P.; Leblanc, M.; Griffin, M.; Ramakrishnan, N.; Linde-Zwirble, W.T. Continuous versus intermittent renal replacement therapy: A meta-analysis. *Intensiv. Care Med.* **2002**, *28*, 29–37. [CrossRef] [PubMed]
17. Soubrier, S.; Leroy, O.; Devos, P.; Nseir, S.; Georges, H.; d'Escrivan, T.; Guery, B. Epidemiology and prognostic factors of critically ill patients treated with hemodiafiltration. *J. Crit. Care* **2006**, *21*, 66–72. [CrossRef] [PubMed]
18. Kim, E.S.; Ham, Y.R.; Jang, W.I.; Jung, J.Y.; Kwon, O.K.; Chung, S.; Choi, D.E.; Na, K.R.; Lee, K.W.; Shin, Y.T. Prognostic factors of acute renal failure patients treated with continuous renal replacement therapy. *Korean J. Nephrol.* **2010**, *29*, 54–63.
19. Gjyzaria, A.; Muzi, L.; Morabito, S. Continuous renal replacement therapy for acute renal failure in critically ill patients and early predictive factors. *BANTAO* **2007**, *5*, 58–60.
20. Lee, S.H.; Kwon, S.K.; Kim, H.Y. Outcome and prognosis in patients receiving continuous renal replacement therapy. *Korean J. Nephrol.* **2010**, *29*, 434–440.
21. Vaara, S.T.; Korhonen, A.M.; Kaukonen, K.M.; Nisula, S.; Inkinen, O.; Hoppu, S.; Laurila, J.J.; Mildh, L.; Reinikainen, M.; Lund, V.; et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: Data from the prospective FINNAKI study. *Crit. Care* **2012**, *16*, R197. [CrossRef] [PubMed]
22. Kashani, K.; Thongprayoon, C.; Cheungpasitporn, W.; Iacovella, G.M.; Akhoundi, A.; Albright, R.C. Association between mortality and replacement solution bicarbonate concentration in continuous renal replacement therapy: A propensity-matched cohort study. *PLoS ONE* **2017**, *12*, e0185064. [CrossRef] [PubMed]
23. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **1987**, *40*, 373–383. [CrossRef]
24. Levey, A.S.; Bosch, J.P.; Lewis, J.B.; Greene, T.; Rogers, N.; Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann. Intern. Med.* **1999**, *130*, 461–470. [CrossRef] [PubMed]
25. Bone, R.C.; Balk, R.A.; Cerra, F.B.; Dellinger, R.P.; Fein, A.M.; Knaus, W.A.; Schein, R.M.; Sibbald, W.J. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* **1992**, *101*, 1644–1655. [CrossRef] [PubMed]
26. Zahar, J.R.; Timsit, J.F.; Garrouste-Orgeas, M.; Français, A.; Vesin, A.; Descorps-Declere, A.; Dubois, Y.; Souweine, B.; Haouache, H.; Goldgran-Toledano, D.; et al. Outcomes in severe sepsis and patients with septic shock: Pathogen species and infection sites are not associated with mortality. *Crit. Care Med.* **2011**, *39*, 1886–1895. [CrossRef] [PubMed]
27. Prasad, B.; Urbanski, M.; Ferguson, T.W.; Karreman, E.; Tangri, N. Early mortality on continuous renal replacement therapy (CRRT): The prairie CRRT study. *Can. J. Kidney Health Dis.* **2016**, *3*, 36. [CrossRef] [PubMed]
28. Gonzalez, C.A.; Pinto, J.L.; Orozco, V.; Contreras, K.; Garcia, P.; Rodriguez, P.; Patiño, J.; Echeverri, J. Early mortality risk factors at the beginning of continuous renal replacement therapy for acute kidney injury. *Cogent Med.* **2018**, *5*, 1407485. [CrossRef]
29. Macedo, E.; Mehta, R.L. Continuous dialysis therapies: Core curriculum 2016. *Am. J. Kidney Dis.* **2016**, *68*, 645–657. [CrossRef] [PubMed]

30. Ronco, C. Continuous renal replacement therapies for the treatment of acute renal failure in intensive care patients. *Clin. Nephrol.* **1993**, *40*, 187–198. [PubMed]
31. Da Hora Passos, R.; Ramos, J.G.; Mendonça, E.J.; Miranda, E.A.; Dutra, F.R.; Coelho, M.F.; Pedroza, A.C.; Correia, L.C.; Batista, P.B.; Macedo, E.; et al. A clinical score to predict mortality in septic acute kidney injury patients requiring continuous renal replacement therapy: The HELENICC score. *BMC Anesthesiol.* **2017**, *17*, 21. [CrossRef] [PubMed]
32. Schetz, M. Classical and alternative indications for continuous renal replacement therapy. *Kidney Int.* **1998**, *S66*, S129.
33. Davenport, A. *Renal Replacement Therapy for the Patient with Acute Traumatic Brain Injury and Severe Acute Kidney Injury, in Acute Kidney Injury*; Karger Publishers: Basel, Switzerland, 2007; pp. 333–339.
34. Schetz, M. Non-renal indications for continuous renal replacement therapy. *Kidney Int.* **1999**, *56*, S88–S94. [CrossRef]
35. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensiv. Care Med.* **2017**, *43*, 304–377. [CrossRef] [PubMed]
36. Oppert, M.; Engel, C.; Brunkhorst, F.M.; Bogatsch, H.; Reinhart, K.; Frei, U.; Eckardt, K.U.; Loeffler, M.; John, S. Acute renal failure in patients with severe sepsis and septic shock—A significant independent risk factor for mortality: Results from the German Prevalence Study. *Nephrol. Dial. Transplant.* **2007**, *23*, 904–909. [CrossRef] [PubMed]
37. Ferreira, F.L.; Bota, D.P.; Bross, A.; Mélot, C.; Vincent, J.L. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* **2001**, *286*, 1754–1758. [CrossRef] [PubMed]
38. Kawarazaki, H.; Uchino, S.; Tokuhira, N.; Ohnuma, T.; Namba, Y.; Katayama, S.; Toki, N.; Takeda, K.; Yasuda, H.; Izawa, J.; et al. Who may not benefit from continuous renal replacement therapy in acute kidney injury? *Hemodial. Int.* **2013**, *17*, 624–632. [CrossRef] [PubMed]
39. Rhee, H.; Jang, K.S.; Park, J.M.; Kang, J.S.; Hwang, N.K.; Kim, I.Y.; Song, S.H.; Seong, E.Y.; Lee, D.W.; Lee, S.B.; et al. Short-and long-term mortality rates of elderly acute kidney injury patients who underwent continuous renal replacement therapy. *PLoS ONE* **2016**, *11*, e0167067. [CrossRef] [PubMed]
40. Pistolesi, V.; Di Napoli, A.; Fiaccadori, E.; Zeppilli, L.; Polistena, F.; Sacco, M.I.; Regolisti, G.; Tritapepe, L.; Pierucci, A.; Morabito, S. Severe acute kidney injury following cardiac surgery: Short-term outcomes in patients undergoing continuous renal replacement therapy (CRRT). *J. Nephrol.* **2016**, *29*, 229–239. [CrossRef] [PubMed]
41. Soni, S.S.; Nagarik, A.P.; Adikey, G.K.; Raman, A. Using continuous renal replacement therapy to manage patients of shock and acute renal failure. *J. Emerg. Trauma Shock* **2009**, *2*, 19. [PubMed]
42. Yoon, J.; Kim, Y.; Yim, H.; Cho, Y.S.; Kym, D.; Hur, J.; Chun, W.; Yang, H.T. Analysis of prognostic factors for acute kidney injury with continuous renal replacement therapy in severely burned patients. *Burns* **2017**, *43*, 1418–1426. [CrossRef] [PubMed]
43. Bae, W.K.; Lim, D.H.; Jeong, J.M.; Jung, H.Y.; Kim, S.K.; Park, J.W.; Bae, E.H.; Ma, S.K.; Kim, S.W.; Kim, N.H.; et al. Continuous renal replacement therapy for the treatment of acute kidney injury. *Korean J. Intern. Med.* **2008**, *23*, 58. [CrossRef] [PubMed]
44. Han, S.S.; Bae, E.; Kim, D.K.; Kim, Y.S.; Han, J.S.; Joo, K.W. Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: A prospective observational study. *BMC Nephrol.* **2016**, *17*, 2. [CrossRef] [PubMed]
45. Lindner, G.; Funk, G.C.; Schwarz, C.; Kneidinger, N.; Kaider, A.; Schneeweiss, B.; Kramer, L.; Druml, W. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am. J. Kidney Dis.* **2007**, *50*, 952–957. [CrossRef] [PubMed]
46. Jung, S.Y.; Kwon, J.; Park, S.; Jhee, J.H.; Yun, H.R.; Kim, H.; Kee, Y.K.; Yoon, C.Y.; Chang, T.I.; Kang, E.W.; et al. Phosphate is a potential biomarker of disease severity and predicts adverse outcomes in acute kidney injury patients undergoing continuous renal replacement therapy. *PLoS ONE* **2018**, *13*, e0191290. [CrossRef] [PubMed]
47. Kraft, M.D.; Btaiche, I.F.; Sacks, G.S.; Kudsk, K.A. Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am. J. Health-Syst. Pharm.* **2005**, *62*, 1663–1682. [CrossRef] [PubMed]

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Effect of Anesthetic Technique on the Occurrence of Acute Kidney Injury after Total Knee Arthroplasty

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Abstract: Recent studies have reported the advantages of spinal anesthesia over general anesthesia in orthopedic patients. However, little is known about the relationship between acute kidney injury (AKI) after total knee arthroplasty (TKA) and anesthetic technique. This study aimed to identify the influence of anesthetic technique on AKI in TKA patients. We also evaluated whether the choice of anesthetic technique affected other clinical outcomes. We retrospectively reviewed medical records of patients who underwent TKA between January 2008 and August 2016. Perioperative data were obtained and analyzed. To reduce the influence of potential confounding factors, propensity score (PS) analysis was performed. A total of 2809 patients and 2987 cases of TKA were included in this study. A crude analysis of the total set demonstrated a significantly lower risk of AKI in the spinal anesthesia group. After PS matching, the spinal anesthesia group showed a tendency for reduced AKI, without statistical significance. Furthermore, the spinal anesthesia group showed a lower risk of pulmonary and vascular complications, and shortened hospital stay after PS matching. In TKA patients, spinal anesthesia had a tendency to reduce AKI. Moreover, spinal anesthesia not only reduced vascular and pulmonary complications, but also shortened hospital stay.

Keywords: acute kidney injury; anesthetic technique; total knee arthroplasty

1. Introduction

Total knee arthroplasty (TKA) is the primary treatment option for advanced inflammatory and degenerative knee osteoarthritis. With an increase in the elderly population, the number of TKAs performed is increasing rapidly, and is expected to continue to increase [1,2]. Even in young patients, the number of TKAs performed is increasing as the surgical technique and durability of the implant have improved [3].

Although controversy remains over the optimal anesthetic technique in perioperative outcomes following TKA, general anesthesia has historically been used for TKA [4]. There is minimal risk of anesthesia failure with general anesthesia; however, although very rare, neuraxial anesthesia, including spinal anesthesia and epidural anesthesia, is associated with neurologic complications, such as radiculopathy, cauda equina syndrome, and paraplegia [5]. In addition, a meta-analysis showed that general anesthesia had no significant risk on perioperative morbidities and mortality compared to regional anesthesia including neuraxial anesthesia and peripheral nerve block in patients undergoing total joint arthroplasty [6]. Moreover, many surgeons and patients were found to prefer general anesthsia over neuraxial anesthesia because of patient anxiety; anesthesiologists also tend to opt for general anesthesia due to more experience with this technique [7].

However, there is increasing evidence that neuraxial anesthesia has potential advantages over general anesthesia. Several previous studies reported that neuraxial anesthesia can reduce the risk of deep vein thrombosis, surgical site infection, and perioperative blood loss in orthopedic patients [8–10]. A recent study identified that 30-day mortality was also reduced after total joint arthroplasty in patients receiving neuraxial anesthesia [11]. Spinal anesthesia also showed benefits especially in patients with multiple comorbidities [11].

Although various studies have analyzed the effect of anesthetic technique on perioperative morbidity and mortality, little is known about the relationship between acute kidney injury (AKI) after TKA and anesthetic technique. The incidence of AKI in patients undergoing TKA is approximately 4–5% and newly developed AKI after noncardiac surgery was found to lengthen postoperative hospital stay and increase mortality [12–14]. Thus, identification of modifiable factors associated with AKI is important to improve patient outcomes.

The current study aimed to identify the influence of anesthetic technique on the incidence of AKI using propensity score (PS) matching. We also evaluated whether the choice of anesthetic technique affected the occurrence of perioperative complications other than AKI.

2. Materials and Methods

This study was approved by the Institutional Review Board of Asan Medical Center (2017-0626; date of approval, 29 May 2017) and written informed consent was waived owing to the retrospective nature of this study. All surgeries were performed by three surgeons at a tertiary center in Seoul, Korea.

2.1. Study Population

We retrospectively reviewed the medical records of patients who underwent TKA between January 2008 and August 2016. A total of 4702 consecutive TKAs were identified from the electronic medical records system. Of these, 401 TKAs were excluded due to estimated preoperative glomerular filtration rate of less than 60 mL/min/1.73 m^2, preoperative serum creatinine (sCr) levels greater than 1.5 mg/dL, or a previous history of renal dysfunction. The remaining 4301 TKAs were performed on 2809 patients. In total, 1317 patients underwent a single TKA surgery. The remaining 1492 patients underwent TKAs on both knees; 555 with staggered operations during one hospitalization, 178 with staged operations at intervals of more than two weeks in two separate hospitalizations, and 759 simultaneous operations.

2.2. Anesthesia

Standard monitoring was performed in the operating room, including electrocardiogram (ECG), SpO_2, non-invasive blood pressure, and body temperature.

In patients receiving TKA under general anesthesia, intravenous propofol (2–3 mL/kg) or thiopental sodium (4–5 mL/kg) with rocuronium (0.6–1.0 mg/kg) was used for induction. After induction, anesthesia was maintained with 1–1.5 minimum alveolar concentration of inhalational agents (sevoflurane or desflurane) with 50% nitrous oxide. Fresh gas flow rate was maintained at 2 L/min and minute ventilation was adjusted with reference to $ETCO_2$. Tidal volume was set at 6–8 mL/kg and respiratory rate was set at 10–12/min without positive end-expiratory pressure (PEEP). In patients with decreased SpO_2, recruitment maneuver was performed and 5 cm H_2O PEEP was applied. After the procedure was completed, the inhalation agent and nitrous oxide were turned off and the lung was ventilated with 100% oxygen. When an attempt of self-respiration appeared, sugammadex or a cholinesterase inhibitor with anticholinergics was administered and extubation was performed.

Spinal anesthesia consisted of 10–15 mg bupivacaine and 10–15 mcg of fentanyl intrathecally after a lumbar puncture at the lateral decubitus position. During the intraoperative period, patients were sedated with midazolam and/or dexmedetomidine and breathed 5–6 L/min oxygen via a simple mask.

In both groups, blood pressure was targeted within normal range. If systolic blood pressure dropped below 80 mmHg, ephedrine (5–10 mg) or phenylephrine (50–100 μg) was injected. In the case of persistent hypotension, continuous infusion of phenylephrine was administered. When the

blood pressure was high despite the adequate anesthetic depth and sufficient analgesia, calcium channel blocker or beta blocker was administered considering the underlying disease of the patients and other vital signs upon the decision-making of a staff anesthesiologist. When severe bradycardia (HR < 40 BPM/min) was observed, atropine (0.5 mg) or glycopyrrolate (0.2 mg) was applied. Crystalloid and colloid solution was infused by calculating the maintenance volume and bleeding, and by considering the volume status of the patient. Transfusion was carried out based on the amount of hemorrhage, the symptom of anemia including hypotension, tachycardia, or change of ECG, and the hematocrit level. For postoperative pain control, IV patient-controlled analgesia with fentanyl was available to most patients.

2.3. Clinical Data

We retrospectively obtained demographic, surgical, preoperative, and clinical outcome data of all patients from the electronic medical records system of our institution. The demographic data included age, sex, body mass index (BMI), and the American Society of Anethesiologists' physical status (ASA PS) classification. Surgical data included the operator and the type of surgical strategy. The surgical strategy was classified as surgery on 1) only one knee (single group), 2) both knees simultaneously (simultaneous group), or 3) both knees sequentially. Patients that underwent surgery on both knees sequentially were divided into two groups according to whether the two surgeries were performed during one or two hospitalization periods (staggered group and staged group, respectively). Preoperative clinical data included medical history, including the presence of diabetes, hypertension, ischemic heart disease, cerebrovascular disease, pulmonary disease, adrenal insufficiency, and the use of the following medications: calcium channel blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, beta blocker, aspirin, antiplatelet agent, HMG-CoA reductase inhibitors, antibiotics, non-steroidal anti-inflammatory drugs, selective COX-2 inhibitor, other analgesics, and steroids. In addition, preoperative laboratory findings, including anemia, platelet, white blood cells, blood sodium level, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and uric acid, as well as transthoracic/transesophageal echocardiographic findings and pulmonary function test (PFT), were also documented.

2.4. Definitions of Outcomes

The primary outcome of this study was the association of the anesthetic technique with the occurrence of AKI in patients following TKA. AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and is described as the change in the sCr level on postoperative days 1 to 7 compared with the baseline sCr level measured before surgery. AKI was defined by alteration of sCr level $\geq$ 0.3 mg/dL within 48 hours, or a rise in sCr level $\geq$ 50% within the prior 7 days.

Intraoperative variables including the use of vasopressor, calcium channel blocker, and beta blocker, the total volume of infused crystalloid and colloid, intraoperative packed red blood cell transfusion, and the lowest mean blood pressure (MBP) were evaluated. In addition, the operation time and the tourniquet time were also calculated.

Other outcome variables were classified postoperatively as follows: cardiovascular complications, including hypotension, arrhythmia, ischemic heart disease, and congestive heart failure; pulmonary complications, including pneumonia, pleural effusion and pneumothorax; vascular complications, including deep vein thrombosis (DVT) with or without pulmonary thromboembolism (PTE); delirium; cerebrovascular accident; surgical site infection; gastrointestinal complications, including gastric ulcer, diarrhea, and elevated liver enzymes; and urologic complications, including voiding difficulty and urinary tract infection. Major complications, defined as complications requiring a surgical, endoscopic, or radiologic intervention, or those that were life-threatening (Clavien–Dindo classification $\geq$ 3), were also analyzed.

2.5. Statistical Analysis

The 2809 patients included in this study were classified into four groups based on surgical strategy. Since we aimed to evaluate the risk of AKI during a hospitalization, cases of two TKAs performed on the same patient, staggered and simultaneous, were considered as one case. However, the two TKAs performed on the same patient in the staged group were considered to be two separate cases. Thus, the total number of cases included in the analysis was 2987.

All data are presented as mean ± standard deviation or median (interquartile range) for continuous variables, or number (percentages) for categorical variables. Since the portion of missing data was insignificant, analyses were performed with only the recorded data without any special processing. Demographic characteristics and preoperative laboratory data were compared using Student's t test or the Mann-Whitney U test for continuous variables. Categorical variables were analyzed with Chi-square or Fisher's exact test.

To reduce the influence of potential confounding factors, PS analysis was performed to modify intergroup differences according to the anesthetic technique. Table 1 shows all demographic and perioperative variables used for estimating the PS. Using greedy matching algorithms, we used a caliper of 0.25 standard deviations of the logit of the PS to match patients at a ratio of 1:1. Model discrimination and model calibration were evaluated with c statistics (0.837) and Hosmer-Lemshow statistics (Chi-square = 8.6005, degrees of freedom = 8, $p = 0.377$), respectively. In addition, patients who received both anesthetic techniques were considered self-matching. We evaluated the balance in demographic, surgical, and preoperative covariates of the PS-matched cohort by the standardized mean difference. All absolute standardized differences after PS were less than 0.1. The risk of clinical outcome variables, including occurrence of morbidity, were analyzed by logistic regression using generalized estimating equations in the total and PS-matched cohort. Moreover, hospital stay and postoperative maximum CRP level of each group was compared between the two groups. Statistically significance was set at $p < 0.05$. Statistical analysis was conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics of all patients included in the total set.

Demographic Data	General (N = 2353)	Spinal (N = 634)	*p*-Value	Standardized Difference
Age (years)	68.6 ± 6.6	69.3 ± 6.4	0.027	0.102
Body mass index (kg/m^2)	26.8 ± 3.5	26.5 ± 3.2	0.048	0.090
Sex, Female/male	2174 / 179 (92.4/7.6)	568 / 66 (89.6 / 10.4)	0.022	0.092
ASA PS †, 1/2/3	129/2157/67 (5.5/91.7/2.9)	21/581/32 (3.3/91.6/5.1)	0.003	0.152
Smoking History Non/current/ex-smoker	2039/52/262 (86.7/2.2/11.1)	325/19/290 (51.3/3/45.7)	<0.001	0.844
Surgical Data				
Surgical strategy, Single/staggered/staged_1st/ staged_2nd/simultaneous	983/380/149/146/695 (41.8/16.2/6.3/6.2/29.5)	334/175/29/32/64 (52.7/27.6/4.6/5.1/10.1)	<0.001	0.553
Surgeon, B/C/K	719/1173/461 (30.6/49.9/19.6)	326/273/35 (51.4/43.1/5.5)	<0.001	0.542
Preoperative Medical History				
Diabetes mellitus	306 (13.0)	105 (16.6)	0.021	0.096
Hypertension	768 (32.6)	261 (41.2)	<0.001	0.173
Ischemic heart disease	164 (7.0)	63 (9.9)	0.012	0.099
Cerebrovascular disease	127 (5.4)	45 (7.1)	0.103	0.066
Pulmonary disease	88 (3.7)	35 (5.5)	0.045	0.078
Adrenal disease	33 (1.4)	7 (1.1)	0.562	0.029

Table 1. *Cont.*

Demographic Data	General (N = 2353)	Spinal (N = 634)	*p*-Value	Standardized Difference
Preoperative Medication History				
Calcium channel blocker	927 (39.4)	243 (38.3)	0.625	0.022
Angiotensin-converting enzyme inhibitor	803 (34.1)	220 (34.7)	0.787	0.012
Beta blocker	360 (15.3)	106 (16.7)	0.382	0.038
Aspirin	512 (21.8)	135 (21.3)	0.800	0.011
Clopidogrel	150 (6.4)	58 (9.2)	0.015	0.096
HMG-CoA reductase inhibitors ‡	600 (25.5)	234 (36.9)	<0.001	0.236
Antibiotics	12 (0.5)	1 (0.2)	0.323	0.089
Nonsteroidal anti-inflammatory drugs	187 (8.0)	33 (5.2)	0.019	0.123
Selective cyclooxygenase-2 inhibitor	408 (17.3)	140 (22.1)	0.006	0.114
Other analgesics	356 (15.1)	116 (18.3)	0.052	0.082
Steroids	51 (2.2)	19 (3.0)	0.220	0.049
Preoperative Laboratory Data				
Anemia	618 (26.3)	147 (23.2)	0.115	0.073
Thrombocytopenia/normal/thrombocytosis	85/2142/126 (3.6/91.0/5.4)	19/590/25 (3.0/93.1/3.9)	0.255	0.077
Leukopenia/normal/leukocytosis	89/2198/66 (3.8/93.4/2.8)	22/598/14 (3.5/94.3/2.2)	0.657	0.042
Hyponatremia/normal/hypernatremia	26/2279/48 (1.1/96.9/2.0)	10/611/13 (1.6/96.4/2.1)	0.626	0.041
Hemoglobin (g/dL)	12.7 ± 1.1	12.8 ± 1.1	0.111	0.071
C-reactive protein (mg/dL)	0.23 ± 0.48	0.21 ± 0.4	0.014	0.052
Aspartate aminotransferase (IU/L)	23.0 ± 8.9	22.4 ± 9.0	0.008	0.064
Alanine aminotransferse (IU/L)	19.9 ± 11.2	20.4 ± 12.0	0.569	0.039
Albumin (g/dL)	3.9 ± 0.3	3.8 ± 0.3	<0.001	0.418
Uric acid (mg/dL)	4.6 ± 1.2	4.6 ± 1.1	0.519	0.029
Abnormality on echocardiogram	279 (11.9)	48 (7.6)	0.002	0.163
Abnormality on pulmonary function test	103 (4.4)	40 (6.4)	0.041	0.081

Data are presented as mean ± standard deviation or median (interquartile range (IQR)) for continuous variables, or number (percentages) for categorical variables. † American Society of Anesthesiologists physical status; ‡ 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

3. Results

A total of 2809 patients and 2987 cases of TKA were analyzed in this study. Demographic, surgical, and preoperative data of the general anesthesia and spinal anesthesia group without PS matching are shown in Table 1. Without PS matching, the two groups showed significant differences in age, BMI, sex, ASA PS, smoking history, operator, surgical strategy, DM, HTN, IHD, pulmonary disease, clopidogrel, HMG-CoA reductase, NSAIDs, selective COX-2 inhibitor, CRP, AST, albumin, and echocardiographic/PFT findings. After PS matching, standardized differences of all covariates were less than 0.1 (Table 2) and there were no significant differences between the two groups.

Intraoperative data are shown in Table 3. In the analysis of the matched set, the spinal anesthesia group showed significantly fewer requirements of calcium channel blocker and beta blocker, while the lowest MBP was higher. The infused volume of crystalloid and the infused volume of colloid were significantly different, and the volume of urine output also showed a difference between the two groups.

The incidence of AKI, based on the KDIGO criteria, was 162 (5.4%) in all cases (Table 4). Among these, 143 (6.1%) and 19 (3.0%) cases of AKI occurred in the general anesthesia and spinal anesthesia groups, respectively. In a crude analysis of the total set, the spinal anesthesia group demonstrated a significantly lower risk for AKI than the general anesthesia group (Odds ratio (OR) = 0.477, 95% confidence interval [CI] 0.293–0.778, $p = 0.003$). However, in the PS matched set analysis, a total of 37 cases of AKI were included in the PS matched sets and the spinal anesthesia group showed lower incidence of AKI that was not statistically significant (OR = 0.529, 95% CI 0.273–1.024, $p = 0.059$). There were 33 cases of stage 1 AKI (serum creatinine ≥ 1.5–1.9 times baseline or ≥ 0.3 mg/dL increase), out of which 20 cases occurred in the general anesthesia group. The three cases of stage 2 AKI (serum creatinine ≥ 2.0–2.9 times baseline) and one case of stage 3 AKI (serum creatinine ≥ 3.0 times

baseline or ≥ 4.0 mg/dL or requirement of renal replacement therapy) occurred only in the general anesthesia group.

Table 4 shows additional clinical outcomes. Delirium and gastrointestinal complications were significantly more frequent in the spinal versus general anesthesia group in the total set analysis. However, these results were different from the PS-matched set analysis. After PS matching, the general anesthesia group showed a significantly higher risk of pulmonary and vascular complications. Hospital stay was significantly shorter in the spinal anesthesia group compared with the general anesthesia group, in both the total set (spinal anesthesia group 13.6 ± 5.2 days, general anesthesia group 14.0 ± 5.2 days, $p < 0.001$) and the PS matched set (spinal anesthesia group 13.6 ± 5.5 days, general anesthesia group 14.3 ± 5.0 days, $p = 0.0067$). In addition, the patients in the spinal anesthesia group showed significantly lower postoperative maximum CRP levels compared to the general anesthesia group in the total set (spinal anesthesia group 7.1 ± 4.6, general anesthesia group 8.4 ± 5.6, $p < 0.001$) and the PS matched set (spinal anesthesia group 6.9 ± 4.5, general anesthesia group 7.9 ± 5.4, $p = 0.001$).

Table 2. Baseline characteristics of the patients included in the propensity score matched set.

Demographic Data	General (N = 467)	Spinal (N = 467)	Standardized Difference
Age	69.4 ± 6.5	69.3 ± 6.4	0.011
Body mass index (kg/m^2)	26.4 ± 3.3	26.4 ± 3.3	0.017
Sex, Female/male	423/44 (90.6/9.4)	416/51 (89.1/10.9)	0.049
ASA PS †, 1/2/3	17/425/25 (3.6/91.0/5.4)	18/426/23 (3.9/91.2/4.9)	0.022
Smoking HistoryNon/current/ex-smoker	340/15/112 (72.8/3.2/24.0)	320/18/129 (68.5/3.9/27.6)	0.094
Surgical Data			
Surgical strategy, Single/staggered/staged_1st/staged_2nd/simultaneous	238/120/19/27/63 (51.0/25.7/4.1/5.8/13.5)	240/110/23/31/63 (51.4/23.6/4.9/6.6/13.5)	0.069
Surgeon, B/C/K	216/208/43 (46.3/44.5/9.2)	204/228/35 (43.7/48.8/7.5)	0.095
Preoperative Medical History			
Diabetes mellitus	74 (15.9)	70 (15.0)	0.023
Hypertension	166 (35.6)	170 (36.4)	0.017
Ischemic heart disease	47 (10.1)	45 (9.6)	0.014
Cerebrovascular disease	29 (6.2)	30 (6.4)	0.008
Pulmonary disease	26 (5.6)	27 (5.8)	0.009
Adrenal disease	7 (1.5)	6 (1.3)	0.020
Preoperative Medication History			
Calcium channel blocker	186 (39.8)	178 (38.1)	0.035
Angiotensin converting enzyme inhibitor	165 (35.3)	162 (34.7)	0.014
Beta blocker	84 (18.0)	77 (16.5)	0.040
Aspirin	101 (21.6)	99 (21.2)	0.010
Clopidogrel	42 (9.0)	39 (8.4)	0.022
HMG-CoA reductase inhibitors ‡	160 (34.3)	150 (32.1)	0.044
Antibiotics	0 (0)	1 (0.2)	0.054
NSAIDs	29 (6.2)	24 (5.1)	0.048
Selective cyclooxygenase-2 inhibitor	102 (21.8)	101 (21.6)	0.005
Other analgesics	94 (20.1)	81 (17.3)	0.072
Steroids	13 (2.8)	11 (2.4)	0.025
Preoperative Laboratory Data			
Anemia	119 (25.5)	106 (22.7)	0.066
Thrombocytopenia/normal/thrombocytosis	18/427/22 (3.9/91.4/4.7)	17/431/19 (3.6/92.3/4.1)	0.034
Leukopenia/normal/leukocytosis	25/432/10 (5.4/92.5/2.1)	21/437/9 (4.5/93.6/1.9)	0.043
Hyponatremia/normal/hypernatremia	7/450/10 (1.5/96.4/2.1)	4/455/8 (0.9/97.4/1.7)	0.068
Hemoglobin (g/dL)	12.7 ± 1.2	12.8 ± 1.1	0.088
C-reactive protein (mg/dL)	0.22 ± 0.38	0.23 ± 0.45	0.008
Aspartate aminotransferase (IU/L)	22.2 ± 7.7	22.6 ± 9.6	0.048
Alanine aminotransferse (IU/L)	20.4 ± 12.2	20.5 ± 12.9	0.010
Albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.3	0.085
Uric acid (mg/dL)	4.7 ± 1.2	4.7 ± 1.1	0.003
Abnormality on echocardiogram	49 (10.5)	45 (9.6)	0.032
Abnormality on pulmonary function test	34 (7.3)	34 (7.3)	0.0

Data are presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables, or number (percentages) for categorical variables. † American Society of Anesthesiologists physical status; ‡ 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor.

Table 3. Intraoperative data of the study groups by anesthetic technique in total and matched sets.

Intraoperative Data	Total Set			Matched Set		
	General Group (n = 2353)	Spinal Group (n = 634)	*p*-Value	General Group (n = 467)	Spinal Group (n = 467)	*p*-Value
Use of vasopressor	430 (18.3)	102 (16.1)	0.202	77 (16.5)	86 (18.4)	0.432
Use of calcium channel blocker	366 (15.6)	58 (9.2)	<0.001	65 (13.9)	34 (7.3)	0.001
Use of beta blocker	516 (21.9)	8 (1.3)	<0.001	95 (20.3)	5 (1.1)	<0.001
Red blood cell transfusion	795 (33.8)	103 (16.3)	<0.001	95 (20.3)	99 (21.2)	0.730
Infused crystalloid (mL)	1014.8 ± 600.1	961.1 ± 551.2	0.016	922.4 ± 574.1	1013.5 ± 599.9	0.012
Infused colloid (mL)	544.6 ± 305.1	382.8 ± 209.0	<0.001	496.7 ± 277.9	402.0 ± 215.0	<0.001
Urine output (mL)	193.4 ± 230.8	379.4 ± 350.6	<0.001	168.0 ± 209.9	366.2 ± 341.8	<0.001
The lowest mean blood pressure (mm Hg)	69.3 ± 8.5	73.1 ± 9.8	<0.001	70.3 ± 8.7	72.6 ± 9.9	<0.001
Operation time (minute)	133.4 ± 42.3	122.5 ± 33.8	<0.001	123.7 ± 34.8	124.4 ± 36.9	0.731
Tourniquet time (minute)	123.1 ± 34.5	105.3 ±30.6	<0.001	114.0 ± 31.0	104.5 ± 31.0	<0.001

Table 4. Comparison of postoperative clinical outcomes in the study groups by anesthetic technique.

Clinical Outcome	Group	Total Set					Matched Set				
		Event	Odds Ratio	95% Confidence Interval		*p*-Value	Event	Odds Ratio	95% Confidence Interval		*p*-Value
Acute kidney injury	General	143	1				24				
	Spinal	19	0.477	0.293	0.778	0.003	13	0.529	0.273	1.024	0.059
Cardiovascular complication	General	29	1				10				
	Spinal	7	0.895	0.390	2.052	0.793	5	0.495	0.166	1.470	0.205
Pulmonary complication	General	38					14				
	Spinal	7	0.680	0.276	1.676	0.402	4	0.280	0.091	0.862	0.027
Deep vein thrombosis/Pulmonary thromboembolism	General	28					11				
	Spinal	3	0.395	0.119	1.309	0.129	2	0.178	0.039	0.813	0.026
Delirium	General	32					7				
	Spinal	19	2.241	1.254	4.004	0.006	15	2.181	0.873	5.450	0.095
Neurologic complication	General	18					3				
	Spinal	6	1.239	0.490	3.133	0.650	6	2.013	0.497	8.146	0.327
Surgical site infection	General	14					4				
	Spinal	6	1.596	0.611	4.171	0.340	6	1.507	0.420	5.409	0.530
Gastrointestinal complication	General	58					6				
	Spinal	26	1.692	1.060	2.701	0.028	14	2.375	0.943	5.980	0.066
Endocrinologic complication	General	3					2				
	Spinal	1	1.237	0.128	11.918	0.854	1	0.499	0.045	5.540	0.571
Urologic complication	General	24					11				
	Spinal	9	1.397	0.641	3.048	0.400	4	0.358	0.122	1.053	0.062
Major complication	General	70					18				
	Spinal	24	1.283	0.800	2.058	0.301	22	1.233	0.654	2.325	0.517
Intensive care unit admission	General	59	1				15				
	Spinal	21	1.332	0.803	2.210	0.267	19	1.278	0.647	2.526	0.480

4. Discussion

In the current study, we found that spinal anesthesia might be protective for AKI based on KDIGO criteria in patients undergoing TKA. Moreover, spinal anesthesia had lower observable risks of pulmonary and vascular complications compared to general anesthesia. Hospital stay was also reduced in patients receiving spinal anesthesia.

Spinal anesthesia showed a trend for a favorable outcome in the occurrence of AKI compared with general anesthesia, although this effect did not reach statistical significance. The protective mechanism of spinal anesthesia is unclear.

First, we suggest that spinal anesthesia may produce these results through sympathetic nerve blockade. The sympathetic nerve fibers originate from the lower thoracic spinal nerves (T7-11). Sympathetic activity is known to have a significant impact on renal function by altering renal hemodynamics, renin release, and sodium handling [15]. Increased sympathetic tone reduces renal blood flow by stimulation of α1 adrenoceptors on renal vasculature and increasing sodium reabsorption by direct effect on the renal tubules [16]. In addition, increased renal sympathetic nerve activity promotes renin release, which is mediated by β-1 adrenoceptors on the juxtaglomerular cells [17]. This series of processes acts to reduce renal blood flow and glomerular filtration rate. In this study, we found that intraoperative urine output was higher in the spinal anesthesia group than in general anesthesia group, even though the amount of fluid administered to both groups was similar. We considered the renal sympathetic nerves blocked, and that the blockade of renal sympathetic activity contributed to the greater urine output, thus resulting in a protective effect for AKI under spinal anesthesia.

Acute postoperative pain following orthopedic surgery is known to be more severe under general anesthesia compared with spinal anesthesia, with greater opioid use also observed with general anesthesia [18–20]. Since the duration of local anesthetics for spinal anesthesia was longer than the duration of TKA, patients generally feel comfortable during the immediate postoperative period. In addition, a previous study suggested that spinal anesthesia lowered the postoperative pain score via preemptive inhibition of afferent nociceptive stimuli and improved organ function [21,22]. Greater postoperative pain in patients receiving general anesthesia increases sympathetic nervous system stimulation, and as a result, the general anesthesia group may have showed a tendency for increased risk for AKI.

A second hypothesis in support of our findings is that the systemic inflammatory response to surgical stress is lower in regional anesthesia than in general anesthesia, resulting in less kidney injury with the spinal technique. The postoperative systemic inflammatory response was reported to be associated with any organ dysfunction, including AKI [23,24]. Inflammatory cytokines inducing neutrophil recruitment and accumulation play a key role in the development of AKI [25,26]. Moreover, the integrity of the endothelial glycocalyx layer, which is closely related to AKI, is disrupted by the inflammatory response [27]. Although controversial, some investigators reported that neuraxial anesthesia suppressed the stress response in elective surgical patients by blocking transmission of pain sensation and sympathetic activation [28–30]. In addition, local anesthetics used for neuraxial anesthesia were shown to have intrinsic anti-inflammatory effects [31,32]. In the current study, changes in CRP level revealed that the inflammatory response in the spinal group was reduced compared to the general group, consistent with previous studies. Therefore, we suggest that the reduced inflammatory response to surgical stress by spinal anesthesia might contribute to the trend of decreased risk for AKI.

Moreover, we found some differences in the intraoperative variables between the two groups. These differences seemed to be derived from the anesthetic techniques since PS matching was performed. A previous study showed that prolonged tourniquet time was related to the increased postoperative complications by leading greater ischemic insult [33]. Therefore, the reduced postoperative complications including AKI in the spinal anesthesia group could be seen as an indirect effect of spinal anesthesia by shortening the tourniquet time.

Besides the tourniquet time, the amount of fluid also showed differences between the two groups. The infused volume of crystalloid solution was greater in the spinal anesthesia group, while the infused

volume of colloid solution was greater in the general anesthesia group. However, the sum of the crystalloid and colloid solution was similar in both groups, so that it was unlikely that the total volume of infused fluid could have had an impact on the occurrence of AKI. In addition, there was also a difference in the lowest MBP between the two groups. Intraoperative hypotension was known to have an association with AKI [34]. However, in this current study, the difference between the two groups was considered clinically insignificant, as the lowest MBP values in each group were higher than 55–60 mmHg, which was considered as cut-off value of hypotensive MBP.

This study showed that spinal anesthesia has advantages over general anesthesia due to reduced postoperative pulmonary complications after TKA. A recent study using a large national database also demonstrated that neuraxial anesthesia decreased the risk of both pulmonary compromise and pneumonia in TKA patients [7]. Respiratory function is disturbed in many aspects from the start of the general anesthesia, and mechanical ventilation under general anesthesia plays a major role in the occurrence of postoperative pulmonary complications [35]. Therefore, we should consider spinal anesthesia first, then general anesthesia, in patients with risk factors for pulmonary complications.

The beneficial effect of neuraxial anesthesia in vascular complication has been well documented [9,36–39]. Among them, Memtsoudis et al. suggested that neuraxial anesthesia has a beneficial effect itself beyond simply avoiding general anesthesia, and speculated that this result is due to alteration of the coagulation profile, blood flow, and stress responses to the surgery [7]. However, a number of studies have also shown that anesthetic technique was not associated with the risk of vascular complication, or that neuraxial anesthesia rather increased this risk [8,40,41]. An important factor leading to these inconsistent results was prophylactic treatment with chemical antithrombotics [41]. The studies reporting benefits of neuraxial anesthesia generally included patients that did not receive a prophylactic agent. At our institution, chemical antithrombotic prophylaxis was not applied and our results are consistent with those of previous studies. When chemical antithrombotic prophylaxis is not used, neuraxial anesthesia may be a better choice than general anesthesia.

Many studies have investigated whether neuraxial anesthesia can reduce the postoperative hospital stay. Although still controversial, a number of studies reported that the length of hospital stay was shorter with neuraxial anesthesia in orthopaedic patients [7,8,42]. Length of hospital stay is a surrogate marker for postoperative complications and use of resources [43]. Thus, the shorter length in the spinal anesthesia group may reflect a better clinical outcome. However, the length of hospital stay was much longer in both the general and spinal groups in this study compared to other studies [7,8,44,45]. This discrepancy is likely due to differences in management protocol. At our institution, patients are discharged after achieving a certain level of rehabilitation. Nonetheless, the spinal anesthesia group did show a shorter length of hospital stay. That is, spinal anesthesia had a beneficial effect on postoperative outcome.

This study has some limitations. First, there were inevitable flaws due to the nature of the retrospective observational design. We cannot conclude causality between general anesthesia and AKI owing to the characteristics of this study design. Second, there might be other confounding factors that were excluded in the analysis. However, we attempted to include as many factors as possible in the PS matching. Third, our definition of a staged/staggered operation might be different from that of other studies. In the current study, we defined a staggered operation as two operations occurring on two separate days during one hospitalization. However, we focused our investigation on the association of anesthetic technique on AKI, and the surgical strategy was used only for the propensity score matching. Thus, the disparity of the definition of a staged/staggered operation did not likely impact the results. Lastly, since we included patients with normal kidney function in this study, the present findings could not be extrapolated to the patients with decreased renal function. Further studies to evaluate the effect of anesthetic technique on AKI would be required.

In conclusion, the incidence of AKI, based on the KDIGO criteria, in patients who underwent total knee arthroplasty was 5.4%. Spinal anesthesia had a tendency to reduce AKI. In addition, spinal

anesthesia reduced vascular and pulmonary complications compared to general anesthesia. Length of hospital stay was also shortened in patients with spinal anesthesia.

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References

1. Koh, I.J.; Kim, T.K.; Chang, C.B.; Cho, H.J.; In, Y. Trends in use of total knee arthroplasty in Korea from 2001 to 2010. *Clin. Orthop. Relat. Res.* **2013**, *471*, 1441–1450. [CrossRef] [PubMed]
2. Kurtz, S.; Ong, K.; Lau, E.; Mowat, F.; Halpern, M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J. Bone Joint Surg. Am.* **2007**, *89*, 780–785. [PubMed]
3. Kim, Y.H.; Kim, J.S.; Choe, J.W.; Kim, H.J. Long-term comparison of fixed-bearing and mobile-bearing total knee replacements in patients younger than fifty-one years of age with osteoarthritis. *J. Bone Joint Surg. Am.* **2012**, *94*, 866–873. [CrossRef] [PubMed]
4. Turnbull, Z.A.; Sastow, D.; Giambrone, G.P.; Tedore, T. Anesthesia for the patient undergoing total knee replacement: Current status and future prospects. *Local Reg. Anesth.* **2017**, *10*, 1–7. [CrossRef] [PubMed]
5. Brull, R.; McCartney, C.J.; Chan, V.W.; El-Beheiry, H. Neurological complications after regional anesthesia: Contemporary estimates of risk. *Anesth. Analg.* **2007**, *104*, 965–974. [CrossRef] [PubMed]
6. Macfarlane, A.J.; Prasad, G.A.; Chan, V.W.; Brull, R. Does regional anesthesia improve outcome after total knee arthroplasty? *Clin. Orthop. Relat. Res.* **2009**, *467*, 2379–2402. [CrossRef] [PubMed]
7. Memtsoudis, S.G.; Sun, X.; Chiu, Y.-L.; Stundner, O.; Liu, S.S.; Banerjee, S.; Mazumdar, M.; Sharrock, N.E. Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. *Anesthesiology* **2013**, *118*, 1046–1058. [CrossRef]
8. Pugely, A.J.; Martin, C.T.; Gao, Y.; Mendoza-Lattes, S.; Callaghan, J.J. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. *J. Bone Joint Surg. Am.* **2013**, *95*, 193–199. [CrossRef]
9. Davis, F.M.; Laurenson, V.G.; Gillespie, W.J.; Wells, J.E.; Foate, J.; Newman, E. Deep vein thrombosis after total hip replacement. A comparison between spinal and general anaesthesia. *J. Bone Joint Surg. Br.* **1989**, *71*, 181–185. [CrossRef]
10. Planes, A.; Vochelle, N.; Fagola, M.; Feret, J.; Bellaud, M. Prevention of deep vein thrombosis after total hip replacement. The effect of low-molecular-weight heparin with spinal and general anaesthesia. *J. Bone Joint Surg. Br.* **1991**, *73*, 418–422. [CrossRef]
11. Stundner, O.; Chiu, Y.L.; Sun, X.; Mazumdar, M.; Fleischut, P.; Poultsides, L.; Gerner, P.; Fritsch, G.; Memtsoudis, S.G. Comparative perioperative outcomes associated with neuraxial versus general anesthesia for simultaneous bilateral total knee arthroplasty. *Reg. Anesth. Pain Med.* **2012**, *37*, 638–644. [CrossRef] [PubMed]
12. Kim, H.J.; Koh, W.U.; Kim, S.G.; Park, H.S.; Song, J.G.; Ro, Y.J.; Yang, H.S. Early postoperative albumin level following total knee arthroplasty is associated with acute kidney injury: A retrospective analysis of 1309 consecutive patients based on kidney disease improving global outcomes criteria. *Medicine* **2016**, *95*, e4489. [CrossRef] [PubMed]
13. Warth, L.C.; Noiseux, N.O.; Hogue, M.H.; Klaassen, A.L.; Liu, S.S.; Callaghan, J.J. Risk of acute kidney injury after primary and revision total hip arthroplasty and total knee arthroplasty using a multimodal approach to perioperative pain control including ketorolac and celecoxib. *J. Arthroplasty* **2016**, *31*, 253–255. [CrossRef] [PubMed]
14. Biteker, M.; Dayan, A.; Tekkesin, A.I.; Can, M.M.; Tayci, I.; Ilhan, E.; Sahin, G. Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. *Am. J. Surg.* **2014**, *207*, 53–59. [CrossRef] [PubMed]
15. Suleiman, M.Y.; Passannante, A.N.; Onder, R.L.; Greene-Helms, W.F.; Perretta, S.G. Alteration of renal blood flow during epidural anesthesia in normal subjects. *Anesth. Analg.* **1997**, *84*, 1076–1080. [CrossRef] [PubMed]

16. DiBona, G.F. Neural control of renal function in health and disease. *Clin. Auton. Res.* **1994**, *4*, 69–74. [CrossRef] [PubMed]
17. Pelayo, J.C.; Tucker, B.J.; Blantz, R.C. Effects of beta-adrenergic stimulation with isoproterenol on glomerular hemodynamics. *Am. J. Physiol.* **1989**, *257*, F866–F873. [CrossRef] [PubMed]
18. Gonano, C.; Leitgeb, U.; Sitzwohl, C.; Ihra, G.; Weinstabl, C.; Kettner, S.C. Spinal versus general anesthesia for orthopedic surgery: Anesthesia drug and supply costs. *Anesth. Analg.* **2006**, *102*, 524–529. [CrossRef]
19. Jellish, W.S.; Thalji, Z.; Stevenson, K.; Shea, J. A prospective randomized study comparing short-and intermediate-term perioperative outcome variables after spinal or general anesthesia for lumbar disk and laminectomy surgery. *Anesth. Analg.* **1996**, *83*, 559–564. [CrossRef]
20. Korhonen, A.-M.; Valanne, J.V.; Jokela, R.M.; Ravaska, P.; Korttila, K.T. A comparison of selective spinal anesthesia with hyperbaric bupivacaine and general anesthesia with desflurane for outpatient knee arthroscopy. *Anesth. Analg.* **2004**, *99*, 1668–1673. [CrossRef]
21. Carr, D.B.; Goudas, L.C. Acute pain. *Lancet* **1999**, *353*, 2051–2058. [CrossRef]
22. Kehlet, H.; Dahl, J.B. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* **2003**, *362*, 1921–1928. [CrossRef]
23. Boehne, M.; Sasse, M.; Karch, A.; Dziuba, F.; Horke, A.; Kaussen, T.; Mikolajczyk, R.; Beerbaum, P.; Jack, T. Systemic inflammatory response syndrome after pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J. Card. Surg.* **2017**, *32*, 116–125. [CrossRef] [PubMed]
24. Park, J.T. Postoperative acute kidney injury. *Korean J. Anesthesiol.* **2017**, *70*, 258–266. [CrossRef] [PubMed]
25. Berry, M.; Clatworthy, M.R. Immunotherapy for acute kidney injury. *Immunotherapy* **2012**, *4*, 323–334. [CrossRef] [PubMed]
26. Nechemia-Arbely, Y.; Barkan, D.; Pizov, G.; Shriki, A.; Rose-John, S.; Galun, E.; Axelrod, J.H. IL-6/IL-6R axis plays a critical role in acute kidney injury. *J. Am. Soc. Nephrol.* **2008**, *19*, 1106–1115. [CrossRef]
27. Song, J.W.; Goligorsky, M.S. Perioperative implication of the endothelial glycocalyx. *Korean J. Anesthesiol.* **2018**, *71*, 92–102. [CrossRef]
28. Milosavljevic, S.B.; Pavlovic, A.P.; Trpkovic, S.V.; Ilić, A.N.; Sekulic, A.D. Influence of spinal and general anesthesia on the metabolic, hormonal, and hemodynamic response in elective surgical patients. *Med. Sci. Monit.* **2014**, *20*, 1833–1840.
29. Buyukkocak, U.; Daphan, C.; Caglayan, O.; Aydinuraz, K.; Kaya, T.; Saygun, O.; Agalar, F. Effects of different anesthetic techniques on serum leptin, C-reactive protein, and cortisol concentrations in anorectal surgery. *Croat. Med. J.* **2006**, *47*, 862–868.
30. Bugada, D.; Ghisi, D.; Mariano, E.R. Continuous regional anesthesia: A review of perioperative outcome benefits. *Minerva Anestesiol.* **2017**, *83*, 1089–1100.
31. Lirk, P.; Picardi, S.; Hollmann, M.W. Local anaesthetics: 10 essentials. *Eur. J. Anaesthesiol.* **2014**, *31*, 575–585. [CrossRef] [PubMed]
32. Lirk, P.; Fiegl, H.; Weber, N.; Hollmann, M. Epigenetics in the perioperative period. *Br. J. Pharmacol.* **2015**, *172*, 2748–2755. [CrossRef] [PubMed]
33. Rasmussen, L.E.; Holm, H.A.; Kristensen, P.W.; Kjaersgaard-Andersen, P. Tourniquet time in total knee arthroplasty. *Knee* **2018**, *25*, 306–313. [CrossRef] [PubMed]
34. Zarbock, A.; Koyner, J.L.; Hoste, E.A.; Kellum, J.A. Update on perioperative acute kidney injury. *Anesth. Analg.* **2018**, *127*, 1236–1245. [CrossRef] [PubMed]
35. Miskovic, A.; Lumb, A.B. Postoperative pulmonary complications. *Br. J. Anaesth.* **2017**, *118*, 317–334. [CrossRef]
36. Turan, A.; Bajracharya, G.R.; Leung, S.; Yazici Kara, M.; Mao, G.; Botsford, T.; Ruetzler, K.; Maheshwari, K.; Ali Sakr Esa, W.; Elsharkawy, H.; et al. Association of neuraxial anesthesia with postoperative venous thromboembolism after noncardiac surgery: A propensity-matched analysis of ACS-NSQIP database. *Anesth. Analg.* **2019**, *128*, 494–501. [CrossRef] [PubMed]
37. Mauermann, W.J.; Shilling, A.M.; Zuo, Z. A comparison of neuraxial block versus general anesthesia for elective total hip replacement: A meta-analysis. *Anesth. Analg.* **2006**, *103*, 1018–1025. [CrossRef]
38. Smith, L.M.; Cozowicz, C.; Uda, Y.; Memtsoudis, S.G.; Barrington, M.J. Neuraxial and combined neuraxial/general anesthesia compared to general anesthesia for major truncal and lower limb surgery: A systematic review and meta-analysis. *Anesth. Analg.* **2017**, *125*, 1931–1945. [CrossRef]
39. Hu, S.; Zhang, Z.Y.; Hua, Y.Q.; Li, J.; Cai, Z.D. A comparison of regional and general anaesthesia for total replacement of the hip or knee: A meta-analysis. *J. Bone Joint Surg. Br.* **2009**, *91*, 935–942. [CrossRef]

40. Walker, J.B.; Nguyen, P.L.; Schmidt, U.H.; Gabriel, R.A. Postoperative outcomes associated with neuraxial vs general anesthesia following bilateral total knee arthroplasty. *J. Arthroplasty* **2017**, *32*, 3632–3636. [CrossRef]
41. Johnson, R.L.; Kopp, S.L.; Burkle, C.M.; Duncan, C.M.; Jacob, A.K.; Erwin, P.J.; Murad, M.H.; Mantilla, C.B. Neuraxial vs general anaesthesia for total hip and total knee arthroplasty: A systematic review of comparative-effectiveness research. *Br. J. Anaesth.* **2016**, *116*, 163–176. [CrossRef] [PubMed]
42. Helwani, M.A.; Avidan, M.S.; Ben Abdallah, A.; Kaiser, D.J.; Clohisy, J.C.; Hall, B.L.; Kaiser, H.A. Effects of regional versus general anesthesia on outcomes after total hip arthroplasty: A retrospective propensity-matched cohort study. *J. Bone Joint Surg. Am.* **2015**, *97*, 186–193. [CrossRef] [PubMed]
43. Cryer, C.; Gulliver, P.; Langley, J.D.; Davie, G. Is length of stay in hospital a stable proxy for injury severity? *Inj. Prev.* **2010**, *16*, 254–260. [CrossRef] [PubMed]
44. McIsaac, D.I.; McCartney, C.J.; Walraven, C.V. Peripheral Nerve Blockade for Primary Total Knee Arthroplasty: A population-based cohort study of outcomes and resource utilization. *Anesthesiology* **2017**, *126*, 312–320. [CrossRef] [PubMed]
45. El Bitar, Y.F.; Illingworth, K.D.; Scaife, S.L.; Horberg, J.V.; Saleh, K.J. Hospital length of stay following primary total knee arthroplasty: Data from the nationwide inpatient sample database. *J. Arthroplasty* **2015**, *30*, 1710–1715. [CrossRef]

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One-Year Progression and Risk Factors for the Development of Chronic Kidney Disease in Septic Shock Patients with Acute Kidney Injury: A Single-Centre Retrospective Cohort Study

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Abstract: (1) Background: Sepsis-associated acute kidney injury (AKI) can lead to permanent kidney damage, although the long-term prognosis in patients with septic shock remains unclear. This study aimed to identify risk factors for the development of chronic kidney disease (CKD) in septic shock patients with AKI. (2) Methods: A single-site, retrospective cohort study was conducted using a registry of adult septic shock patients. Data from patients who had developed AKI between January 2011 and April 2017 were extracted, and 1-year follow-up data were analysed to identify patients who developed CKD. (3) Results: Among 2208 patients with septic shock, 839 (38%) had AKI on admission (stage 1: 163 (19%), stage 2: 339 (40%), stage 3: 337 (40%)). After one year, kidney function had recovered in 27% of patients, and 6% had progressed to CKD. In patients with stage 1 AKI, 10% developed CKD, and mortality was 13% at one year; in patients with stage 2 and 3 AKI, the CKD rate was 6%, and the mortality rate was 42% and 47%, respectively. Old age, female, diabetes, low haemoglobin levels and a high creatinine level at discharge were seen to be risk factors for the development of CKD. (4) Conclusions: AKI severity correlated with mortality, but it did not correlate with the development of CKD, and patients progressed to CKD, even when initial AKI stage was not severe. Physicians should focus on the recovery of renal function, and ensure the careful follow-up of patients with risk factors for the development of CKD.

Keywords: septic shock; acute kidney injury; acute kidney disease; chronic kidney disease; follow-up

1. Introduction

Sepsis is one of the most common causes of mortality in critically ill patients worldwide [1–3]. Septic shock, the most severe form of sepsis, can lead to multi-system organ failure and is a major risk factor for the development of acute kidney injury (AKI), accounting for more than 50% of cases [4,5]. Although septic AKI has been considered a temporary syndrome [5,6], a growing body of evidence suggests that AKI is likely to lead to continuous or permanent kidney damage, and it can progress to end-stage kidney disease [7,8]. In patients with sepsis and septic shock, the presence of AKI has been shown to be a poor prognostic factor that is associated with higher rates of mortality and short-term adverse consequences, including the prolonged duration of mechanical ventilation, increased intensive care unit stay and death [9,10]. However, few studies have included long-term follow-up periods [11,12], and data describing the relationship between initial severity and the development of chronic kidney disease (CKD) in patients with sepsis-induced AKI are limited [13].

To address this issue, we evaluated data from the Asan Medical Center Emergency Department Septic Shock Registry, to determine the development of CKD in septic shock patients with AKI, and to identify risk factors associated with the development of this condition.

2. Materials and Methods

2.1. Setting and Study Population

This single-center, retrospective, observational, registry-based study was conducted at the Asan Medical Center Emergency Department in South Korea, using data obtained from patients diagnosed between January 2011 and April 2017. The Asan Medical Center is an academic tertiary referral center with 2700 beds; approximately 100,000 patients visit the emergency department annually. The study protocol was approved by the institutional research ethics committee (Study No. 2016-0548), and the requirement for informed consent was waived, due to the retrospective nature of the study.

Adult patients ($\geq$18 years of age) with septic shock were enrolled from the Asan Medical Center Septic Shock Registry. Septic shock was defined as the presence of refractory hypotension (mean arterial pressure $\leq$70 mmHg) requiring treatment with vasopressors, or a blood lactate concentration $\geq$4 mmol/L despite sufficient fluid loading [14]. We excluded individuals who were younger than 18 years and pregnant individuals. Moreover, in addition to evaluate the effect of newly developed AKI to CKD, we also excluded patients who had previously been diagnosed with CKD and end-stage renal disease (ESRD) requiring renal replacement therapy (RRT).

2.2. Data Collection and Definition

Data regarding patient age, sex, previous medical history, laboratory results and infection sites based on clinical and radiological examination were obtained from the registry. Previous CKD or ESRD patients who had outpatient or inpatient diagnosis of pre-existing CKD and ESRD, had code related with hemodialysis and who had a prior diagnosis of AKI or a baseline-estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73 m^2 were identified via electronic medical records. AKI on initial admission was defined in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [15], i.e., an increase in serum creatinine (Cr) of 0.3 mg/dL within 48 h, or an increase in creatinine to 1.5 times the lowest known creatinine level during the preceding one week to one year. If baseline Cr levels were not available, an estimated baseline was calculated using the simplified modification of diet in renal disease (MDRD) formula, assuming that a given patient without known renal disease had a normal glomerular filtration rate (GFR) of approximately 75–100 mL/min/1.73 m^2. Serum Cr levels were assessed in all patients at least once each day during the hospital stay, and baseline, initial, peaks within 48 h and discharge values, were recorded. Maximum KDIGO refers to the worst KDIGO stage observed over the 48 h period following admission. Baseline Cr levels were measured preceding one week to one year before admission, and the initial level was measured at admission.

To evaluate the CKD status after one year, serum Cr and eGFR levels were obtained after discharge from the electronic medical records of all patients, 12 $\pm$ 3 months from initial admission. Moreover, in order to reduce missing diagnoses, we collected data of inpatient or outpatient diagnoses of CKD or ESRD and codes related to hemodialysis, via medical records. All eGFRs were calculated by MDRD (GFR = 175 $\times$ serum $Cr^{-1.154}$ $\times$ $age^{-0.203}$ $\times$ 1.212 (if patient is black) $\times$ 0.742 (if female)). When multiple records were present, the highest serum Cr and the lowest GFR values were recorded. CKD risk (based on GFR values, mL/min/1.73 m^2) was then classified according to the KDIGO guidelines: G1 $\geq$90, G2 = 60–89, G3a = 45–59, G3b = 30–44, G4 = 15–29 and G5 <15 [16]. Patients classified as G3a, G3b, G4 and G5 were included in the analysis; those with G1 and G2 disease were excluded, as they were considered to be at a low risk of developing ESRD. The date of the patient's death was extracted from the National Health Insurance Service in South Korea. The primary study outcome

was the development of CKD according to the initial and the maximum KDIGO AKI stage. Secondary outcomes included all-cause mortality and RRT dependence within the 1-year follow-up period.

2.3. Statistical Analyses

Statistical analyses were performed using SPSS Statistics for Windows, version 23 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as the median and interquartile range. Categorical variables were analysed using the chi-square test or Fisher's exact test. The normality of distribution was examined using the Kolmogorov–Smirnov test. The Mann–Whitney *U* test was used for the comparison of CKD and non-CKD groups after one year of follow-up. Variables with an entry-level significance of $p < 0.2$ in the univariate analysis were included in a stepwise multivariate analysis, because an entry-level of less than 0.2 was more informative than that of 0.1. Possible interactions and collinearities were also tested. To adjust for confounding variables, and to assess possible effect modification, separate multiple logistic regression analyses were performed. The results were reported as odds ratios (OR) and 95% confidence intervals (CI). A *p*-value <0.05 was considered to be statistically significant.

3. Results

3.1. Patient Characteristics

Between 1 January 2011 and 31 April 2017, 2208 adult patients were enrolled in the Asan Medical Center Emergency Medicine Septic Shock Registry (Figure 1). Of these, 255 who had a pre-existing diagnosis of CKD or ESRD, and 1114 patients with septic shock without AKI, were excluded. The remaining 839 patients (38%) with AKI were categorised according to their KDIGO classification on the day of admission. Among these 839 patients, 163 (19%) had stage 1, 339 (40%) stage 2 and 337 (40%) stage 3. According to the maximum KDIGO criteria, 117 (14%) had stage 1, 337 (40%) stage 2 and 385 (46%) stage 3. Within the first 48 h, maximum serum creatinine was recorded and 35 patients were reassigned from stage 1 to stage 2; 48 patients were additionally included in the stage 3 group. Among them, 151 patients applied continuous RRT during admission, and six patients needed intermittent hemodialysis after stopping continuous RRT.

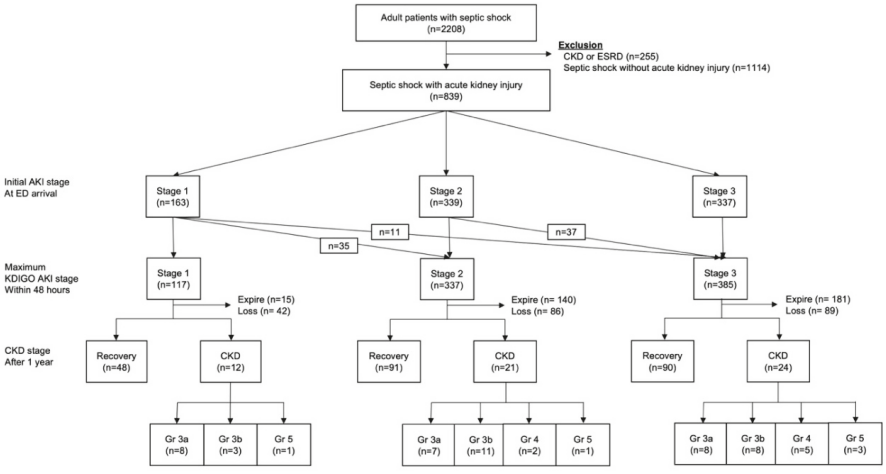

Figure 1. Flowchart of the study population.

The demographic, clinical and laboratory characteristics of patients who developed/did not develop CKD after one year (CKD and non-CKD groups) are summarised in Table 1. Overall, patients

were predominantly male (63.3%), with a median age of 64 years. Hypertension and diabetes were more common in the CKD group than the non-CKD group (47.4% vs. 32.8%, $p = 0.045$; 52.6% vs. 23.6%, $p < 0.001$, respectively). No significant differences were seen in other underlying diseases between the two groups. Pulmonary (21.6%) and hepatobiliary (30.9%) infections were most common in both groups, and no statistically significant differences were seen in the locations of the infection sites. Regarding laboratory values, baseline, initial, peak and discharge creatinine, blood urea nitrogen and hemoglobin levels tended to be higher in the CKD group than in the non-CKD group.

Table 1. Characteristics of patients.

Characteristics	Total n = 286	Non-CKD after 1 Year n = 229	CKD after 1 Year n = 57	p-Value
Age	63.7 (56.0–72.0)	64.0 (55.0–70.0)	71.0 (61.3–77.8)	0.001
Male	181 (63.3)	152 (66.4)	29 (50.9)	0.033
Underlying disease				
HTN	102 (35.7)	75 (32.8)	27 (47.4)	0.045
Stroke	24 (8.4)	18 (7.9)	6 (10.5)	0.592
DM	84 (29.4)	54 (23.6)	30 (52.6)	<0.001
Coronary artery disease	22 (7.7)	14 (6.1)	8 (14.0)	0.054
Chronic pulmonary disease	29 (10.1)	22 (9.6)	7 (12.3)	0.623
Liver cirrhosis	43 (15.0)	37 (16.2)	6 (10.5)	0.312
Malignancy	79 (27.6)	56 (25.8)	20 (35.1)	0.186
Infection site				
Unknown	4 (4.1)	2 (8.8)	2 (2.7)	0.788
Pulmonary	21 (21.6)	15 (20.5)	6 (25.0)	0.776
Urinary	23 (23.7)	18 (24.7)	5 (20.8)	0.788
Gastrointestine	15 (15.5)	13 (17.8)	2 (8.3)	0.345
Hepatobiliary	30 (30.9)	21 (28.8)	9 (37.5)	0.452
Others	11 (11.3)	9 (12.3)	2 (8.3)	0.572
Laboratory				
WBC ($\times 10^3$/uL)	10.5 (5.1–17.5)	10.5 (5.7–18.0)	10.6 (4.0–14.9)	0.491
Hb (g/dL)	11.5 (9.3–13.2)	11.9 (9.9–13.6)	14.93 (10.6–22.6)	<0.001
PLT ($\times 10^3$/uL)	137.0 (72.5–207.0)	138.0 (75.5–207.0)	130.0 (66.25–210.5)	0.921
BUN (mg/dL)	32.0 (24.8–45.0)	31.0 (23.0–40.5)	36.0 (29.0–53.0)	0.017
Baseline Cr (mg/dL)	0.72 (0.63–0.86)	0.70 (0.61–0.82)	0.80 (0.72–0.98)	<0.001
Initial Cr (mg/dL)	1.8 (1.4–2.5)	1.8 (1.4–2.4)	2.1 (1.5–3.0)	0.037
Peak Cr (mg/dL)	2.0 (1.5–2.7)	1.9 (1.5–2.6)	2.4 (1.6–3.5)	0.002
Discharge Cr (mg/dL)	0.9 (0.7–1.1)	0.8 (0.6–1.0)	1.1 (0.9–1.8)	<0.001
Lactate (mmol/L)	3.3 (2.0–5.5)	3.3 (2.0–5.6)	3.0 (1.8–4.5)	0.389
CRP (mg/dL)	15.3 (5.9–22.2)	16.1 (6.7–22.3)	11.9 (5.13–22.0)	0.278

Data are presented as n (%) or median with interquartile ranges. HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; WBC = white blood cells; Hb = hemoglobin; PLT = platelet; BUN = blood urea nitrogen; Cr = creatinine; CRP = c-reactive protein.

3.2. KDIGO Stages and Outcomes

Clinical outcomes in the CKD and non-CKD groups are shown in Figure 1. Among the 117 stage 1 patients, 15 (13%) died, 42 (36%) were lost to follow-up, 48 (41%) recovered full kidney function and 12 (20%) developed CKD (KDIGO CKD stage G3a, n = 8 patients; G3b, n = 3; G5, n = 1). Of the 337 stage 2 patients, 140 (42%) died, 86 (26%) were lost to follow-up within one year, 91 (27%) recovered full kidney function and 21 (6%) developed CKD (stage G3a, n = 7; G3b, n = 11; G4, n = 2; G5, n = 1). Of the 385 stage 3 patients, 181 (47%) died, 89 (23%) were lost to follow-up, 90 (23%) recovered full kidney function and 24 (6%) developed CKD (stage G3a, n = 8; G3b, n = 8; G4, n = 5; G5, n = 3).

The adjusted ORs of the initial and maximum KDIGO AKI stage for CKD development and all-cause mortality within 1 year are shown in Table 2. Notably, there were no significant differences in the occurrence of CKD by KDIGO classification between the initial and maximum criteria. The OR for CKD development according to the AKI stages increased proportionally, but it was not statistically significant. Meanwhile, all-cause mortality proportionally increased according to KDIGO classification by the initial and maximum Cr levels.

Table 2. Adjusted odds ratios of the AKI stage for CKD development in patients with sepsis-induced AKI.

Variables	Multivariate Analysis		
	OR	95% CI	*p*-Value
CKD Development			
Initial Cr			
KDIGO stage 1	Reference		
KDIGO stage 2	0.783	0.375–1.635	0.515
KDIGO stage 3	0.924	0.444–1.923	0.832
Maximum Cr			
KDIGO stage 1	Reference		
KDIGO stage 2	0.879	0.396–1.950	0.751
KDIGO stage 3	1.111	0.513–2.405	0.789
All-Cause Mortality			
Initial Cr			
KDIGO stage 1	Reference		
KDIGO stage 2	2.637	1.719–4.046	<0.001
KDIGO stage 3	2.933	1.913–4.499	<0.001
Maximum Cr			
KDIGO stage 1	Reference		
KDIGO stage 2	4.832	2.696–8.668	<0.001
KDIGO stage 3	5.909	3.316–10.530	<0.001

AKI = acute kidney injury; CKD = chronic kidney disease; OR = odds ratio; CI = confidence interval; Cr = creatinine; KDIGO = Kidney Disease Improving Global Outcomes.

3.3. Risk Factors for the Development of CKD

A multivariate logistic regression of factors associated with the occurrence of CKD development within one year is shown in Table 3. Older age (adjusted OR: 1.070, 95% CI: 1.033–1.108, $p < 0.001$), diabetes (adjusted OR: 2.620, 95% CI: 1.352–5.078, $p = 0.004$), low hemoglobin levels (adjusted OR: 0.840, 95% CI: 0.744–0.949, $p = 0.005$) and higher discharge creatinine levels (adjusted OR: 2.686, 95% CI: 1.499–4.812, $p < 0.001$) were associated with the development of CKD.

Table 3. Multivariate logistic regression of factors associated with the occurrence of CKD after one year.

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	1.066	1.027–1.107	<0.001	1.070	1.033–1.108	<0.001
HTN	0.996	0.487–2.039	0.991			
DM	2.656	1.341–5.257	0.005	2.620	1.352–5.078	0.004
CAD	1.914	0.638–5.745	0.247			
LC	0.992	0.360–2.730	0.987			
Malignancy	1.250	0.601–2.600	0.551			
Hb	0.833	0.734–0.946	0.005	0.840	0.744–0.949	0.005
Discharge Cr	2.503	1.371–4.569	0.003	2.686	1.499–4.812	<0.001

Abbreviations: OR = odds ratio; CI = confidence interval; HTN = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; LC = liver cirrhosis; Hb = hemoglobin; Cr = creatinine.

4. Discussion

In this study, we evaluated the development of CKD in patients with septic shock-associated AKI. In patients who survived and for whom 1-year follow-up data were available, 80% (229/286) recovered full renal function within 1 year and 20% (57/286) had progressed to CKD; 2% (5/286) were dependent on RRT. Long-term all-cause mortality was 40% (336/839), and while the severity of the KDIGO AKI stage was correlated with mortality, it did not correlate with the development of CKD.

In the current study, the incidence of AKI in patients with septic shock was 38% on admission, which is consistent with previous studies reporting an incidence of approximately 35% [17]. AKI can accelerate the progression of CKD [7,18,19], but little is known about the association between AKI severity and the development of CKD. Ishani et al. showed that CKD developed in 6.6%–10.5% of elderly patients with AKI [8]. In addition, they found that elderly individuals, particularly those with previously diagnosed CKD, were at significantly greater risk for end-stage renal disease, suggesting that episodes of AKI may accelerate the progression of renal disease [8].

Few studies have assessed the relationship between AKI severity and CKD progression, and this association therefore remains the subject of some debate [20–22]. Chawla et al. hypothesised that the severity of AKI, according to the Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) criteria, correlates with the progression of CKD [23]. In addition, a recent meta-analysis reported that the risk of CKD increased proportionally with mild, moderate and severe AKI (adjusted hazard ratio: 2.0, 3.3 and 28.2, respectively) [18]. However, in the current study, all three stages of AKI were associated with similar rates of recovery and CKD development, suggesting that physicians should focus on the recovery of renal function, even when the initial AKI is not severe. The differing results seen in the present study, in comparison with previous reports, may reflect confounding variables, such as the severity of infection, immune function, duration of exposure to nephrotoxic drugs and timing of RRT initiation, which were not assessed in the current study.

Risk factors for CKD after AKI were seen to include older age, diabetes and higher creatinine level at discharge. Higher creatine levels at discharge indicate delayed or lack of renal function recovery, despite the resolution of the initial infection. Manish et al. suggested that early reversible AKI within the first day of admission was associated with a better survival rate than was no, new or persistent AKI [12]. By contrast, Jones et al. demonstrated that even reversible AKI is strongly associated with an increased risk of progression to CKD [24]. Identifying a direct causative mechanism between AKI and CKD may be impossible, but recent studies demonstrated that persistent kidney injury induced by septic AKI is coupled with systemic inflammation. Renal repair can lead to malfunctions in inflammation and fibrosis and vascular rarefaction that leads to continuous cell and tissue disruption [25,26]. Considering this, protein biomarkers such as neutrophil gelatinase-associated lipocalin and interleukin 6 are likely to have an important role in assessing kidney injury, and aiding the discovery of new treatment targets [26–28].

The current study has several limitations. First, the results are limited by the retrospective study design, and as the data were obtained from a single center, it may not be possible to generalise the findings to other populations. Secondly, because of the long-term study period, patients may not have received consistent prehospital and hospital treatment, which may have affected the outcomes. Thirdly, the diagnosis and classification of AKI based only on serum creatinine values may not have captured all relevant cases of AKI, as extremes in muscle mass or dietary protein consumption may affect serum creatinine, and may not reflect true kidney functioning [29]. A recent study demonstrated that the use of serum creatinine only, urine output only or both factors of the KDIGO criteria showed differing outcomes; for example, hospital mortality within the three groups was 9.2% (serum creatinine only), 7.5% (urine output only) and 26.7% (both serum creatinine and urine output) [30]. Moreover, previous CKD or ESRD, or patients with high risk factors (pre-existing proteinuria, albuminuria, decreased urine output, or long-term usage of medication, which could induce renal dysfunction) could be included in study population. Also, not all patients had baseline serum creatinine or eGFR, so we could not confirm to what extent septic shock was responsible for kidney dysfunction. Because our data did not have urine analysis and renal ultrasonography, which contain other important clues to diagnosis CKD development, there was a potential risk of not having an accurate total number of CKD patients upon follow up. In addition, there is a risk of CKD misclassification, as only single timepoint data were used during the follow-up. Finally, a considerable number of patients (217 of 839, 25%) were lost to follow-up, which may have impacted on the results obtained. To make up for this problem, we compared the baseline characteristics between the study group and the follow-up loss

group, and there were no significant differences between the two groups. Moreover, we conducted a sensitivity analysis (Supplementary 1), and found that the trend of ORs for discharge creatinine did not change significantly. These results indirectly imply that follow-up loss patients did not make up a significant bias to our result. However, our results still had the possibility to change if follow-up loss data were included.

5. Conclusions

In conclusion, AKI severity was correlated with mortality, but it did not correlate with the development of CKD, and patients progressed to CKD, even when the initial AKI stage was not severe. Physicians should focus on the recovery of renal function, and ensure the careful follow-up of patients with risk factors for the development of CKD.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/12/554/s1, Supplementary 1. Univariate logistic regression of factors associated with the occurrence of CKD after 1 year including follow-up loss patients (sensitivity analysis).

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References

1. Knoop, S.T.; Skrede, S.; Langeland, N.; Flaatten, H.K. Epidemiology and impact on all-cause mortality of sepsis in Norwegian hospitals: A national retrospective study. *PLoS ONE* **2017**, *12*, e0187990. [CrossRef] [PubMed]
2. Kaukonen, K.-M.; Bailey, M.; Suzuki, S.; Pilcher, D.; Bellomo, R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* **2014**, *311*, 1308–1309. [CrossRef] [PubMed]
3. Meyer, N.; Harhay, M.O.; Small, D.S.; Prescott, H.C.; Bowles, K.H.; Gaieski, D.F.; Mikkelsen, M.E. Temporal trends in incidence, sepsis-related mortality, and hospital-based acute care after sepsis. *Crit. Care Med.* **2018**, *46*, 354–360. [CrossRef] [PubMed]
4. Fujishima, S. Organ dysfunction as a new standard for defining sepsis. *Inflamm. Regen.* **2016**. [CrossRef] [PubMed]
5. Alobaidi, R.; Basu, R.K.; Goldstein, S.L.; Bagshaw, S.M. Sepsis-associated acute kidney injury. *Semin. Nephrol.* **2015**, *35*, 2–11. [CrossRef] [PubMed]
6. Zarjou, A.; Agarwal, A. Sepsis and acute kidney injury. *J. Am. Soc. Nephrol.* **2011**, *22*, 999–1006. [CrossRef] [PubMed]
7. Kellum, J.A.; Sileanu, F.E.; Bihorac, A.; Hoste, E.A.J.; Chawla, L.S. Recovery after acute kidney injury. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 784–791. [CrossRef]
8. Ishani, A.; Xue, J.L.; Himmelfarb, J.; Eggers, P.W.; Kimmel, P.L.; Molitoris, B.A.; Collins, A.J. Acute kidney injury increases risk of ESRD among elderly. *J. Am. Soc. Nephrol.* **2009**, *20*, 223–228. [CrossRef]
9. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* **2017**, *43*, 304–377. [CrossRef]
10. Yearly, D.M.; Kellum, J.A.; Huang, D.T.; Barnato, A.E.; Weissfeld, L.A.; Pike, F.; Terndrup, T.; Wang, H.E.; Hou, P.C.; LoVecchio, F.; et al. A randomized trial of protocol-based care for early septic shock. *N. Engl. J. Med.* **2014**, *370*, 1683–1693.
11. Kim, W.Y.; Huh, J.W.; Lim, C.M.; Koh, Y.S.; Hong, S.B. Analysis of progression in risk, injury, failure, loss, and end-stage renal disease classification on outcome in patients with severe sepsis and septic shock. *J. Crit. Care* **2012**, *27*, 104.e1–104.e7. [CrossRef] [PubMed]

12. Sood, M.M.; Shafer, L.A.; Ho, J.; Reslerova, M.; Martinka, G.; Keenan, S.; Dial, S.; Wood, G.; Rigatto, C.; Kumar, A. Early reversible acute kidney injury is associated with improved survival in septic shock. *J. Crit. Care* **2014**, *29*, 711–717. [CrossRef] [PubMed]
13. Xu, J.-R.; Zhu, J.-M.; Jiang, J.; Ding, X.-Q.; Fang, Y.; Shen, B.; Liu, Z.-H.; Zou, J.-Z.; Liu, L.; Wang, C.-S.; et al. Risk factors for long-term mortality and progressive chronic kidney disease associated with acute kidney injury after cardiac surgery. *Medicine* **2015**, *94*, e2025. [CrossRef] [PubMed]
14. Levy, M.M.; Fink, M.P.; Marshall, J.C.; Abraham, E.; Angus, D.; Cook, D.; Cohen, J.; Opal, S.M.; Vincent, J.-L.; Ramsay, G. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit. Care Med.* **2003**, *31*, 1250–1256. [CrossRef] [PubMed]
15. KDIGO. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Available online: https://kdigo.org/guidelines/ (accessed on 15 December 2018).
16. KDIGO. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Available online: https://kdigo.org/guidelines/ (accessed on 15 December 2018).
17. Singbartl, K.; Kellum, J.A. AKI in the ICU: Definition, epidemiology, risk stratification, and outcomes. *Kidney Int.* **2012**, *81*, 819–825. [CrossRef] [PubMed]
18. Coca, S.G.; Singanamala, S.; Parikh, C.R. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int.* **2012**, *81*, 442–448. [CrossRef] [PubMed]
19. Pereira, B.J.; Barreto, S.; Gentil, T.; Assis, L.S.; Soeiro, E.M.; de Castro, I.; Laranja, S.M. Risk factors for the progression of chronic kidney disease after acute kidney injury. *J. Bras. Nefrol.* **2017**, *39*, 1–7. [CrossRef]
20. Fujii, T.; Uchino, S.; Doi, K.; Sato, T.; Kawamura, T. Diagnosis, management, and prognosis of patients with acute kidney injury in Japanese intensive care units: The JAKID study. *J. Crit. Care* **2018**, *47*, 1–7. [CrossRef]
21. Chawla, L.S.; Amdur, R.L.; Amodeo, S.; Kimmel, P.L.; Palant, C.E. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int.* **2011**, *79*, 1361–1369. [CrossRef]
22. Heung, M.; Chawla, L.S. Acute kidney injury: Gateway to chronic kidney disease. *Nephron Clin. Pract.* **2014**, *127*, 30–34. [CrossRef]
23. Chawla, L.S.; Amdur, R.L.; Shaw, A.D.; Faselis, C.; Palant, C.E.; Kimmel, P.L. Association between acute kidney injury and long-term renal and cardiovascular outcomes in United States Veterans. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 448–456. [CrossRef] [PubMed]
24. Jones, J.; Holmen, J.; De Graauw, J.; Jovanovich, A.; Thornton, S.; Chonchol, M. Association of complete recovery from acute kidney injury with incident CKD Stage 3 and all-cause mortality. *Am. J. Kidney Dis.* **2012**, *60*, 402–408. [CrossRef] [PubMed]
25. Murugan, R.; Wen, X.; Shah, N.; Lee, M.; Kong, L.; Pike, F.; Keener, C.; Unruh, M.; Finkel, K.; Vijayan, A.; et al. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. *Nephrol. Dial. Transplant.* **2014**, *29*, 1854–1864. [CrossRef] [PubMed]
26. Mårtensson, J.; Vaara, S.T.; Pettilä, V.; Ala-Kokko, T.; Karlsson, S.; Inkinen, O.; Uusaro, A.; Larsson, A.; Bell, M. Assessment of plasma endostatin to predict acute kidney injury in critically ill patients. *Acta Anaesthesiol. Scand.* **2017**, *61*, 1286–1295. [CrossRef] [PubMed]
27. Kellum, J.A.; Prowle, J.R. Paradigms of acute kidney injury in the intensive care setting. *Nat. Rev. Nephrol.* **2018**, *14*, 217–230. [CrossRef] [PubMed]
28. Forni, L.G.; Darmon, M.; Ostermann, M.; Straaten, H.M.O.-V.; Pettilä, V.; Prowle, J.R.; Schetz, M.; Joannidis, M. Renal recovery after acute kidney injury. *Intensive Care Med.* **2017**, *43*, 855–866. [CrossRef] [PubMed]
29. Carlier, M.; Dumoulin, A.; Janssen, A.; Picavet, S.; Vanthuyne, S.; Van Eynde, R.; Vanholder, R.; Delanghe, J.; De Schoenmakere, G.; De Waele, J.J.; et al. Comparison of different equations to assess glomerular filtration in critically ill patients. *Intensive Care Med.* **2015**, *41*, 427–435. [CrossRef] [PubMed]
30. Kaddourah, A.; Basu, R.K.; Bagshaw, S.M.; Goldstein, S.L. Epidemiology of acute kidney injury in critically ill children and young adults. *N. Engl. J. Med.* **2017**, *376*, 11–20. [CrossRef] [PubMed]

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Effect of Diabetes Mellitus on Acute Kidney Injury after Minimally Invasive Partial Nephrectomy: A Case-Matched Retrospective Analysis

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Abstract: Postoperative acute kidney injury (AKI) is still a concern in partial nephrectomy (PN), even with the development of minimally invasive technique. We aimed to compare AKI incidence between patients with and without diabetes mellitus (DM) and to determine the predictive factors for postoperative AKI. This case-matched retrospective study included 884 patients with preoperative creatinine levels ≤1.4 mg/dL who underwent laparoscopic or robot-assisted laparoscopic PN between December 2005 and May 2018. Propensity score matching was employed to match patients with and without DM in a 1:3 ratio (101 and 303 patients, respectively). Of 884 patients, 20.4% had postoperative AKI. After propensity score matching, the incidence of postoperative AKI in DM and non-DM patients was 30.7% and 14.9%, respectively ($P < 0.001$). In multivariate analysis, male sex and warm ischemia time (WIT) >25 min were significantly associated with postoperative AKI in patients with and without DM. In patients with DM, hemoglobin A1c (HbA1c) >7% was a predictive factor for AKI, odds ratio (OR) = 4.59 (95% CI, 1.47–14.36). In conclusion, DM increased the risk of AKI after minimally invasive PN; male sex, longer WIT, and elevated HbA1c were independent risk factors for AKI in patients with DM.

Keywords: diabetes mellitus; acute kidney injury; nephrectomy; minimally invasive surgical procedures; risk factors

1. Introduction

Partial nephrectomy (PN) is the current gold standard treatment for small, localized renal tumors owing to reduced risk of acute and chronic kidney dysfunction compared with radical nephrectomy [1,2]. Nevertheless, the incidence rate of acute kidney injury (AKI) after PN is 12%–54% depending on the definition of AKI [2–4]. In case of robot assisted PN, the incidence of postoperative AKI was reported as 24%–27% [5,6]. Therefore, postoperative AKI remains a concern in minimally invasive PN, as parenchymal mass reduction and/or ischemic injury due to vascular clamping cannot be avoided [4].

Diabetes mellitus (DM) has an increasing global prevalence and is the leading cause of chronic kidney disease [7]. Moreover, patients with DM are at an increased risk of acute kidney dysfunction

throughout their lifetime [8]. Furthermore, DM is a recognized risk factor for AKI in the postoperative setting, such as in cardiac [9] and non-cardiac surgeries [10,11]. Previous studies investigating risk factors for AKI in all patients who underwent PN did not distinguish the open technique from the minimally invasive approach [3,4,12–15]. Only one study evaluated the effect of warm ischemia time (WIT) on AKI in robot-assisted laparoscopic PN [5]. Therefore, data on risk factors for AKI after minimally invasive PN are limited. Furthermore, no study has determined whether patients with DM have an increased risk of AKI after minimally invasive PN. The present study aimed to compare the AKI incidence between patients with and without DM and to investigate the predictive factors for AKI in these patients after laparoscopic and robot-assisted laparoscopic PN.

2. Material and Methods

2.1. Patients

This case-matched retrospective analysis was performed after obtaining approval from the institutional review board and hospital research ethics committee (Yonsei University Health System, Seoul, Korea; IRB protocol No. 4-2018-0678, approved at August 29, 2018) with informed consent form from the patients being waived off. A total of 991 patients who underwent laparoscopic or robot-assisted laparoscopic PN between December 2005 and May 2018 were identified from the electronic medical records of a single institution, of which 58 were excluded owing to the type of operation; specifically, 18 patients underwent other combined procedures, whereas 5 and 35 patients were converted to open and radical nephrectomy, respectively. Furthermore, 20 patients with an American Society of Anesthesiologists (ASA) physical status ≥IV, 24 patients with an underlying chronic kidney disease or preoperative creatinine level >1.4 mg/dL, and 5 patients who underwent reoperation because of bleeding within 24 hours postoperatively were excluded from the analysis. Finally, 884 patients were identified, and propensity score matching was performed to match patients with and without DM in a 1:3 ratio (101 and 303 patients, respectively). In propensity score matching, hypertension, cerebrovascular disease, and coronary artery disease were used as covariates (Figure 1).

Standard general anesthesia was provided to all patients. Propofol, remifentanil, and rocuronium were used for anesthesia induction, whereas sevoflurane or desflurane and remifentanil were used for anesthesia maintenance. Administered colloid solution was 6% hydroxyethyl starch 130/0.4 (Volulyte® or Voluven®, Fresenius-Kabi, Seoul, Korea). Laparoscopic or robot-assisted laparoscopic PN was performed in accordance with our institution's protocol [16]. Tumor bed closure was performed using renorrhaphy with absorbable synthetic braided sutures or absorbable barbed sutures according to the surgeon's preference. In cases with calyceal opening, additional suturing was also performed to maintain watertightness.

2.2. Data Collection

All data were collected from electronic medical records. Demographic data included age, sex, body mass index, ASA physical status, and underlying diseases, such as diabetes controlled with oral medication or insulin, hypertension, cerebrovascular disease, and coronary artery disease. Cerebrovascular disease was defined as transient ischemic attack, stroke, history of carotid artery stent, and cerebral hemorrhage. Preoperative laboratory data included creatinine, hematocrit, and hemoglobin (Hb) A1c levels. Operative data included the type of operation, operative time, WIT, volume of intraoperatively administered fluid, intraoperative use of a colloid solution or packed red blood cells, and intraoperative urine output. Data on serum creatinine level and estimated glomerular filtration rate (eGFR) were collected before surgery, immediately after surgery, and at 1 day, 2 days, 1 month, and 3 months after surgery. The eGFR value was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

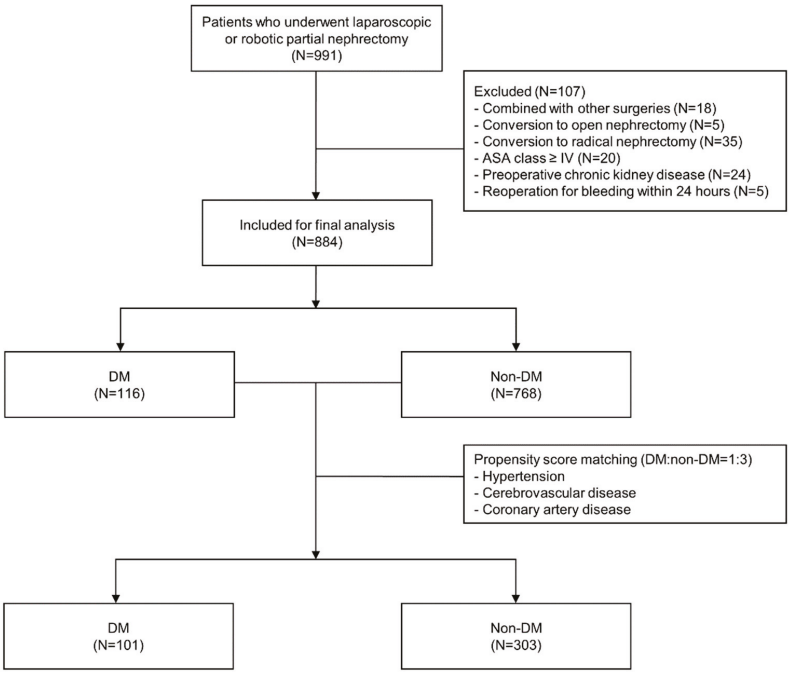

Figure 1. Flow diagram of patient selection. ASA—American Society of Anesthesiologists; DM—diabetes mellitus.

2.3. Primary and Secondary Outcomes

The primary outcome was comparison of AKI incidence between patients with and without DM after laparoscopic and robot-assisted laparoscopic PN. AKI was defined as an absolute increase in serum creatinine level by ≥0.3 mg/dL or ≥50% increase from the preoperative value within the first 48 h after surgery [17]. AKI was further categorized into three stages according to the acute kidney injury network classification: Stage 1, an increase in serum creatinine level ≥0.3 mg/dL or ≥150%–200% (1.5–2-fold) from the baseline value; stage 2, an increase in serum creatinine level >200%–300% (2–3-fold) from the baseline value; and stage 3, an increase in serum creatinine level >300% (3-fold) from the baseline value [17]. Additionally, we investigated predictive factors for AKI in patients with and without DM after laparoscopic and robot-assisted laparoscopic PN as the secondary outcome.

2.4. Statistical Analysis

Continuous variables are presented as mean (SD), whereas categorical variables are expressed as the number of patients in percentage. Continuous and categorical variables were evaluated using independent *t*-test and chi-squared test, respectively. Propensity score matching using a 1:3 ratio was performed to adjust the baseline characteristics of patients with and without DM. Multivariate logistic regression was employed to identify risk factors for AKI in patients with and without DM. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

In the analysis of all patients (N = 884) prior to matching, the incidence rate of AKI after minimally invasive PN was 20.4%, and the following variables were identified as independent risk factors for

AKI (Table 1): Male sex, DM, longer operative duration, WIT >25 min, and higher intraoperative urine output.

Table 1. Univariate and multivariate analyses of risk factors for acute kidney injury after minimally invasive partial nephrectomy (N = 884).

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, year	0.99 (0.98–1.01)	0.292		
Male sex	3.84 (2.51–5.87)	<0.001	4.57 (2.40–8.72)	<0.001
Body mass index, kg/m^2	1.02 (0.99–1.05)	0.151		
ASA physical status				
I	1			
II	0.95 (0.66–1.36)	0.772		
III	1.39 (0.74–2.63)	0.309		
Co-morbidities				
Diabetes mellitus	2.56 (1.68–3.92)	<0.001	2.85 (1.71–4.74)	<0.001
Hypertension	1.39 (0.99–1.95)	0.056	1.10 (0.73–1.65)	0.654
Cerebrovascular disease	1.19 (0.43–3.27)	0.738		
Coronary artery disease	2.20 (0.92–5.28)	0.077	1.39 (0.52–3.69)	0.507
Preoperative lab value				
Creatinine, mg/dL	7.07 (2.78–18.03)	<0.001	0.79 (0.20–3.09)	0.734
Hematocrit, %	1.06 (1.02–1.10)	0.002	1.00 (0.95–1.05)	0.912
Hemoglobin A1c				
≤7%	1			
>7%	1.63 (0.76–3.50)	0.214		
Type of operation				
Laparoscopic	1			
Robotic	0.98 (0.67–1.44)	0.907		
Operation time, 60 min increase	1.44 (1.30–1.61)	<0.001	1.26 (1.08–1.47)	0.003
Warm ischemia time				
≤25 min	1		1	
>25 min	3.25 (2.30–4.58)	<0.001	2.81 (1.92–4.10)	<0.001
Intraoperative I & O				
Fluid input, 500 mL increase	1.46 (1.30–1.65)	<0.001	1.09 (0.91–1.31)	0.349
Colloid administration	1.22 (0.88–1.70)	0.238		
RBC transfusion	2.61 (1.28–5.32)	0.008	1.72 (0.71–4.19)	0.230
Urine output, 100 mL increase	1.06 (1.02–1.10)	0.002	1.06 (1.02–1.11)	0.008
Blood loss, 300 mL increase	1.55 (1.33–1.80)	<0.001		

OR—odds ratio; CI—confidence interval; ASA—American Society of Anesthesiologists; RBC—red blood cells; I & O—input and output.

Among patients with a concomitant disease, only DM was shown to be a risk factor for AKI. Hence, we decided to investigate the effect of DM on AKI using propensity score matching. Prior to matching, the number of patients with DM who were older and had hypertension, cerebrovascular disease, and coronary artery disease was higher than that of patients without DM (Table 2). However, after matching, the demographic characteristics of patients with and without DM were similar except for the ASA physical status (Table 2) and the distribution of patients with and without DM was fairly uniform (Figure 2).

Table 2. Demographic characteristics after propensity score matching.

Variables	After Case Matching (N = 404)			Before Case Matching (N = 884)		
	DM (N = 101)	Non–DM (N = 303)	*P* value	DM (N = 116)	Non–DM (N = 768)	*P* value
Age, year	58.7 (9.2)	58.8 (9.6)	0.887	60.0 (9.8)	51.5 (12.5)	<0.001
Male sex	69 (68%)	182 (60%)	0.139	78 (67%)	472 (61%)	0.231
Body mass index, kg/m^2	26.8 (11.7)	25.0 (3.2)	0.131	26.6 (11.0)	24.6 (3.6)	0.065
ASA physical status			<0.001			<0.001
I	0	49 (16%)		0	295 (38%)	
II	91 (90%)	223 (74%)		100 (86%)	427 (56%)	
III	10 (10%)	31 (10%)		16 (14%)	46 (6%)	
Co-morbidities						
DM with oral medication	98 (97%)			113 (97%)		
DM with insulin	3 (3%)			3 (3%)		
Hypertension	68 (67%)	206 (68%)	0.902	83 (72%)	234 (30%)	<0.001
Cerebrovascular disease	4 (4%)	13 (4%)	>0.999	7 (6%)	15 (2%)	0.018
Coronary artery disease	4 (4%)	6 (2%)	0.276	8 (7%)	15 (2%)	0.006
Preoperative lab value						
Creatinine, mg/dL	0.8 (0.2)	0.8 (0.2)	0.821	0.8 (0.2)	0.8 (0.2)	0.530
Hematocrit, %	42.2 (5.1)	42.2 (4.5)	0.988	41.9 (5.1)	42.4 (4.4)	0.262
Hemoglobin A1c, %	7.3 (1.3)			7.3 (1.4)		
Type of operation			0.604			0.478
Laparoscopic	29 (29%)	79 (26%)		31 (27%)	182 (24%)	
Robotic	72 (71%)	224 (74%)		85 (73%)	586 (76%)	
Operation time, min	289.5 (78.3)	287.5 (98.0)	0.838	288.2 (78.2)	284.9 (91.2)	0.676
Warm ischemia time			0.952			0.511
≤25 min	64 (63%)	191 (63%)		72 (62%)	452 (59%)	
>25 min	37 (37%)	112 (37%)		44 (38%)	316 (41%)	
Intraoperative I & O						
Fluid input, mL	1793.5 (652.6)	1845.2 (658.8)	0.494	1812.9 (640.1)	1853.6 (652.8)	0.531
Patients administered with colloid, n	44 (44%)	125 (41%)	0.684	51 (44%)	326 (42%)	0.758
Patients transfused with RBC, n	7 (7%)	9 (3%)	0.135	10 (9%)	24 (3%)	0.009
Urine output, mL	583.7 (361.4)	563.7 (393.7)	0.652	609.6 (442.3)	593.9 (422.1)	0.710
Blood loss, mL	286.4 (337.7)	254.9 (303.4)	0.380	294.3 (336.8)	245.0 (288.6)	0.137

Values are presented as mean (SD) or number of patients (%). DM—diabetes mellitus; ASA—American Society of Anesthesiologists; RBC—red blood cells; I & O—input and output.

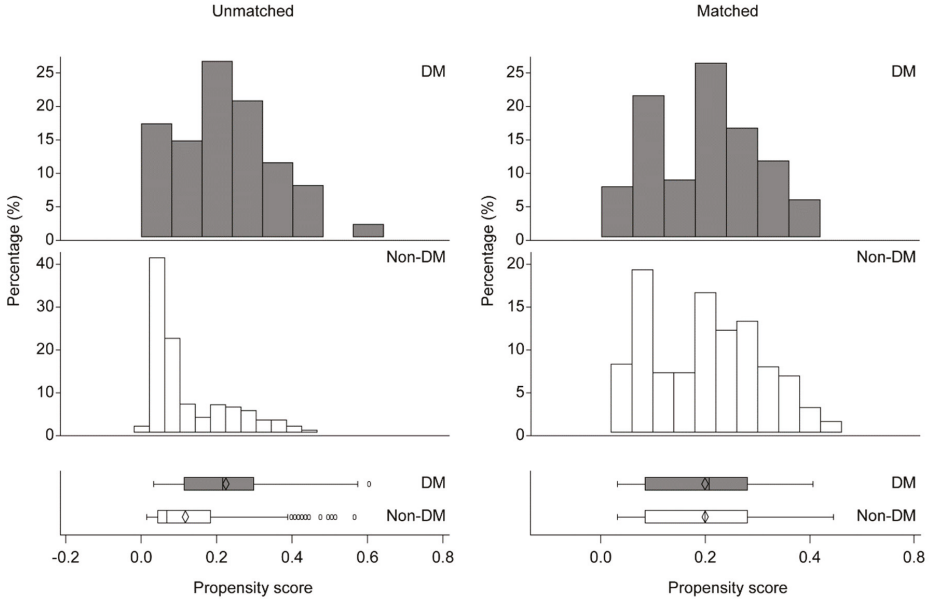

Figure 2. Distribution of propensity scores of patients with and without diabetes mellitus (DM) before and after matching. DM, Diabetes mellitus.

After matching, the incidence rate of postoperative AKI was significantly higher in patients with DM than in those without DM (total: 30.7% vs. 14.9%, $P < 0.001$; stage 1: 29.7% vs. 14.2%, $P < 0.001$; stage 2: 1.0% vs. 0.7%, $P > 0.999$) (Figure 3). No patient developed stage 3 of AKI.

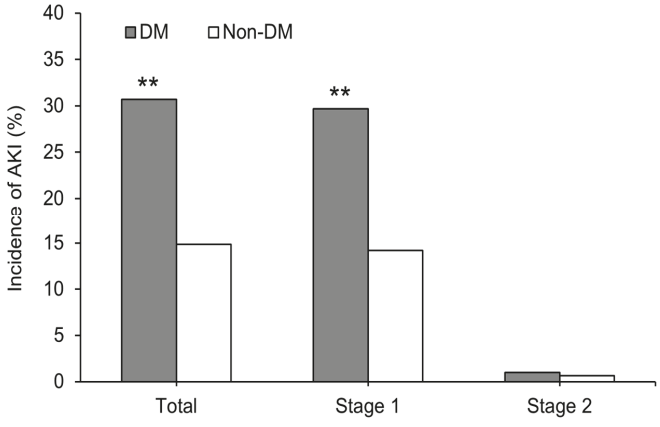

Figure 3. Incidence of acute kidney injury after minimally invasive partial nephrectomy according to the acute kidney injury network criteria. $^{**}P < 0.001$ versus non-DM patients. DM, Diabetes mellitus; AKI, acute kidney injury; stage 1, increase in the serum creatinine level ≥0.3 mg/dL or ≥150%–200% (1.5–2-fold) from baseline; stage 2, increase in the serum creatinine level >200%–300% (2–3-fold) from baseline.

Results of the univariate and multivariate analyses of risk factors for AKI in patients with and without DM are summarized in Table 3. Male sex and WIT >25 min were determined to pose a significantly higher risk of postoperative AKI in patients with and without DM. In patients with DM, preoperative HbA1c >7% was a predictive factor for AKI: Odds ratio (OR) = 4.59 (95% confidence interval (CI), 1.47–14.36). When patients were classified according to DM and sex, the probabilities of AKI were as follows: Females without DM, OR = 1; females with DM, OR = 0.95 (95% CI: 0.16–5.59); males without DM, OR = 4.12 (95% CI: 1.32–12.86); and males with DM, OR = 14.46 (95% CI: 4.62–45.25) (Table 4).

The perioperative serum creatinine level and eGFR until three months after surgery are shown in Figure 4. Although no significant difference in serum creatinine level and eGFR was observed between patients with and without DM at each time point, there were significant intergroup differences over time ($P_{Group \times Time} = 0.016$ and 0.026, respectively).

Table 3. Univariate and multivariate analyses of risk factors for acute kidney injury after minimally invasive partial nephrectomy in patients with and without DM.

Variables	DM (N = 101)				Non–DM (N = 303)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, year	1.00 (0.96–1.05)	0.947			0.99 (0.96–1.03)	0.581		
Male sex	10.87 (2.41–49.18)	0.002	19.58 (2.47–155.35)	0.005	4.89 (2.00–11.99)	0.001	4.52 (1.32–15.48)	0.016
Body mass index, kg/m^2	0.99 (0.96–1.04)	0.973			1.06 (0.96–1.17)	0.236		
ASA physical status								
I					1			
II	1				0.51 (0.24–1.12)	0.093		
III	2.50 (0.67–9.36)	0.174			0.38 (0.10–1.51)	0.170		
Co-morbidities								
Hypertension	2.03 (0.77–5.35)	0.154			1.10 (0.55–2.22)	0.787		
Cerebrovascular disease	0.74 (0.07–7.45)	0.802			1.10 (0.24–5.16)	0.900		
Coronary artery disease	7.39 (0.74–74.13)	0.089	10.41 (0.79–136.42)	0.074	0.45 (0.02 –10.23)	0.616	0.39 (0.02–9.25)	0.557
Preoperative lab value								
Creatinine, mg/dL	21.28 (1.36–332.47)	0.029	5.46 (0.14–219.15)	0.367	7.37 (1.26–43.09)	0.027	0.25 (0.02–3.50)	0.301
Hematocrit, %	1.08 (0.99–1.18)	0.090	0.94 (0.83–1.08)	0.391	1.09 (1.02–1.18)	0.017	1.04 (0.95–1.13)	0.418
Hemoglobin A1c								
≤7%	1							
>7%	2.11 (0.89–5.01)	0.090	4.59 (1.47–14.36)	0.009				
Type of operation								
Laparoscopic	1				1			
Robotic	1.57 (0.59–4.19)	0.367			1.03 (0.49–2.16)	0.937		
Operation time, 60 min increase	1.35 (0.97–1.88)	0.077	1.24 (0.75–2.05)	0.408	1.45 (1.21–1.74)	<0.001	1.18 (0.90–1.56)	0.235
Warm ischemia time								
≤25 min	1		1		1		1	
>25 min	2.49 (1.04–5.94)	0.040	3.57 (1.17–10.94)	0.026	3.09 (1.59–6.01)	0.001	2.56 (1.24–5.26)	0.011
Intraoperative I & O								
Fluid input, 500 mL increase	1.31 (0.95–1.81)	0.101	0.93 (0.60–1.44)	0.752	1.63 (1.29–2.05)	<0.001	1.21 (0.87–1.68)	0.251
Colloid administration	1.33 (0.57–3.10)	0.516			0.92 (0.48–1.78)	0.805		
RBC transfusion	1.77 (0.37–8.42)	0.474	4.28 (0.40–46.09)	0.230	5.23 (1.35–20.33)	0.017	5.13 (0.96–27.42)	0.056
Urine output, 100 mL increase	0.91 (0.80–1.05)	0.185			1.07 (0.99–1.15)	0.097		
Blood loss, 300 mL increase	1.58 (1.07–2.33)	0.023			1.56 (1.20–2.04)	0.001		

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; RBC, red blood cells; I & O, input and output.

Table 4. Incidence and odds ratio of acute kidney injury after minimally invasive partial nephrectomy based on the presence of DM and sex.

	Total patients, n	AKI incidence, n (%)	OR (95% CI)	*P* value
Non-DM female	121	8 (6.6%)	1	
DM female	32	2 (6.3%)	0.95 (0.16–5.59)	0.958
Non-DM male	182	37 (20.3%)	4.12 (1.32–12.86)	0.015
DM male	69	29 (42.0%)	14.46 (4.62–45.25)	<0.001

Values are presented as number of patients (%). AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus.

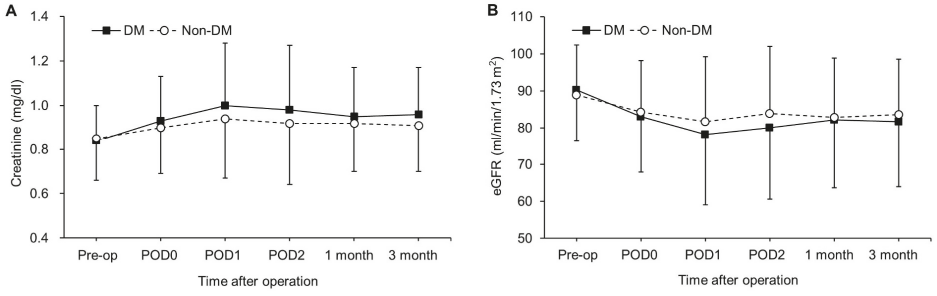

Figure 4. Changes in the serum creatinine level (**A**) and estimated glomerular filtration rate (**B**) until three months postoperatively. Values are presented as a mean (SD). No significant differences were observed between patients with and without DM at each time point. DM, Diabetes mellitus; eGFR, estimated glomerular filtration rate; Pre-op—preoperatively; POD0—postoperative day 0 (immediately after the operation); POD1—postoperative day 1—POD2, postoperative day 2.

4. Discussion

This is the first retrospective case-matched study to clarify whether patients with DM have an increased risk of AKI and evaluate risk factors for AKI in patients with and without DM after minimally invasive PN. The main findings were as follows: (1) DM was a strong predictive factor for AKI after minimally invasive PN. (2) The incidence rate of postoperative AKI was significantly higher in patients with DM than in those without DM, even after adjustment for other factors. (3) Male sex and WIT >25 min were predictive factors for AKI in both patients with and without DM. (4) Preoperative HbA1c >7% was a predictive factor for AKI in patients with DM

Although PN is associated with a reduced risk of postoperative AKI compared with radical nephrectomy owing to being a nephron-sparing surgery [15], the incidence rate of AKI after PN has been reported to be 12%–54% [2–4]. Although AKI incidence varies depending on the definition used, this incidence rate is definitely higher than that after non-cardiovascular surgery (1%–11%) [10,11]. In our study, the incidence rate of AKI in 884 patients who underwent laparoscopic or robot-assisted laparoscopic PN was 20.4%, which is comparable to the previously reported incidence rate of 24%–27% after robot-assisted laparoscopic PN [5,6]. Postoperative AKI is known as a high-risk factor for new-onset chronic kidney disease and is associated with increased morbidity and mortality after nephrectomy and non-cardiovascular surgery [10,11,18,19]. Therefore, attention should be paid to AKI after PN even with the development of the minimally invasive technique, and identification of patients at risk before surgery is important.

Several studies have investigated predictive factors for AKI after PN, which included open and minimally invasive techniques [3,4,12–15]. Longer WIT and operative duration as well as patient-related factors, such as old age, male sex, obesity, impaired preoperative kidney function, and history of hypertension were identified as risk factors for postoperative AKI [3,4,12–15,20,21]. In our study, which analyzed risk factors after minimally invasive PN only, WIT >25 min, longer operative duration,

and patient-related factors, such as male sex, presence of DM, and high intraoperative urine output were revealed to be independent predictors of postoperative AKI. A previous study that included intraoperative urine output as one of the variables for analysis showed that a low urine output is a risk factor for AKI after PN [3]. The high urine output in the present study could be attributed to the use of diuretics typically prescribed by surgeons in difficult cases, which could be the reason for the different result in our study. As urine output in anesthetized patients has been proven to be a poor indicator of fluid balance and is not a predictive factor for AKI after general surgery [11], further studies on the relationship between intraoperative urine output and AKI after PN are required to establish a definite conclusion.

Although our study is the first to identify DM as a risk factor for AKI in PN, previous studies have already reported DM as a risk factor for AKI after general surgeries [10,11]. One study, which enrolled 7564 non-cardiovascular surgical patients and applied the same definition of AKI that we used, reported an OR of 1.51 (95% CI, 1.11–2.06) for AKI development in patients with DM [11]. In comparison, the OR for AKI development in patients with DM in our study was 2.85 (95% CI, 1.71–4.74). Moreover, even after adjustment for other factors by propensity score matching, the incidence rate of AKI was significantly higher in patients with DM (30.7%) than in those without DM (14.9%). Several experimental studies have indicated the susceptibility to renal ischemia/reperfusion (I/R) injury in DM [22–24]. Compared with the nondiabetic kidney, the diabetic kidney exhibited severe damage, including increased tubular cell apoptosis, tubulointerstitial fibrosis, and decreased tubular proliferation after renal I/R [22,23]. Moreover, reperfusion after renal ischemia was markedly delayed in diabetic mice than that in nondiabetic mice [24]. Therefore, the combination of these factors might have made patients with DM more susceptible to AKI in our study.

WIT is recognized as a strong contributing factor for AKI after PN [3–5,12,13,20,21]. WIT >25 min results in irreversible damage that is diffusely distributed throughout the operated kidney, even at six months after PN [25]. Porpiglia and colleagues [26] reported that every minute of warm ischemia could diminish the postoperative kidney function; moreover, they identified 25 min as a safe cut-off for WIT in laparoscopic PN. In line with previous results, WIT > 25 min was a predictive factor for AKI in patients with and without DM.

Previous studies showed that male sex is a risk factor for AKI after PN as well as general surgery [10,12,14,20,27]. Consistent with prior results, we observed a significantly higher risk of postoperative AKI among male patients with and without DM. Sexual dimorphism exists in renal I/R injury, and sex hormones (i.e., ratio of testosterone to estrogen) are considered as the primary factor. Park and colleagues [28] showed that the presence of testosterone rather than the absence of estrogen is crucial in sex difference with respect to susceptibility to renal I/R injury via an increase in inflammation and functional injury to the kidney. Moreover, estrogen displayed a protective effect against renal I/R injury via activation of nitric oxide synthases, inhibition of endothelin-1 production, and depression of the renal sympathetic nervous system [28–30]. Thus, the combination of male sex and DM might have resulted in synergistic effects, and this might have led to our result that male patients with DM had approximately 14 times higher risk of developing AKI than female patients without DM.

HbA1c measurement is a standard method for assessing blood glucose management in patients with DM and it reflects the average blood glucose level over the past 2–3 months. The patients with an HbA1c level of 7% or more had a significantly increased risk of renal failure as well as cerebrovascular accidents, wound infection, and hospital death after coronary artery bypass surgery [31]. However, no study has determined whether elevated preoperative HbA1c increases AKI after PN. Our study is the first to demonstrate that preoperative HbA1c >7% was associated with increased risk for AKI after minimally invasive PN in patients with DM.

The present study has limitations, its main drawback being its retrospective observational nature; thus, it is susceptible to bias and other confounding factors. The baseline difference between patients with and without DM can confound analyses of AKI incidence and risk factors for AKI. In fact, prior to matching, the number of patients with DM who were older and had hypertension, cerebrovascular

disease, and coronary artery disease was higher than that of patients without DM; however, these data were adjusted after propensity score matching. Although this study cannot replace a randomized trial, propensity score matching is a powerful tool for adjusting for confounding variables and reducing selection bias [32]. Therefore, this study is valuable in that it is the first study to compare patients with and without DM with respect to postoperative AKI using propensity score matching. Second, long-term functional outcomes of patients with AKI were not evaluated in the current study. Since postoperative AKI is known as a high-risk factor for new-onset chronic kidney disease [19], long-term follow-up studies are required.

In conclusion, patients with DM had an increased risk of developing AKI after minimally invasive PN, even after adjustment for other factors. Male patients with DM were most susceptible to AKI. WIT >25 min and preoperative HbA1c >7% were associated with AKI in patients with DM. Therefore, caution should be taken to reduce WIT during minimally invasive PN, especially in male patients with DM combined with elevated preoperative HbA1c.

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References

1. Lau, W.K.; Blute, M.L.; Weaver, A.L.; Torres, V.E.; Zincke, H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin. Proc.* **2000**, *75*, 1236–1242. [CrossRef] [PubMed]
2. Suer, E.; Burgu, B.; Gokce, M.I.; Turkolmez, K.; Beduk, Y.; Baltaci, S. Comparison of radical and partial nephrectomy in terms of renal function: A retrospective cohort study. *Scand. J. Urol. Nephrol.* **2011**, *45*, 24–29. [CrossRef]
3. Rajan, S.; Babazade, R.; Govindarajan, S.R.; Pal, R.; You, J.; Mascha, E.J.; Khanna, A.; Yang, M.; Marcano, F.D.; Singh, A.K.; et al. Perioperative factors associated with acute kidney injury after partial nephrectomy. *Br. J. Anaesth.* **2016**, *116*, 70–76. [CrossRef]
4. Zhang, Z.; Zhao, J.; Dong, W.; Remer, E.; Li, J.; Demirjian, S.; Zabell, J.; Campbell, S.C. Acute kidney injury after partial nephrectomy: Role of parenchymal mass reduction and ischemia and impact on subsequent functional recovery. *Eur. Urol.* **2016**, *69*, 745–752. [CrossRef] [PubMed]
5. Rosen, D.C.; Kannappan, M.; Paulucci, D.J.; Beksac, A.T.; Attallah, K.; Abaza, R.; Eun, D.D.; Bhandari, A.; Hemal, A.K.; Porter, J.; et al. Reevaluating warm ischemia time as a predictor of renal function outcomes after robotic partial nephrectomy. *Urology* **2018**, *120*, 156–161. [CrossRef]
6. Lee, B.; Lee, S.Y.; Kim, N.Y.; Rha, K.H.; Choi, Y.D.; Park, S.; Kim, S.Y. Effect of ulinastatin on postoperative renal function in patients undergoing robot-assisted laparoscopic partial nephrectomy: A randomized trial. *Surg. Endosc.* **2017**, *31*, 3728–3736. [CrossRef]
7. National Kidney, F. Kdoqi clinical practice guideline for diabetes and ckd: 2012 update. *Am. J. Kidney Dis.* **2012**, *60*, 850–886.
8. Girman, C.J.; Kou, T.D.; Brodovicz, K.; Alexander, C.M.; O'Neill, E.A.; Engel, S.; Williams-Herman, D.E.; Katz, L. Risk of acute renal failure in patients with type 2 diabetes mellitus. *Diabet. Med.* **2012**, *29*, 614–621. [CrossRef] [PubMed]
9. Wang, Y.; Bellomo, R. Cardiac surgery-associated acute kidney injury: Risk factors, pathophysiology and treatment. *Nat. Rev. Nephrol.* **2017**, *13*, 697–711. [CrossRef]
10. Kheterpal, S.; Tremper, K.K.; Heung, M.; Rosenberg, A.L.; Englesbe, M.; Shanks, A.M.; Campbell, D.A., Jr. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: Results from a national data set. *Anesthesiology* **2009**, *110*, 505–515. [CrossRef] [PubMed]

11. Pourafkari, L.; Arora, P.; Porhomayon, J.; Dosluoglu, H.H.; Arora, P.; Nader, N.D. Acute kidney injury after non-cardiovascular surgery: Risk factors and impact on development of chronic kidney disease and long-term mortality. *Curr. Med. Res. Opin.* **2018**, *34*, 1829–1837. [CrossRef] [PubMed]
12. Lane, B.R.; Babineau, D.C.; Poggio, E.D.; Weight, C.J.; Larson, B.T.; Gill, I.S.; Novick, A.C. Factors predicting renal functional outcome after partial nephrectomy. *J. Urol.* **2008**, *180*, 2363–2368. [CrossRef] [PubMed]
13. Volpe, A.; Blute, M.L.; Ficarra, V.; Gill, I.S.; Kutikov, A.; Porpiglia, F.; Rogers, C.; Touijer, K.A.; Van Poppel, H.; Thompson, R.H. Renal ischemia and function after partial nephrectomy: A collaborative review of the literature. *Eur. Urol.* **2015**, *68*, 61–74. [CrossRef]
14. Schmid, M.; Krishna, N.; Ravi, P.; Meyer, C.P.; Becker, A.; Dalela, D.; Sood, A.; Chun, F.K.; Kibel, A.S.; Menon, M.; et al. Trends of acute kidney injury after radical or partial nephrectomy for renal cell carcinoma. *Urol. Oncol.* **2016**, *34*, 293.e1–293.e10. [CrossRef] [PubMed]
15. Schmid, M.; Abd-El-Barr, A.E.; Gandaglia, G.; Sood, A.; Olugbade, K., Jr.; Ruhotina, N.; Sammon, J.D.; Varda, B.; Chang, S.L.; Kibel, A.S.; et al. Predictors of 30-day acute kidney injury following radical and partial nephrectomy for renal cell carcinoma. *Urol. Oncol.* **2014**, *32*, 1259–1266. [CrossRef]
16. Jeong, W.; Park, S.Y.; Lorenzo, E.I.; Oh, C.K.; Han, W.K.; Rha, K.H. Laparoscopic partial nephrectomy versus robot-assisted laparoscopic partial nephrectomy. *J Endourol.* **2009**, *23*, 1457–1460. [CrossRef] [PubMed]
17. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* **2007**, *11*, R31. [CrossRef] [PubMed]
18. Weight, C.J.; Larson, B.T.; Fergany, A.F.; Gao, T.; Lane, B.R.; Campbell, S.C.; Kaouk, J.H.; Klein, E.A.; Novick, A.C. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized ct1b renal masses. *J. Urol.* **2010**, *183*, 1317–1323. [CrossRef]
19. Cho, A.; Lee, J.E.; Kwon, G.Y.; Huh, W.; Lee, H.M.; Kim, Y.G.; Kim, D.J.; Oh, H.Y.; Choi, H.Y. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol. Dial. Transplant.* **2011**, *26*, 3496–3501. [CrossRef] [PubMed]
20. Zaher Bahouth, E.S.; Nativ, O.; Halachmi, S.; Moskovitz, B.; Abassi, Z.; Nativ, O. Relationship between clinical factors and the occurrence of post-operative acute kidney injury in patients undergoing nephron-sparing surgery. *JMCM* **2018**, *1*, 47–50.
21. Nativ, O.; Bahouth, Z.; Sabo, E.; Halachmi, S.; Moskovitz, B.; Hellou, E.G.; Abassi, Z.; Nativ, O. Method used for tumor bed closure (suture vs. Sealant), ischemia time and duration of surgery are independent predictors of post-nephron sparing surgery acute kidney injury. *Urol. Int.* **2018**, *101*, 184–189. [CrossRef] [PubMed]
22. Nakazawa, J.; Isshiki, K.; Sugimoto, T.; Araki, S.; Kume, S.; Yokomaku, Y.; Chin-Kanasaki, M.; Sakaguchi, M.; Koya, D.; Haneda, M.; et al. Renoprotective effects of asialoerythropoietin in diabetic mice against ischaemia-reperfusion-induced acute kidney injury. *Nephrology* **2010**, *15*, 93–101. [CrossRef] [PubMed]
23. Peng, J.; Li, X.; Zhang, D.; Chen, J.K.; Su, Y.; Smith, S.B.; Dong, Z. Hyperglycemia, p53, and mitochondrial pathway of apoptosis are involved in the susceptibility of diabetic models to ischemic acute kidney injury. *Kidney Int.* **2015**, *87*, 137–150. [CrossRef] [PubMed]
24. Shi, H.; Patschan, D.; Epstein, T.; Goligorsky, M.S.; Winaver, J. Delayed recovery of renal regional blood flow in diabetic mice subjected to acute ischemic kidney injury. *Am. J. Physiol. Renal Physiol.* **2007**, *293*, F1512–F1517. [CrossRef] [PubMed]
25. Funahashi, Y.; Hattori, R.; Yamamoto, T.; Kamihira, O.; Kato, K.; Gotoh, M. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. *Eur. Urol.* **2009**, *55*, 209–215. [CrossRef] [PubMed]
26. Porpiglia, F.; Fiori, C.; Bertolo, R.; Angusti, T.; Piccoli, G.B.; Podio, V.; Russo, R. The effects of warm ischaemia time on renal function after laparoscopic partial nephrectomy in patients with normal contralateral kidney. *World J. Urol.* **2012**, *30*, 257–263. [CrossRef] [PubMed]
27. Bell, S.; Dekker, F.W.; Vadiveloo, T.; Marwick, C.; Deshmukh, H.; Donnan, P.T.; Van Diepen, M. Risk of postoperative acute kidney injury in patients undergoing orthopaedic surgery—development and validation of a risk score and effect of acute kidney injury on survival: Observational cohort study. *BMJ* **2015**, *351*, h5639. [CrossRef]
28. Park, K.M.; Kim, J.I.; Ahn, Y.; Bonventre, A.J.; Bonventre, J.V. Testosterone is responsible for enhanced susceptibility of males to ischemic renal injury. *J. Biol. Chem.* **2004**, *279*, 52282–52292. [CrossRef]

29. Muller, V.; Losonczy, G.; Heemann, U.; Vannay, A.; Fekete, A.; Reusz, G.; Tulassay, T.; Szabo, A.J. Sexual dimorphism in renal ischemia-reperfusion injury in rats: Possible role of endothelin. *Kidney Int.* **2002**, *62*, 1364–1371. [CrossRef]
30. Tanaka, R.; Tsutsui, H.; Ohkita, M.; Takaoka, M.; Yukimura, T.; Matsumura, Y. Sex differences in ischemia/reperfusion-induced acute kidney injury are dependent on the renal sympathetic nervous system. *Eur. J. Pharmacol.* **2013**, *714*, 397–404. [CrossRef]
31. Halkos, M.E.; Puskas, J.D.; Lattouf, O.M.; Kilgo, P.; Kerendi, F.; Song, H.K.; Guyton, R.A.; Thourani, V.H. Elevated preoperative hemoglobin a1c level is predictive of adverse events after coronary artery bypass surgery. *J. Thorac. Cardiovasc. Surg.* **2008**, *136*, 631–640. [CrossRef]
32. Morgan, C.J. Reducing bias using propensity score matching. *J. Nucl. Cardiol.* **2018**, *25*, 404–406. [CrossRef]

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Intraoperative Oliguria with Decreased SvO_2 Predicts Acute Kidney Injury after Living Donor Liver Transplantation

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Abstract: Acute kidney injury (AKI) is a frequent complication after living donor liver transplantation (LDLT), and is associated with increased mortality. However, the association between intraoperative oliguria and the risk of AKI remains uncertain for LDLT. We sought to determine the association between intraoperative oliguria alone and oliguria coupled with hemodynamic derangement and the risk of AKI after LDLT. We evaluated the hemodynamic variables, including mean arterial pressure, cardiac index, and mixed venous oxygen saturation (SvO_2). We reviewed 583 adult patients without baseline renal dysfunction and who did not receive hydroxyethyl starch during surgery. AKI was defined using the Kidney Disease Improving Global Outcomes criteria according to the serum creatinine criteria. Multivariable logistic regression analysis was performed with and without oliguria and oliguria coupled with a decrease in SvO_2. The performance was compared with respect to the area under the receiver operating characteristic curve (AUC). Intraoperative oliguria <0.5 and <0.3 mL/kg/h were significantly associated with the risk of AKI; however, their performance in predicting AKI was poor. The AUC of single predictors increased significantly when oliguria was combined with decreased SvO_2 (AUC 0.72; 95% confidence interval (CI) 0.68–0.75 vs. AUC of oliguria alone 0.61; 95% CI 0.56–0.61; $p < 0.0001$; vs. AUC of SvO_2 alone 0.66; 95% CI 0.61–0.70; $p < 0.0001$). Addition of oliguria coupled with SvO_2 reduction also increased the AUC of multivariable prediction (AUC 0.87; 95% CI 0.84–0.90 vs. AUC with oliguria 0.73; 95% CI 0.69–0.77; $p < 0.0001$; vs. AUC with neither oliguria nor SvO_2 reduction 0.68; 95% CI 0.64–0.72; $p < 0.0001$). Intraoperative oliguria coupled with a decrease in SvO_2 may suggest the risk of AKI after LDLT more reliably than oliguria alone or decrease in SvO_2 alone. Intraoperative oliguria should be interpreted in conjunction with SvO_2 to predict AKI in patients with normal preoperative renal function and who did not receive hydroxyethyl starch during surgery.

Keywords: acute kidney injury; urine output; hemodynamics; living-donor liver transplantation

1. Introduction

The incidence of acute kidney injury (AKI) after orthotopic liver transplantation has been reported to be as high as 64% [1–4]. AKI is an important complication associated with poor graft survival and increased mortality [1,2,5–8]. Furthermore, post-transplant AKI is associated with the development of chronic kidney disease [3,9,10].

Diagnosis of AKI is based on elevation of serum creatinine and/or decrease in urine output in the currently available KDIGO (Kidney Disease Improving Global Outcomes) criteria [7,11].

However, serum creatinine and urine output criteria have been criticized due to inaccurate reflection of glomerular filtration rate, insensitivity to detect acute change in renal function, [12,13] and being influenced by many factors including use of diuretics and volume status. In this regard, biomarkers to detect the development of AKI early after surgery have been investigated and showed promising performance for early detection [14]. However, the accuracy of the biomarkers are still controversial and there is still no biomarker with performance as good as that of troponin for detecting myocardial infarction [14].

The current urine output criteria of AKI suggest that a urine flow rate of <0.5 mL/kg/h lasting for more than 6 h indicates stage 1 AKI [7,11]. A rate of 0.3 mL/kg/h indicates stage 3 AKI. These criteria are widely regarded as the cutoff values to determine AKI in critically ill patients [15,16]. However, urine output criteria are regarded as unreliable in predicting AKI after surgery, because oliguria may develop during surgery due to decreased preload or nephrotoxic drug in addition to intrarenal oliguria [17]. AKI may develop in the absence of oliguria and oliguria may develop due to external obstruction of urinary tract [18,19]. Furthermore, during living donor liver transplantation (LDLT), urine output is influenced by many other factors, including baseline hepatorenal syndrome, cardiac preload condition, hemodynamics, sympathetic tone, and endocrine factors such as anti-diuretic hormones and aldosterone. Therefore, clinical significance of oliguria that is associated with postoperative AKI may be different from the currently available diagnostic criteria.

The etiology of acute kidney injury during surgery includes hemodynamic instability that may result in decreased renal perfusion. During LDLT, intraoperative hemodynamic variables including continuous arterial pressure, cardiac index, and mixed venous oxygen saturation (SvO_2) from pulmonary artery catheter are frequently monitored, although less invasive monitoring is increasingly used. Oliguria coupled with the deterioration in these hemodynamic variables may predict AKI better than oliguria alone because the other causes of oliguria that are not associated with AKI could be excluded. Oliguria developed from poor renal perfusion and oxygen delivery may be more strongly associated with AKI after LDLT.

Therefore, in the present study, we aimed to investigate the specific impact of intraoperative oliguria on the risk of AKI after LDLT determined by KDIGO criteria. We also hypothesized that oliguria coupled with low mean arterial blood pressure, low cardiac index, or low SvO_2 may predict AKI after LDLT better than oliguria alone. The objective of this retrospective study was to compare the association of intraoperative oliguria alone with oliguria observed with hemodynamic deterioration on the risk of AKI after LDLT.

2. Materials and Methods

2.1. Study Design

This retrospective observational study was approved by the institutional review board of Seoul National University Hospital (1608-073-784). We reviewed the electronic medical records of 1211 consecutive adult patients who had undergone liver transplantation at our institution between 2004 and 2015. The need for informed consent was waived because the study had a retrospective design. Patients who received deceased donor liver transplantation (n = 367), those who had baseline renal dysfunction with an estimated glomerular filtration rate of <60 mL/min/1.73m^2 and/or with hepatorenal syndrome (n = 73), and those who received hydroxyethyl starch during surgery (n = 188) were excluded from the analysis. The remaining 583 patients who had undergone LDLT were analyzed.

2.2. Anesthesia, Surgical Technique and Immunosuppression

During the study period, the anesthesia protocol of our institution was as follows. Anesthesia was induced and maintained using propofol, rocuronium, and sevoflurane. Volume-controlled ventilation was maintained, with a tidal volume of 6–8 mL kg^{-1} and a FiO_2 of 0.5. Arterial-line catheters were inserted into the radial and femoral arteries. A Swan-Ganz catheter was inserted

through a 9-Fr Advanced Venous Access catheter (Edward Lifesciences, Irvine, CA, USA) that was placed in the right internal jugular vein. Continuous cardiac index and right ventricle-associated variables were monitored using the Vigilance II monitor (Edward Lifesciences, Irvine, CA, USA). The cause of hypotension was determined on the basis of cardiac index, stroke volume variation, SvO_2 and systemic vascular resistance and was treated using either (1) ephedrine and continuous dopamine, (2) phenylephrine and norepinephrine, and/or (3) epinephrine. Donor grafts were prepared using a histidine-tryptophan-ketoglutarate solution. The piggyback technique was used to anastomose the graft and donor vessels. End-to-end anastomosis of the hepatic artery and duct-to-duct anastomosis of the bile duct were carried out in succession. During surgery, immunosuppression was induced using 500 mg of methylprednisolone (Solumedrol, Pfizer, Ballerup, Denmark) and 20 mg of intravenous basiliximab (Simulect, Novartis Pharma B.V., Arnhem, The Netherlands). During the postoperative period, immunosuppression was induced using calcineurin inhibitors of either tacrolimus or cyclosporine with mycophenolate mofetil.

When intraoperative oliguria occurred during the study period, we administered crystalloid solutions to increase preload when surgical bleeding is evident or preload indices including central venous pressure, pulmonary artery occlusion pressure, and/or right ventricular end-diastolic volume indicated intravascular hypovolemia. Vasopressor was used to increase renal perfusion pressure when urine output decreased with euvolemia. Diuretics were used only when intravascular volume overload was suspected with elevated central venous pressure, pulmonary artery occlusion pressure, and/or right ventricular end-diastolic volume. Diuretics were not used to treat intraoperative oliguria.

The following crystalloid fluids were used to optimize the preload during LDLT before 2010: lactated Ringer's solution, normal saline, and plasmalyte, and hydroxyethyl starch (Voluven, Fresenius Kabi, Germany). The administration rate of crystalloid during LDLT was adjusted according to the hemodynamic preload index of central venous pressure, pulmonary artery occlusion pressure, and stroke volume variation. The hematocrit threshold for red blood cell transfusion was 20% during LDLT throughout the study period. Intraoperative diuretics (furosemide; 10–20 mg) were used in patients with persistent positive fluid balance and when volume overload was suspected due to a pulmonary artery wedge pressure greater 18 mmHg.

2.3. Data Collection

Based on previous literature, demographic and perioperative variables known to be related to postoperative renal dysfunction or AKI were collected [1,4,5,20–22]. Preoperatively, the Model for End-stage Liver Disease (MELD) score, the Child-Turcotte-Pugh (CTP) score, and the Child classification were determined for all recipients [23]. The following variables were also collected: history of hypertension, diabetes mellitus, ABO blood type incompatibility, preoperative serum albumin, preoperative diuretic medication, graft macrosteatosis, graft ischemic time, postoperative platelet count, intraoperative blood loss, intraoperative transfusion volume, intraoperative diuretics use, and mean tacrolimus trough concentration during the first week after surgery [20,24]. The mean urine output during surgery was calculated by averaging the intraoperative data obtained from the electronic medical records. Urine output was measured hourly in a urine bag connected to a Foley catheter.

The resting arterial blood pressure before anesthesia induction was used as baseline blood pressure. The initially measured cardiac index and SvO_2 by pulmonary artery catheter and the Vigilance II monitor were used as a baseline. Sudden decrease in mean arterial pressure, cardiac index, and SvO_2 lower than 20% from baseline for at least one measurement was identified and recorded as a categorized variable.

The primary outcome variable was postoperative AKI, as defined using the KDIGO criteria, which have been validated in patients undergoing LDLT [10]. We determined postoperative AKI based on the maximal change in serum creatinine level during the first seven postoperative days [25]. No urine output criteria were used due to the purpose of our study. Although the oliguria criteria of

KDIGO requires that oliguria last more than 6 h, oliguria was determined based on the average urine out during surgery, regardless of its duration, in our study.

2.4. Statistical Analysis

SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) and STATA/MP version 15.1 (StataCorp, College Station, TX, USA) were used to analyze the data. In all analyses, p-values < 0.05 were considered statistically significant. The Kolmogorov-Smirnov test was used to determine the normality of the data. All the continuous covariates listed in Table 1 followed non-parametric distribution. To compare all continuous variables in Table 1 and the urine output between those with and without AKI, the Mann-Whitney U test was used. Data were missing in fewer than 5% of records. We imputed the missing values according to the incidence of missing data. If the incidence of missing was < 1%, the missing data were substituted by the mean for continuous variables and by the mode for incidence variables. Missing values of variables with a ratio of missing data >1% and <5% were replaced by hot-deck imputation.

Table 1. Patient characteristics and perioperative parameters.

Characteristic	No AKI Group (n = 378)	AKI Group (n = 205)	p-Values
Demographic data			
Age, years	53 (47–58)	53 (49–58)	0.405
Female, n	85 (22.5)	63 (30.7)	0.029
Body-mass index, kg/m^2	22.9 (21.0–24.8)	23.3 (21.6–26.1)	0.008
Background medical status			
Hypertension, n	39 (10.3)	12 (5.9)	0.069
Diabetes mellitus, n	47 (12.4)	22 (10.7)	0.544
Alcoholic liver cirrhosis, n	44 (11.6)	25 (12.2)	0.843
HBV hepatitis, n	159 (42.1)	71 (34.6)	0.080
HCV hepatitis, n	25 (6.6)	12 (5.9)	0.719
Hepatocellular carcinoma, n	209 (55.3)	113 (55.1)	0.969
Cholestatic disease, n	7 (1.9)	6 (2.9)	0.401
Preoperative hemoglobin, g/dL	11.5 (9.7–13.2)	10.2 (8.9–11.9)	<0.001
Preoperative serum albumin level, g/dL	3.0 (2.5–3.6)	2.8 (2.5–3.2)	0.002
Preoperative serum creatinine, mg/dL	0.90 (0.75–1.10)	0.85 (0.68–1.04)	0.014
Preoperative estimated glomerular filtration rate, mL/min	88 (70–109)	94 (75–122)	0.021
MELD score	13 (9–21)	17 (11–21)	0.001
Child-Turcotte-Pugh score	8 (6–11)	9 (7–11)	<0.001
Child class, n (A/ B/ C)	109 (33.5)/96 (29.5)/120 (36.9)	28 (16.2)/61 (35.3)/84 (48.6)	<0.001
Preoperative LVEF. %	65 (61–68)	65 (62–68)	0.254
Preoperative beta-blocker, n	29 (7.7)	13 (6.3)	0.645
Preoperative diuretics, n	16 (4.2)	12 (5.9)	0.382
Donor/ graft factors			
Age, years	31 (23–41)	30 (23–38)	0.302
Estimated GRWR	1.17 (1.01–1.46)	1.16 (1.00–1.41	0.396
ABO incompatible, n	19 (5.0)	10 (4.9)	0.937
Operation and anesthesia details			
Operation time, h	7.0 (6.1–8.2)	7.6 (6.5–8.6)	0.001
Cold ischemic time, min	71 (58–83)	78 (65–95)	<0.001
Warm ischemic time, min	31 (23–40)	32 (26–41)	0.142
Intraoperative furosemide use, n	71 (18.8)	52 (25.4)	0.063
Intraoperative furosemide dose, mg	0 (0–0)	0 (0–5)	0.040
Intraoperative use of epinephrine, n	148 (39.2)	81 (39.5)	0.933
Intraoperative dose of epinephrine, mcg	0 (0–10)	0 (0–5)	0.603
Intraoperative mean blood glucose, mg/dL	163 (144–178)	164 (145–183)	0.216
Intraoperative highest blood glucose, mg/dL	211 (194–230)	218 (200–238)	0.012
Mean trough level of tacrolimus during posmiddleerative first week (ng/mL)	6.2 (3.2–8.5)	6.5 (3.4–9.1)	0.098

Table 1. *Cont.*

Characteristic	No AKI Group (n = 378)	AKI Group (n = 205)	p-Values
Bleeding and transfusion amount			
pRBC transfusion, units	4 (0–10)	6 (3–12)	<0.001
FFP transfusion, units	4 (0–8)	6 (2–12)	<0.001
Blood loss per body weight, mL/kg	33 (18–64)	47 (23–91)	<0.001
Input and output during surgery			
Intraoperative average urine flow rate, mL/kg/h	1.36 (0.89–2.08)	1.15 (0.76–1.72)	0.007
Crystalloid administration, mL/kg	53 (37–73)	57 (40–85)	0.007
Net fluid balance during surgery, mL/kg	31 (13–52)	36 (18–59)	0.072

The values are expressed as the mean (standard deviation) or median [interquartile range] or number (%). AKI = acute kidney injury; MELD score = model for end-stage liver disease score; GRWR = graft to recipient body weight ratio; pRBC = packed red blood cell; FFP = fresh frozen plasma. Net fluid balance was calculated by total input subtracted by total output.

The following is a summary of our statistical analysis. First, we determined the cutoff of intraoperative mean urine output by multivariable logistic regression analysis. Second, according to oliguria using the cutoff, we compared the predictive ability of the oliguria alone with that of oliguria coupled with a decrease in mean arterial pressure, cardiac index, and SvO_2. Third, we evaluated whether the oliguria coupled with hemodynamic derangement could enhance the AUC of the multivariable prediction model for AKI after LDLT.

Multivariable logistic regression analysis was performed (1) to find an optimal cutoff of oliguria, and (2) to evaluate the association between perioperative variables and postoperative AKI. The following variables were considered potential risk factors of AKI after LDLT in addition to oliguria and hemodynamic variables: age, sex, body-mass index, year of operation, MELD score, CTP score, hypertension, diabetes mellitus, preoperative hemoglobin level, preoperative serum albumin, preoperative serum creatinine, ABO blood type incompatibility, operation time, graft ischemic time, preoperative diuretics use, intraoperative blood loss, intraoperative crystalloid and colloid administration, transfusion amount and total dose of diuretics administered during surgery. We did not perform any univariable screening before the multivariable analysis. A p-value < 0.20 was used to select for significant predictors in the multivariable analysis, with the backward stepwise variable selection. We also performed multivariable logistic regression analysis without stepwise variable selection.

Three different cutoffs of intraoperative mean intraoperative urine flow rate including 1.0, 0.5, and 0.3 mL/kg/h were evaluated, because oliguria less than these cutoffs was significantly associated with postoperative AKI in our preliminary multivariable logistic regression analysis using perioperative baseline variables with mean urine output with different cutoffs (Supplemental Table S1).

To compare the predictive ability of oliguria using these cutoffs with that of oliguria coupled with three hemodynamic variables, the area under the receiver operating characteristic curve (AUC) was calculated for every single potential predictor. Also, performance measurements including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were compared.

Multivariable logistic regression analysis was performed again by adding the predictors of oliguria coupled with hemodynamic variables. Then, the AUCs of a multivariable prediction model with and without these oliguria coupled with hemodynamic variables were compared to evaluate whether these combined predictors could increase the predictive ability of multivariable prediction model. The comparison between AUCs was performed using De Long' s method [26].

3. Results

During the first postoperative week, AKI, as determined using the KDIGO criteria, occurred in 205 patients (35.2%), and stage ≥2 AKI occurred in 43 patients (7.4%). Patient demographics and perioperative variables were compared between the patients with and without AKI in Table 1. The distribution of mean intraoperative mean urine flow rate is shown in Supplemental Figure S1.

The median (interquartile ranges) of mean urine output were 1.15 (0.76–1.71) for those with AKI and 1.36 (0.89–2.08) for those without AKI. The mean intraoperative urine output was significantly lower in patients with AKI than in those without AKI ($p = 0.007$).

The odds ratios, 95% CI and their p-values according to oliguria with different cutoffs are shown in Supplemental Table S1. Multivariable logistic regression analysis showed that oliguria <0.5 and <0.3 mL/kg/h were significantly associated with AKI.

The performances to predict postoperative AKI of a single variable of oliguria, a single variable of 20% decrease in hemodynamic variables, and their combined variables were compared in terms of AUC, sensitivity, specificity, PPV, and NPV (Table 2). Three different cutoffs of 0.3, 0.5, and 1.0 mL/kg/h were used, and hemodynamic variables included mean arterial pressure, cardiac index, and SvO_2. AUC was largest for oliguria <0.5 mL/kg/h with SvO_2 reduction (AUC = 0.72, 95% CI 0.68–0.75).

Table 2. Comparisons of performance of risk factors between the oliguria with different cutoffs alone, 20% decreased hemodynamic variables alone, and their combined variables.

Oliguria	Coupled Hemodynamic Variable	AUC (95% CI)	p-Value	Sensitivity	Specificity	PPV	NPV
<0.3	None	0.55 (0.50–0.60)	0.031	16.1	94.7	62.3	60.5
<0.5	None	0.60 (0.56–0.64)	<0.001	49.8	56.6	50.1	64.7
<1.0	None	0.55 (0.50–0.60)	0.040	53.7	48.7	38.3	69.8
No	SvO_2	0.66 (0.61–0.70)	<0.001	57.1	79.1	59.7	77.3
No	Cardiac index	0.56 (0.52–0.61)	0.011	62.0	50.8	40.6	71.1
No	Mean arterial pressure	0.53 (0.48–0.58)	0.219	52.2	54.0	38.1	67.5
<0.3	SvO_2	0.61 (0.56–0.66)	<0.001	11.3	97.4	82.5	50.0
<0.3	Cardiac index	0.55 (0.50–0.60)	0.046	16.1	93.9	58.9	67.4
<0.3	Mean arterial pressure	0.53 (0.48–0.58)	0.191	13.2	91.4	51.9	66.5
<0.5	SvO_2	0.72 (0.68–0.75)	<0.001	59.1	86.5	69.6	78.8
<0.5	Cardiac index	0.56 (0.52–0.60)	0.011	37.6	75.1	45.0	68.9
<0.5	Mean arterial pressure	0.53 (0.49–0.57)	0.276	29.3	73.2	40.0	65.5
<1.0	SvO_2	0.58 (0.53–0.63)	0.001	37.1	79.1	49.0	69.9
<1.0	Cardiac index	0.52 (0.47–0.57)	0.418	39.5	64.6	37.7	66.3
<1.0	Mean arterial pressure	0.50 (0.45–0.55)	0.929	30.2	69.3	34.8	64.7

AUC = area under the receiver operating characteristic curve, CI = confidence interval, SvO_2 = mixed venous oxygen saturation, PPV = positive predictive value, NPV = negative predictive value. Coupled hemodynamic variables mean 20% decrease of the hemodynamic variables compared to baseline. AUC of the univariable analysis was reported. P-value are the results of testing the null hypothesis of AUC is 0.50.

The AUCs of four single predictors of oliguria <0.5 mL/kg/h alone, oliguria coupled with mean arterial pressure reduction, oliguria with cardiac index reduction, and oliguria with SvO_2 reduction were compared in Figure 1. AUC of oliguria $\leq$0.5 mL/kg/h with SvO_2 20% reduction was significantly greater than all other variables (oliguria with SvO_2 reduction: AUC 0.72, 95% CI 0.68–0.75 vs. oliguria alone: 0.60, 95% CI 0.56–0.64, $p < 0.001$; vs. oliguria with mean arterial pressure reduction: 0.53, 95% CI 0.49–0.57, $p < 0.001$; vs. oliguria with cardiac index reduction: 0.56, 95% CI 0.52–0.60, $p < 0.001$).

The results of multivariable logistic regression analysis to predict postoperative AKI with and without including oliguria <0.5 mL/kg/h coupled with SvO_2 reduction are shown in Table 3. The Nagelkerke's R^2 of the model with and without oliguria with SvO_2 reduction were 0.16 and 0.39, respectively. Both models showed good calibration (Hosmer-Lemeshow goodness of fit: chi-square = 2.33, 8.76 and $p = 0.264, 0.567$, respectively). The results of multivariable logistic regression analysis without stepwise variable selection are shown in Supplemental Table S1.

The AUCs of (1) the multivariable prediction without oliguria or SvO_2, (2) multivariable prediction with oliguria <0.5 mL/kg/h, and (3) multivariable prediction with oliguria <0.5 mL/kg/h coupled with SvO_2 reduction are compared in Figure 2 (AUC of oliguria coupled with SvO_2 reduction: 0.87, 95% CI 0.84–0.90 vs. AUC without oliguria or SvO_2 reduction: 0.68, 95% CI 0.64–0.72, $p < 0.0001$; vs. AUC with oliguria: 0.73, 95% CI 0.69–0.77, $p < 0.0001$).

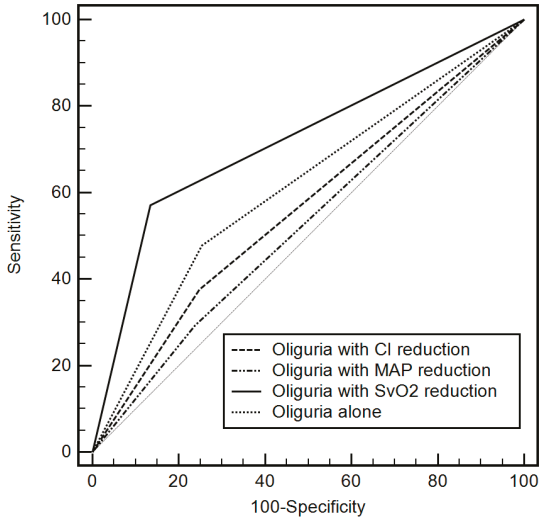

Figure 1. Comparison of area under the receiver operating characteristic curve between the four predictors of oliguria alone and oliguria coupled with hemodynamic variables including mean arterial pressure (MAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2). Oliguria used a cutoff of 0.5 mL/kg/h and hemodynamic variables used 20% reduction from their baseline values. AUC of oliguria $\leq$ 0.5 mL/kg/h with SvO_2 20% reduction was significantly greater than all other variables (oliguria coupled with SvO_2 reduction: AUC 0.72, 95% CI 0.68–0.75 vs. oliguria alone: 0.60, 95% CI 0.56–0.64, $p < 0.001$; vs. oliguria coupled with mean arterial pressure reduction: 0.53, 95% CI 0.49–0.57, $p < 0.001$; vs. oliguria coupled with cardiac index reduction: 0.56, 95% CI 0.52–0.60, $p < 0.001$).

Table 3. Multivariable logistic regression analysis to predict acute kidney injury after liver transplantation with and without oliguria or hemodynamic variables.

Variable	Odds Ratio	95% CI	*p*-Value
Without urine output or hemodynamic variables			
Body-mass index, kg/m^2	1.09	1.03–1.16	0.004
Preoperative hemoglobin, g/dL	0.86	0.77–0.95	0.004
Preoperative albumin, g/dL	0.88	0.68–1.15	0.158
Operation time, h	1.07	0.94–1.22	0.123
Cold ischemic time, min	1.02	1.01–1.03	<0.001
Red blood cell transfusion, unit	1.10	1.05–1.12	0.010
Crystalloid administration, per 10 mL/kg	1.07	1.00–1.15	0.068
Including urine output coupled with hemodynamic variables			
Body-mass index, kg/m^2	1.12	1.05–1.20	0.001
Preoperative hemoglobin, g/dL	0.89	0.79–0.99	0.041
Preoperative diuretics	1.68	0.58–4.89	0.139
Operation time, h	1.12	0.91–1.34	0.236
Cold ischemic time, min	1.02	1.01–1.03	0.003
Crystalloid administration, per 10 mL/kg	1.08	1.02–1.15	0.011
SvO_2 reduction with oliguria <0.5 mL/kg/h	7.64	4.82–12.11	<0.001

Two separate logistic regression analysis was performed with and without intraoperative mean urine flow rate and intraoperative hemodynamic variables. CI = confidence interval. Stepwise backward variable selection was used and cutoff of $p < 0.20$ was used to select the variables.

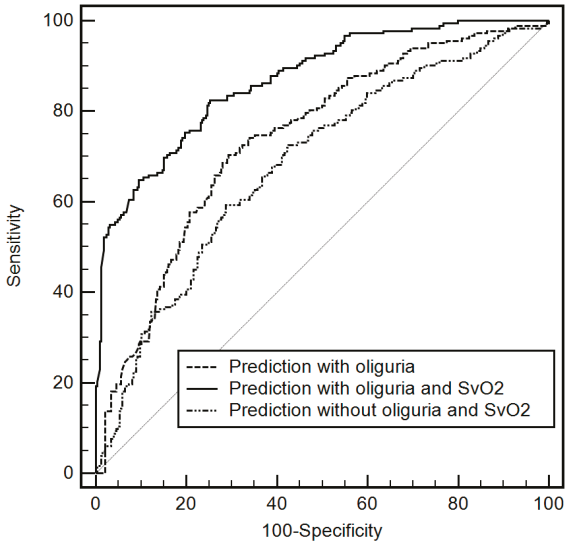

Figure 2. Comparison of area under the receiver operating characteristic curve between the multivariable prediction models (1) without oliguria or mixed venous oxygen saturation (SvO_2) reduction, (2) with oliguria, and (3) with oliguria coupled with SvO_2 reduction. AUC of model with oliguria coupled with SvO_2 reduction was significantly greater than AUCs of model without SvO_2 reduction (AUC with oliguria coupled with SvO_2 reduction: 0.87, 95% CI 0.84–0.90 vs. AUC without oliguria or SvO_2 reduction: 0.68, 95% CI 0.64–0.72, $p < 0.0001$; vs. AUC with oliguria: 0.73, 95% CI 0.69–0.77, $p < 0.0001$).

4. Discussion

To our knowledge, the present study was the first to evaluate the association between intraoperative mean urine output, hemodynamic variables, and AKI after LDLT. Although there was a significant association between oliguria <1.0, <0.5 and <0.3 mL/kg/h and risk of AKI, the predictive ability of oliguria alone was relatively poor and did not add substantial additional discriminative power in multivariable prediction. However, when oliguria developed in association with decreased SvO_2, the AUC of a single predictor significantly increased, while oliguria coupled with mean arterial blood pressure or cardiac index failed to increase the AUC. These results suggested that oliguria accompanied by a reduction in SvO_2 during LDLT may be more strongly associated with the development of AKI than oliguria or reduction in SvO_2 alone. The AUC of multivariable prediction showed similar results and the model including oliguria coupled with decreased SvO_2 showed significantly higher performance in terms of AUC and Nagelkerke's R^2. Although oliguria alone is not specific and has little value in predicting AKI after LDLT, oliguria coupled with a decrease in cardiac output or SvO_2 could significantly increase the sensitivity and predictive ability for AKI after LDLT. However, our results should not be applied to the patients with poor baseline renal function including hepatorenal syndrome and the patients who received hydroxyethyl starch during surgery. Also, our results should be interpreted cautiously, because our oliguria was determined by the intraoperative mean value and the duration of oliguria was not considered.

The urine output criteria of the RIFLE criteria (Risk, Injury, Failure, Loss of function, and End-stage renal disease) and the AKIN (AKI network) criteria are widely used to diagnose AKI [7]. The clinical implications of the oliguria criteria have been validated in a critical care setting [27,28]. However, intraoperative oliguria is regarded as less predictive of postoperative AKI compared to non-surgical settings [29]. AKI determined by serum creatinine may develop without oliguria, and AKI may not

develop despite the intraoperative oliguria. Furthermore, recent studies have suggested that the urine output criteria for AKI in surgical patients may be different from the previous commonly used value of 0.5 mL/kg/h [30,31].

Several studies have attempted to derive urine output thresholds that identify AKI in surgical patients [30–32]. Using a methodology that was similar to ours, one retrospective study in cardiac surgical patients undergoing cardiopulmonary bypass identified a urine flow rate of <1.5 mL/kg/h as a cutoff that was associated with AKI risk [30]. Another retrospective study involving major abdominal surgery reported that <0.3 mL/kg/h was the threshold of the risk of AKI [31]. As such, the threshold urine output to diagnose AKI may vary depending on the surgical setting. Therefore, we first identified the optimal cutoff of oliguria that is significantly associated with AKI after LDLT in our study sample. However, in these studies, the predictive ability of intraoperative oliguria has not been evaluated fully.

Along with the usual <0.5 or <0.3 mL/kg/h cutoff of oliguria, our analysis suggested significant associations between low urine flow rate of <1.0 mL/kg/h and risk of AKI after LDLT. We evaluated the cutoff of oliguria up to 3.0 mL/kg/h because previous studies reported different cutoffs of oliguria during surgery [30–32] (Supplemental Table S2). The significant threshold of <1.0 mL/kg/h may be influenced by the intraoperative diuretics use. More than 20% of our patients received diuretics before or intraoperatively. Our subgroup analysis after excluding all patients who administered diuretics pre- or intraoperatively (n = 435) showed that <1.0 mL/kg/h was not significantly associated with postoperative AKI (Supplemental Table S3).

The performance of oliguria in predicting AKI defined by creatinine criteria was poor at any cutoff (Table 2). AUC was only between 0.55 to 0.60, with low sensitivity and specificity. Addition of oliguria <1.5 mL/kg/h did not significantly improve the predictive ability of multivariable prediction model for AKI. It seems that oliguria during LDLT is neither a sensitive nor specific marker of AKI—i.e., the patients with the same mean urine flow rate may or may not develop AKI. Although hemodynamic variables of SvO_2 showed a slightly better performance as a single predictor, the other hemodynamic variables did not. However, oliguria coupled with a decrease in SvO_2 showed a significantly better performance as a single predictor and enhanced the predictive ability of multivariable prediction when included in the multivariable logistic model.

A low SvO_2 may suggest poor oxygen delivery to the kidney [33]. During LDLT, decreased preload by intraoperative bleeding may decrease cardiac output and thereby impair renal perfusion. An ischemia/reperfusion injury of the kidney may develop especially during liver graft reperfusion [34]. A low SvO_2 during LDLT reflects decreased oxygen delivery by low cardiac output to the major organs including kidney. When oliguria developed in a patient who experienced a decrease in SvO_2, the oliguria of the patient is more likely to be caused by poor renal perfusion and oxygen delivery to the kidney. Meanwhile, the oliguria alone may not be associated with poor oxygen delivery to the kidney but associated with an extrarenal cause such as a transient decrease in preload or urinary tract obstruction.

However, decrease in cardiac index or mean arterial pressure combined with oliguria did not increase AUC to predict AKI after LDLT. Mean arterial pressure is not a sensitive marker to measure the cardiac output and oxygen delivery to the major organ especially in patients with significant cirrhosis or during and after reperfusion with unequal vasodilation [35]. Cardiac index could be more important than mean arterial pressure. However, in patients with liver cirrhosis, 20% decrease in cardiac index may not be meaningful in patients with cirrhosis and hyperdynamic hemodynamics with already elevated baseline cardiac output. Also, a previous study reported that there was a poor correlation between cardiac index and SvO_2 during liver transplantation [36].

Several urinary or serum biomarkers were reported to be sensitive to predict AKI after surgery [37–39]. The performance of neutrophil gelatinase-associated lipocalin (NGAL) to predict AKI after surgery in terms of AUC was reported to be 0.82 to 0.83 after cardiac surgery [40]. The AUC of urinary NGAL on postoperative day one to predict AKI after liver transplantation was 0.79 [41]. Considering these AUC, the performance of our multivariable prediction could be regarded as similar

to that of NGAL. In addition to NGAL, many other promising biomarkers have been reported including kidney injury molecule-1 (KIM-1), interleukin-18, liver-type fatty-acid binding protein (L-FABP), angiotensinogen [42], tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein-3 (IGFBP-3) [38,43]. Two recent studies reported that biomarker-guided implementation of KDIGO interventions could decrease the incidence of AKI after cardiac and major abdominal surgery [44,45]. However, the performance of these biomarkers are still controversial [46] and there seems to be a long way to go before incorporating the biomarkers into our routine perioperative practice.

Hemodynamic optimization may protect renal function in surgical patient [47]. Our results may suggest that hemodynamic goals should not be managed step-by-step—i.e., firstly, optimize preload; secondly, optimize contractility; thirdly, optimize afterload, and so on—and should be interpreted comprehensively. Goal-directed therapy algorithm usually establishes several hemodynamic goals first and do not pay attention to the remaining goals until the first goal, usually preload index, is achieved. However, hemodynamic goals including preload, afterload, and oxygenation index, as well as urine output, are associated with each other. Therefore, we suggest that intraoperative urine flow rate should be interpreted in conjunction with other hemodynamic parameters such as cardiac index or SvO_2. However, routine use of pulmonary artery catheter has been a subject of debate. A previous multicenter trial reported no difference in mortality in high-risk surgical patients with and without hemodynamic management guided by pulmonary artery catheter [48]. Pulmonary artery catheter was associated with higher risk of pulmonary embolism. The use of less invasive monitoring with central venous oxygen saturation may substitute the SvO_2 monitoring with pulmonary artery catheter [49].

There was a significant difference in gender distribution between the patients with and without AKI (Table 1). The incidence of female was significantly higher in the AKI group compared to the no-AKI group, which was consistent with a previous study [50], albeit not in other studies [1,20]. However, female was not an independent predictor in our multivariable analysis, suggesting that female gender is associated with other significant covariates. We compared the independent predictors identified in our multivariable analysis between male and female groups (Supplemental Table S3) and found that female was associated with significantly lower preoperative hemoglobin, and larger intraoperative crystalloid administration compared to male group in our study population.

The present study had several limitations. Firstly, it was a single-center retrospective analysis, and urine flow rate data collected from the medical records may have been inaccurate. Furthermore, our cutoff for urine output may not be extrapolated to other institutions with different fluid management strategy and different baseline medical conditions, although multivariable adjustment was performed in this study. The intraoperative urine output may differ markedly depending on the intraoperative goal of fluid management, transfusion amount and intraoperative diuretics or hydroxyethyl starch use. Secondly, in our analysis, we used a mean urine flow rate during surgery rather than hourly urine output. However, oliguria lasting for longer than 6 h is required for the KDIGO criteria. Furthermore, there may be critical periods during LDLT, such as the anhepatic or reperfusion period, which involve unstable hemodynamics and severe metabolic acidosis [34]. In future studies, duration of oliguria as well as phases of LDLT when oliguria developed should be considered when investigating the association of oliguria with AKI. Different oliguria cutoffs should be considered including 1.0 mL/kg/h. Thirdly, we did not consider the duration of a decrease in hemodynamic variables. We evaluated the association between the decrease in hemodynamic variables for at least one measurement and AKI. Our electronic record has data of most hemodynamic variables in 5-min intervals. Further studies may investigate the possible dose-response relationship between the duration of hemodynamic deterioration and the risk of AKI. Fourthly, since our study was a retrospective analysis and intraoperative mean urine output was used for analysis, the temporal relationship between oliguria and decrease in hemodynamic variables could not be identified. The risk of AKI may be different between oliguria following deterioration in hemodynamic variables and oliguria with no temporal relationship hemodynamic derangement.

5. Conclusions

Intraoperative oliguria alone could not accurately predict AKI after LDLT determined by creatinine criteria, although there were significant associations using a cutoff of oliguria <1.0, <0.5 and <0.3 mL/kg/h. However, when oliguria with these cutoffs was found with decreased intraoperative SvO_2, the performance to predict AKI improved significantly and the predictive ability of multivariable prediction model was significantly enhanced. Decrease in cardiac index or mean arterial blood pressure combined with oliguria did not significantly increase the AUC to predict AKI after LDLT. Intraoperative oliguria interpreted in conjunction with a decrease in SvO_2 may suggest the risk of AKI after LDLT more reliably in patients with normal baseline renal function and who did not receive hydroxyethyl starch during transplantation surgery.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/1/29/s1, Supplemental Table S1. Multivariable logistic regression analysis to predict acute kidney injury after liver transplantation without stepwise variable selection. Supplemental Table S2. Odds ratios (95% confidence intervals) and their P-values according to the categorized intraoperative urine flow rate with different cutoffs determined by both the univariable and multivariable logistic regression analysis for acute kidney injury. Supplemental Table S3. Subgroup analysis for the patients who had not received diuretics either before or during surgery (n = 435). Odds ratios (95% confidence intervals) and their p-values according to the categorized intraoperative urine flow rate with different cutoffs determined by both the univariable and multivariable logistic regression analysis for acute kidney injury were shown. Supplemental Table S4. Comparisons of independent predictors of the multivariable logistic regression analysis of our study between male and female. Supplemental Figure S1. Distribution of mean urine flow rate during liver transplantation surgery in all patients (upper), and box and whisker plots of urine flow rate during liver transplantation surgery with and without postoperative acute kidney injury (lower).

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References

1. Utsumi, M.; Umeda, Y.; Sadamori, H.; Nagasaka, T.; Takaki, A.; Matsuda, H.; Shinoura, S.; Yoshida, R.; Nobuoka, D.; Satoh, D.; et al. Risk factors for acute renal injury in living donor liver transplantation: Evaluation of the RIFLE criteria. *Transpl. Int.* **2013**, *26*, 842–852. [CrossRef] [PubMed]
2. Zhu, M.; Li, Y.; Xia, Q.; Wang, S.; Qiu, Y.; Che, M.; Dai, H.; Qian, J.; Ni, Z.; Axelsson, J.; et al. Strong impact of acute kidney injury on survival after liver transplantation. *Transplant. Proc.* **2010**, *42*, 3634–3638. [CrossRef] [PubMed]
3. Ferreira, A.C.; Nolasco, F.; Carvalho, D.; Sampaio, S.; Baptista, A.; Pessegueiro, P.; Monteiro, E.; Mourão, L.; Barroso, E. Impact of RIFLE classification in liver transplantation. *Clin. Transplant.* **2010**, *24*, 394–400. [CrossRef] [PubMed]
4. Chen, J.; Singhapricha, T.; Hu, K.Q.; Hong, J.C.; Steadman, R.H.; Busuttil, R.W.; Xia, V.W. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: A matched study. *Transplantation* **2011**, *91*, 348–353. [CrossRef] [PubMed]
5. Lebron Gallardo, M.; Herrera Gutierrez, M.E.; Seller Perez, G.; Curiel Balsera, E.; Fernandez Ortega, J.F.; Quesada Garcia, G. Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transpl.* **2004**, *10*, 1379–1385. [CrossRef] [PubMed]
6. Barri, Y.M.; Sanchez, E.Q.; Jennings, L.W.; Melton, L.B.; Hays, S.; Levy, M.F.; Klintmalm, G.B. Acute kidney injury following liver transplantation: Definition and outcome. *Liver Transpl.* **2009**, *15*, 475–483. [CrossRef] [PubMed]
7. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef]
8. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef]

9. Paramesh, A.S.; Roayaie, S.; Doan, Y.; Schwartz, M.E.; Emre, S.; Fishbein, T.; Florman, S.; Gondolesi, G.E.; Krieger, N.; Ames, S.; et al. Post-liver transplant acute renal failure: Factors predicting development of end-stage renal disease. *Clin. Transplant.* **2004**, *18*, 94–99. [CrossRef]
10. Trinh, E.; Alam, A.; Tchervenkov, J.; Cantarovich, M. Impact of acute kidney injury following liver transplantation on long-term outcomes. *Clin. Transplant.* **2017**, *31*, e12863. [CrossRef]
11. Shin, S.R.; Kim, W.H.; Kim, D.J.; Shin, I.W.; Sohn, J.T. Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery. *Biomed. Res. Int.* **2016**, *2016*, 2985148. [CrossRef] [PubMed]
12. Bellomo, R.; Kellum, J.A.; Ronco, C. Defining acute renal failure: Physiological principles. *Intensive Care Med.* **2004**, *30*, 33–37. [CrossRef] [PubMed]
13. Murray, P.T.; Le Gall, J.R.; Dos Reis Miranda, D.; Pinsky, M.R.; Tetta, C. Physiologic endpoints (efficacy) for acute renal failure studies. *Curr. Opin. Crit. Care* **2002**, *8*, 519–525. [CrossRef] [PubMed]
14. Alge, J.L.; Arthur, J.M. Biomarkers of AKI: A review of mechanistic relevance and potential therapeutic implications. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 147–155. [CrossRef] [PubMed]
15. Chenitz, K.B.; Lane-Fall, M.B. Decreased urine output and acute kidney injury in the postanesthesia care unit. *Anesthesiol. Clin.* **2012**, *30*, 513–526. [CrossRef] [PubMed]
16. Katayama, S.; Koyama, K.; Goto, Y.; Koinuma, T.; Tonai, K.; Shima, J.; Wada, M.; Nunomiya, S. Body weight definitions for evaluating a urinary diagnosis of acute kidney injury in patients with sepsis. *BMC Nephrol.* **2018**, *19*, 101. [CrossRef] [PubMed]
17. Gaffney, A.M.; Sladen, R.N. Acute kidney injury in cardiac surgery. *Curr. Opin. Anaesthesiol.* **2015**, *28*, 50–59. [CrossRef] [PubMed]
18. Anderson, R.J.; Linas, S.L.; Berns, A.S.; Henrich, W.L.; Miller, T.R.; Gabow, P.A.; Schrier, R.W. Nonoliguric acute renal failure. *N. Engl. J. Med.* **1977**, *296*, 1134–1138. [CrossRef] [PubMed]
19. Klahr, S. Pathophysiology of obstructive nephropathy. *Kidney Int.* **1983**, *23*, 414–426. [CrossRef] [PubMed]
20. Park, M.H.; Shim, H.S.; Kim, W.H.; Kim, H.J.; Kim, D.J.; Lee, S.H.; Kim, C.S.; Gwak, M.S.; Kim, G.S. Clinical Risk Scoring Models for Prediction of Acute Kidney Injury after Living Donor Liver Transplantation: A Retrospective Observational Study. *PLoS ONE* **2015**, *10*, e0136230. [CrossRef] [PubMed]
21. Lee, H.C.; Yoon, S.; Yang, S.M.; Kim, W.; Ryu, H.G.; Jung, C.W.; Suh, K.S.; Lee, K. Prediction of Acute Kidney Injury after Liver Transplantation: Machine Learning Approaches vs. Logistic Regression Model. *J. Clin. Med.* **2018**, *7*, 428. [CrossRef] [PubMed]
22. Chen, Y.Y.; Wu, V.C.; Huang, W.C.; Yeh, Y.C.; Wu, M.S.; Huang, C.C.; Wu, K.D.; Fang, J.T.; Wu, C.J.; CAKS Group. Norepinephrine Administration Is Associated with Higher Mortality in Dialysis Requiring Acute Kidney Injury Patients with Septic Shock. *J. Clin. Med.* **2018**, *7*, 274. [CrossRef] [PubMed]
23. Selzner, M.; Kashfi, A.; Cattral, M.S.; Selzner, N.; McGilvray, I.D.; Greig, P.D.; Levy, G.A.; Renner, E.L.; Grant, D.R. Live donor liver transplantation in high MELD score recipients. *Ann. Surg.* **2010**, *251*, 153–157. [CrossRef] [PubMed]
24. Goren, O.; Matot, I. Perioperative acute kidney injury. *Br. J. Anaesth.* **2015**, *115* (Suppl. S2), ii3–ii14. [CrossRef] [PubMed]
25. Cockcroft, D.W.; Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* **1976**, *16*, 31–41. [CrossRef] [PubMed]
26. DeLong, E.R.; DeLong, D.M.; Clarke-Pearson, D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* **1988**, *44*, 837–845. [CrossRef] [PubMed]
27. Guerin, C.; Girard, R.; Selli, J.M.; Perdrix, J.P.; Ayzac, L. Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. Rhone-Alpes Area Study Group on Acute Renal Failure. *Am. J. Respir. Crit. Care Med.* **2000**, *161*, 872–879. [CrossRef]
28. Teixeira, C.; Garzotto, F.; Piccinni, P.; Brienza, N.; Iannuzzi, M.; Gramaticopolo, S.; Forfori, F.; Pelaia, P.; Rocco, M.; Ronco, C.; et al. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. *Crit. Care* **2013**, *17*, R14. [CrossRef]
29. Alpert, R.A.; Roizen, M.F.; Hamilton, W.K.; Stoney, R.J.; Ehrenfeld, W.K.; Poler, S.M.; Wylie, E.J. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery* **1984**, *95*, 707–711. [CrossRef]

30. Hori, D.; Katz, N.M.; Fine, D.M.; Ono, M.; Barodka, V.M.; Lester, L.C.; Yenokyan, G.; Hogue, C.W. Defining oliguria during cardiopulmonary bypass and its relationship with cardiac surgery-associated acute kidney injury. *Br. J. Anaesth.* **2016**, *117*, 733–740. [CrossRef]
31. Mizota, T.; Yamamoto, Y.; Hamada, M.; Matsukawa, S.; Shimizu, S.; Kai, S. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. *Br. J. Anaesth.* **2017**, *119*, 1127–1134. [CrossRef] [PubMed]
32. Kunst, G.; Ostermann, M. Intraoperative permissive oliguria - how much is too much? *Br. J. Anaesth.* **2017**, *119*, 1075–1077. [CrossRef] [PubMed]
33. Mayer, K.; Trzeciak, S.; Puri, N.K. Assessment of the adequacy of oxygen delivery. *Curr. Opin. Crit. Care* **2016**, *22*, 437–443. [CrossRef] [PubMed]
34. Adelmann, D.; Kronish, K.; Ramsay, M.A. Anesthesia for Liver Transplantation. *Anesthesiol. Clin.* **2017**, *35*, 491–508. [CrossRef] [PubMed]
35. Rudnick, M.R.; Marchi, L.D.; Plotkin, J.S. Hemodynamic monitoring during liver transplantation: A state of the art review. *World, J. Hepatol.* **2015**, *7*, 1302–1311. [CrossRef] [PubMed]
36. Acosta, F.; Sansano, T.; Palenciano, C.G.; Roqués, V.; Clavel, N.; González, P.; Robles, R.; Bueno, F.S.; Ramírez, P.; Parrilla, P. Does mixed venous oxygen saturation reflect the changes in cardiac output during liver transplantation? *Transplant. Proc.* **2002**, *34*, 277. [CrossRef]
37. De Geus, H.R.; Betjes, M.G.; Bakker, J. Biomarkers for the prediction of acute kidney injury: A narrative review on current status and future challenges. *Clin. Kidney, J.* **2012**, *5*, 102–108. [CrossRef] [PubMed]
38. Parikh, C.R.; Moledina, D.G.; Coca, S.G.; Thiessen-Philbrook, H.R.; Garg, A.X. Application of new acute kidney injury biomarkers in human randomized controlled trials. *Kidney Int.* **2016**, *89*, 1372–1379. [CrossRef] [PubMed]
39. Merchant, M.L.; Brier, M.E.; Slaughter, M.S.; Klein, J.B.; McLeish, K.R. Biomarker enhanced risk prediction for development of AKI after cardiac surgery. *BMC Nephrol.* **2018**, *19*, 102. [CrossRef] [PubMed]
40. Haase-Fielitz, A.; Haase, M.; Devarajan, P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: A critical evaluation of current status. *Ann. Clin. Biochem.* **2014**, *51*, 335–351. [CrossRef] [PubMed]
41. Baron-Stefaniak, J.; Schiefer, J.; Miller, E.J.; Berlakovich, G.A.; Baron, D.M.; Faybik, P. Comparison of macrophage migration inhibitory factor and neutrophil gelatinase-associated lipocalin-2 to predict acute kidney injury after liver transplantation: An observational pilot study. *PLoS ONE* **2017**, *12*, e0183162. [CrossRef] [PubMed]
42. Yang, X.; Chen, C.; Tian, J.; Zha, Y.; Xiong, Y.; Sun, Z.; Chen, P.; Li, J.; Yang, T.; Ma, C.; et al. Urinary Angiotensinogen Level Predicts AKI in Acute Decompensated Heart Failure: A Prospective, Two-Stage Study. *J. Am. Soc. Nephrol.* **2015**, *26*, 2032–2041. [CrossRef] [PubMed]
43. Meersch, M.; Schmidt, C.; Van Aken, H.; Martens, S.; Rossaint, J.; Singbartl, K.; Görlich, D.; Kellum, J.A.; Zarbock, A. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS ONE* **2014**, *9*, e93460. [CrossRef] [PubMed]
44. Göcze, I.; Jauch, D.; Götz, M.; Kennedy, P.; Jung, B.; Zeman, F.; Gnewuch, C.; Graf, B.M.; Gnann, W.; Banas, B.; et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. *Ann. Surg.* **2018**, *267*, 1013–1020. [CrossRef] [PubMed]
45. Meersch, M.; Schmidt, C.; Hoffmeier, A.; Van Aken, H.; Wempe, C.; Gerss, J.; Zarbock, A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med.* **2017**, *43*, 1551–1561. [CrossRef] [PubMed]
46. Meersch, M.; Schmidt, C.; Zarbock, A. Perioperative Acute Kidney Injury: An Under-Recognized Problem. *Anesth Analg.* **2017**, *125*, 1223–1232. [CrossRef] [PubMed]
47. Brienza, N.; Giglio, M.T.; Marucci, M.; Fiore, T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit. Care Med.* **2009**, *37*, 2079–2090. [CrossRef]
48. Sandham, J.D.; Hull, R.D.; Brant, R.F.; Knox, L.; Pineo, G.F.; Doig, C.J.; Laporta, D.P.; Viner, S.; Passerini, L.; Devitt, H.; et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N. Engl. J. Med.* **2003**, *348*, 5–14. [CrossRef]

49. El-Masry, A.; Mukhtar, A.M.; el-Sherbeny, A.M.; Fathy, M.; el-Meteini, M. Comparison of central venous oxygen saturation and mixed venous oxygen saturation during liver transplantation. *Anaesthesia* **2009**, *64*, 378–382. [CrossRef]
50. Hilmi, I.A.; Damian, D.; Al-Khafaji, A.; Planinsic, R.; Boucek, C.; Sakai, T.; Chang, C.C.; Kellum, J.A. Acute kidney injury following orthotopic liver transplantation: Incidence, risk factors, and effects on patient and graft outcomes. *Br. J. Anaesth.* **2015**, *114*, 919–926. [CrossRef]

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Diagnostic Performance of Cyclophilin A in Cardiac Surgery-Associated Acute Kidney Injury

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Abstract: Acute kidney injury (AKI) is associated with increased morbidity and mortality and is frequently encountered in cardiovascular surgical intensive care units (CVS-ICU). In this study, we aimed at investigating the utility of cyclophilin A (CypA) for the early detection of postoperative AKI in patients undergoing cardiac surgery. This was a prospective observational study conducted in a CVS-ICU of a tertiary care university hospital. All prospective clinical and laboratory data were evaluated as predictors of AKI. Serum and urine CypA, as well as urine neutrophil gelatinase-associated lipocalin (uNGAL), were examined within 6 h after cardiac surgery. The discriminative power for the prediction of AKI was evaluated using the area under the receiver operator characteristic curve (AUROC). We found that both serum CypA and urine CypA were significantly higher in the AKI group than in the non-AKI group. For discriminating AKI and dialysis-requiring AKI, serum CypA demonstrated acceptable AUROC values (0.689 and 0.738, respectively). The discrimination ability of urine CypA for predicting AKI was modest, but it was acceptable for predicting dialysis-requiring AKI (AUROC = 0.762). uNGAL best predicted the development of AKI, but its sensitivity was not good. A combination of serum CypA and uNGAL enhanced the overall performance for predicting the future development of AKI and dialysis-requiring AKI. Our results suggest that CypA is suitable as a biomarker for the early detection of postoperative AKI in CVS–ICU. However, it has better discriminating ability when combined with uNGAL for predicting AKI in CVS-ICU patients.

Keywords: cardiovascular surgical intensive care units; cardiac surgery; acute kidney injury; cyclophilin A; neutrophil gelatinase-associated lipocalin

1. Introduction

Acute kidney injury (AKI) is a severe complication after cardiac surgery and significantly affects morbidity and mortality [1,2]. Up to 15–40% of patients undergoing cardiac surgery develop AKI, with 1–6% requiring renal replacement therapy (RRT) [1–4]. The mortality rate in cardiac surgery patients with a severe, RRT-requiring AKI can be as high as 60% [3,4]. Even minor increases in serum

creatinine (SCr) levels (that is, 20–25% from preoperative baseline) following cardiac surgery are associated with increased mortality [5,6]. AKI is associated with not only postoperative mortality but long-term complications, such as increased risks of myocardial infarction, heart failure, mediastinitis, and stroke [2,7–9]. Therefore, novel biomarkers that can predict the development and severity of AKI earlier after cardiac surgery are important tools in clinical practice.

Recently, a secreted molecule, cyclophilin A (CypA), was found to have a physiological and pathological role in cardiovascular diseases, including atherosclerosis, acute coronary syndrome, and aortic aneurysm [10–14]. Extracellular CypA has been found to promote either the development of atherosclerosis or the vulnerability of atherosclerotic plaques by enhancing vascular oxidative stress and inflammation [14]. CypA has also been shown to be a damage-associated molecular pattern molecule that can initiate and perpetuate the inflammatory response [15]. It can stimulate inflammatory cell recruitment and subsequent tissue injury through binding to membrane receptor CD147 [16]. Critically, Dear et al., by using a mouse model of sepsis based on cecal ligation and puncture, found that inhibition of CypA receptor CD147 attenuates sepsis-induced acute renal failure [17]. Furthermore, the increased secretion of CypA from human proximal tubular cells has been demonstrated after exposure to harmful insults, such as free radical treatment [18]. Thus, it is conceivable that urine CypA might be a potential early marker of kidney injury.

Our hypothesis was that serum CypA can be a crucial mediator leading to adverse outcomes in patients after cardiac surgery. Therefore, this study aimed to evaluate whether serum or urine CypA could be a potential marker to predict AKI after cardiac surgery.

2. Materials and Methods

2.1. Study Design

We conducted a prospective, observational study in the CVS-ICU at a tertiary care referral center in Taiwan between September 2015 and December 2016. Patients who received cardiac surgery were enrolled in this investigation. A total of 186 patients were included and divided into the AKI and non-AKI groups. Patients who had an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, were receiving dialysis, were aged < 18 years, or reported any prior organ transplantation were excluded. To ensure early detection, only those who underwent cardiac surgery and were admitted to the CVS-ICU within 72 h were enrolled. Demographic data, clinical characteristics, and echocardiographic data were collected. Routine biochemistry test results, such as white blood cell, hemoglobin, creatinine (Cr), and alanine aminotransferase levels were measured by the central laboratory of Chang Gung Memorial Hospital. Based on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury, AKI was defined under either of the following criteria: increase in SCr by ≥0.3mg/dL within 48 h or increase in SCr to ≥1.5 times the baseline within 7 days. In addition, the severity of AKI was staged according to the KDIGO guidelines [19]. The study protocol was approved by the local Institutional Review Board (number 103-1993B).

2.2. Clinical Assessment

All the patients received standard medical therapy after cardiac surgery. The cardiac surgical details included coronary artery bypass grafting (CABG), valve surgery, and aortic surgery. Surgical risk was assessed using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II score [20]. To determine the predictive value of potential biomarkers for AKI, the primary outcome was the development of AKI within 7 days after cardiac surgery. To assess the prognostic utility of potential biomarkers, new-onset dialysis-requiring AKI and 90-day mortality were considered secondary outcomes. After hospital discharge, a 6-month follow-up examination was performed by reviewing the electronic medical records or using telephone interviews as needed.

2.3. Sampling and Quantifying Urine Neutrophil Gelatinase-Associated Lipocalin (uNGAL) and Cyclophilin A (CypA)

Urine samples were collected in sterile non-heparinized tubes immediately after cardiac surgery and then centrifuged at 5000× *g* for 30 min at 4 °C to remove cells and debris. The clarified supernatants were stored at −80 °C until analysis. CypA and uNGAL were measured by an enzyme-linked immunosorbent assay using kits purchased from Cusabio Biotech (Carlsbad, CA, USA) and R&D Systems (DLCN20; Minneapolis, MN, USA), respectively, according to the manufacturers' specifications.

2.4. Statistical Analysis

Continuous data, such as preoperative laboratory value, were expressed as means ± standard deviations. Since most biomarkers did not fit a normal distribution, we expressed them as median and interquartile range. Data of continuous variables for the AKI and non-AKI groups were compared using the Student's *t*-test or Mann–Whitney U test. Fisher's exact test was used to compare the categorical variables. The trends of uNGAL/Cr and serum CypA across chronic kidney disease (CKD) stages was assessed by the Jonckheere–Terpstra trend test. Pairwise comparisons among the CKD stages were made by the Kruskal–Wallis test with Bonferroni adjustment. The discrimination abilities of several markers (i.e., serum CypA, uNGAL/Cr, serum CypA + uNGAL/Cr, and urine CypA/Cr) in diagnosing outcomes (including AKI, hemodialysis, and 90-day mortality) were assessed using the area under the receiver operating characteristic curve (AUROC). Subsequently, optimal cut-off points and the corresponding sensitivities/specificities were obtained according to the Youden index. The areas under the curve (AUCs) of different markers were compared by the DeLong test. All tests were two-tailed, and $p < 0.05$ was considered statistically significant. No adjustment for multiple testing (multiplicity) was made in this study. Data analyses were conducted using SPSS 22 (IBM SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Study Population Characteristics

Overall, 186 adult patients (116 men and 70 women) with a mean age of 60 years were investigated. AKI was diagnosed in 92 (49.5%) patients. The patient characteristics, including age, sex, preoperative laboratory data, and surgical details, are listed in Table 1. Diabetes mellitus and congestive heart failure were recorded in 32.8% and 19.9% of the patients, respectively, during recruitment. The AKI patients exhibited significantly higher EuroSCORE II than the non-AKI patients ($p = 0.018$). Furthermore, the AKI patients exhibited lower platelet and albumin levels and higher Cr levels at baseline than the non-AKI patients ($p < 0.05$; Table 1). No significant differences were seen in other clinical and biochemical parameters between the AKI and non-AKI groups after the cardiac surgeries.

Table 1. Baseline characteristics of the patients with and without AKI after cardiac surgeries.

Characteristics	All Patients	AKI	Non-AKI	*p*
Patient number	186	92	94	-
Age, year	60.0 ± 14.6	60.7 ± 14.8	59.3 ± 14.5	0.504
Male gender, *n* (%)	116 (62.4)	55 (59.8)	61 (64.9)	0.545
Diabetes mellitus, *n* (%)	61 (32.8)	33 (35.9)	28 (29.8)	0.436
CHF NYHA III/IV, *n* (%)	37 (19.9)	22 (23.9)	15 (16.0)	0.201
Mean arterial pressure, mmHg	90.3 ± 14.4	89.5 ± 15.4	91.0 ± 13.3	0.475
LVEF, %	60.9 ± 15.5	59.9 ± 15.9	61.8 ± 15.3	0.394

Table 1. *Cont.*

Characteristics	All Patients	AKI	Non-AKI	*p*
Preoperative laboratory data				
Leukocyte count, 1000/mL	7.8 ± 3.4	7.7 ± 3.6	7.9 ± 3.2	0.730
Hemoglobin, g/dL	12.6 ± 2.4	12.3 ± 2.7	12.9 ± 2.0	0.083
Platelet count, 1000/mL	201 ± 75	189 ± 81	212 ± 66	0.038
ALT, u/L	30.2 ± 34.8	31.2 ± 43.3	29.1 ± 24.0	0.691
Serum creatinine, mg/dL	1.1 ± 1.0	1.3 ± 1.3	0.9 ± 0.4	0.013
Albumin, mg/dL	3.9 ± 0.5	3.9 ± 0.6	4.0 ± 0.4	0.044
EuroSCORE II	6.7 (6.1)	8.0 (7.2)	5.5 (4.5)	0.018
Surgical detail, *n* (%)				0.162
CABG	61 (32.8)	24 (26.1)	37 (39.4)	
Valve surgery	64 (34.4)	33 (35.9)	31 (33.0)	
CABG + valve surgery	17 (9.1)	12 (13.0)	5 (5.3)	
Aorta	34 (18.3)	19 (20.7)	15 (16.0)	
Others	10 (5.4)	4 (4.3)	6 (6.4)	

Continuous data are presented as means ± SDs or medians (interquartile range); AKI, acute kidney injury; CHF, congestive heart failure; NYHA, New York Heart Association; ALT, alanine aminotransferase; CABG, coronary artery bypass grafting.

Table 2 summarizes the postoperative biomarkers and clinical outcomes of the patients with and without AKI in this study. In the AKI and non-AKI groups, the median serum CypA levels were 5.8 ng/mL and 4.0 ng/mL ($p < 0.001$), respectively; the median uNGAL levels were 91 ng/mL and 31 ng/mL ($p < 0.001$), respectively; and the median urine CypA levels were 0.24 ng/mL and 0.17 ng/mL ($p = 0.035$), respectively. To compensate for perioperative variation in urine dilution, urine CypA and uNGAL were adjusted according to urine Cr. The median urine CypA/Cr levels in the AKI and non-AKI groups were 0.004 ng/mL and 0.002 ng/mL ($p = 0.003$), respectively, and the median uNGAL/Cr levels in the two groups were 1.73 ng/mL and 0.43 ng/mL ($p < 0.001$), respectively. Eventually, eleven (12%) of the AKI patients underwent hemodialysis. There were seven (7.6%) and five (5.4%) patients in the AKI group suffered from post-operative bleeding and sepsis respectively. Overall, 12 (6.5%) patients died within 90 days. Patients in the AKI group had a longer hospital stay and a higher incidence of postoperative bleeding and mortality than did those in the non-AKI group.

Table 2. Postoperative biomarkers and outcomes of the patients with and without AKI after cardiac surgeries.

Characteristics	All Patients	AKI	Non-AKI	*p*
Patient number	186	92	94	-
Postoperative biomarkers				
Urine NGAL, ng/mL	44 (104)	91 (141)	31 (39)	<0.001
Urine NGAL/urine creatinine	0.73 (1.9)	1.73 (6.51)	0.43 (0.65)	<0.001
CypA, ng/mL	5.2 (3.3)	5.8 (3.9)	4.0 (4.3)	<0.001
Urine CypA, ng/mL	0.19 (0.29)	0.24 (0.40)	0.17 (0.24)	0.035
Urine CypA/urine creatinine	0.003 (0.007)	0.004 (0.013)	0.002 (0.005)	0.003
Peak serum creatinine, mg/dL	1.6 ± 1.3	2.3 ± 1.8	1.0 ± 0.4	<0.001
Outcome				
AKI stage 1/2/3	-	48/23/21	-	-
Renal replacement therapy, *n* (%)	12 (6.5)	11 (12.0)	1 (1.1)	0.002
Postoperative bleeding, *n* (%)	8 (4.3)	7 (7.6)	1 (1.1)	0.034
Postoperative sepsis, *n* (%)	6 (3.2)	5 (5.4)	1 (1.1)	0.116
Stay of hospital, days	21.4 (15.0)	28.0 (18.5)	14.9 (11.0)	<0.001
Mortality in 90 days, *n* (%)	12 (6.5)	10 (10.9)	2 (2.1)	0.018

Continuous data are presented as means ± SDs or medians (interquartile range); AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin; CypA, cyclophilin A.

The patients in the AKI group exhibited significantly higher serum CypA and normalized uNGAL levels than those in the non-AKI group. The level of normalized uNGAL increased along with the more severe AKI stage, but there was no significant difference between the KDIGO 1 and KDIGO 2 stages (Figure 1A). The level of serum CypA was significantly different between the AKI and non-AKI groups, but there was no significant difference among the KDIGO stages 1–3 (Figure 1B).

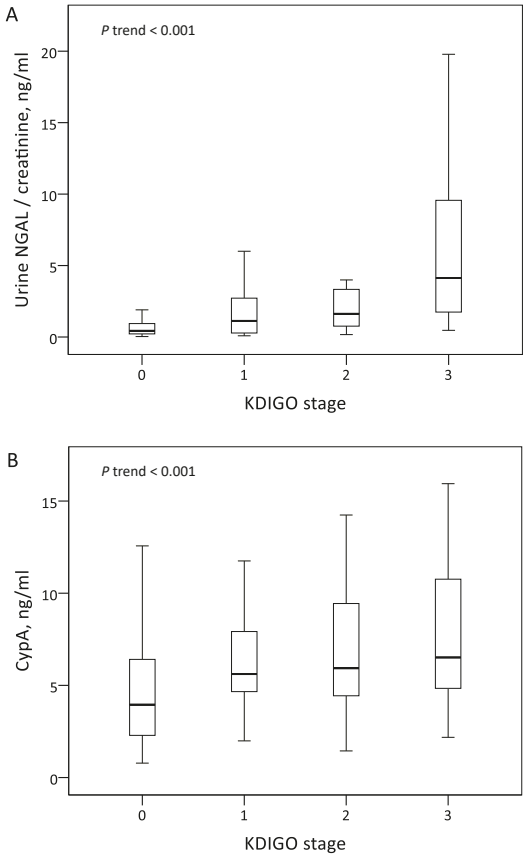

Figure 1. Levels of urine NGAL normalized by urine creatinine (**A**) and serum CypA (**B**) across KDIGO stages. Abbreviations: CypA, cyclophilin A; NGAL, neutrophil gelatinase-associated lipocalin; KDIGO, Kidney Disease Improving Global Outcomes.

3.2. Discrimination Abilities of Serum CypA and Normalized uNGAL in Detecting AKI, Dialysis-Requiring AKI, and 90-Day Mortality

The performances of serum CypA and normalized uNGAL in the detection of outcomes were assessed through AUROC analysis, as shown in Figure 2A–C. The ROC analysis of serum CypA and normalized uNGAL revealed AUROC values of 0.689 (95% confidence interval [CI], 0.618–0.755) and 0.752 (95% CI, 0.684–0.812), respectively, for predicting the future development of AKI. The combination of serum CypA and normalized uNGAL showed the highest AUC of 0.787 (95% CI, 0.721–0.843) in diagnosing AKI. In terms of using a single marker to predict dialysis-requiring AKI, serum CypA and normalized uNGAL had AUROCs of 0.738 (95% CI, 0.668–0.799) and 0.835 (95% CI, 0.773–0.885), respectively. Normalized urine CypA had an AUROC of 0.762 and exhibited a good specificity of 83.9%

for a cutoff value of 0.012. The combination of CypA and normalized uNGAL showed the highest AUC of 0.848 (95% CI, 0.788–0.896).

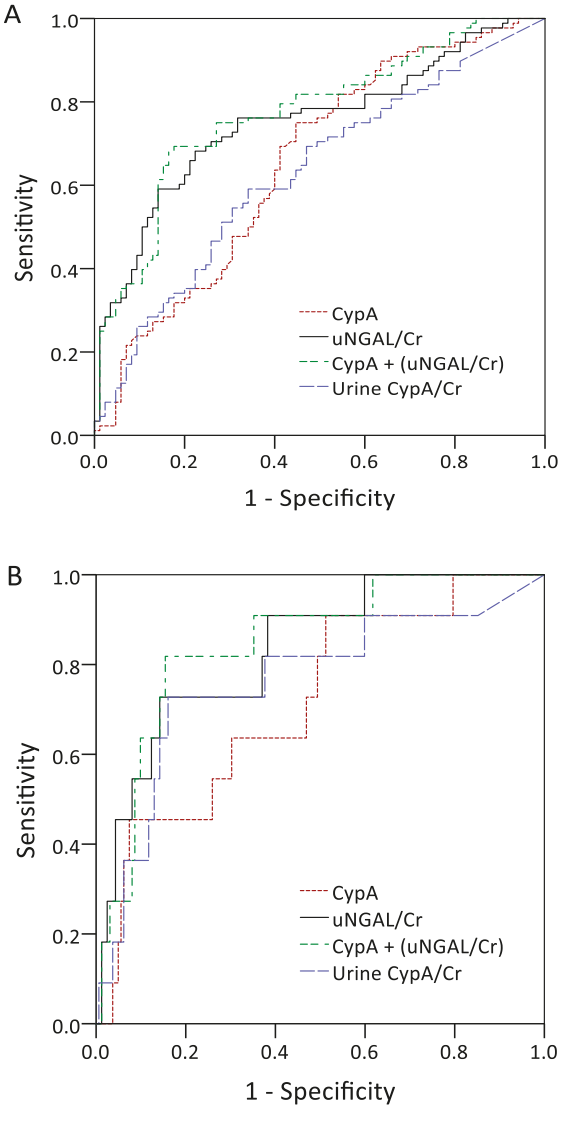

Figure 2. *Cont.*

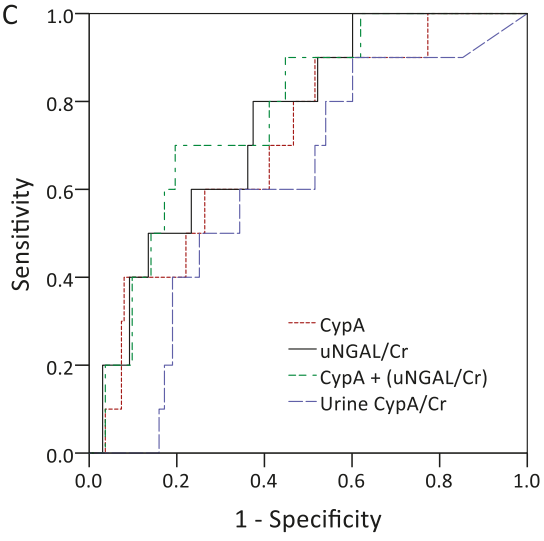

Figure 2. Area under the curves for serum CypA, urine NGAL normalized by urine Cr, serum CypA plus urine NGAL normalized by urine Cr, and urine CypA normalized by urine Cr in discriminating acute kidney injury (**A**), dialysis-requiring acute kidney injury (**B**), and 90-day mortality (**C**). Abbreviations: CypA, cyclophilin A; NGAL, neutrophil gelatinase-associated lipocalin; Cr, creatinine.

As for the detection of AKI, CypA exhibited a sensitivity of 76.1% and a specificity of 58.5% for a threshold value of 4.36 ng/mL, whereas normalized uNGAL exhibited a poor sensitivity of 68.5% and a specificity of 76.6% for a cut-off value of 0.85 (Table 3). However, there was no significant difference in the 90-day survival rates between the subgroups of high/low serum CypA and normalized uNGAL.

Table 3. Diagnostic property of markers in discriminating outcomes.

Outcome/Marker	AUC (95% CI)	Cut-Off #	Sensitivity (95% CI)	Specificity (95% CI)
Acute kidney injury				
CypA	68.9 (61.8–75.5)	>4.36	76.1 (66.1–84.4)	58.5 (47.9–68.6)
Urine NGAL/Cr	75.2 (68.4–81.2)	>0.85	68.5 (58.0–77.8)	76.6 (66.7–84.7)
CypA + (urine NGAL/Cr)	78.7 (72.1–84.3)	NA	NA	NA
Urine CypA/Cr	63.0 (55.3–70.2)	>0.003	59.1 (48.1–69.5)	65.9 (54.8–75.8)
Dialysis-requiring AKI				
CypA	73.8 (66.8–79.9)	>4.84	91.7 (61.5–99.8)	50.0 (42.3–57.7)
Urine NGAL/Cr	83.5 (77.3–88.5)	>3.09	75.0 (42.8–94.5)	85.1 (78.9–90.0)
CypA + (urine NGAL/Cr)	84.8 (78.8–89.6)	NA	NA	NA
Urine CypA/Cr	76.2 (69.2–82.3)	>0.012	72.7 (39.0–94.0)	83.9 (77.4–89.2)
90-day mortality				
CypA	67.0 (59.7–73.7)	>4.84	83.3 (51.6–97.9)	49.4 (41.8–57.1)
Urine NGAL/Cr	75.4 (68.5–81.4)	>1.12	83.3 (51.6–97.9)	62.6 (55.0–69.8)
CypA + (urine NGAL/Cr)	73.1 (66.2–79.4)	NA	NA	NA
Urine CypA/Cr	61.1 (53.4–68.4)	>0.0016	90.0 (55.5–99.7)	39.9 (32.3–47.8)

AUC, area under the curve; CI, confidence interval; CypA, cyclophilin A; NGAL, neutrophil gelatinase-associated lipocalin; Cr, creatinine; AKI, acute kidney injury; NA, not applicable; #, number by Youden index.

4. Discussion

The development of AKI is associated with unfavorable outcomes and high mortality in patients undergoing cardiac surgery. Because renal dysfunction is known as a well-established predictor of all-cause mortality in cardiac surgery, biomarkers for the early detection of AKI after cardiac

surgery would be valuable for clinical practices, such as decision making, patient counseling, and optimization of post-operative care [21]. NGAL has been the most popular biomarker for the early identification of AKI following cardiac surgery. However, compared with the excellent discrimination reported in pediatric patients, studies of urinary NGAL in adult patients reported only moderate discrimination, with an AUROC of 0.72 (95% confidence interval, 0.66–0.79) [22]. Thus, new biomarkers with better performance are urgently needed. Strategies combining biomarkers with different types of pathophysiological relevance may also be beneficial in risk stratification. In this study, we found that both serum CypA and normalized urine CypA were elevated in the patients who developed AKI after sample collection. As we have shown, serum CypA is suitable for the early detection of AKI in patients undergoing cardiac surgery, with a good sensitivity and acceptable discriminative power comparable to those of normalized uNGAL. A combination of serum CypA and normalized uNGAL enhanced the overall performance for predicting the development of AKI and dialysis-requiring AKI, with AUROC values of 0.787 and 0.848, respectively.

Cyclophilins are a family of ubiquitous proteins that are evolutionarily well conserved and present in all prokaryotes and eukaryotes [23]. The most abundant member of this family is CypA, which accounts for about 0.1–0.6% of total cytosolic proteins [24]. Although CypA is present intracellularly and was originally identified as the primary cytosolic binding protein of the immunosuppressive drug cyclosporin A, it has been found to be secreted from cells in response to inflammatory stimuli, such as hypoxia, infection, and oxidative stress [25–28]. Secreted CypA has been demonstrated to be a damage-associated molecular pattern molecule that has a potent chemotactic effect on leukocytes, and, in turn, perpetuates the inflammatory response [15,27]. Moreover, high levels of extracellular CypA have also been detected in several different human inflammatory diseases, such as rheumatoid arthritis [29,30] and sepsis [17,31], and found to be correlated with the severity of those diseases. Our data are in accordance with these findings. The distinctive characteristics of cardiac surgery, including aortic clamping and cardiopulmonary bypass, which induce a systemic inflammatory response lead to the development of AKI [32]. Notably, our study also revealed that urine CypA is elevated in patients with AKI. Because CypA is an 18-kDa protein that theoretically can be freely filtered by renal glomeruli, higher levels of urine CypA in patients with AKI may just reflect an increase in serum CypA levels. An alternative explanation is that the actual source of urine CypA may be the injured renal tubular cells. Studies have demonstrated that CypA is highly expressed in the kidney, especially in the proximal tubular epithelial cells [33]. Tsai et al. also demonstrated that CypA is released by human proximal tubular cells in a dose-dependent manner after exposure to free radical treatment [18]. However, our study showed that normalized urine CypA only exhibited modest discrimination ability for predicting AKI, with an AUROC of 0.63. In addition, although normalized urine CypA exhibited a good specificity of 83.9% in predicting dialysis-requiring AKI for a cutoff value of 0.012, its overall performance was not better than that of the well-known marker normalized urine NGAL. Intriguingly, previous studies reported that not only urine soluble components, but human urine exosomes, contain CypA [15]. Whether the exosomal part of urine CypA can exhibit better discrimination power than soluble part of urine CypA alone in stratifying AKI risk needs further investigation.

Our study found that serum CypA levels were higher in the patients who subsequently developed AKI than in those who did not, but the levels were not significantly different among the AKI KDIGO stages 1–3. This might be explained by the notion that the AKI severity is more associated with changes in the serum CypA level over time than with the level at a single time. Indeed, some of the elevation in serum CypA levels in our patients might just reflect their underlying cardiac diseases. Extracellular CypA was previously found to contribute to cardiovascular diseases as a novel player not only through its proinflammatory actions but through its proatherogenic properties [10,11,34]. Yan et al. reported that serum CypA concentrations in patients with unstable angina and acute myocardial infarction were significantly higher than those in patients with stable angina and controls [12]. Serum CypA levels were also previously found to be associated with the clinical outcomes of coronary

artery disease [35], ST-elevated myocardial infarction [36], and heart failure [37]. In addition to coronary artery disease, extracellular CypA was identified as a mediator in abdominal aortic aneurysm (AAA) progression. In human AAA lesions, CypA was highly expressed, especially in the area that expresses active metalloproteinase 2 (MMP-2) [14]. Using human AAA-derived vascular smooth muscle cells, angiotensin II induces the release of CypA and enhances vascular inflammation by activating MMP activity, which was significantly reduced by treatment with the CypA inhibitor. Based on these evidences, we hypothesized that increased serum CypA levels may partly be a consequence of underlying cardiovascular diseases, and that patients with more severe cardiovascular diseases might have hemodynamic instability, leading to higher baseline renal dysfunction. Further studies using preoperative serum CypA levels or serum CypA dynamics are needed to help clarify the relationship between CypA and the outcomes of cardiac surgery.

Our study showed that normalized uNGAL best predicted the development of AKI, and the level of normalized uNGAL increased along with the more severe AKI stage. This finding is consistent with previous reports that uNGAL is an early predictive biomarker of AKI following cardiac surgery [38,39]. NGAL was originally identified from neutrophils as a shuttle for iron transport, and its upregulation has been demonstrated in the proximal renal tubule after exposure to harmful insults, such as ischemia [40]. Consequently, increased level of NGAL is rapidly detectable in the urine before SCr is elevated, presumably resulting from acute tubular damage. Although the discrimination ability of CypA levels regarding the development of AKI was not superior to that of normalized uNGAL levels, our study found that normalized uNGAL had only modest sensitivity in predicting AKI and dialysis-requiring AKI. Meanwhile, we further found that the combination of these two biomarkers provides the most accurate predictive ability in these patients, suggesting that their combination is a reasonable strategy to improve the diagnostic performance of biomarkers. Our study also found a moderate discrimination ability of normalized urine CypA when predicting dialysis-requiring AKI, with comparable sensitivity and specificity ability when compared to the well-known marker normalized uNGAL. However, this study only considered AKI identified within a 7-day period; thus, studies focusing on longer-term outcomes, such as acute kidney disease [41], are warranted to clarify the potential pathogenic role of serum CypA or urine CypA in cardiac surgery-related kidney injury.

This study has several limitations. First, only one measurement of the CypA and NGAL levels was used in this cross-sectional study to predict the development of AKI. Repeated measurements to detect persistent or secondary kidney damage may improve the predictive ability. Second, the roles and expression of CypA in AKI require further investigation. Using animal models to evaluate the origin of CypA in urine may help determine the pathogenic role of urine CypA. Third, this research was conducted on a heterogeneous population with different cardiovascular diseases, and no subgroup analysis was conducted to explore the relationships between a specific disease type and the biomarkers. We also did not analyze the relationships between CypA levels and medications that may interfere with CypA levels. Finally, given the small sample size and observational design, additional prospective trials are warranted to explore the role of CypA in different etiologies of AKI.

In summary, both serum CypA and normalized uNGAL are suitable for the early detection of AKI in patients undergoing cardiac surgery, as both have acceptable discriminative power. Moreover, the combination of these two markers provides the highest AUROC and could serve as a new non-invasive test for use in clinical applications to differentiate AKI and RRT, potentially shortening the time to the initiation of appropriate therapy. Relatedly, the careful consideration of the appropriate medication, choice of therapy, and early intervention in patients exhibiting increased biomarker levels may improve AKI outcomes.

Author Contributions: C.-C.L. and C.-H.C. made substantial contribution to conception and design of the study. Y.-L.C., G.K. and S.-W.C. assisted in analysis and interpretation of the data. Y.-J.L. and Y.-T.C. assisted in laboratory analysis and interpretation of results. C.-C.L. and C.-H.C. wrote the manuscript and prepared the figures. C.-H.C., Y.-J.L. and Y.-C.T. supervised the study. All authors have read and agreed to the published version of the manuscript.

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References

1. Hobson, C.E.; Yavas, S.; Segal, M.S.; Schold, J.D.; Tribble, C.G.; Layon, A.J.; Bihorac, A. Acute Kidney Injury Is Associated With Increased Long-Term Mortality After Cardiothoracic Surgery. *Circulation* **2009**, *119*, 2444–2453. [CrossRef] [PubMed]
2. Rydén, L.; Ahnve, S.; Bell, M.; Hammar, N.; Ivert, T.; Holzmann, M.J. Acute kidney injury following coronary artery bypass grafting: Early mortality and postoperative complications. *Scand. Cardiovasc. J.* **2012**, *46*, 114–120. [CrossRef] [PubMed]
3. Chertow, G.M.; Levy, E.M.; Hammermeister, K.E.; Grover, F.; Daley, J. Independent Association between Acute Renal Failure and Mortality following Cardiac Surgery. *Am. J. Med.* **1998**, *104*, 343–348. [CrossRef]
4. Zanardo, G.; Michielon, P.; Paccagnella, A.; Rosi, P.; Caló, M.; Salandin, V.; Da Ros, A.; Michieletto, F.; Simini, G. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J. Thorac. Cardiovasc. Surg.* **1994**, *107*, 1489–1495. [CrossRef]
5. Mangano, C.M.; Diamondstone, L.S.; Ramsay, J.G.; Aggarwal, A.; Herskowitz, A.; Mangano, D.T. Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann. Intern. Med.* **1998**, *128*, 194–203. [CrossRef] [PubMed]
6. Liotta, M.; Olsson, D.; Sartipy, U.; Holzmann, M.J. Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting. *Am. J. Cardiol.* **2014**, *113*, 70–75. [CrossRef]
7. Olsson, D.; Sartipy, U.; Braunschweig, F.; Holzmann, M.J. Acute Kidney Injury Following Coronary Artery Bypass Surgery and Long-term Risk of Heart Failure. *Circ. Heart Fail.* **2013**, *6*, 83–90. [CrossRef]
8. Rydén, L.; Ahnve, S.; Bell, M.; Hammar, N.; Ivert, T.; Sartipy, U.; Holzmann, M.J. Acute kidney injury after coronary artery bypass grafting and long-term risk of myocardial infarction and death. *Int. J. Cardiol.* **2014**, *172*, 190–195. [CrossRef]
9. Pickering, J.W.; James, M.T.; Palmer, S.C. Acute Kidney Injury and Prognosis After Cardiopulmonary Bypass: A Meta-analysis of Cohort Studies. *Am. J. Kidney Dis.* **2015**, *65*, 283–293. [CrossRef]
10. Nigro, P.; Satoh, K.; O'Dell, M.R.; Soe, N.N.; Cui, Z.; Mohan, A.; Abe, J.-I.; Alexis, J.D.; Sparks, J.D.; Berk, B.C. Cyclophilin A is an inflammatory mediator that promotes atherosclerosis in apolipoprotein E–deficient mice. *J. Exp. Med.* **2011**, *208*, 53–66. [CrossRef]
11. Rezzani, R.; Favero, G.; Stacchiotti, A.; Rodella, L.F. Endothelial and vascular smooth muscle cell dysfunction mediated by cyclophylin A and the atheroprotective effects of melatonin. *Life Sci.* **2013**, *92*, 875–882. [CrossRef] [PubMed]
12. Yan, J.; Zang, X.; Chen, R.; Yuan, W.; Gong, J.; Wang, C.; Li, Y. The clinical implications of increased cyclophilin A levels in patients with acute coronary syndromes. *Clin. Chim. Acta* **2012**, *413*, 691–695. [CrossRef] [PubMed]
13. Satoh, K.; Fukumoto, Y.; Sugimura, K.; Miura, Y.; Aoki, T.; Nochioka, K.; Tatebe, S.; Miyamichi-Yamamoto, S.; Shimizu, T.; Osaki, S.; et al. Plasma Cyclophilin A Is a Novel Biomarker for Coronary Artery Disease. *Circ. J.* **2013**, *77*, 447–455. [CrossRef] [PubMed]
14. Satoh, K.; Nigro, P.; Matoba, T.; O'Dell, M.R.; Cui, Z.; Shi, X.; Mohan, A.; Yan, C.; Abe, J.; Illig, K.A.; et al. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. *Nat. Med.* **2009**, *15*, 649–656. [CrossRef] [PubMed]
15. Dear, J.W.; Simpson, K.J.; Nicolai, M.P.; Catterson, J.H.; Street, J.; Huizinga, T.; Craig, D.G.; Dhaliwal, K.; Webb, S.; Bateman, D.N.; et al. Cyclophilin A is a damage-associated molecular pattern molecule that mediates acetaminophen-induced liver injury. *J. Immunol.* **2011**, *187*, 3347–3352. [CrossRef]
16. Seizer, P.; Geisler, T.; Bigalke, B.; Schneider, M.; Klingel, K.; Kandolf, R.; Stellos, K.; Schreieck, J.; Gawaz, M.; May, A.E. EMMPRIN and its ligand cyclophilin A as novel diagnostic markers in inflammatory cardiomyopathy. *Int. J. Cardiol.* **2013**, *163*, 299–304. [CrossRef]

17. Dear, J.W.; Leelahavanichkul, A.; Aponte, A.; Hu, X.; Constant, S.L.; Hewitt, S.M.; Yuen, P.S.; Star, R.A. Liver proteomics for therapeutic drug discovery: Inhibition of the cyclophilin receptor CD147 attenuates sepsis-induced acute renal failure. *Crit. Care Med.* **2007**, *35*, 2319–2328. [CrossRef]
18. Tsai, S.F.; Su, C.W.; Wu, M.J.; Chen, C.H.; Fu, C.P.; Liu, C.S.; Hsieh, M. Urinary Cyclophilin A as a New Marker for Diabetic Nephropathy: A Cross-Sectional Analysis of Diabetes Mellitus. *Medicine* **2015**, *94*, e1802. [CrossRef]
19. Palevsky, P.M.; Liu, K.D.; Brophy, P.D.; Chawla, L.S.; Parikh, C.R.; Thakar, C.V.; Tolwani, A.J.; Waikar, S.S.; Weisbord, S.D. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Am. J. Kidney Dis.* **2013**, *61*, 649–672. [CrossRef]
20. Nashef, S.A.M.; Roques, F.; Sharples, L.D.; Nilsson, J.; Smith, C.; Goldstone, A.R.; Lockowandt, U. EuroSCORE II. *Eur. J. Cardio-Thorac. Surg.* **2012**, *41*, 734–745. [CrossRef]
21. Lee, C.C.; Chang, C.H.; Chen, S.W.; Fan, P.C.; Chang, S.W.; Chen, Y.T.; Nan, Y.Y.; Lin, P.J.; Tsai, F.C. Preoperative risk assessment improves biomarker detection for predicting acute kidney injury after cardiac surgery. *PLoS ONE* **2018**, *13*, e0203447. [CrossRef] [PubMed]
22. Ho, J.; Tangri, N.; Komenda, P.; Kaushal, A.; Sood, M.; Brar, R.; Gill, K.; Walker, S.; MacDonald, K.; Hiebert, B.M.; et al. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. *Am. J. Kidney Dis.* **2015**, *66*, 993–1005. [CrossRef] [PubMed]
23. Wang, P.; Heitman, J. The cyclophilins. *Genome Biol.* **2005**, *6*. [CrossRef]
24. Dornan, J.; Taylor, P.; Walkinshaw, M.D. Structures of immunophilins and their ligand complexes. *Curr. Top. Med. Chem.* **2003**, *3*, 1392–1409. [CrossRef] [PubMed]
25. Handschumacher, R.E.; Harding, M.W.; Rice, J.; Drugge, R.J.; Speicher, D.W. Cyclophilin: A specific cytosolic binding protein for cyclosporin A. *Science* **1984**, *226*, 544–547. [CrossRef] [PubMed]
26. Jin, Z.-G.; Melaragno, M.G.; Liao, D.-F.; Yan, C.; Haendeler, J.; Suh, Y.-A.; Lambeth, J.D.; Berk, B.C. Cyclophilin A Is a Secreted Growth Factor Induced by Oxidative Stress. *Circ. Res.* **2000**, *87*, 789–796. [CrossRef]
27. Sherry, B.; Yarlett, N.; Strupp, A.; Cerami, A. Identification of cyclophilin as a proinflammatory secretory product of lipopolysaccharide-activated macrophages. 1992, 89, 3511–3515. *Proc. Natl. Acad. Sci. USA*.
28. Suzuki, J.; Jin, Z.-G.; Meoli, D.F.; Matoba, T.; Berk, B.C. Cyclophilin A Is Secreted by a Vesicular Pathway in Vascular Smooth Muscle Cells. *Circ. Res.* **2006**, *98*, 811–817. [CrossRef]
29. Billich, A.; Winkler, G.; Aschauer, H.; Rot, A.; Peichl, P. Presence of cyclophilin A in synovial fluids of patients with rheumatoid arthritis. *J. Exp. Med.* **1997**, *185*, 975–980. [CrossRef]
30. Wang, L.; Wang, C.H.; Jia, J.F.; Ma, X.K.; Li, Y.; Zhu, H.B.; Tang, H.; Chen, Z.N.; Zhu, P. Contribution of cyclophilin A to the regulation of inflammatory processes in rheumatoid arthritis. *J. Clin. Immunol.* **2010**, *30*, 24–33. [CrossRef]
31. Tegeder, I.; Schumacher, A.; John, S.; Geiger, H.; Geisslinger, G.; Bang, H.; Brune, K. Elevated serum cyclophilin levels in patients with severe sepsis. *J. Clin. Immunol.* **1997**, *17*, 380–386. [CrossRef] [PubMed]
32. O'Neal, J.B.; Shaw, A.D.; Billings, F.T. Acute kidney injury following cardiac surgery: Current understanding and future directions. *Crit. Care* **2016**, *20*, 187. [CrossRef] [PubMed]
33. Demeule, M.; Laplante, A.; Sepehr-Arae, A.; Murphy, G.M.; Wenger, R.M.; Beliveau, R. Association of cyclophilin A with renal brush border membranes: Redistribution by cyclosporine A. *Kidney Int.* **2000**, *57*, 1590–1598. [CrossRef] [PubMed]
34. Seizer, P.; Schönberger, T.; Schött, M.; Lang, M.R.; Langer, H.F.; Bigalke, B.; Krämer, B.F.; Borst, O.; Daub, K.; Heidenreich, O.; et al. EMMPRIN and its ligand cyclophilin A regulate MT1-MMP, MMP-9 and M-CSF during foam cell formation. *Atherosclerosis* **2010**, *209*, 51–57. [CrossRef] [PubMed]
35. Ohtsuki, T.; Satoh, K.; Omura, J.; Kikuchi, N.; Satoh, T.; Kurosawa, R.; Nogi, M.; Sunamura, S.; Yaoita, N.; Aoki, T.; et al. Prognostic Impacts of Plasma Levels of Cyclophilin A in Patients with Coronary Artery Disease. *Arter. Thromb. Vasc. Biol.* **2017**, *37*, 685–693. [CrossRef]
36. Huang, C.-H.; Chang, C.-C.; Kuo, C.-L.; Huang, C.-S.; Lin, C.-S.; Liu, C.-S. Decrease in Plasma Cyclophilin A Concentration at 1 Month after Myocardial Infarction Predicts Better Left Ventricular Performance and Synchronicity at 6 Months: A Pilot Study in Patients with ST Elevation Myocardial Infarction. *Int. J. Biol. Sci.* **2015**, *11*, 38–47. [CrossRef]

37. Zuern, C.S.; Müller, K.A.L.; Seizer, P.; Geisler, T.; Banya, W.; Klingel, K.; Kandolf, R.; Bauer, A.; Gawaz, M.; May, A.E. Cyclophilin A predicts clinical outcome in patients with congestive heart failure undergoing endomyocardial biopsy. *Eur. J. Heart Fail.* **2013**, *15*, 176–184. [CrossRef]
38. Bennett, M.; Dent, C.L.; Ma, Q.; Dastrala, S.; Grenier, F.; Workman, R.; Syed, H.; Ali, S.; Barasch, J.; Devarajan, P. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: A prospective study. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 665–673. [CrossRef]
39. Parikh, C.R.; Coca, S.G.; Thiessen-Philbrook, H.; Shlipak, M.G.; Koyner, J.L.; Wang, Z.; Edelstein, C.L.; Devarajan, P.; Patel, U.D.; Zappitelli, M.; et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J. Am. Soc. Nephrol.* **2011**, *22*, 1748–1757. [CrossRef]
40. Paragas, N.; Qiu, A.; Zhang, Q.; Samstein, B.; Deng, S.X.; Schmidt-Ott, K.M.; Viltard, M.; Yu, W.; Forster, C.S.; Gong, G.; et al. The Ngal reporter mouse detects the response of the kidney to injury in real time. *Nat. Med.* **2011**, *17*, 216–222. [CrossRef]
41. Chawla, L.S.; Bellomo, R.; Bihorac, A.; Goldstein, S.L.; Siew, E.D.; Bagshaw, S.M.; Bittleman, D.; Cruz, D.; Endre, Z.; Fitzgerald, R.L.; et al. Acute kidney disease and renal recovery: Consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat. Rev. Nephrol.* **2017**, *13*, 241–257. [CrossRef] [PubMed]

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Derivation and Validation of Machine Learning Approaches to Predict Acute Kidney Injury after Cardiac Surgery

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Abstract: Machine learning approaches were introduced for better or comparable predictive ability than statistical analysis to predict postoperative outcomes. We sought to compare the performance of machine learning approaches with that of logistic regression analysis to predict acute kidney injury after cardiac surgery. We retrospectively reviewed 2010 patients who underwent open heart surgery and thoracic aortic surgery. Baseline medical condition, intraoperative anesthesia, and surgery-related data were obtained. The primary outcome was postoperative acute kidney injury (AKI) defined according to the Kidney Disease Improving Global Outcomes criteria. The following machine learning techniques were used: decision tree, random forest, extreme gradient boosting, support vector machine, neural network classifier, and deep learning. The performance of these techniques was compared with that of logistic regression analysis regarding the area under the receiver-operating characteristic curve (AUC). During the first postoperative week, AKI occurred in 770 patients (38.3%). The best performance regarding AUC was achieved by the gradient boosting machine to predict the AKI of all stages (0.78, 95% confidence interval (CI) 0.75–0.80) or stage 2 or 3 AKI. The AUC of logistic regression analysis was 0.69 (95% CI 0.66–0.72). Decision tree, random forest, and support vector machine showed similar performance to logistic regression. In our comprehensive comparison of machine learning approaches with logistic regression analysis, gradient boosting technique showed the best performance with the highest AUC and lower error rate. We developed an Internet–based risk estimator which could be used for real-time processing of patient data to estimate the risk of AKI at the end of surgery.

Keywords: acute kidney injury; cardiovascular surgery; machine learning

1. Introduction

Generalized linear models, such as logistic regression analysis, have been used to predict postoperative morbidity. However, the logistic regression model requires the statistical assumption of a linear relationship between the covariates and the risk of morbidity. Furthermore, the limitation of overfitting and multicollinearity of regression analysis preclude the analysis of many explanatory variables. These limitations have restricted the analysis model to select a small set of variables that are known to be clinically relevant.

Recently, the machine learning technique has been applied in areas of medicine, including detecting a specific clinical finding on medical imaging and has shown excellent performance with high sensitivity and specificity [1,2]. Additionally, there were reports about the use of machine learning

techniques to predict postoperative clinical outcomes including specific morbidity or in-hospital mortality [3–5]. Machine learning techniques showed better performance and low error rates to predict clinical outcomes compared to the logistic regression or Cox regression analysis. However, there was also a study reporting that the machine learning technique did not show a better performance that a previous risk prediction model for in-hospital mortality [5].

Postoperative acute kidney injury (AKI) after cardiovascular surgery is known to be a relevant complication because it is associated with increased long-term mortality and development of chronic kidney disease [6–8]. To find a risk factor and develop a risk prediction model, previous studies reported the results of multivariable logistic regression analysis [9–17]. Although many risk factors and risk scores were reported by multivariable logistic regression analysis, their performance in terms of the area under the receiver operating characteristic curves (AUC) was about 0.70 to 0.83 with room for further improvement [9,10,13,14,18]. Furthermore, previous prediction models may have included an insufficient number of perioperative variables owing to overfitting and multi-collinearity of the logistic regression analysis. Additionally, the potential non-linear relationship between the covariates and the risk of outcome cannot be considered. However, machine learning techniques are relatively free of these limitations of statistical analysis and may demonstrate better performance than that of logistic regression analysis.

Therefore, we attempted to directly compare the performance and error rate of prediction with machine learning techniques with that of prediction with multivariable logistic regression analysis. We hypothesized that prediction with machine learning techniques involving many perioperative variables may demonstrate better performance and low error rate than that of logistic regression analysis. We evaluated as many machine learning techniques as possible that are currently available in the statistical software package R (version 3.4.4., R Development Core Team, Vienna, Austria) because the R software package is easily and freely accessible to investigators and many packages for machine learning approaches are currently available.

2. Materials and Methods

2.1. Study Design

This retrospective observational study was approved by the institutional review board of Seoul National University Hospital (1805-170-948). We retrospectively reviewed the electronic medical records of 2010 consecutive patients who underwent coronary artery surgery, valve replacement, or thoracic aortic surgery at our institution between 2008 and 2015. The need for informed consent was waived because of the retrospective design of the study.

2.2. Anesthesia, Surgical Technique

General anesthesia was maintained using a target-controlled infusion of propofol and remifentanil, or inhalational anesthetics during the study period. Standard monitoring devices were applied, including pulmonary artery catheters (Swan-Ganz CCOmbo CCO/SvO2™; Edward Lifesciences LLC, Irvine, CA, USA), in all patients.

2.3. Data Collection

On the basis of previous studies, data related to demographic or perioperative variables known to be related to postoperative renal dysfunction were collected (Table 1) [6,9–17,19–23]. The following perioperative clinical variables were collected: patient demographics, medical history, medication history, baseline laboratory finding, surgery type, operation time, type of anesthesia, intraoperative fluid and colloid administration, intraoperative transfusion amount, and intraoperative hemodynamic variables.

Table 1. Patient characteristics and postoperative renal function in the dataset.

Variables	All	Training Set	Test Set	*p*-Value
Patient population, *n*	2010	1005	1005	
Demographic data				
Age (years)	64 (56–71)	64 (56–71)	64 (55–71)	0.884
Female (*n*)	553 (27.5)	279 (27.8)	274 (27.3)	0.803
Body-mass index (kg/m^2)	23.8 (21.6–25.9)	23.9 (21.7–25.9)	23.7 (21.5–25.9)	0.563
Surgery type				
Coronary artery bypass (*n*)	911 (45.3)	473 (47.1)	438 (43.6)	0.117
Valvular heart surgery (*n*)	1052 (52.3)	503 (50.0)	549 (54.6)	0.060
Thoracic aortic surgery (*n*)	47 (2.3)	29 (2.9)	18 (1.8)	0.104
Emergency (*n*)	51 (2.5)	26 (2.6)	25 (2.5)	0.887
Previous cardiac surgery (*n*)	149 (7.4)	75 (7.5)	74 (7.4)	0.932
Medical history				
Hypertension (*n*)	1057 (52.6)	538 (53.5)	519 (51.6)	0.396
Diabetes mellitus (*n*)	588 (29.3)	302 (30.0)	286 (28.5)	0.433
Three vessel disease (*n*)	602 (30.0)	306 (30.4)	296 (29.5)	0.626
Previous coronary stent insertion (*n*)	235 (11.7)	118 (11.7)	117 (11.6)	0.945
Cerebrovascular accident (*n*)	228 (11.3)	101 (10.0)	127 (12.6)	0.078
COPD (*n*)	100 (5.0)	49 (4.9)	51 (5.1)	0.837
Pulmonary hypertension (*n*)	129 (6.4)	60 (6.0)	69 (6.9)	0.413
Chronic kidney disease (*n*)	121 (6.0)	57 (5.7)	64 (6.4)	0.512
Preoperative Medication				
ACEi (*n*)	114 (5.7)	58 (5.8)	56 (5.6)	0.847
ARB (*n*)	249 (12.4)	122 (12.1)	127 (12.6)	0.735
β-blocker (*n*)	289 (19.4)	199 (19.8)	190 (18.9)	0.611
Diuretics (*n*)	297 (14.8)	133 (13.2)	164 (16.3)	0.059
Calcium channel blocker (*n*)	287 (14.3)	151 (15.0)	136 (13.5)	0.339
Statins (*n*)	506 (25.2)	255 (25.4)	251 (25.0)	0.837
Aspirin (*n*)	957 (47.6)	498 (49.6)	459 (45.7)	0.090
Baseline laboratory findings				
Preoperative LVEF (%)	58 (52–63)	58 (53–63)	57 (52–63)	0.427
Hematocrit (%)	38 (34–42)	38 (34–42)	38 (34–42)	0.844
Serum creatinine (mg/dL)	0.94 (0.80–1.12)	0.93 (0.80–1.10)	0.94 (0.80–1.13)	0.613
Serum Albumin (g/dL)	4.1 (3.8–4.3)	4.1 (3.9–4.3)	4.1 (3.8–4.3)	0.183
Serum uric acid (mg/dL)	4.6 (3.7–5.6)	4.6 (3.7–5.7)	4.5 (3.6–5.5)	0.190
Blood glucose (mg/dL)	115 (96–146)	116 (96–146)	113 (96–147)	0.500
Surgery and anaesthesia details				
Operation time (h)	6.25 (5.33–7.25)	6.25 (5.41–7.27)	6.25 (5.33–7.24)	0.654
Anesthesia time (h)	7.50 (6.25–8.50)	7.50 (6.50–8.50)	7.50 (6.50–8.42)	0.608
Total intravenous anesthesia (*n*)	1858 (92.4)	937 (93.2)	921 (91.6)	0.206
Inhalational anesthesia (*n*)	152 (7.6)	68 (6.8)	84 (8.4)	0.206
Intraoperative crystalloid infusion (L)	2150 (1150–3000)	2200 (1100–3100)	2150 (1200–2950)	0.656
Intraoperative colloid use (mL)	900 (350–1500)	1000 (350–1550)	800 (350–1500)	0.067
pRBC transfusion during surgery (units)	2 (0–3)	2 (0–3)	2 (0–3)	0.725
FFP transfusion during surgery (units)	0 (0–3)	0 (0–3)	0 (0–3)	0.589
Intraoperative mean arterial pressure (mmHg)	72 (67–78)	72 (67–78)	72 (67–78)	0.974
Intraoperative mean cardiac index (L/min)	2.3 (2.1–2.7)	2.3 (2.1–2.7)	2.3 (2.1–2.7)	0.257
Intraoperative mean SvO_2 (%)	73 (69–76)	73 (69–76)	73 (68–76)	0.207
Intraoperative diuretics use (*n*)	204 (10.1)	91 (9.1)	113 (11.2)	0.107
Postoperative renal function				
AKI according to KDIGO criteria (*n*)				0.596
Stage 1	591 (29.4)	282 (28.1)	309 (30.7)	
Stage 2	114 (5.7)	60 (6.0)	54 (5.4)	
Stage 3	65 (3.2)	33 (3.3)	32 (3.2)	
Hemodialysis dependent (*n*)	125 (6.2)	60 (6.0)	65 (6.5)	0.644
GFR at postoperative day one (ml/min/1.73m^2)	79 (58–94)	79 (57–95)	78 (58–94)	0.864

Data are presented as median (interquartile range) or number (%). COPD = chronic obstructive pulmonary disease, ACEi = angiotensin-converting-enzyme inhibitor, AKI = acute kidney injury, ARB = angiotensin II receptor blocker, LVEF = left ventricular ejection fraction, pRBC = packed red blood cell transfusion, FFP = fresh-frozen plasma, SvO_2 = mixed venous oxygen saturation, KDIGO = kidney disease improving global outcomes, GFR = glomerular filtration rate.

The primary outcome variable was postoperative AKI defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which was determined according to the maximal change in serum creatinine level during the first seven postoperative days [6,24]. The most recent serum creatinine level measured before surgery was used as the baseline value. The detailed diagnostic criteria are shown in Table S1. We did not use the urine output criteria because previous studies suggested that different cutoffs of oliguria may be required for AKI after surgery [25,26]. We also analyzed the stage 2 or 3 AKI as secondary outcomes because stage 1 AKI may only be transient and functional and stage 2 or 3 AKI is more strongly associated with patient mortality [27]. The prediction of severe stages of AKI would be practically more important.

2.4. Statistical Analysis

R software version 3.4.4. (R Development Core Team, Vienna, Austria) was used for our analysis. The following R packages for machine learning approaches were used: Tree, rpart, ROSE (Random Over-Sampling Examples), randomForest, DMwR (Data Mining with R), XGBoost (eXtreme Gradient Boosting), e1071, UBL (utility-based learning), Kernlab, nnet, neuralnet, and h2o. Tree, rpart, and ROSE packages with CART (Classification And Regression Tree) analysis were used for decision tree analysis; randomForest and DMwR were used for random forest; XGboost was used for extreme gradient boosting; e1071, UBL, and kernlab were used for support vector machine; nnet and neuralnet were used for neural network regression; and h2o was used for deep belief networks (Text S1). Seventy-two explanatory variables including variables in Table 1 were used to machine learning. Our sample was randomly divided into a training and test set with a ratio of 1:1. The coefficients of machine learning techniques were trained with the training set and tested with the test set. Our primary analysis attempted to compare the predictive accuracy of machine learning approaches with traditional analytic techniques for classification, and previous risk scores for AKI after cardiac surgery [9–16]. To evaluate and compare the predictive accuracy of prediction by machine learning techniques and logistic regression models, we calculated the areas under the receiver operating characteristics curve (AUCs) [28,29] and compared AUCs of all classifiers and models using De Long's method [30]. We also compared the error rate, which was defined as the sum of the number of cases with false positive and false negative divided by the size of the test set. The error rates of the logistic regression model and other previous risk scores were calculated by using a cutoff where the sum of sensitivity and specificity was maximal.

For decision tree analysis, the number of terminal nodes was determined considering the scree plot showing the relationship between the tree size and coefficient of variance. We considered several decision trees with some terminal nodes that were associated with a small coefficient of variance. The final decision tree model that is clinically acceptable was chosen. The decision tree was pruned based on cross-validated error results using the complexity parameter associated with the minimal error. The ROSE package generates a synthetic balanced dataset with both over- and under-sampling and allows strengthening of the subsequent estimation of any binary outcomes [31].

The randomForest package provided a variable importance plot which shows the relative importance of the explanatory variables according to the mean decrease in accuracy or Gini. DMwR package is a technique to improve predictive ability by increasing the number of positive cases, which is called SMOTE (Synthetic Minority Over-sampling Technique). The XGBoost provides extreme and efficient gradient boosting [32–34]. The e1071 package was used for the support vector machine. The UBL package provides an over-sampling technique of SMOTE, which was also used to handle the class imbalance in the training set for the support vector machine [35]. The parameters of the support vector machine for classification was tuned based on balance data after SMOTE. The best parameters were determined to be a gamma of 0.1 at a cost of 10. The kernlab package provided the least square support vector machine. The neuralnet package provided the neural network classification and the number of hidden layers was defined as 6 with minimal error. The h2o deep learning package was used for deep learning.

Multivariable logistic regression analysis, including the variables in Table 1, was performed to identify independent predictors used for the development of a multivariable prediction model. To avoid multicollinearity, variables that were closely correlated with each other were excluded before being entered into the multivariable analysis. Backward stepwise variable selection was conducted using cutoff of $p < 0.10$. Previous risk scores of Palomba, Wijeysundera, Mehta, Thakar, Brown, Aronson, Fortescue, and Rhamanian et al. [9–16] were also applied to our study data and their performance was also compared with logistic models of ours, as well as other machine learning techniques. As a sensitivity analysis, logistic regression analysis without stepwise variable selection was performed to evaluate the performance.

Missing data were noted in <8% of records. We imputed the missing values according to the incidence of the missing values for each predictor. If the incidence of the missing was <2%, the missing values were substituted by the mean of continuous variables and by the mode for the incidence variable. The missing values of variables with a missing ratio of >2% and <8% were replaced using multiple imputations. Multiple imputations were performed separately in the training and test dataset. Multiple imputed training and test datasets were combined for a single run of the machine learning classifiers or logistic regression analysis.

We developed a risk estimator based on our gradient boosting model [36]. This estimator calculates the risk of developing AKI after cardiac surgery and classifies the risk into three classes of low, moderate, and high risk of AKI.

3. Results

A total of 2010 cases including 911 (45.3%) coronary artery bypass and 1052 (52.3%) valve replacement surgery cases were included in our analysis. During the first seven postoperative days, AKI, as determined according to the KDIGO criteria, was observed in 770 patients (38.3%) and stage 2 or 3 AKI developed in 179 patients (8.9%). The incidence of AKI was 37.3% (375/1005) for the training set and 39.3% (395/1005) for the test set. The incidences of stage 2 or 3 AKI were 9.3% (93/1005) and 8.6% (86/1005) for training and test set, respectively. Patient demographics and surgery-related variables in both training and test set are compared in Table 1.

The error rate and AUCs of all machine techniques, logistic regression model, and risk scores to predict AKI of all stages in the test data set were compared in Table 2 and Figure 1. Extreme gradient boosting classification showed the lowest test error rate (26.0%) and the largest AUC (0.78, 95% confidence interval (CI) 0.75–0.80), which was significantly greater than AUCs of other machine learning techniques or risk scores compared ($p < 0.001$). The deep belief network classifier showed the highest test error rate (47.2%) and smallest test AUC (0.55) among all machine learning techniques compared. The error rate and AUCs to predict AKI of stage 2 or 3 in the test set were compared in Table S2. Gradient boosting classification showed lowest test error rate (8.5%) and the largest AUC (0.74). The results of multivariable logistic regression analysis with and without stepwise variable selection was shown in Table 3 and Table S3. The AUC of the multivariable logistic prediction model with stepwise variable selection was 0.69 (95% CI 0.66 to 0.72) and the model without variable selection showed similar AUC (Table 2).

Table 2. Comparison of area under receiver-operating characteristic curve among the different models.

Model	Software or R Packages	Error Rate of Test Data Set	AUC in the Test Set
Machine learning techniques			
Decision tree, CART	tree, rpart	28.9%	0.71 (0.67–0.74)
ROSE decision tree	ROSE	30.6%	0.66 (0.65–0.72)
Random forest model	randomForest	30.4%	0.68 (0.64–0.71)
Random forest SMOTE model	DMwR	33.5%	0.68 (0.65–0.71)
Gradient boosting classification	XGBoost	26.0%	0.78 (0.75–0.80) *
Support vector machine, classifier	e1071	31.4%	0.67 (0.63–0.70)
Support vector machine, SMOTE model	UBL	33.3%	0.68 (0.65–0.71)
Support vector machine, least square	Kernlab	30.2%	0.69 (0.66–0.72)
Neural network classifier	nnet	38.4%	0.64 (0.61–0.68)
Neural network classifier	neuralnet	43.9%	0.57 (0.53–0.61)
Deep belief network	h2o	47.2%	0.55 (0.51–0.59)
Risk scores from logistic regression analysis			
Logistic regression model, stepwise variable selection	R	33.6%	0.69 (0.66–0.72)
Logistic regression model, without variable selection	R	32.8%	0.70 (0.68–0.73)
AKICS score	R	43.4%	0.57 (0.53–0.60)
Wijeysundera and colleagues	R	45.2%	0.55 (0.51–0.59)
Metha and colleagues	R	45.8%	0.55 (0.52–0.59)
Thakar and colleagues	R	45.3%	0.56 (0.53–0.60)
Brown and colleagues	R	43.1%	0.58 (0.54–0.61)
Aronson and colleagues	R	43.3%	0.58 (0.51–0.62)
Fortescue and colleagues	R	44.2%	0.56 (0.52–0.60)
Rhamanian and colleagues	R	47.0%	0.55 (0.52–0.58)

Error rate was defined as sum of the number of cases with false positive and false negative divided by all test set. * Significantly greater than AUC = area under the receiver operating characteristic curve, CART = Classification And Regression Tree, ROSE = Random Over-Sampling Examples, SMOTE = Synthetic Minority Over-sampling Technique, DMwR = Data Mining with R, XGBoost = eXtreme Gradient Boosting, UBL = utility-based learning, AKICS = acute kidney injury following cardiac surgery.

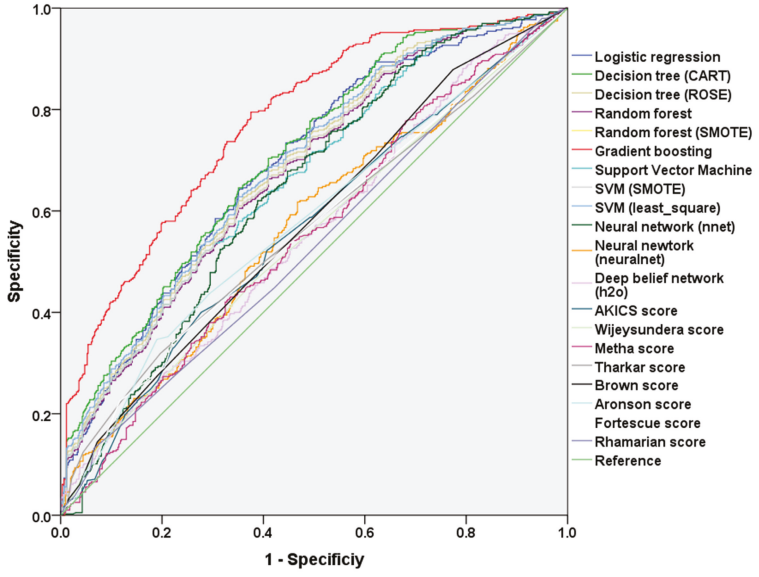

Figure 1. Comparison of AUC among the different machine learning models and logistic regression model. AKICS = acute kidney injury after cardiac surgery.

Table 3. Development of multivariable logistic regression model to predict acute kidney injury using stepwise variable selection.

Variable	Beta-Coefficient	Odds Ratio	95% CI	*p*-Value
Age per 10 year	0.128	1.14	1.04–1.61	0.004
History of hypertension	0.320	1.38	1.12–1.69	0.002
Baseline chronic kidney disease	0.907	2.48	1.62–3.78	<0.001
Preoperative E/e´ > 15	0.454	1.58	1.27–1.96	<0.001
Preoperative hematocrit, %	−0.062	0.94	0.92–0.96	<0.001
Surgery time, per 1 h	0.073	1.08	1.01–1.15	0.036
Intraoperative red blood cell transfusion, unit	0.056	1.06	1.01–1.11	0.022
Intraoperative fresh frozen plasma transfusion, unit	0.085	1.09	1.03–1.15	0.001
Intraoperative diuretics use	0.630	1.88	1.36–2.60	<0.001

Multivariable logistic regression analysis was performed using all the variables in Table 1. Stepwise backward variable selection process was used for this analysis using cutoff of *p*-value of less than 0.10. Nagelkerke's R^2 was 0.32 and Hosmer-Lemeshow goodness-of-fit test showed good calibration (chi-square = 12.1, $p = 0.231$). CI = confidence interval, E/e´ = ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus.

Simple decision tree model showing the classification of patients with and without AKI is shown in Figure 2. The importance matrix plot of gradient boosting is shown in Figure 3 and the amount of Intraoperative red blood cells transfusion and preoperative hematocrit level were ranked the first and second. The variables of importance plot of random forest model was shown in Figure S1. The same variables were ranked first and second in terms of both mean decreases in accuracy and Gini. The matrix of classification of extreme gradient boosting was visualized in Figure S2. Figure S3 shows an example of the support vector machine classification plot.

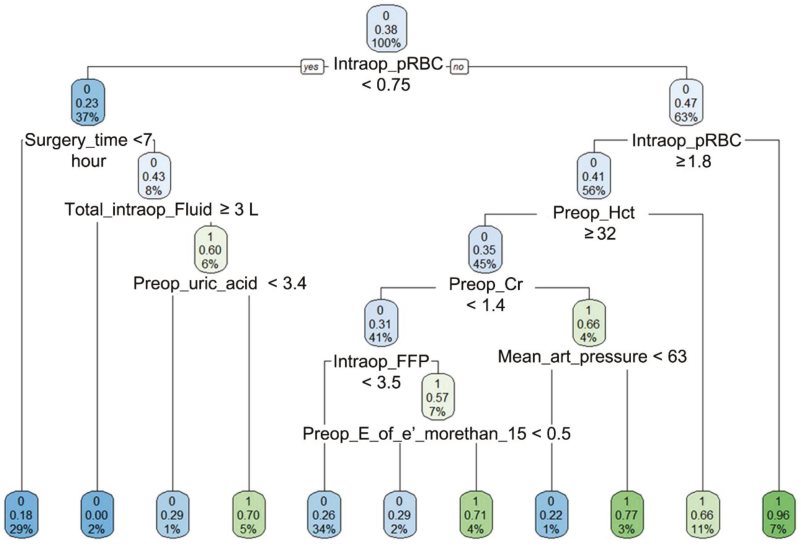

Figure 2. Simple decision tree model showing the classification of patients with (1) and without (0) acute kidney injury (AKI). The numbers with two decimals in each cell means the probability of developing AKI in each classification tree. The blue or green color becomes dense when it is more likely to develop acute kidney injury or not. The % number in the boxes denotes the percentage of patients with each discriminating variable from CART (Classification And Regression Tree) analysis. Intraop = intraoperative, preop = preoperative, pRBC = packed red blood cells, Hct = hematocrit, Cr = creatinine, FFP = fresh frozen plasma, E_or_e_prime = preoperative ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus.

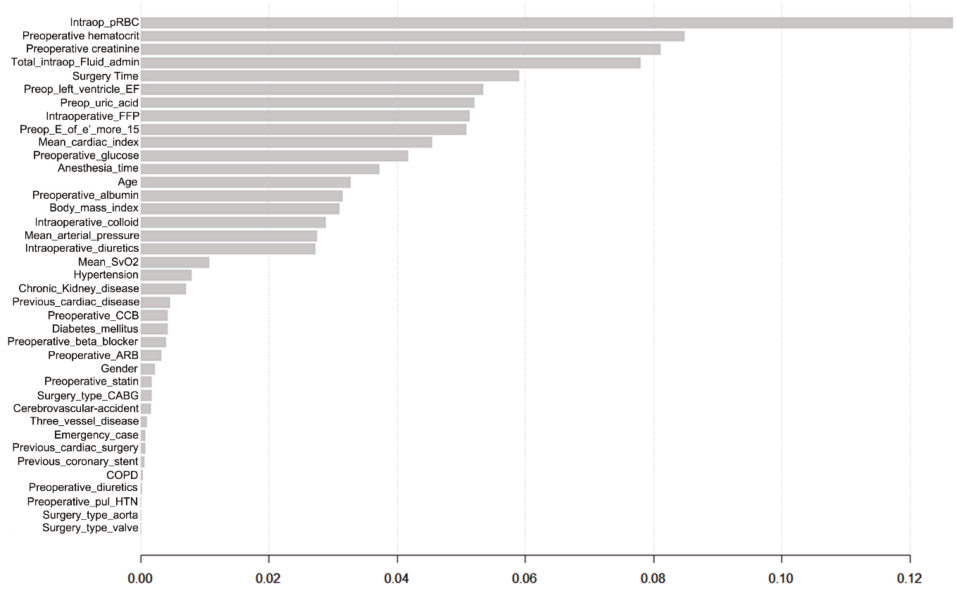

Figure 3. Importance matrix plot of the gradient boosting machine. This figure shows the importance of each covariates in the final model. ARB = angiotensin receptor blocker, BMI = body-mass index, CABG = coronary artery bypass graft, CCB = calcium channel blocker, CKD = chronic kidney disease, Cr = creatinine, CVA = history of cerebrovascular accident, EF = ejection fraction, E_or_e_prime = preoperative ratio of early transmitral flow velocity to early diastolic velocity of the mitral annulus, FFP = fresh frozen plasma, hct = hematocrit, HTN = hypertension, intraop = intraoperative, mean SvO2 = intraoperative mean mixed venous oxygen saturation, three_VD = three vessel coronary disease, preop = preoperative, pRBC = packed red blood cells.

4. Discussion

We compared the predictive accuracy of the prediction for AKI after cardiovascular surgery among the machine learning techniques, traditional statistical approach, and previous risk scoring models. We included currently available machine learning techniques, including decision tree, random forest, support vector machines, neural networks, and deep belief networks. Logistic regression analysis was used as the traditional approach. The results showed that extreme gradient boosting machine showed the lowest error rate and largest AUC among all techniques and risk scores, which was consistent for the prediction of stage 2 or 3 AKI. Extreme gradient boosting machine based prediction may result in significant improvement in the prediction of AKI after cardiac surgery. A risk estimator based on our gradient boosting model was developed for clinical use to determine the risk of AKI at the end of surgery.

Extreme gradient boosting showed the best predictive ability in our analysis [32,33,37]. While the random forest builds an ensemble of independent recursive partitioning tress of unlimited depth, extreme gradient boosting builds a sequential series of shallow trees, where each tree corrects for the residuals in the predictions made by all the previous tress (Figure S2). Gradient boosting uses techniques to reduce overfitting such as shrinkage and column resampling. After each step of boosting, the algorithm scales the newly added weights, which reduces the influence of each tree and allowing the model to learn better. Column resampling considers only a random subset of descriptors in building a given tree, which also fastens the training process by reducing the number of descriptors to consider [32]. It may be determined in further multicenter larger studies whether the better performance of boosting could be applied to data of other institutions or other surgical populations.

Decision tree analysis showed a similar performance to that of logistic regression model in our study. Decision trees are a hierarchical model that are comprised of decision rules based on the optimal feature cutoff values. It recursively classifies independent variables into different small groups based on the Gini impurity measure or entropy, while logistic regression analysis analyzes the interaction of included variables [38–40]. The odds ratio of a specific risk factor in a logistic regression model is applied to all study population rather than a single subgroup, while each branch of the decision tree may have different covariates from another branch. Variable selection in the process of decision tree is not based on probabilistic methods, which may result in overestimation of the importance of explanatory variables or may miss other potential confounders [41]. Decision trees can improve the predictive ability achieved by logistic regression models under certain circumstances. With sufficiently many terminal nodes with a low coefficient of variance, the decision tree model enables the detection of some individual cases that would have been unnoticed applying conventional logistic regression models. However, the clinical interpretation of variable selection and their cutoffs is often difficult, because the decision tree classification does not consider the clinical relevance. Decision trees are susceptible to fluctuations in the training set and are, thus, prone to overfitting and poor generalizability [4]. Additionally, decision tree models may not be practically useful if it includes too many variables. However, for the low error rate and high AUC, more classifying variables are needed.

The performance of random forest was also similar to that of logistic regression analysis in our dataset. Random forest is considered to have advantages, especially in handling electronic medical records. It is an extension to traditional decision tree classifiers [42], and attempts to mitigate the limitations of decision tree through an ensemble-based technique using multiple decision trees. Each tree is constructed from a random subset of the original training data and a random subset of a total number of variables is analyzed at each node for splitting. Random forests can minimize the problem of overfitting by taking the mode of decisions of a large number of these randomly generated trees [43]. Other advantages of random forests to analyze electronic medical records include running efficiently on large samples with thousands of input variables, the ability to accommodate different data scales, and robustness to the inclusion of irrelevant variables. There was no significant performance gain of the random forest over that of the simple decision tree in our study, which may be because the number of input variables was insufficient to demonstrate any difference in performance.

The deep neural network model showed a good performance to predict in-hospital mortality in a previous study, although it was not superior to previous risk score [5]. Contrary to our expectations, the performance of neural network in our study was inferior to the performances of all other machine learning techniques. This may be explained because our data for learning the relationship between the covariates and risk of AKI may not be sufficient. Although the multilayer perceptron is mathematically proven to be able to approximate any nonlinear function, it requires a large amount of learning data. Therefore, the dataset of our study may not be large enough and the number of covariates was not sufficient to train the multilayer perceptron [44].

The performance of previous eight risk scoring models was poor in our test dataset [9–16]. The AUCs of these risk scores were similar possibly because similar predictors were used to construct the risk score [6], and the poor performance may be due to the small number of predictors and lack of intraoperative variables, such as transfusion amounts or hemodynamic variables. A previous study showed that the performance of the logistic regression model could be improved when we consider many perioperative variables as possible [19].

Several previous studies reported that the AUCs of machine learning techniques were not superior to previous risk scores or logistic regression models to predict postoperative mortality [5,45]. However, our study demonstrated that the AUCs of machine learning techniques could be significantly greater than the AUC of logistic regression model to predict AKI. Previous studies compared the predictive ability for in-hospital mortality in a population with a very low incidence (<1%) [5,45]. The difference in AUC or error rate may be small for an outcome with low incidence, and this small

difference in performance would be difficult to be demonstrated. It seems that any difference in error rate and AUC would be more pronounced in our study sample with a postoperative AKI of higher incidence (38.3%). This could also be the reason why the SMOTE model of random forests or support vector machines did not significantly increase the AUC in our test dataset. SMOTE model increases the incidence of outcome cases and balancing the case with and without outcome variables. However, our test set already had a nearly balanced dataset for AKI.

The importance matrix plot of the gradient boosting machine shows the similar predictors that were known to be associated with the development of AKI after cardiac surgery [6,9–14,16,19–21,46]. However, the plot additionally gives the relative importance of each predictor, which was similar to the variance importance plot of random forest model. This analysis may help to find a new risk factor for postoperative morbidity or mortality.

Our study has several limitations. First, our analysis used only single-center data and included a relatively small number of cases and covariates. The performance of machine learning techniques might be different when they are applied to a much larger sample with a different distribution of the covariates. The external validity of our results may be limited. Furthermore, important predictors may be different according to different institutions. However, the relative performance of logistic regression and machine learning techniques would be similar to our results. Each institution may need to develop their own prediction model with the machine learning approach, by using historical data from their electronic medical records and updating the model periodically. Real-time processing of patient data would produce risk prediction for each patient after surgery. Second, machine learning techniques are often difficult to interpret the results. Inferences about the explanatory variables are more difficult than logistic regression analysis [4]. However, the gradient boosting machine and random forest provided for some interpretability through the importance matrix plot and variable importance plot. Third, it is not certain that our results could translate into improved clinical outcomes for the patients. Most of our important variables reported are not clinically modifiable and accurate risk prediction may not be followed by improved patient outcomes. However, further prospective trials may evaluate whether adjustment of potentially modifiable predictors, such as hemodynamic variables could decrease the risk of AKI [46–48].

5. Conclusions

In conclusion, our study demonstrated that the machine learning technique of extreme gradient boosting showed significantly better performance than the traditional logistic regression analysis or previous risk scores in predicting both AKI of all stages and stage 2 or 3 AKI after cardiac surgery. Gradient boosting machine may be used for real-time processing of patient data to estimate the risk of AKI after cardiac surgery at the end of surgery. Our Internet-based risk estimator may help to evaluate the risk of AKI at the end of surgery. However, prospective multicenter trials are required to validate the better prediction by gradient boosting. Further studies may apply extreme gradient boosting machine to the other important clinical outcomes after cardiac surgeries and may prospectively validate our results.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/10/322/s1, Figure S1, Variable importance plot using the random forest model. The abbreviations were the same as the legends of Figure 3; Figure S2, Gradient boosting tree plot showing the matrix of classification. Extreme gradient boosting builds a sequential series of shallow trees; Figure S3, Support vector machine classification plot. This figure shows a simple two-dimensional visual illustration of support vector machine classification. Each triangle and circle means a binomial classification of acute kidney injury or not. The open circle or triangle means a correct classification and closed circle or triangle means an incorrect classification. This figure was drawn by Kernlab package of R; Table S1, KDIGO (Kidney Disease Improving Global Outcomes) serum creatinine diagnostic criteria of acute kidney injury; Table S2, Comparison of area under receiver-operating characteristic curve among the different models for predicting stage 2 or 3 acute kidney injury; Table S3, Results of multivariable logistic regression analysis for acute kidney injury without stepwise variable selection; Text S1, R source code to perform machine learning techniques.

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References

1. Bejnordi, B.E.; Veta, M.; van Diest, P.J.; van Ginneken, B.; Karssemeijer, N.; Litjens, G.; van der Laak, J.A.W.M. Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer. *Jama* **2017**, *318*, 2199–2210. [CrossRef] [PubMed]
2. Ting, D.S.W.; Cheung, C.Y.L.; Lim, G.; Tan, G.S.W.; Quang, N.D.; Gan, A.; Hamzah, H.; Garcia-Franco, R.; San Yeo, I.Y.; Lee, S.Y.; et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. *Jama* **2017**, *318*, 2211–2223. [CrossRef] [PubMed]
3. Fei, Y.; Hu, J.; Li, W.Q.; Wang, W.; Zong, G.Q. Artificial neural networks predict the incidence of portosplenomesenteric venous thrombosis in patients with acute pancreatitis. *J. Thromb. Haemost.* **2017**, *15*, 439–445. [CrossRef] [PubMed]
4. Taylor, R.A.; Pare, J.R.; Venkatesh, A.K.; Mowafi, H.; Melnick, E.R.; Fleischman, W.; Hall, M.K. Prediction of In-hospital Mortality in Emergency Department Patients with Sepsis: A Local Big Data-Driven, Machine Learning Approach. *Acad. Emerg. Med.* **2016**, *23*, 269–278. [CrossRef] [PubMed]
5. Lee, C.K.; Hofer, I.; Gabel, E.; Baldi, P.; Cannesson, M. Development and Validation of a Deep Neural Network Model for Prediction of Postoperative In-hospital Mortality. *Anesthesiology* **2018**, in press. [CrossRef] [PubMed]
6. Shin, S.R.; Kim, W.H.; Kim, D.J.; Shin, I.W.; Sohn, J.T. Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery. *Biomed Res. Int.* **2016**, *2016*, 2985148. [CrossRef] [PubMed]
7. Hobson, C.E.; Yavas, S.; Segal, M.S.; Schold, J.D.; Tribble, C.G.; Layon, A.J.; Bihorac, A. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* **2009**, *119*, 2444–2453. [CrossRef] [PubMed]
8. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef] [PubMed]
9. Thakar, C.V.; Arrigain, S.; Worley, S.; Yared, J.P.; Paganini, E.P. A clinical score to predict acute renal failure after cardiac surgery. *J. Am. Soc. Nephrol.* **2005**, *16*, 162–168. [CrossRef] [PubMed]
10. Mehta, R.H.; Grab, J.D.; O'Brien, S.M.; Bridges, C.R.; Gammie, J.S.; Haan, C.K.; Ferguson, T.B.; Peterson, E.D. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* **2006**, *114*, 2208–2216. [CrossRef] [PubMed]
11. Palomba, H.; de Castro, I.; Neto, A.L.; Lage, S.; Yu, L. Acute kidney injury prediction following elective cardiac surgery: AKICS Score. *Kidney Int.* **2007**, *72*, 624–631. [CrossRef] [PubMed]
12. Wijeysundera, D.N.; Karkouti, K.; Dupuis, J.Y.; Rao, V.; Chan, C.T.; Granton, J.T.; Beattie, W.S. Derivation and validation of a simplified predictive index for renal replacement therapy after cardiac surgery. *Jama* **2007**, *297*, 1801–1809. [CrossRef] [PubMed]
13. Aronson, S.; Fontes, M.L.; Miao, Y.; Mangano, D.T. Risk index for perioperative renal dysfunction/failure: Critical dependence on pulse pressure hypertension. *Circulation* **2007**, *115*, 733–742. [CrossRef] [PubMed]
14. Brown, J.R.; Cochran, R.P.; Leavitt, B.J.; Dacey, L.J.; Ross, C.S.; MacKenzie, T.A.; Kunzelman, K.S.; Kramer, R.S.; Hernandez, F.; Helm, R.E.; et al. Multivariable prediction of renal insufficiency developing after cardiac surgery. *Circulation* **2007**, *116*, I139–I143. [CrossRef] [PubMed]
15. Fortescue, E.B.; Bates, D.W.; Chertow, G.M. Predicting acute renal failure after coronary bypass surgery: Cross-validation of two risk-stratification algorithms. *Kidney Int.* **2000**, *57*, 2594–2602. [CrossRef] [PubMed]
16. Rahmanian, P.B.; Kwiecien, G.; Langebartels, G.; Madershahian, N.; Wittwer, T.; Wahlers, T. Logistic risk model predicting postoperative renal failure requiring dialysis in cardiac surgery patients. *Eur. J. Cardiothorac. Surg.* **2011**, *40*, 701–707. [PubMed]

17. Vives, M.; Callejas, R.; Duque, P.; Echarri, G.; Wijeysundera, D.N.; Hernandez, A.; Sabate, A.; Bes-Rastrollo, M.; Monedero, P. Modern hydroxyethyl starch and acute kidney injury after cardiac surgery: A prospective multicentre cohort. *Br. J. Anaesth.* **2016**, *117*, 458–463. [CrossRef] [PubMed]
18. Kim, W.H.; Lee, J.H.; Kim, E.; Kim, G.; Kim, H.J.; Lim, H.W. Can We Really Predict Postoperative Acute Kidney Injury after Aortic Surgery? Diagnostic Accuracy of Risk Scores Using Gray Zone Approach. *Thorac. Cardiovasc. Surg.* **2016**, *64*, 281–289. [CrossRef] [PubMed]
19. Parolari, A.; Pesce, L.L.; Pacini, D.; Mazzanti, V.; Salis, S.; Sciacovelli, C.; Rossi, F.; Alamanni, F. Risk factors for perioperative acute kidney injury after adult cardiac surgery: Role of perioperative management. *Ann. Thorac. Surg.* **2012**, *93*, 584–591. [CrossRef] [PubMed]
20. Kim, W.H.; Lee, S.M.; Choi, J.W.; Kim, E.H.; Lee, J.H.; Jung, J.W.; Ahn, J.H.; Sung, K.I.; Kim, C.S.; Cho, H.S. Simplified clinical risk score to predict acute kidney injury after aortic surgery. *J. Cardiothorac. Vasc. Anesth.* **2013**, *27*, 1158–1166. [CrossRef] [PubMed]
21. Kim, W.H.; Park, M.H.; Kim, H.J.; Lim, H.Y.; Shim, H.S.; Sohn, J.T.; Kim, C.S.; Lee, S.M. Potentially modifiable risk factors for acute kidney injury after surgery on the thoracic aorta: A propensity score matched case-control study. *Medicine* **2015**, *94*, e273. [CrossRef] [PubMed]
22. Hur, M.; Koo, C.H.; Lee, H.C.; Park, S.K.; Kim, M.; Kim, W.H.; Kim, C.S.; Lee, S.M. Preoperative aspirin use and acute kidney injury after cardiac surgery: A propensity-score matched observational study. *PLoS ONE* **2017**, *12*, E0177201. [CrossRef] [PubMed]
23. Hur, M.; Nam, K.; Jo, W.Y.; Kim, G.; Kim, W.H.; Bahk, J.H. Association Between Elevated Echocardiographic Index of Left Ventricular Filling Pressure and Acute Kidney Injury After Off-Pump Coronary Artery Surgery. *Circ. J.* **2018**, *82*, 857–865. [CrossRef] [PubMed]
24. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef] [PubMed]
25. Hori, D.; Katz, N.M.; Fine, D.M.; Ono, M.; Barodka, V.M.; Lester, L.C.; Yenokyan, G.; Hogue, C.W. Defining oliguria during cardiopulmonary bypass and its relationship with cardiac surgery-associated acute kidney injury. *Br. J. Anaesth.* **2016**, *117*, 733–740. [CrossRef] [PubMed]
26. Mizota, T.; Yamamoto, Y.; Hamada, M.; Matsukawa, S.; Shimizu, S.; Kai, S. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. *Br. J. Anaesth.* **2017**, *119*, 1127–1134. [CrossRef] [PubMed]
27. Kellum, J.A.; Zarbock, A.; Nadim, M.K. What endpoints should be used for clinical studies in acute kidney injury? *Intensive Care Med.* **2017**, *43*, 901–903. [CrossRef] [PubMed]
28. Hanley, J.A.; McNeil, B.J. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* **1982**, *143*, 29–36. [CrossRef] [PubMed]
29. Zou, K.H.; O'Malley, A.J.; Mauri, L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. *Circulation* **2007**, *115*, 654–657. [CrossRef] [PubMed]
30. DeLong, E.R.; DeLong, D.M.; Clarke-Pearson, D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* **1988**, *44*, 837–845. [CrossRef] [PubMed]
31. Zavrsnik, J.; Kokol, P.; Maleiae, I.; Kancler, K.; Mernik, M.; Bigec, M. ROSE: Decision trees, automatic learning and their applications in cardiac medicine. *Medinfo* **1995**, *8*, 1688. [PubMed]
32. Sheridan, R.P.; Wang, W.M.; Liaw, A.; Ma, J.; Gifford, E.M. Extreme Gradient Boosting as a Method for Quantitative Structure-Activity Relationships. *J. Chem. Inf. Model.* **2016**, *56*, 2353–2360. [CrossRef] [PubMed]
33. Gao, C.; Sun, H.; Wang, T.; Tang, M.; Bohnen, N.I.; Muller, M.L.; Herman, T.; Giladi, N.; Kalinin, A.; Spino, C.; et al. Model-based and Model-free Machine Learning Techniques for Diagnostic Prediction and Classification of Clinical Outcomes in Parkinson's Disease. *Sci. Rep.* **2018**, *8*, 7129. [CrossRef] [PubMed]
34. Available online: https://github.com/dmlc/xgboost (accessed on 3 October 2018).
35. Chawla, N.V.; Bowyer, K.W.; Hall, L.O.; Kegelmeyer, W.P. SMOTE: Synthetic minority over-sampling technique. *J. Artif. Intell. Res.* **2002**, *16*, 321–357. [CrossRef]
36. Available online: https://vitaldb.net/aki (accessed on 3 Octber 2018).
37. Lei, T.; Sun, H.; Kang, Y.; Zhu, F.; Liu, H.; Zhou, W.; Wang, Z.; Li, D.; Li, Y.; Hou, T. ADMET Evaluation in Drug Discovery. 18. Reliable Prediction of Chemical-Induced Urinary Tract Toxicity by Boosting Machine Learning Approaches. *Mol. Pharm.* **2017**, *14*, 3935–3953. [CrossRef] [PubMed]

38. Aviles-Jurado, F.X.; Leon, X. Prognostic factors in head and neck squamous cell carcinoma: Comparison of CHAID decision trees technology and Cox analysis. *Head Neck* **2013**, *35*, 877–883. [CrossRef] [PubMed]
39. Kasbekar, P.U.; Goel, P.; Jadhav, S.P. A Decision Tree Analysis of Diabetic Foot Amputation Risk in Indian Patients. *Front. Endocrinol.* **2017**, *8*, 25. [CrossRef] [PubMed]
40. Zintzaras, E.; Bai, M.; Douligeris, C.; Kowald, A.; Kanavaros, P. A tree-based decision rule for identifying profile groups of cases without predefined classes: Application in diffuse large B.-cell lymphomas. *Comput. Biol. Med.* **2007**, *37*, 637–641. [CrossRef] [PubMed]
41. Lemon, S.C.; Roy, J.; Clark, M.A.; Friedmann, P.D.; Rakowski, W. Classification and regression tree analysis in public health: Methodological review and comparison with logistic regression. *Ann. Behav. Med.* **2003**, *26*, 172–181. [CrossRef] [PubMed]
42. Li, K.; Yu, N.; Li, P.; Song, S.; Wu, Y.; Li, Y.; Liu, M. Multi-label spacecraft electrical signal classification method based on DBN and random forest. *PLoS ONE* **2017**, *12*, E0176614. [CrossRef] [PubMed]
43. Hsu, P.L.; Robbins, H. Complete Convergence and the Law of Large Numbers. *Proc. Natl. Acad. Sci. USA* **1947**, *33*, 25–31. [CrossRef] [PubMed]
44. Hornik, K. Approximation capabilities of multilayer feedforward networks. *Neural. Networks.* **1991**, *4*, 251–257. [CrossRef]
45. Kuo, P.J.; Wu, S.C.; Chien, P.C.; Rau, C.S.; Chen, Y.C.; Hsieh, H.Y.; Hsieh, C.H. Derivation and validation of different machine-learning models in mortality prediction of trauma in motorcycle riders: A cross-sectional retrospective study in southern Taiwan. *BMJ Open* **2018**, *8*, e018252. [CrossRef] [PubMed]
46. Karkouti, K.; Wijeysundera, D.N.; Yau, T.M.; Callum, J.L.; Cheng, D.C.; Crowther, M.; Dupuis, J.Y.; Fremes, S.E.; Kent, B.; Laflamme, C.; et al. Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. *Circulation* **2009**, *119*, 495–502. [CrossRef] [PubMed]
47. Lee, E.H.; Kim, W.J.; Kim, J.Y.; Chin, J.H.; Choi, D.K.; Sim, J.Y.; Choo, S.J.; Chung, C.H.; Lee, J.W.; Choi, I.C. Effect of Exogenous Albumin on the Incidence of Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Surgery with a Preoperative Albumin Level of Less Than 4.0 g/dl. *Anesthesiology* **2016**, *124*, 1001–1011. [CrossRef] [PubMed]
48. Yoo, Y.C.; Shim, J.K.; Kim, J.C.; Jo, Y.Y.; Lee, J.H.; Kwak, Y.L. Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. *Anesthesiology* **2011**, *115*, 929–937. [CrossRef] [PubMed]

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General Anesthetic Agents and Renal Function after Nephrectomy

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Abstract: The association between the choice of general anesthetic agents and the risk of acute kidney injury (AKI) and long-term renal dysfunction after nephrectomy has not yet been evaluated. We reviewed 1087 cases of partial or radical nephrectomy. The incidence of postoperative AKI, new-onset chronic kidney disease (CKD) and CKD upstaging were compared between general anesthetic agent groups (propofol, sevoflurane, and desflurane). Four different propensity score analyses were performed to minimize confounding for each pair of comparison (propofol vs. sevoflurane; propofol vs. desflurane; sevoflurane vs. desflurane; propofol vs. volatile agents). Study outcomes were compared before and after matching. Kaplan-Meier survival curve analysis was performed to compare renal survival determined by the development of new-onset CKD between groups up to 36 months after nephrectomy. Propofol was associated with a lower incidence of AKI (propofol 23.2% vs. sevoflurane 39.5%, $p = 0.004$; vs. propofol 21.0% vs. desflurane 34.3%, $p = 0.031$), a lower incidence of CKD upstaging (propofol 27.2% vs. sevoflurane 58.4%, $p < 0.001$; propofol 32.4% vs. desflurane 48.6%, $p = 0.017$) and better three-year renal survival after nephrectomy compared to sevoflurane or desflurane group (Log-rank test propofol vs. sevoflurane $p < 0.001$; vs. desflurane $p = 0.015$) after matching. Propofol was also associated with a lower incidence of new-onset CKD after nephrectomy compared to sevoflurane after matching ($p < 0.001$). There were no significant differences between sevoflurane and desflurane. However, subgroup analysis of partial nephrectomy showed a significant difference only in CKD upstaging. In conclusion, propofol, compared to volatile agents, could be a better general anesthetic agent for nephrectomy to attenuate postoperative renal dysfunction. However, limitations of the retrospective study design and inconsistent results of the subgroup analysis preclude firm conclusions.

Keywords: nephrectomy; acute kidney injury; chronic kidney disease; sevoflurane; desflurane; propofol

1. Introduction

Kidney cancer, more than 90% of which is renal cell carcinoma (RCC), is common in both men and women [1]. Although partial or radical nephrectomy is the standard treatment for localized RCC [2], postoperative acute kidney injury (AKI) remains a common complication with a risk of evolving chronic kidney disease (CKD) [3,4] and the distant organ dysfunction [5]. Postoperative AKI and CKD after nephrectomy result in the prolonged length of hospital stay, increased medical cost

and mortality [4,6,7]. Since acute postoperative renal dysfunction is associated with other delayed morbidities, it would be important to identify and correct potentially reversible risk factors of AKI [8].

Previous studies investigated perioperative predictors for AKI and CKD after nephrectomy [9–12]. However, to our knowledge, previously reported risk factors were generally not modifiable except ischemic time during renal arterial clamping, cold ischemia during partial nephrectomy, and intraoperative hypotension [9,13–15]. Effective interventions to decrease the risk of renal functional decline after nephrectomy are still required [16]. As another modifiable risk factor, the choice of general anesthetic agents would be important. General anesthetic agents may affect the postoperative renal function by the following mechanisms. Propofol, a widely used intravenous anesthetic agent, could prevent renal ischemia/reperfusion injury by anti-oxidative effect and progression of renal fibrosis by downregulating inducible nitric oxide synthase expression [17,18]. Although there were concerns regarding compound A-associated nephrotoxicity, many previous studies demonstrated the safety of sevoflurane. [19]. Conversely, sevoflurane had a protective effect on acute renal injury due to its anti-inflammatory effect in a previous animal study [20]. Therefore, propofol or sevoflurane may be associated with better postoperative renal function compared to other general anesthetics after nephrectomy. However, there have been no previous reports regarding the effect of general anesthetic agents on the postoperative renal function and it is unknown whether the choice of general anesthetic agents influences the risk of AKI or long-term renal function after partial or radical nephrectomy.

Therefore, we attempted to investigate the association between the choice of general anesthetic agents and the risk of AKI and long-term renal function after nephrectomy [21]. We hypothesized that the incidences of AKI and new-onset CKD after general anesthesia with propofol may be lower than the incidences with sevoflurane or desflurane. To this aim, we conducted a retrospective cohort study to investigate the potential association between different anesthetic agents and the incidences of AKI and new-onset CKD after partial or radical nephrectomy.

2. Materials and Methods

2.1. Study Design

This retrospective observational study was approved by the institutional review board (IRB) of Seoul National University Hospital (1905-089-1034). The requirement for written informed consent was waived by the IRB due to the retrospective design of this study. Studies were conducted in accordance with the approved guidelines and regulations.

2.2. Data Collection

After approval from the IRB, we reviewed the electronic medical records of 1087 adult patients underwent radical or partial nephrectomy due to a renal mass at our hospital between 2010 and 2014. Demographic or perioperative variables known to be associated with AKI or CKD after nephrectomy were collected (Table 1) [9,10,12]. The cohort was divided into three groups according to the anesthetic agents commonly used for maintenance of general anesthesia; propofol, sevoflurane, and desflurane. The patients who received agents other than these ($n = 0$) or whose main agent was changed during surgery ($n = 0$) or whose renal function after surgery was not followed up at least two times after surgery three months apart were excluded from our analysis ($n = 0$).

Table 1. Patient characteristics and perioperative parameters.

Characteristics	Propofol (n = 130)	Sevoflurane (n = 644)	Desflurane (n = 313)	p-Value
Demographic data				
Age, years	55 (47–62)	57 (48–67)	58 (49–66)	0.12
Female, n	34 (26.2)	199 (30.9)	87 (27.8)	0.42
Body-mass index, kg/m^2	24.5 (22.4–26.6)	24.5 (22.6–26.6)	24.5 (22.5–26.6)	0.98
Current smoker, n	22 (16.9)	85 (13.2)	59 (18.8)	0.06
Background medical status				
ASA 1/2/3/4	69 (53.1)/55 (42.3)/6 (4.6)/0	317 (49.2)/280 (43.5)/47 (7.3)/0	119 (38.0)/181 (57.8)/12 (3.8)/1 (0.3)	<0.001
Hypertension, n	46 (35.4)	292 (45.3)	131 (41.9)	0.10
Diabetes mellitus, n	16 (12.3)	99 (15.4)	53 (16.9)	0.47
Cerebrovascular accident, n	4 (3.1)	17 (2.6)	4 (1.3)	0.34
Liver disease, n	11 (8.5)	22 (3.4)	13 (4.2)	0.03
Ischemic heart disease, n	2 (1.5)	11 (1.7)	2 (0.6)	0.41
Hyperlipidemia, n	8 (6.2)	59 (9.2)	34 (10.9)	0.29
Preoperative eGFR (mL/min/1.73 m^2)	82 (73–89)	81 (69–92)	77 (68–90)	0.068
Preoperative stage of CKD				0.09
1 (eGFR ≥ 90 mL/min/1.73 m^2)	29 (22.3)	193 (30.0)	79 (25.2)	0.179
2 (60–89 mL/min/1.73 m^2)	91 (71.0)	365 (56.7)	185 (59.1)	
3a (45–59 mL/min/1.73 m^2)	4 (3.1)	47 (7.3)	29 (9.3)	
3b (30–44 mL/min/1.73 m^2)	4 (3.1)	13 (2.0)	7 (2.2)	
4 (15–30 mL/min/1.73 m^2)	1 (0.8)	3 (0.5)	2 (0.6)	
5 (< 15 mL/min/1.73 m^2)	1 (0.8)	23 (3.6)	11 (3.5)	
Preoperative proteinuria, n	9 (6.9)	43 (6.7)	31 (9.9)	0.20
Preoperative hemoglobin, g/dL	14.3 (12.8–15.1)	13.7 (12.5–14.8)	13.8 (12.5–14.9)	0.04
Preoperative albumin, g/dL	4.4 (4.2–4.7)	4.4 (4.1–4.6)	4.4 (4.2–4.6)	0.20
ECOG performance status				0.001
0/1/2/3	121/6/3/0	536/82/23/2	285/25/1/2	
Clinical stage				
T 1a/1b	103 (79.2)/ 14 (10.8)	416 (64.6)/ 126 (19.6)	231 (73.8)/ 25 (8.0)	0.23
T 2a/2b	7 (5.4)/-	65 (10.1)/ 15 (2.3)	35 (11.2)/ 6 (1.9)	
T 3a/3b/3c	3 (2.3)/2 (1.5)/1 (0.8)	12 (1.9)/4 (0.6)/6 (0.9)	4 (1.3)/6 (1.9)/6 (1.9)	
N 0/1	129 (99.2)/ 1 (0.8)	616 (95.7)/ 28 (4.3)	298 (95.2)/ 15 (4.8)	0.10
M 0/1	123 (94.6)/ 7 (5.4)	619 (96.1)/ 25 (3.9)	303 (96.8)/ 10 (3.2)	0.30
Operation and anesthesia related				
Surgery type				0.07
Radical nephrectomy, n	44 (33.8)	286 (44.4)	139 (44.4)	
Partial nephrectomy, n	86 (66.2)	358 (55.6)	174 (55.6)	
Surgical approach				<0.001
Laparoscopic, n	10 (7.7)	130 (20.2)	51 (16.3)	
Hand-assisted laparoscopic, n	2 (1.5)	22 (3.4)	11 (3.5)	
Robot-assisted, n	62 (47.7)	40 (6.2)	32 (10.2)	
Open, n	56 (43.1)	452 (70.2)	219 (70.0)	
Operation time, hour	2.8 (2.3–3.3)	2.2 (1.7–2.8)	2.2 (1.7–2.9)	<0.001
Renal ischemic time, min *	27 (21.5–35.5)	24.6 (20.0–31.0)	22.4 (17.4–27.5)	<0.001
Ischemia type *				0.13
Cold ischemia	1 (1.2)	22 (6.1)	7 (4.0)	
Warm ischemia	85 (98.8)	336 (93.9)	167 (96.0)	
Intraoperative vasopressor use, n	5 (3.8)	10 (1.6)	7 (2.2)	0.55
pRBC transfusion, n	15 (11.5)	68 (10.6)	40 (12.8)	0.59
Crystalloid administration, mL/kg	18.8 (12.3–24.9)	18.7 (14.2–25.0)	18.1 (12.5–25.2)	0.17
Colloid administration, mL/kg	0 (0–5.8)	0 (0–5.0)	0 (0–5.5)	0.78

The values are presented as the median (interquartile range) or number (%). * These values are for only partial nephrectomy. Liver disease includes hepatitis or liver cirrhosis. ASA = American society of Anesthesiologist physical classification, CKD = chronic kidney disease, ECOG performance status = Eastern Cooperative Oncology Group performance status, eGFR = estimated glomerular filtration rate, pRBC = packed red blood cell.

2.3. Anesthesia and Surgical Techniques

The anesthetic protocols of our hospital during the study period were as follows. In the propofol group, general anesthesia was induced and maintained with a target-controlled infusion of propofol using infusion pump (Orchestra®; Fresenius Vial, Brezins, France). In the volatile agent groups, anesthesia was induced with propofol 1–2 mg/kg and maintained with either sevoflurane (2–4 vol %) or desflurane (5–7 vol %). In all groups, remifentanil was continuously infused throughout the surgery for balanced anesthesia, adjusted to maintain arterial pressure within 20% of baseline ward pressure. If arterial pressure was less than 20% of baseline despite adequate fluid administration and urine output, vasopressor including phenylephrine or norepinephrine was infused. The choice of anesthetic agents for anesthetic maintenance was made according to the anesthesiologists' discretion. The decision was made according to the attending anesthesiologist's preference regardless of patients' comorbidity or baseline medical status. Patients were mechanically ventilated with a volume-controlled mode with a tidal volume of 6–8 mL/kg and a FiO_2 of 0.4 to 0.5. Nephrectomies were conducted by open, laparoscopic, or robot-assisted techniques. Decisions regarding the type of surgical approach were made based on tumor characteristics. For partial nephrectomy, surgical resection was performed after clamping the main renal artery or arteries. The renal vein was clamped selectively. Saline ice slush was used for cold ischemia. Mannitol was administered intraoperatively within 30 min prior to renal vascular clamping.

2.4. Outcome Variables

The primary outcome of our study was the incidence of AKI after nephrectomy. Postoperative AKI was diagnosed by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which was determined by the maximal change of the serum creatinine level during the first seven postoperative days (Stage 1: 1.5–1.9; stage 2: 2–2.9; stage 3: More than 3-fold increase from baseline) [22,23]. The most recent preoperative serum creatinine level was defined as the baseline value.

The secondary outcomes included the incidence of new-onset CKD stage 3a or high (eGFR < 60 mL/min/1.73 m^2), CKD upstaging after nephrectomy, the incidence of postoperative complications, and length of hospital stay. Postoperative new-onset CKD was diagnosed by the creatinine criteria of KDIGO criteria, which was determined when the estimated glomerular filtration rate (eGFR) decreased below 60 mL/min/1.73 m^2 for three months or more [24]. We calculated eGFR from serum creatinine level using the Modification of Diet in Renal Disease (MDRD) study equation [25]. The most recent preoperative eGFR was defined as the baseline value. CKD upstaging was determined when the CKD stage follow-up was higher than the baseline until 3 years after nephrectomy.

2.5. Statistical Analysis

Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc Statistical Software version 18.6 (MedCalc Software bvba, Ostend, Belgium). A p-value of less than 0.05 was considered statistically significant. The Kolmogorov-Smirnov test was performed to determine the normality of the continuous variables. Continuous data are described as the mean (SD) or median (25 and 75 percentiles) and were compared by the independent t-test or the Mann-Whitney U test or one-way analysis of variance (ANOVA). In the pairwise comparisons between two anesthetic groups, Bonferroni correction was used by dividing the critical p-value by the number of comparisons to minimize the chance of a type 1 error. p-value < 0.017 was considered statistically significant. Categorical data are described as number (%) and were compared by the chi-square test or Fisher's exact test. Missing data were less than 5% of the total records. We used simple imputation with median and mode. Missing values of continuous variables were replaced by the age-and sex-specific median values, and incidence data were assigned the most frequent age and sex-specific modes. The followings are main analyses of our study to evaluate the association between the general anesthetic agents and clinical outcomes.

Firstly, to reduce the influence of confounding variables, four different propensity score matching analyses were performed to adjust for intergroup differences; Propofol vs. Sevoflurane, Propofol vs. Desflurane, Sevoflurane vs. Desflurane, and Propofol vs. volatile agents. The following variables were used as contributors to the propensity score: Sex, age, body-mass index, current smoking, history of hypertension, diabetes mellitus, cerebrovascular disease, chronic hepatitis or cirrhosis, ischemic heart disease, dyslipidemia, preoperative hemoglobin, serum albumin, eGFR, TNM stage of renal cell carcinoma, year of surgery, open surgery (vs. laparoscopic surgery), radical nephrectomy (vs. partial nephrectomy), operation time, unit number of packed red cell transfusion, crystalloid and colloid administration and need for vasopressor infusion. All patients were matched at a 1:1 ratio using the nearest neighbor method with a caliper width of 0.2 of the pooled standard deviation of the logit of the propensity score. To evaluate the balance of the matched patients, the standardized mean difference for each contributor was compared before and after matching. In each propensity-matched cohort, we directly compared the incidences of postoperative AKI and other secondary outcomes.

Secondly, to evaluate the effect of general anesthetic agents on long-term renal function, Kaplan-Meier survival curve analyses were performed. Renal survival was determined by the development of new-onset CKD stage 3a or higher and the survival was compared between different anesthetic agent groups before and after matching. Patients were followed for up to 36 months and the log-rank test was used for inter-group comparison.

Thirdly, we performed a subgroup analysis for the patients who underwent partial nephrectomy. We compared our primary and secondary outcomes between the propofol and volatile agent groups.

Although power calculation was not conducted prior to analysis, available power was calculated with the number of patients used in our analysis. With 130 and 644 patients used to compare the incidence of AKI between propofol and sevoflurane group and incidences of AKI of the two groups observed in our study, there was about 84.7% power to detect the observed difference in AKI. However, power decreased to 76.0% in the matched cohort between propofol and sevoflurane.

3. Results

Among 1087 patients included in our analysis, 130 patients (12.0%) received propofol and 957 patients (88.0%: Sevoflurane 59.2%, Desflurane 28.8%) received volatile agent to maintain general anesthesia. After propensity score matching, 125 pairs of patients were matched between the propofol and sevoflurane group, 105 pairs between the propofol and desflurane group, and 307 pairs between the sevoflurane and desflurane group (Figure 1). Patient characteristics and perioperative parameters are summarized in Table 1. Histograms and covariate balance plots of the distribution of standardized differences of covariates between groups before and after matching are shown in Supplemental Figures S1–S4 according to the different pairs of matching.

There were significant differences in the incidences of postoperative AKI, new-onset CKD stage 3a or high and CKD upstaging between the propofol and volatile groups. (Tables 2 and 3) However, there was no significant difference between the sevoflurane and desflurane groups (Table 4). After propensity score matching, the propofol group still showed significantly less frequent postoperative AKI, new-onset CKD stage 3a or high, and CKD upstaging than the sevoflurane group (Table 2). The propofol group also showed significantly less frequent postoperative AKI and CKD upstaging than the desflurane group (Table 3). Between sevoflurane and desflurane groups, there was no significant difference (Table 4). When the sevoflurane and desflurane groups were combined into the volatile group, the propofol group showed significantly less frequent postoperative AKI and CKD upstaging than the volatile group before and after matching (Supplemental Table S1).

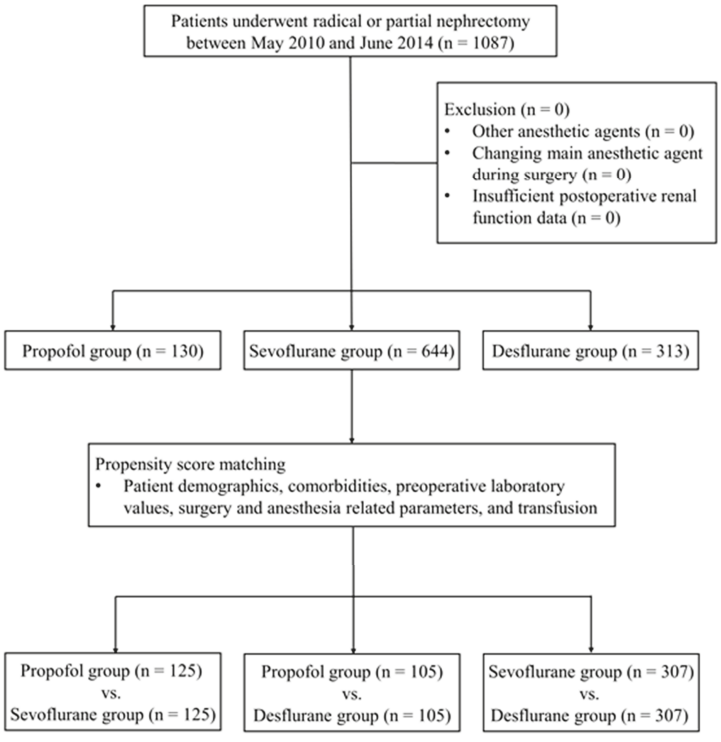

Figure 1. Flow diagram of the present study.

Table 2. Comparison of incidence of primary and secondary outcomes between patients according to the main anesthetic agents during surgery before and after propensity score matching.

Outcomes	Propofol	Sevoflurane	Risk Difference, %	*p*-Value
Number of patients before matching	130	644		
Postoperative AKI, *n*	29 (22.3)	229 (35.6)	−13 (−5 to −21)	0.032
Stage 1	24 (18.5)	203 (31.5)	−13 (−5 to −21)	
Stage 2	1 (0.8)	2 (0.3)	0.5 (−1.1 to 2.0)	
Stage 3	4 (3.1)	24 (3.7)	−0.6 (−3.9 to 2.7)	
Postoperative new-onset CKD stage 3a or high, *n*	33 (25.4)	296 (46.0)	−21 (−12 to −29)	<0.001
CKD upstaging, *n*	38 (29.2)	307 (47.7)	−18 (−10 to −27)	<0.001
Number of patients after matching	125	125		
Postoperative AKI, *n*	29 (23.2)	50 (39.5)	−17 (−5 to −28)	0.004
Stage 1	24 (19.2)	45 (36.0)	−17 (−6 to −28)	
Stage 2	1 (0.8)	-	-	
Stage 3	4 (3.2)	5 (4.0)	−0.8 (−5.4 to 3.8)	
Postoperative new-onset CKD stage 3a or high, *n*	33 (26.4)	61 (48.8)	−22 (−11 to −34)	<0.001
CKD upstaging, *n*	34 (27.2)	73 (58.4)	−31 (−20 to −43)	<0.001

The values are presented as the median (interquartile range) or number (%). AKI = acute kidney injury determined by KDIGO creatinine criteria, CKD = chronic kidney disease.

Table 3. Comparison of incidence of primary and secondary outcomes between patients according to the main anesthetic agents during surgery before and after propensity score matching.

Outcomes	Propofol	Desflurane	Risk Difference, %	*p*-Value
Number of patients before matching	130	313		
Postoperative AKI, *n*	29 (22.3)	113 (36.1)	−14 (−5 to −22)	0.042
Stage 1	24 (18.5)	100 (31.9)	−13 (−5 to −22)	
Stage 2	1 (0.8)	3 (1.0)	−0.2 (−2.0 to 1.7)	
Stage 3	4 (3.1)	10 (3.2)	−0.1 (−3.7 to 3.4)	
Postoperative new-onset CKD stage 3a or high, *n*	33 (25.4)	131 (41.9)	−16 (−7 to −26)	0.001
CKD upstaging, *n*	38 (29.2)	141 (45.0)	−16 (−6 to −25)	0.002
Number of patients after matching	105	105		
Postoperative AKI, *n*	22 (21.0)	36 (34.3)	−13 (−1 to −25)	0.031
Stage 1	19 (18.1)	31 (29.5)	−11 (−0.1 to −23)	
Stage 2	1 (1.0)	-	-	
Stage 3	2 (1.9)	5 (4.8)	−2.9 (−7.7 to 2.0)	
Postoperative new-onset CKD stage 3a or high, *n*	24 (22.9)	35 (33.3)	−10 (−23 to 2)	0.09
CKD upstaging, *n*	34 (32.4)	51 (48.6)	−16 (−29 to −3)	0.017

The values are presented as the median (interquartile range) or number (%). AKI = acute kidney injury determined by KDIGO creatinine criteria, CKD = chronic kidney disease.

Table 4. Comparison of incidence of primary and secondary outcomes between patients according to the main anesthetic agents during surgery before and after propensity score matching.

Outcomes	Sevoflurane	Desflurane	Risk Difference, %	*p*-Value
Number of patients before matching	644	313		
Postoperative AKI, *n*	229 (35.6)	113 (36.1)	−0.5 (−7.0 to 5.9)	0.98
Stage 1	203 (31.5)	100 (31.9)	−0.4 (−6.7 to 5.9)	
Stage 2	2 (0.3)	3 (1.0)	−0.6 (−1.8 to 0.5)	
Stage 3	24 (3.7)	10 (3.2)	0.5 (−1.9 to 3.0)	
Postoperative new-onset CKD stage 3a or high, *n*	296 (46.0)	131 (41.9)	4.1 (−2.6 to 10.8)	0.23
CKD upstaging, *n*	307 (47.7)	141 (45.0)	2.7 (−4.1 to 9.4)	0.45
Number of patients after matching	307	307		
Postoperative AKI, *n*	103 (33.6)	110 (35.8)	−2.3 (−9.8 to 5.2)	0.55
Stage 1	93 (30.3)	99 (32.2)	−2.0 (−9.3 to 5.4)	
Stage 2	-	3 (1.0)	-	
Stage 3	10 (3.3)	8 (2.6)	0.7 (−2.0 to 3.3)	
Postoperative new-onset CKD stage 3a or high, *n*	136 (44.3)	127 (41.4)	2.9 (−4.9 to 10.8)	0.46
CKD upstaging, *n*	147 (47.9)	139 (45.3)	2.6 (−5.3 to 10.5)	0.52

The values are presented as the median (interquartile range) or number (%). AKI = acute kidney injury determined by KDIGO creatinine criteria, CKD = chronic kidney disease.

Kaplan-Meier survival analyses of the entire cohort showed significant differences in renal survival between the propofol and other volatile groups (Log-rank test: vs. sevoflurane, $p < 0.001$; vs. desflurane, $p < 0.001$) (Figure 2). After matching, there were significant differences in survival between the propofol and volatile agent groups (vs. sevoflurane, $p < 0.001$; vs. desflurane, $p = 0.015$) (Figure 2). However, no significant difference was observed between the sevoflurane and desflurane groups before and after

matching (Figure 2). Regarding combined volatile group, there was a significant difference in renal survival between the propofol and volatile group ($p < 0.001$) (Supplementary Figure S5). The significant difference was also observed after matching ($p = 0.032$).

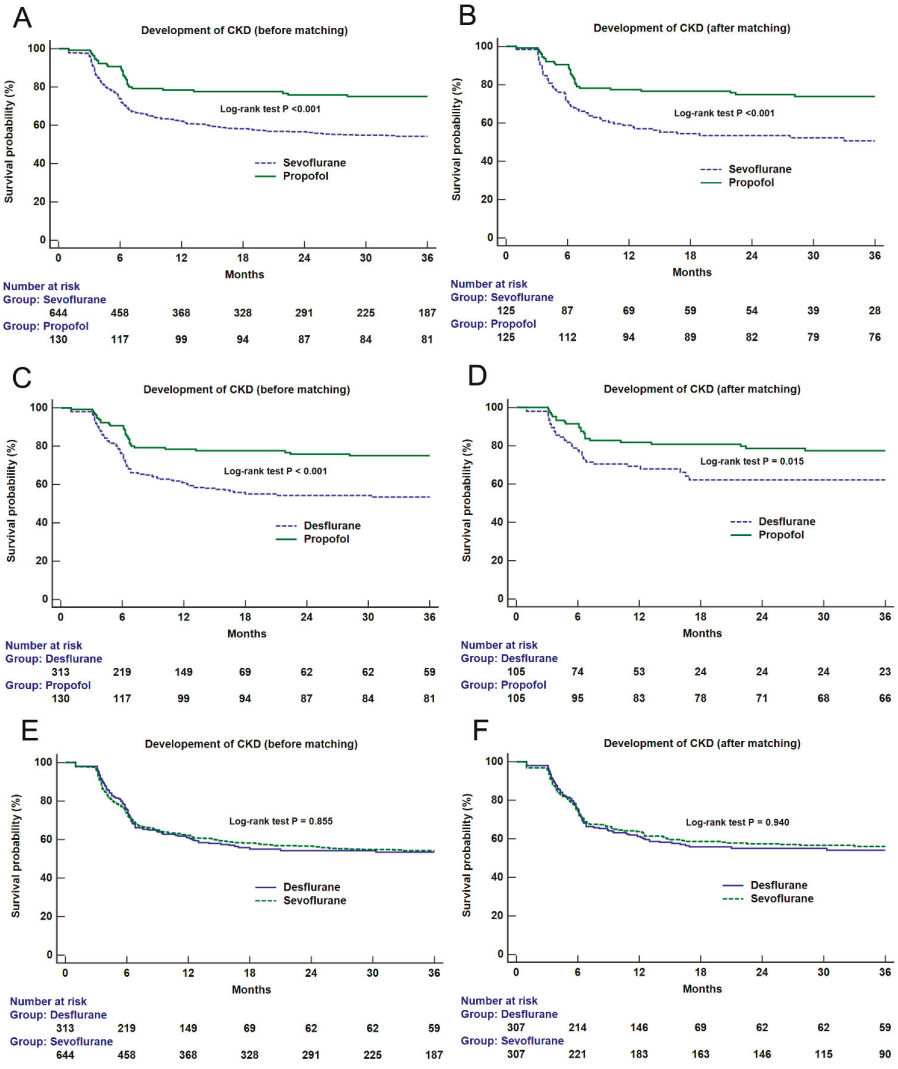

Figure 2. Kaplan-Meier survival curve analyses of new-onset chronic kidney disease stage 3a or high according to the main anesthetic agent groups (propofol vs. sevoflurane, upper, before (**A**) and after (**B**) matching; propofol vs. desflurane, middle, before (**C**) and after (**D**) matching; sevoflurane vs. desflurane, lower, before (**E**) and after (**F**) matching). The results of the log-rank test between groups are shown on the figure.

The results of the subgroup analysis of partial nephrectomy were shown in Supplemental Table S2 and Supplemental Figures S6 and S7. We also performed propensity score matching in the subgroup and obtained 67 pairs of matched cases. No significant difference in the incidence of postoperative AKI

or new-onset CKD was found between the propofol and volatile groups. However, the propofol group showed significantly less frequent postoperative CKD upstaging than the volatile group.

4. Discussion

We investigated the association between general anesthetic agents and postoperative renal functional outcomes in patients undergoing nephrectomy. The incidences of postoperative AKI and CKD upstaging were significantly and consistently lower in the propofol group compared to the sevoflurane or desflurane group before and after propensity score matching. The three-year postoperative incidence of new-onset CKD stage 3a or high was also significantly lower in the propofol group than the sevoflurane group after matching. There was no significant difference between sevoflurane and desflurane groups. Propofol was associated with better both short- and long-term renal function after nephrectomy compared to the volatile agents. However, subgroup analysis of partial nephrectomy did not show consistent results. Our results should be interpreted cautiously given the limitations of single-center retrospective design.

There was a significant association between the choice of general anesthetic agent and the incidence of AKI after nephrectomy in our study, favoring the propofol group. Several possible mechanisms can be elucidated on the basis of previous animal experiments. Propofol reduced postoperative AKI by attenuating oxidative stress in a rat model [26]. Propofol conferred a protective effect against renal ischemia-reperfusion injury by modulating inflammatory cytokines [27,28]. Considering the mechanisms of renal dysfunction after partial nephrectomy involves the ischemia-reperfusion injury by vascular clamping [29], propofol could be beneficial to attenuate AKI after nephrectomy. By reducing the incidence of AKI, propofol could attenuate the risk of CKD subsequently, as AKI is a potent risk factor of postoperative CKD [3,30].

The safety issue of sevoflurane has been raised since its introduction due to potential nephrotoxicity of its metabolite, compound A. However, despite the nephrotoxicity proven in an animal study, clinical studies demonstrated the safety of sevoflurane regarding renal function [19,31]. In a recent randomized trial conducted in patients undergoing kidney transplantation, there was no significant difference in graft outcome between the sevoflurane and propofol groups [32]. Conversely, previous animal studies reported the renal protective effect of sevoflurane [33,34]. However, to our knowledge, there was no previous animal or clinical study comparing propofol and sevoflurane during nephrectomy. The influence of anesthetic agent on renal function may be greater during nephrectomy with frequent and significant postoperative renal functional decline [13,35].

Recent studies reported results advocating propofol, which are consistent with our findings. A previous randomized study reported that the propofol-based anesthesia reduced the incidence of postoperative AKI compared to the sevoflurane group after valvular heart surgery [36]. They measured plasma inflammatory markers and suggested the reno-protective effect was mediated by the anti-inflammatory action of propofol. Propofol-based anesthesia reduced postoperative urinary kidney-specific proteins and serum pro-inflammatory cytokines compared to sevoflurane-based anesthesia in patients undergoing open abdominal aortic aneurysm repair [37]. In addition, in a retrospective study conducted on 4320 patients undergoing colorectal surgery, propofol decreased the incidence of postoperative AKI when compared to sevoflurane [38].

There were also studies reporting no effect of general anesthetic agents on postoperative renal function in other surgical populations. However, the number of studies which reported neutral effect was small. Although study design was different, a previous randomized trial showed no significant differences in renal function between sevoflurane, desflurane, and propofol after elective surgery [39]. However, this study involved only a small number of patients and did not limit the type of surgery. There was also no significant difference in the incidence of postoperative AKI after lung surgery between the propofol and sevoflurane in a recent retrospective study [40]. However, the incidence of AKI after lung surgery was as low as 3.5% and larger number of patients are required for sufficient study power.

We performed propensity score analysis and used intraoperative vasopressor infusion as the contributor to the propensity score because vasopressor use could reflect intraoperative hypotension and was reported as an independent risk factor of postoperative AKI [41]. However, a recent retrospective study reported that intraoperative vasopressor infusion was not associated with AKI [42]. Vasopressor infusion during surgery could be a mediator to the development of AKI rather than a confounder because we infuse vasopressor to treat hypotension but vasopressor could also cause AKI [43].

The strength of our study is that we investigated the incidence of new-onset CKD after nephrectomy for 36 months after nephrectomy. Demographic and genetic factors, comorbidity, pre-existing renal disease, and surgical technique are associated with the development of CKD after nephrectomy [14]. However, there have been no reports of the association of anesthetic agents in the surgical population with long-term renal function. Although this was a single-center retrospective study, we demonstrated the possible benefit of propofol to mitigate the risk of CKD as well as AKI compared to volatile agents through rigorous adjustment of possible confounding factors. Matching was performed pairwise like a network analysis including matching for three different pairs of general anesthetics. The consistent results between different pair of network comparison supported our conclusion. However, we did not obtain significant difference in the incidence of AKI and new-onset CKD in the subgroup of partial nephrectomy. The incidence of AKI after partial nephrectomy is lower than the incidence after radical nephrectomy [11]. The incidences of AKI after partial and radical nephrectomy in our study were 16.0% and 58.0%, respectively. The incidences of new-onset CKD after partial and radical nephrectomy were 22.0% and 69.1%, respectively. As the incidences of AKI and CKD after partial nephrectomy are much lower than radical nephrectomy, a larger number of patients than our study would be required to detect any difference in the incidence of AKI or CKD after partial nephrectomy. Therefore, our subgroup analysis of partial nephrectomy may lack sufficient power.

The results of our study should be interpreted cautiously under several limitations. First, it was a single-center retrospective analysis. Unmeasured or unknown confounders may have affected our study results. However, the pair-wise propensity score matching was used to minimize confounding. Sensitivity analyses of secondary outcomes yielded consistent results. Secondly, we did not exclude the patients with pre-existing CKD stage 3a or high not to decrease the study power. This might affect the incidence of AKI because preoperative CKD is known to be an important risk factor of postoperative AKI [44]. Furthermore, acute-on-chronic kidney injury is a different disease entity from AKI [45]. However, to minimize confounding by the baseline renal function, we used preoperative eGFR and serum albumin as contributors to the propensity score analysis. Furthermore, our secondary outcome of CKD upstaging could detect the renal functional decline even in the patients with baseline CKD. Thirdly, we used only serum creatinine concentration except urine output to diagnose the AKI. However, urine output criteria may be inaccurate due to mannitol infusion during partial nephrectomy [11]. Fourthly, we included all types of surgical approach, which was reported to be associated with postoperative AKI [10]. However, we could not perform the subgroup analysis according to the type of surgical approach due to the small number of patients in each surgical category. We only performed a propensity score analysis using the type of surgical approach and operation time as contributors. Fifthly, mannitol was routinely administered in our patients undergoing partial nephrectomy, but a recent randomized trial showed no effect of mannitol infusion on postoperative renal function [46]. However, since mannitol infusion did not affect postoperative eGFR [46] and we did not use the urine output criteria of AKI, the effect of mannitol on our study results would be insignificant. Sixthly, in the volatile groups, propofol bolus dose was used to induce anesthesia and this might have some residual effect in the volatile groups. However, propofol is distributed and eliminated rapidly after single bolus injection [47]. Therefore, the dose of propofol (1–2 mg/kg) used during anesthesia induction would not be a significant confounder for our analysis. Lastly, we performed post hoc power analysis instead of prior power analysis due to the limited number of patients. A sufficient number of patients were not included for the primary outcome according to our post hoc power calculation.

5. Conclusions

In our propensity score-matched comparison of the general anesthetic agents in patients undergoing radical and partial nephrectomy, propofol was associated with a lower incidence of postoperative AKI and CKD upstaging compared to sevoflurane or desflurane. The three-year renal survival after nephrectomy was also significantly better for propofol compared to volatile agents. Therefore, in patients receiving nephrectomy, propofol may be the reasonable general anesthetic agent to mitigate postoperative renal functional deterioration compared to volatile agents. However, inconsistent subgroup analysis of partial nephrectomy and significant limitations of our study design preclude a firm conclusion.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/10/1530/s1, Table S1: Comparison of incidence of primary and secondary outcomes between patients according to the main anesthetic agents (propofol vs. volatile agents) during surgery before and after propensity score matching, Table S2: Comparison of incidence of primary and secondary outcomes between patients according to the main anesthetic agents (propofol vs. volatile agents) before and after propensity score matching in the subgroup of partial nephrectomy, Figure S1: Histograms (left) and covariate balance plot (right) of distribution of standardized differences of covariates between the patients who received propofol and sevoflurane during surgery in all cohort, Figure S2: Histograms (left) and covariate balance plot (right) of distribution of standardized differences of covariates between the patients who received propofol and desflurane during surgery in all cohort, Figure S3: Histograms (left) and covariate balance plot (right) of distribution of standardized differences of covariates between the patients who received sevoflurane and desflurane during surgery in all cohort, Figure S4: Histograms (left) and covariate balance plot (right) of distribution of standardized differences of covariates between the patients who received propofol and volatile agents during surgery in all cohort, Figure S5: Kaplan-Meier survival curve analysis of new-onset chronic kidney disease according to the main anesthetic agents (TIVA vs. volatile agents) before (A) and after (B) propensity score matching in all cohort, Figure S6: Histograms (left) and covariate balance plot (right) of distribution of standardized differences of covariates between the patients who received propofol and volatile agents during surgery in the subgroup of partial nephrectomy, Figure S7: Kaplan-Meier survival curve analysis of new-onset chronic kidney disease according to the main anesthetic agents (TIVA vs. volatile agents) before (A) and after (B) propensity score matching in the subgroup of partial nephrectomy.

Author Contributions: Data curation, formal analysis, investigation, visualization, writing-original draft, H-J.L.; writing review and editing, J.B., Y.K., H.S.J., S.Y.; supervision, writing review and editing, J-T.K.; data curation, writing—review and editing, C.W.J.; conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, W.H.K.

Conflicts of Interest: The authors declared that they have no conflicts of interest.

References

1. Znaor, A.; Lortet-Tieulent, J.; Laversanne, M.; Jemal, A.; Bray, F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur. Urol.* **2015**, *67*, 519–530. [CrossRef] [PubMed]
2. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Dabestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyk, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma, the 2019 Update. *Eur. Urol.* **2019**, *75*, 799–810. [CrossRef] [PubMed]
3. Garofalo, C.; Liberti, M.E.; Russo, D.; Russo, L.; Fuiano, G.; Cianfrone, P.; Conte, G.; De Nicola, L.; Minutolo, R.; Borrelli, S. Effect of post-nephrectomy acute kidney injury on renal outcome, a retrospective long-term study. *World J. Urol.* **2018**, *36*, 59–63. [CrossRef] [PubMed]
4. Schmid, M.; Krishna, N.; Ravi, P.; Meyer, C.P.; Becker, A.; Dalela, D.; Sood, A.; Chun, F.K.H.; Kibel, A.S.; Menon, M.; et al. Trends of acute kidney injury after radical or partial nephrectomy for renal cell carcinoma. *Urol. Oncol.* **2016**, *34*, 293-e1–293-e10. [CrossRef] [PubMed]
5. Grams, M.E.; Rabb, H. The distant organ effects of acute kidney injury. *Kidney Int.* **2012**, *81*, 942–948. [CrossRef] [PubMed]
6. Weight, C.J.; Larson, B.T.; Fergany, A.F.; Gao, T.; Lane, B.R.; Campbell, S.C.; Kaouk, J.H.; Klein, E.A.; Novick, A.C. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J. Urol.* **2010**, *183*, 1317–1323. [CrossRef] [PubMed]

7. Hobson, C.; Ozrazgat-Baslanti, T.; Kuxhausen, A.; Thottakkara, P.; Efron, P.A.; Moore, F.A.; Moldawer, L.L.; Segal, M.S.; Bihorac, A. Cost and Mortality Associated with Postoperative Acute Kidney Injury. *Ann. Surg.* **2015**, *261*, 1207–1214. [CrossRef]
8. Bellomo, R.; Kellum, J.A.; Ronco, C. Acute kidney injury. *Lancet* **2012**, *380*, 756–766. [CrossRef]
9. Rajan, S.; Babazade, R.; Govindarajan, S.R.; Pal, R.; You, J.; Mascha, E.J.; Khanna, A.; Yang, M.; Marcano, F.D.; Singh, A.K.; et al. Perioperative factors associated with acute kidney injury after partial nephrectomy. *Br. J. Anaesth.* **2016**, *116*, 70–76. [CrossRef]
10. Schmid, M.; Gandaglia, G.; Sood, A.; Olugbade, K., Jr.; Ruhotina, N.; Sammon, J.D.; Varda, B.; Chang, S.L.; Kibel, A.S.; Chun, F.K.; et al. Predictors of 30-day acute kidney injury following radical and partial nephrectomy for renal cell carcinoma. *Urol. Oncol.* **2014**, *32*, 1259–1266. [CrossRef]
11. Hur, M.; Park, S.K.; Yoo, S.; Choi, S.N.; Jeong, C.W.; Kim, W.H.; Kim, J.T.; Kwak, C.; Bahk, J.H. The association between intraoperative urine output and postoperative acute kidney injury differs between partial and radical nephrectomy. *Sci. Rep.* **2019**, *9*, 760. [CrossRef] [PubMed]
12. Kim, N.Y.; Hong, J.H.; Koh, D.H.; Lee, J.; Nam, H.J.; Kim, S.Y. Effect of Diabetes Mellitus on Acute Kidney Injury after Minimally Invasive Partial Nephrectomy, A Case-Matched Retrospective Analysis. *J. Clin. Med.* **2019**, *8*, 468. [CrossRef] [PubMed]
13. Mir, M.C.; Ercole, C.; Takagi, T.; Zhang, Z.; Velet, L.; Remer, E.M.; Demirjian, S.; Campbell, S.C. Decline in renal function after partial nephrectomy, etiology and prevention. *J. Urol.* **2015**, *193*, 1889–1898. [CrossRef] [PubMed]
14. Li, L.; Lau, W.L.; Rhee, C.M.; Harley, K.; Kovesdy, C.P.; Sim, J.J.; Jacobsen, S.; Chang, A.; Landman, J.; Kalantar-Zadeh, K. Risk of chronic kidney disease after cancer nephrectomy. *Nat. Rev. Nephrol.* **2014**, *10*, 135–145. [CrossRef] [PubMed]
15. Salmasi, V.; Maheshwari, K.; Yang, D.; Mascha, E.J.; Singh, A.; Sessler, D.I.; Kurz, A. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac SurgeryA retrospective cohort analysis. *Anesthesiology* **2017**, *126*, 47–65. [CrossRef] [PubMed]
16. Kil, H.; Kim, J.; Choi, Y.; Lee, H.; Kim, T. Effect of Combined Treatment of Ketorolac and Remote Ischemic Preconditioning on Renal Ischemia-Reperfusion Injury in Patients Undergoing Partial Nephrectomy, Pilot Study. *J. Clin. Med.* **2018**, *7*, E470. [CrossRef] [PubMed]
17. Song, L.; Shi, S.; Jiang, W.; Liu, X.; He, Y. Protective role of propofol on the kidney during early unilateral ureteral obstruction through inhibition of epithelial-mesenchymal transition. *Am. J. Transl. Res.* **2016**, *8*, 460. [PubMed]
18. Li, Y.; Zhong, D.; Lei, L.; Jia, Y.; Zhou, H.; Yang, B. Propofol prevents renal ischemia-reperfusion injury via inhibiting the oxidative stress pathways. *Cell. Physiol. Biochem.* **2015**, *37*, 14–26. [CrossRef] [PubMed]
19. Gentz, B.A.; Malan, T.P. Renal toxicity with sevoflurane. *Drugs* **2001**, *61*, 2155–2162. [CrossRef]
20. Kong, H.Y.; Zhu, S.M.; Wang, L.Q.; He, Y.; Xie, H.Y.; Zheng, S.S. Sevoflurane protects against acute kidney injury in a small-size liver transplantation model. *Am. J. Nephrol.* **2010**, *32*, 347–355. [CrossRef]
21. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef] [PubMed]
22. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef] [PubMed]
23. Shin, S.R.; Kim, W.H.; Kim, D.J.; Shin, I.W.; Sohn, J.T. Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery. *BioMed Res. Int.* **2016**, *2016*, 2985148. [CrossRef] [PubMed]
24. Eknoyan, G.; Lameire, N.; Eckardt, K.; Kasiske, B.; Wheeler, D.; Levin, A.; Stevens, P.E.; Bilous, R.W.; Lamb, E.J.; Coresh, J.; et al. Kidney Disease, Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* **2013**, *3*, 1–150.
25. Levey, A.S.; Coresh, J.; Greene, T.; Stevens, L.A.; Zhang, Y.L.; Hendriksen, S.; Kusek, J.W.; Van Lente, F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann. Intern. Med.* **2006**, *145*, 247–254. [CrossRef] [PubMed]

26. Luo, C.; Yuan, D.; Li, X.; Yao, W.; Luo, G.; Chi, X.; Li, H.; Irwin, M.G.; Xia, Z.; Hei, Z. Propofol attenuated acute kidney injury after orthotopic liver transplantation via inhibiting gap junction composed of connexin 32. *Anesthesiology* **2015**, *122*, 72–86. [CrossRef] [PubMed]
27. Hsing, C.-H.; Chou, W.; Wang, J.-J.; Chen, H.-W.; Yeh, C.-H. Propofol increases bone morphogenetic protein-7 and decreases oxidative stress in sepsis-induced acute kidney injury. *Nephrol. Dial. Transplant.* **2010**, *26*, 1162–1172. [CrossRef] [PubMed]
28. Sánchez-Conde, P.; Rodriguez-Lopez, J.M.; Nicolás, J.L.; Lozano, F.S.; García-Criado, F.J.; Cascajo, C.; González-Sarmiento, R.; Muriel, C. The comparative abilities of propofol and sevoflurane to modulate inflammation and oxidative stress in the kidney after aortic cross-clamping. *Anesth. Analg.* **2008**, *106*, 371–378. [CrossRef] [PubMed]
29. Zabell, J.R.; Wu, J.; Suk-Ouichai, C.; Campbell, S.C. Renal ischemia and functional outcomes following partial nephrectomy. *Urol. Clin.* **2017**, *44*, 243–255. [CrossRef]
30. Cho, A.; Lee, J.E.; Kwon, G.Y.; Huh, W.; Lee, H.M.; Kim, Y.G.; Kim, D.J.; Oh, H.Y.; Choi, H.Y. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol. Dial. Transplant.* **2011**, *26*, 3496–3501. [CrossRef]
31. Kharasch, E.D.; Frink, E.J.; Artru, A., Jr.; Michalowski, P.; Rooke, G.A.; Nogami, W. Long-duration low-flow sevoflurane and isoflurane effects on postoperative renal and hepatic function. *Anesth. Analg.* **2001**, *93*, 1511–1520. [CrossRef] [PubMed]
32. Nieuwenhuijs-Moeke, G.J.; Nieuwenhuijs, V.B.; Seelen, M.A.J.; Berger, S.P.; Van Den Heuvel, M.C.; Burgerhof, J.G.M.; Ottens, P.J.; Ploeg, R.J.; Leuvenink, H.G.D.; Struys, M.M.R.F. Propofol-based anaesthesia versus sevoflurane-based anaesthesia for living donor kidney transplantation, results of the VAPOR-1 randomized controlled trial. *Br. J. Anaesth.* **2017**, *118*, 720–732. [CrossRef] [PubMed]
33. Lee, H.T.; Chen, S.W.; Doetschman, T.C.; Deng, C.; D'Agati, V.D.; Kim, M. Sevoflurane protects against renal ischemia and reperfusion injury in mice via the transforming growth factor-β1 pathway. *Am. J. Physiol. Renal Physiol.* **2008**, *295*, F128–F136. [CrossRef] [PubMed]
34. Lee, H.T.; Kim, M.; Song, J.H.; Chen, S.W.; Gubitosa, G.; Emala, C.W. Sevoflurane-mediated TGF-β1 signaling in renal proximal tubule cells. *Am. J. Physiol. Renal Physiol.* **2008**, *294*, F371–F378. [CrossRef] [PubMed]
35. Scosyrev, E.; Messing, E.M.; Sylvester, R.; Campbell, S.; Van Poppel, H. Renal function after nephron-sparing surgery versus radical nephrectomy, results from EORTC randomized trial 30904. *Eur. Urol.* **2014**, *65*, 372–377. [CrossRef]
36. Yoo, Y.C.; Shim, J.K.; Song, Y.; Yang, S.Y.; Kwak, Y.L. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. *Kidney Int.* **2014**, *86*, 414–422. [CrossRef]
37. Ammar, A.; Mahmoud, K. Comparative effect of propofol versus sevoflurane on renal ischemia/reperfusion injury after elective open abdominal aortic aneurysm repair. *Saudi J. Anaesth.* **2016**, *10*, 301.
38. Bang, J.Y.; Lee, J.; Oh, J.; Song, J.G.; Hwang, G.S. The Influence of Propofol and Sevoflurane on Acute Kidney Injury after Colorectal Surgery, A Retrospective Cohort Study. *Anesth. Analg.* **2016**, *123*, 363–370. [CrossRef]
39. Ebert, T.J.; Arain, S.R. Renal responses to low-flow desflurane, sevoflurane, and propofol in patients. *Anesthesiology* **2000**, *93*, 1401–1406. [CrossRef]
40. Oh, T.K.; Kim, J.; Han, S.; Kim, K.; Jheon, S.; Ji, E. Effect of sevoflurane-based or propofol-based anaesthesia on the incidence of postoperative acute kidney injury, A retrospective propensity score-matched analysis. *Eur. J. Anaesthesiol.* **2019**, *36*, 649–655.
41. Kheterpal, S.; Tremper, K.K.; Englesbe, M.J.; O'Reilly, M.; Shanks, A.M.; Fetterman, D.M.; Rosenberg, A.L.; Swartz, R.D. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology* **2007**, *107*, 892–902. [CrossRef] [PubMed]
42. Farag, E.; Makarova, N.; Argalious, M.; Cywinski, J.B.; Benzel, E.; Kalfas, I.; Sessler, D.I. Vasopressor infusion during prone spine surgery and acute renal injury, A retrospective cohort analysis. *Anesth. Analg.* **2019**, *219*, 896–904. [CrossRef] [PubMed]
43. Mascha, E.J.; Dalton, J.E.; Kurz, A.; Saager, L. Statistical grand rounds, understanding the mechanism, mediation analysis in randomized and nonrandomized studies. *Anesth. Analg.* **2013**, *117*, 980–994. [CrossRef]
44. Kheterpal, S.; Tremper, K.K.; Heung, M.; Rosenberg, A.L.; Englesbe, M.; Shanks, A.M.; Campbell, D.A. Development and validation of an acute kidney injury risk index for patients undergoing general surgery, results from a national data set. *Anesthesiology* **2009**, *110*, 505–515. [CrossRef]

45. Stucker, F.; Ponte, B.; De la Fuente, V.; Alves, C.; Rutschmann, O.; Carballo, S.; Vuilleumier, N.; Martin, P.Y.; Perneger, T.; Saudan, P. Risk factors for community-acquired acute kidney injury in patients with and without chronic kidney injury and impact of its initial management on prognosis, a prospective observational study. *BMC Nephrol.* **2017**, *18*, 380. [CrossRef] [PubMed]
46. Spaliviero, M.; Power, N.E.; Murray, K.S.; Sjoberg, D.D.; Benfante, N.E.; Bernstein, M.L.; Wren, J.; Russo, P.; Coleman, J.A. Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function, a double-blind, clinically-integrated, randomized trial. *Eur. Urol.* **2018**, *73*, 53–59. [CrossRef] [PubMed]
47. Cockshott, I.D.; Briggs, L.P.; Douglas, E.J.; White, M. Pharmacokinetics of propofol in female patients, studies using single bolus injections. *Br. J. Anaesth.* **1987**, *59*, 1103–1110. [CrossRef] [PubMed]

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Continuous Renal Replacement Therapy (CRRT) in Children and the Specialized CRRT Team: A 14-Year Single-Center Study

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Abstract: Continuous renal replacement therapy (CRRT) has been used as an important intervention in critically ill children. Our center has the only specialized CRRT team (SCT) for children in Korea, which consists of pediatric intensivists, a pediatric nephrologist and CRRT-specialized-nurses. This study was a retrospective single-center analysis, including all pediatric patients admitted to the intensive care unit (ICU) of Severance hospital in Korea and received CRRT between 2003 and 2016, grouped as before SCT (group A, $n = 51$) and after SCT (group B, $n = 212$). We obtained the data for sex, age, weight, diagnosis, blood flow rate or type of CRRT machine used, administration of inotropic agents or anticoagulants, and ICU duration before CRRT (hours). A total of 263 patients were included. The age was significantly younger ($p < 0.001$) and blood flow rate was lower ($p = 0.001$) in group B than group A. Vasopressors ($p < 0.001$), continuous veno-venous hemodiafiltration (CVVHDF) ($p < 0.001$), nafamostat mesilate ($p < 0.001$), and extracorporeal membrane oxygenation (ECMO)-CRRT ($p = 0.004$) were more frequently used in group B. Based on our 14-year experience, we conclude that SCT operation could have played an important role in increasing the amount of CRRT utilization.

Keywords: continuous renal replacement therapy (CRRT); specialized CRRT team (SCT); retrospective study

1. Introduction

Acute kidney injury (AKI) is defined according to the elevated plasma creatinine level and decreased urine output [1–4]. It shows diverse clinical manifestations ranging from asymptomatic, through anuria, to multiple organ dysfunctions [5,6]. The prevalence of AKI has been reported to be about 30%–60% for critically ill patients in an intensive care unit (ICU) [7]. In 2017, Kaddourah et al. reported that AKI developed in 26.9%, and severe AKI (renal replacement therapy required) developed in 11.6% of the children in ICU during the first seven days after ICU admission [8]. They

also described that AKI itself may crucial to the associated morbidity and mortality and the mortality rate in severe AKI group could be up to 20% [8].

From this point of view, since continuous renal replacement therapy (CRRT) was first introduced by Kramer et al. in 1977 [9], and pediatric CRRT was first used in 1985 [10]; it has been the most important renal replacement modality in critically ill patients. Although both hemodialysis (HD) and peritoneal dialysis (PD) are established interventions for patients who require renal replacement, CRRT is known to be a more efficient therapy for stabilizing circulatory, acid-base, and electrolyte balance when the patient has unstable vital parameters [11].

As well as technological advances, other attempts in worldwide have been made to drive the success of the CRRT in the critical patient with AKI. In adult patients, Ronco et al. firstly emphasized the importance of a multidisciplinary approach, including collaboration between various clinical teams [12,13]. After then, several centers opened a specialized CRRT team (SCT) to manage CRRT [14], and two recent observational studies showed that patients had improved CRRT outcomes after the SCT approach [15,16].

Despite several studies that have been published demonstrating that CRRT is a very important therapy for critically ill children so far [17–19], there have been no reports about the real efficacy of a SCT in the clinic and managing results. Our center is the biggest tertiary care center in Korea with over 14 years of experience in CRRT and has the only specialized CRRT team (SCT) for children in Korea, which consists of pediatric intensivists, a pediatric nephrologist, and CRRT-specialized nurses. Because the SCT was started in August 2008, the objective of this study was to compare and analyze the factors before and after starting SCT management.

2. Methods

2.1. Search Strategy

Medical records of 291 patients were collected from January 1, 2003 to April 30, 2016. Of these, 28 underwent more than one CRRT treatment run. Final analysis was done by removing duplicates and leaving only the longest CRRT run.

During the study period, patients undergoing CRRT were included and grouped as before SCT (group A) and after SCT (group B). Group A included patients treated from March 2003 to July 2008 and group B those from August 2008 to April 2016. Before SCT, pediatric CRRT was run by occasional operators, but after the SCT began, ICU nurses joined and began to work as the member of SCT. Double-lumen catheters ranging between 6.5 and 13.5 F in diameter (Gambro Healthcare, Lakewood, CO, USA) were inserted into the central veins depending on the child's age and weight. Polyarylethersulfone hollow-fiber hemofilters (PAES; the Prismaflex® HF20, Gambro Lundia AB, Lund, Sweden) and polyacrilonytrile hollow-fiber hemofilters (① AN69® membrane before the year 2010; the Prismaflex® M-10/60/100, Gambro Lundia AB, Lund, Sweden; ② AN69® ST membrane since the year 2010; the Prismaflex® ST-60/100, Gambro Lundia AB, Lund, Sweden) were used in all patients, depending on the patient's weight. HF-20 or M-10 were used in children weighing less than 10 kg; ST-60 or M-60 were used in patients weighing 10–20 kg, and ST-100 or M-100 were used in children weighing more than 20 kg. Commercially prepared bicarbonate-buffered hemofiltration replacement fluid (Hemosol B0; Gambro Healthcare, Seoul, Korea; potassium free), was used as a dialysate and replacement fluid. Potassium chloride (KCl) was added if the patient has a risk of hypokalemia (20 mEq KCl mix in the 5L Hemozol® when serum potassium level ranged from 3.6 to 4.5 mEg/L and 40 mEq KCl mix in the 5L Hemozol® when serum potassium level lowered than 3.6 mEg/L). The blood flow rate was set as 5 mL/kg/min [18]. The predilution replacement fluid rate or dialysate rate was set at a rate of 2000 mL/1.73 m^2/hour [18]. The mode of CRRT was selected from one of the following, depending on the patient's status of solute imbalance: continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration

(CVVHDF). These were determined by the pediatric nephrologist and pediatric intensivist through in-depth discussion.

The time to initiate CRRT was decided by the pediatric intensivist, depending on each patient's clinical condition, such as anuria, oliguria (<0.5 mL/kg/hour), or positive fluid balance, regardless of administration of high doses of diuretics (furosemide more than 1 mg/kg/hour). Anticoagulation was not administered during CRRT initiation; however, our protocol establishes that if the filter was blocked within 12 hours of CRRT initiation, anticoagulation agents such as continuous heparin or nafamostat mesilate infusion via the pre-blood pump port were used. The percentage of fluid overload at CRRT initiation (%FO) was calculated using the following formula [20]:

$$\%FO = (\text{Fluid In} - \text{Fluid Out})/(\text{ICU admission weight}) \times 100\% \quad (1)$$

At the initiation of CRRT, the following data were obtained for all patients: sex, age, diagnosis, underlying patient conditions, blood flow rate, use of inotropic agents, anticoagulants, and hours to starting CRRT.

2.2. Definition of SCT

The SCT is a specialized team of physicians and nurses who perform pediatric CRRT. It includes a pediatric nephrologist, pediatric intensivists, nephrologists (internal medicine), and five CRRT-specialized nurses. The pediatric intensivist oversees the critical care and overall decisions on critically ill children–related problems. The pediatric nephrologist determines the distribution of CRRT machines depending upon the daily status of adult and pediatric inpatients in the ICU in consultation with the pediatric intensivist and the nephrologists for adults. CRRT-specialized nurses undergo a CRRT-specialized training course, which includes the basic principles, practical operations, alarm control, and troubleshooting of CRRT; checking hemodynamic stability and CRRT kit status; and management of CRRT catheter-related problems. They work three shifts daily, and their role is separate from that of ICU bedside nurses and chronic HD nurses. They regularly monitor the hemodynamic status and CRRT-related problems of children undergoing CRRT. They are in contact with the machine company and monitor periodic inspections to prevent problems of the CRRT machine itself. Every month, the members of the SCT have a conference, where they share their clinical experiences and provide educational feedback on pediatric CRRT.

2.3. Statistical Analysis

Statistical analyses were performed using the SPSS for Windows version 18.0 (IBM Corp., Armonk, NY, USA). An independent *t*-test was used for continuous variables, and they were expressed as means ± standard deviations. Chi-square test and Fisher's exact test were used to analyze the categorical variables. All differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Characteristics of Patients

The demographics and characteristics of the patients treated with CRRT are presented in Table 1. Two hundred and sixty-three patients were included, 212 in group A and 51 in group B. The overall mean age was significantly lower in group B than in group A ($p < 0.001$). There were significantly more patients in group B, especially those aged 1 to 11 months, 3 to 5 years, and 11 to 14 years ($p = 0.003$, $p = 0.022$, $p = 0.013$, respectively).

The use of inotropic agents at CRRT initiation was also significantly higher in group B than in group A ($p < 0.001$). The differences in the male-to-female ratio (17/34 versus 87/125) and the mean durations in the ICU before CRRT initiation were not significantly different between the two groups ($p > 0.05$).

Table 1. Characteristics of patients receiving continuous renal replacement therapy (CRRT).

Variables	Number of Patients (%)		*p*-Value
	Group A (n = 51)	Group B (n = 212)	
Age	5.0 ± 0.0	3.01 ± 0.21	<0.001
<1 month	0 (0.0%)	8 (3.8%)	0.361
1–11 month	1 (2.0%)	37 (17.5%)	0.003
1–2 year	5 (9.8%)	43 (20.3%)	0.082
3–5 year	15 (29.4%)	33 (15.6%)	0.022
6–10 year	12 (23.5%)	38 (17.9%)	0.360
11–14 year	14 (27.5%)	28 (13.2%)	0.013
15–18 year	4 (7.8%)	25 (11.8%)	0.419
Sex			0.312
Male	17 (33.3%)	87 (41.0%)	0.312
Vasopressors at CRRT initiation			<0.001
0	14 (27.5%)	154 (72.6%)	<0.001
>1	37 (72.5%)	58 (27.4%)	<0.001
ICU duration before CRRT (hours)	6.72 ± 6.39	5.78 ± 6.80	0.476

CRRT: continuous renal replacement therapy; ICU: intensive care unit.

The diagnoses of patients who received CRRT were renal disease (e.g., nephrotic syndrome and hemolytic uremic syndrome (HUS)), malignancy and drug intoxication. Cardiac diseases were significantly higher in group B than in group A (p = 0.001), and they negatively affect outcome. Malignancy was the most common underlying disease in both groups (70.6% in group A and 36.3% in group B). In contrast to cardiac disease, malignancy was more frequent in group A than in group B, with a statistically significant difference (p < 0.001) (Table 2).

Table 2. Underlying diseases of patients receiving CRRT.

Parameter	Number of Patients (%)		*p*-Value
	Group A (n = 51)	Group B (n = 212)	
Neurologic disease	5 (9.8%)	43 (20.3%)	0.112
Cardiac disease	2 (3.8%)	31 (14.6%)	0.001
Renal disease	3 (5.8%)	16 (7.5%)	1.000
Nephrotic syndrome	1 (1.9%)	2 (0.9%)	1.000
Obstructive uropathy	0 (0.0%)	2 (0.9%)	1.000
HUS	1 (1.9%)	3 (1.4%)	0.580
Rhabdomyolysis	0 (0.0%)	4 (1.9%)	1.000
Denys-Drash syndrome	1 (1.9%)	1 (0.5%)	0.351
AKI on CKD †	0 (0.0%)	4 (1.9%)	1.000
Liver disease	1 (2.0%)	20 (9.4%)	0.088
Malignancy	36 (70.6%)	77 (36.3%)	<0.001
No tumor lysis syndrome	35 (68.7%)	72 (34.0%)	<0.001
Tumor lysis syndrome	1 (1.9%)	5 (2.3%)	1.000
Drug intoxication	0 (0.0%)	1 (0.5%)	1.000
Pulmonary disease	1 (2.0%)	11 (5.2%)	0.471
Metabolic disease	1 (2.0%)	1 (0.5%)	0.351
Immune deficiency	0 (0.0%)	1 (0.5%)	1.000
Sepsis	1 (2.0%)	11 (5.2%)	0.471
Other	1 (2.0%)	0 (0.0%)	0.194

CRRT: continuous renal replacement therapy; HUS: hemolytic uremic syndrome; AKI: acute kidney injury; CKD: chronic kidney disease. † Patients who are CKD stage 3–5, not depending upon the cause of CKD. These patients received CRRT due to aggravation of AKI.

The indications for initiating CRRT are listed in Table 3. The most common indications for CRRT in both groups were oliguria refractory to diuretic treatment (54.9% in group A and 49.5% in group B). Fluid overload and sepsis were marked significantly higher in group B than in group A ($p = 0.041$, $p = 0.027$, respectively).

Table 3. Indications of initiating CRRT.

Indication	Total Number of Patients (%) *		*p*-Value
	Group A ($n = 51$)	Group B ($n = 212$)	
Oliguria	28(54.9%)	105(49.5%)	0.491
Fluid overload	28(54.9%)	83(39.2%)	0.041
Uremia	27(52.9%)	96(45.3%)	0.325
Metabolic acidosis	3(5.9%)	30(14.2%)	0.156
Electrolyte imbalance	8(15.7%)	20(9.4%)	0.208
Sepsis	9(17.6%)	16(7.5%)	0.027
Others †	1(2.0%)	8(3.8%)	1.000

CRRT: continuous renal replacement therapy. * Duplicates are allowed. † Other indications contain kidney transplantation, applied immediately after continuous ambulatory peritoneal dialysis catheter insertion, rhabdomyolysis, operation, etc.

Table 4 demonstrates a comparison of the laboratory variables between the group A and B. There were statistically significant differences between the groups in white blood cell counts ($p = 0.022$) and platelet counts ($p < 0.001$). Other parameters, including blood urea nitrogen (BUN) and creatinine, had no significant difference ($p > 0.05$).

Table 4. Laboratory results of patients receiving CRRT.

Parameter	Group A ($n = 51$)	Group B ($n = 212$)	*p*-Value
Complete blood count			
WBC (/mm^3)	6584.78 ± 8331.47	12822.82 ± 12368.29	0.022
Hemoglobin (g/L)	9.32 ± 2.53	9.63 ± 2.31	0.569
Hematocrit (%)	26.83 ± 7.52	29.33 ± 7.53	0.147
Platelet count (×10^3/μL)	81.30 ± 61.36	160.84 ± 149.86	<0.001
Coagulation tests			
Prothrombin Time (s)	30.53 ± 35.66	28.14 ± 29.32	0.737
aPTT (s)	71.00 ± 50.98	72.87 ± 55.14	0.884
ABGA			
pH	7.33 ± 0.17	7.27 ± 0.18	0.147
pCO_2 (mmHg)	44.21 ± 26.20	41.98 ± 25.57	0.704
pO_2 (mmHg)	92.20 ± 73.53	99.97 ± 67.20	0.619
Lactate (mg/dL)	4.20 ± 0.00	7.03 ± 5.90	0.634
Routine chemistry			
Glucose (mg/dL)	135.32 ± 103.59	144.63 ± 82.83	0.644
Potassium (mg/dL)	4.11 ± 1.18	4.43 ± 1.50	0.342
tCO_2 (mg/dL)	20.27 ± 8.09	17.29 ± 7.17	0.081
BUN (mg/dL)	32.60 ± 18.43	39.21 ± 38.54	0.433
Creatinine (mg/dL)	1.53 ± 1.30	1.97 ± 2.95	0.497

WBC: white blood cell; aPTT: activated partial thromboplastin time; ABGA: arterial blood gas analysis; pH: acidity; pCO_2: partial pressure of carbon dioxide; pO_2: partial pressure of oxygen; tCO_2: total carbon dioxide; BUN: blood urea nitrogen.

3.2. Technical Characteristics of CRRT

The details of the technical characteristics of CRRT are shown in Table 5. In the univariate analyses, more children in group B significantly received a combination of diffusion and convection (CVVHDF)

($p < 0.001$) and fewer received the diffusion-only CRRT modality (CVVHD) ($p < 0.001$). In both groups, only one patient received the convective modality (CVVH).

Table 5. Technical characteristics of CRRT.

Characteristics	Number of Patients (%)		*p*-Value
	Group A ($n = 51$)	Group B ($n = 212$)	
Modality			<0.001
CVVH	0 (0.7%)	1 (0.5%)	1.000
CVVHD	47 (92.2%)	17 (8.0%)	<0.001
CVVHDF	4 (7.8%)	194 (91.5%)	<0.001
Anticoagulation			<0.001
No anticoagulation	29 (56.9%)	119 (56.1%)	0.925
Heparin	19 (37.2%)	22 (10.4%)	<0.001
Nafamostat mesilate	2 (3.9%)	60 (28.3%)	<0.001
Nafamostat mesilate → Heparin	0 (0.0%)	6 (2.8%)	0.600
Heparin → Nafamostat mesilate	1 (2.0%)	5 (2.4%)	1.000
Initial catheter position			<0.001
Left femoral	13 (25.5%)	70 (33.0%)	0.299
Right femoral	21 (41.2%)	54 (25.5%)	0.026
Right internal jugular	1 (2.0%)	26 (12.3%)	0.036
Left internal jugular	0 (0.0%)	19 (9.0%)	0.029
Subclavian	7 (13.7%)	16 (7.5%)	0.131
ECMO (PCPS)	0 (0.0%)	27 (12.7%)	0.004
No information *	9 (17.6%)	0 (0.0%)	<0.001
Blood flow rate (mL/min)	89.86 ± 36.13	70.64 ± 29.59	0.001
Range	30–180	15–120	0.001

CRRT: continuous renal replacement therapy; CVVH: continuous veno-venous hemofiltration. CVVHD: continuous veno-venous hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration ECMO: extracorporeal membrane oxygenation; PCPS: percutaneous cardiopulmonary support. * There was no information about catheter position in the patient chart.

A total of 148 (56.3%) patients were initiated on CRRT without anticoagulants. More patients in group B were initiated on CRRT with a single infusion of nafamostat mesilate ($p < 0.001$) and a single dose of heparin ($p < 0.001$) once the hemofilter clotted within 12 hours. When anticoagulation started, six (2.8%) patients in group B were switched from heparin to nafamostat mesylate, and five (2.4%) patients were switched from nafamostat mesilate to heparin, but it was not statistically significant ($p > 0.05$). The mean blood flow rate was lower in group B than in group A ($p = 0.001$).

The most common sites of insertion of the initial hemocatheter are the right and left femoral veins in groups A and B, respectively. Since the administration of extracorporeal membrane oxygenation (ECMO)-CRRT to a patient in January 2, 2012, all 27 (12.7%) patients who underwent simultaneous ECMO and CRRT belonged in group B ($p = 0.004$). In most of such cases, the CRRT pump was cannulated into the ECMO circuit. There were only two cases in 2013, including the first case; however, the number of cases had been increasing dramatically over the years following the increase in the rate of CRRT utilization (Figure 1).

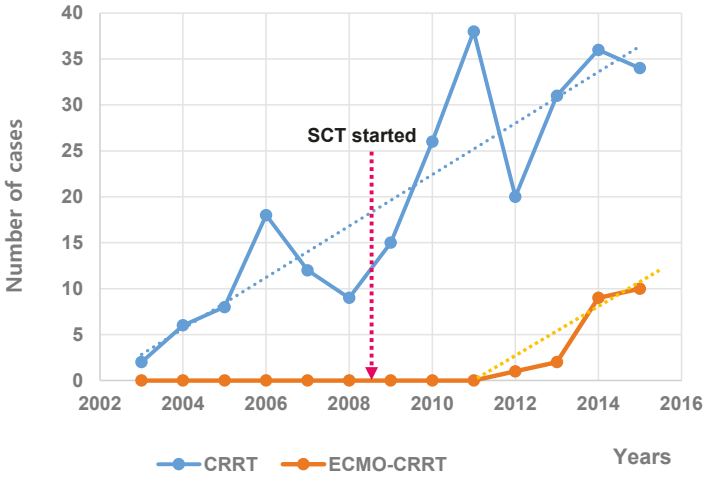

Figure 1. Distribution of CRRT and ECMO-CRRT numbers according to the years. CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane oxygenation; SCT: specialized CRRT team.

Three different types of CRRT machines were used in pediatric patients: the MultiFiltrate™ CRRT device (FMC), PRISMA® (Gambro Healthcare, Lakewood, CO, USA), and PRISMAFLEX® (Gambro Healthcare). Both PRISMA® and PRISMAFLEX® were more frequently used in group B than in group A, with a statistically significant difference ($p < 0.001$, $p < 0.001$). Only one patient received CRRT with the FMC machine (Table 6).

Table 6. Distribution of CRRT machines which used to patients.

CRRT Machines	Number of Patients (%)		*p*-Value
	Group A (n = 51)	Group B (n = 212)	
PRISMA ®	51 (100.0%)	166 (78.3%)	<0.001
PRISMAFLEX ®	0 (0.0%)	45 (21.2%)	<0.001
FMC ®	0 (0.0%)	1 (0.5%)	1.000

CRRT: continuous renal replacement therapy.

Table 7 shows a comparison of the outcomes and parameters between two groups. There were no differences in the duration between CRRT, number of filters used and transfusion during CRRT treatment run, and urine output. Mortality also showed no statistically significance between both groups ($p > 0.05$).

Table 7. Comparison of outcomes and parameters between the groups in patients receiving CRRT.

Valuables	Group A (n = 51)	Group B (n = 212)	*p*-Value
Duration of CRRT ± SD (days)	6.72 ± 6.39	5.85 ± 6.83	0.508
Number of filter use during CRRT ± SD (n) †	3.67 ± 3.66	4.79 ± 4.39	0.091
Number of TF during CRRT ± SD (n) †	0.53 ± 1.50	0.20 ± 0.59	0.133
%FO at CRRT (%)	5.97 ± 7.61	7.35 ± 8.40	0.348
Urine output rate at CRRT (mL/kg/h)	1.24 ± 1.53	1.49 ± 1.80	0.427
CRRT mortality, n (%)	34 (66.7%)	150 (70.8%)	0.863

CRRT: continuous renal replacement therapy; TF: transfusion; %FO: percent of fluid overload; SD: standard deviation.
† Number of filters used and TFs during CRRT were counted per patient.

4. Discussion

In our study, the increase in the use of CRRT followed the general world trend. In our center, there are about 10 cases of PD, including acute peritoneal dialysis and continuous ambulatory peritoneal dialysis, and about 10 cases of intermittent HD annually. In the same periods in which CRRT data were compared, from March 2003 to July 2008, patients treated with PD and HD numbered 90. On the other hand, from August 2008 to April 2016, patients treated with PD and HD numbered 160. Confirming the general trend, CRRT increased more in group B than group A. The possible reasons are: (1) Before CRRT was developed, only PD could be applied to children, but PD could be dangerous for children in poor condition when inserting PD catheter through the abdomen by major surgery. Compared to PD surgery, hemo-catheter insertion is easier to insert with short duration. (2) We could further consider applying CRRT in ICU because HD has hemodynamic problems in children lighter than 20 kg with unstable vital signs.

CRRT is an important treatment modality in the field of intensive care. In critically ill children, appropriate treatment has a significant impact on their survival or prognosis. However, research on CRRT has been delayed compared to that on HD or PD worldwide because CRRT must be administered for 24 hours a day, almost all CRRT machines can only be used in the ICU, and a skilled physician is needed to operate these machines. Like elsewhere, in Korea, the numbers of skilled pediatric nephrologists, pediatric intensivists, and well-trained CRRT-specialized nurses are very small, and the number of pediatric patients is much smaller than that of adults. These factors make research on pediatric CRRT difficult.

According to our results, most patients undergoing CRRT were younger than 10 (73.0%), and there were significantly more infants aged 1 to 11 months and children aged 3 to 5 years after initiating SCT ($p = 0.003$, $p = 0.022$). Furthermore, eight neonates were newly started on CRRT. Young patients develop acute kidney injury (AKI) in the early stage, which might progress rapidly, thus requiring renal replacement. If children develop AKI, they should be carefully monitored in the ICU, and early initiation of CRRT should be considered. The intervention of a SCT exclusively dedicated to pediatric CRRT can avoid the dispersion of knowledge by concentrating the expertise in the hands of few, highly specialized operators, thereby maximally exploiting the information coming from a restricted number of patients.

The most common positions for catheter insertion were the left and right femoral veins (60.1%). Probably, as the number of younger patients increases, the femoral site is more easily accessible without ultrasonographic guidance. Besides, as the technique improved, entrance into the right and left internal jugular veins, which was previously difficult, became significantly easier after SCT ($p = 0.036$, $p = 0.029$). Along with the worldwide trend, we increased the number of patients treated with CRRT in recent years (see Figure 1). Before SCT, some patients were initiated on CRRT in the emergency room or in the ward rather than in the ICU. The advent of a SCT allowed us a more specific control over a larger number of patients, standardization of procedures, and catheter related problems. Although not measurable, this may have had a positive impact on patient treatment.

For acceptable number of patients, there were more who started CRRT without vasopressors, and less started on vasopressors in group B, indicating, likely, the early use of CRRT ($p < 0.001$). Our study also showed a significant reduction in blood flow rate significantly after the start of the SCT activity ($p = 0.001$). A possible explanation is the improvement of the machine and filter performance, together with the ability of the SCT to cope with the improvement of technology, in order to obtain adequate results with lesser blood flow rates, and consequently, less hemodynamic stress. SCT may allow for improving diagnose the early AKI, giving early application of CRRT, facilitating decision-making and standardized safe extracorporeal therapy.

Similar to other studies [17,18], the CVVHDF mode was the most common modality used in our study. The initial version of CRRT, which used continuous arteriovenous (AV) filtration modes, is very different from the present one. Because the AV mode is maintained by the patient's own cardiac output, it showed a high access complication rate; thus, it was not widely applied [21]. Since 2000,

after the development of external venovenous circuit pumps, the number of cases using CRRT greatly increased, and it is now a standard therapy for AKI. It effectively resolves fluid retention and improves the electrolyte imbalance simultaneously, especially the CVVHDF mode, which is the most recent modality among the external venovenous modes. In a similar context, the use of PRISMAFLEX®, a more specialized CRRT machine for children, also has increased.

There were 27 (10.3%) patients on percutaneous cardiopulmonary support or with ECMO connected to CRRT. In particular, since the first success of ECMO-CRRT in 2012, the rate of ECMO-CRRT utilization has increased rapidly (Figure 1). As mentioned above, this may be due to the fact that the CRRT backup of the SCT has performed well following the development of ECMO technology. The methods of CRRT connection to ECMO, duration of use, and the difference in survival rate were not separately analyzed in this study. Additional studies should be undertaken if plasmapheresis is performed simultaneously with CRRT in patients with liver disease.

The major difference in the use of anticoagulants is that citrate was used in patients with a bleeding tendency in the US study [17], whereas nafamostat mesilate is used in Korea because citrate is not licensed in Korea. In some studies, nafamostat mesilate has been known to have fewer complications, such as hypocalcemia, compared to citrate [22,23]. Because well-trained CRRT-specialized nurses are more efficient in handling nafamostat mesilate, the use of nafamostat mesilate significantly increased after the SCT was established ($p < 0.001$). In Korea, compared with Japan or China, especially in single-group institutions like ours, it is surprising and unusual that nafamostat mesilate has been largely used without notable side effects so far.

Fluid overload or oliguria was an important indication for initiating CRRT in this study. %FO was not significant in the univariate analysis ($p = 0.348$); however, higher %FO indication to CRRT in group B probably reflects an improved sensitization to the %FO importance in outcome determination; i.e., what is expectable in more current times. Although %FO was an important factor to initiate CRRT in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry study [17], it was not very significant in this study. This could be because the %FO was not accurately measured before and after CRRT.

The limitations of our study are as follows: Since this was a single-center study, it might have had some bias. Moreover, this was a retrospective study. Over this study period, there were significant changes in the development of machines, technique, and proficiency of the SCT, including the pediatric physicians and CRRT-specialized nurses. In addition, although the number of patients with CRRT increased, it could not be associated with SCT because of other factors, such as increased number of beds in ICU, CRRT machines, and critically ill patients in our center compared to other hospitals. Moreover, univariate analysis of both neonates and 1 to 2-year-old infants showed no statistical significance ($p = 0.361$, $p = 0.082$), but no accurate reason for this could be identified. This could be due to a bias in the process of collecting data and selecting patients.

Nevertheless, Severance Hospital is one of the five major hospitals in Korea, and the number of patients who underwent CRRT in this single center is almost similar to the number of patients in 13 major hospitals in the US. In addition, the study period was relatively longer than that of the ppCRRT (14 versus 5 years), reflecting almost all of the cases of pediatric CRRT in Korea. Moreover, since this was a study of Korean children, it also reflects specific ethnic and national characteristics compared with the US studies. The application of SCT to pediatric patients under the collaboration of pediatric nephrologists, pediatric intensivists, and CRRT-specialized nurses has not been reported worldwide and has never been reported in the US.

There have been no multicentric CRRT studies in pediatric patients worldwide, apart from the US ppCRRT. Since 2005, when ppCRRT was implemented, there has been no significant research on pediatric CRRT. Based on this study, an effort should be made in Korea to design an index to predict the mortality and increase the survival of patients.

5. Conclusions

The creation of a homogenous group with common tasks, interests, and devotion is essential in managing pediatric CRRT. This is the first study to have identified that the SCT and the organic collaboration of pediatric nephrologists, pediatric intensivists, and CRRT-specialized nurses could have widened the indication of CRRT for critically ill children with AKI and improved management of our patients.

Although CRRT is used as a first-line treatment for severe AKI in developed countries, it has not yet been introduced in less developed countries. In this global point of view, thorough CRRT training, introduction, and application for physicians are necessary. Further prospective studies will be necessary to evaluate the additional factors for sensitive markers of a SCT efficacy.

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Conflicts of Interest: The authors disclose no conflicts of interest.

References

1. Kellum, J.A.; Lameire, N.; Aspelin, P.; Barsoum, R.S.; Burdmann, E.A.; Goldstein, S.L.; Herzog, C.A.; Joannidis, M.; Kribben, A.; Levey, A.S.; et al. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int.* **2012**, *2* (Suppl. S1), 1–138.
2. Hoste, E.A.; Clermont, G.; Kersten, A.; Venkataraman, R.; Angus, D.C.; De Bacquer, D.; Kellum, J.A. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit. Care* **2006**, *10*, R73. [CrossRef]
3. Selewski, D.T.; Cornell, T.T.; Heung, M.; Troost, J.P.; Ehrmann, B.J.; Lombel, R.M.; Blatt, N.B.; Luckritz, K.; Hieber, S.; Gajarski, R.; et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med.* **2014**, *40*, 1481–1488. [CrossRef]
4. Sutherland, S.M.; Byrnes, J.J.; Kothari, M.; Longhurst, C.A.; Dutta, S.; Garcia, P.; Goldstein, S.L. AKI in hospitalized children: Comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 554–561. [CrossRef] [PubMed]
5. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morg-era, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multina-tional, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef] [PubMed]
6. Mehta, R.L.; Burdmann, E.A.; Cerdá, J.; Feehally, J.; Finkelstein, F.; García-García, G.; Godin, M.; Jha, V.; Lameire, N.H.; Levin, N.W.; et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: A multinational cross-sectional study. *Lancet* **2016**, *387*, 2017–2025. [CrossRef]
7. Lameire, N.H.; Bagga, A.; Cruz, D.; De Maeseneer, J.; Endre, Z.; Kellum, J.A.; Liu, K.D.; Mehta, R.L.; Pannu, N.; Van Biesen, W.; et al. Acute kidney injury: An increasing global concern. *Lancet* **2013**, *382*, 170–179. [CrossRef]

8. Kaddourah, A.; Basu, R.K.; Bagshaw, S.M.; Goldstein, S.L. AWARE Investigators. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N. Engl. J. Med.* **2017**, *376*, 11–20. [CrossRef]
9. Kramer, P.; Wigger, W.; Rieger, J.; Matthaei, D.; Scheler, F. Arteriovenous haemofiltration: A new and simple method for treatment of over-hydrated patients resistant to diuretics. *Klin. Wochenschr.* **1977**, *55*, 1121–1122. [CrossRef]
10. Ronco, C.; Brendolan, A.; Bragantini, L.; Chiaramonte, S.; Fabris, A.; Feriani, M.; Frigiola, A.; La Greca, G. Treatment of acute renal failure in the newborn by continuous arteriovenous hemofiltration. *Trans. Am. Soc. Artif. Intern. Organs* **1985**, *31*, 634–638.
11. Riegel, W.; Habicht, A.; Ulrich, C.; Kohler, H. Hepatoactive substances eliminated by continuous venovenous hemofiltration in acute renal failure patients. *Kidney Int. Suppl.* **1999**, *72*, S67–S70. [CrossRef]
12. Ronco, C.; Bellomo, R. Critical care nephrology: The time has come. *Nephrol. Dial. Transplant.* **1998**, *13*, 264–267. [CrossRef] [PubMed]
13. Endre, Z.H. The role of nephrologist in the intensive care unit. *Blood. Purif.* **2017**, *43*, 78–81. [CrossRef]
14. Gilbert, R.W.; Caruso, D.M.; Foster, K.N.; Canulla, M.V.; Nelson, M.L.; Gilbert, E.A. Development of a continuous renal replacement program in critically ill patients. *Am. J. Surg.* **2002**, *184*, 526–532. [CrossRef]
15. Kee, Y.K.; Kim, E.J.; Park, K.S.; Han, S.G.; Han, I.M.; Yoon, C.Y.; Lee, E.; Joo, Y.S.; Kim, D.Y.; Lee, M.J.; et al. The effect of specialized continuous renal replacement therapy team in acute kidney injury patients treatment. *Yonsei Med. J.* **2015**, *56*, 658–665. [CrossRef]
16. Oh, H.J.; Lee, M.J.; Kim, C.H.; Kim, D.Y.; Lee, H.S.; Park, J.T.; Na, S.; Han, S.H.; Kang, S.-W.; Koh, S.O.; et al. The benefit of specialized team approaches in patients with acute kidney injury undergoing continuous renal replacement therapy: Propensity score matched analysis. *Crit. Care* **2014**, *18*, 454. [CrossRef]
17. Goldstein, S.L.; Somers, M.J.; Brophy, P.D.; Bunchman, T.E.; Baum, M.; Blowey, D.; Mahan, J.D.; Flores, F.X.; Fortenberry, J.D.; Chua, A.; et al. The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry: Design, development and data assessed. *Int. J. Artif. Organs* **2005**, *427*, 9–14. [CrossRef]
18. Symons, J.M.; Chua, A.N.; Somers, M.J.; Baum, M.A.; Bunchman, T.E.; Benfield, M.R.; Brophy, P.D.; Blowey, D.; Fortenberry, J.D.; Chand, D.; et al. Demographic characteristics of pediatric continuous renal replacement therapy: A report of the prospective pediatric continuous renal replacement therapy registry. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 732–738. [CrossRef]
19. Goldstein, S.L.; Somers, M.J.; Baum, M.A.; Symons, J.M.; Brophy, P.D.; Blowey, D.; Bunchman, T.E.; Baker, C.; Mottes, T.; Mcafee, N.; et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int.* **2005**, *67*, 653–658. [CrossRef]
20. Goldstein, S.L.; Currier, H.; Graf, C.; Cosio, C.C.; Brewer, E.D.; Sachdeva, R. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* **2001**, *107*, 1309–1312. [CrossRef]
21. Pannu, N.; Gibney, R.N. Renal replacement therapy in the intensive care unit. *Ther. Clin. Risk Manag.* **2005**, *1*, 141–150. [CrossRef]
22. Chadha, V.; Garg, U.; Warady, B.A.; Alon, U.S. Citrate clearance in children receiving continuous venovenous renal replacement therapy. *Pediatr. Nephrol.* **2002**, *16*, 819–824. [CrossRef]
23. Choi, J.Y.; Kang, Y.J.; Jang, H.M.; Jung, H.Y.; Cho, J.H.; Park, S.H.; Kim, Y.L.; Kim, C.D. Nafamostat Mesilate as an Anticoagulant During Continuous Renal Replacement Therapy in Patients with High Bleeding Risk: A Randomized Clinical Trial. *Medicine* **2015**, *94*, e2392. [CrossRef] [PubMed]

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Acute Kidney Injury after Lung Transplantation: A Systematic Review and Meta-Analysis

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Abstract: Background: Lung transplantation has been increasingly performed worldwide and is considered an effective therapy for patients with various causes of end-stage lung diseases. We performed a systematic review to assess the incidence and impact of acute kidney injury (AKI) and severe AKI requiring renal replacement therapy (RRT) in patients after lung transplantation. Methods: A literature search was conducted utilizing Ovid MEDLINE, EMBASE, and Cochrane Database from inception through June 2019. We included studies that evaluated the incidence of AKI, severe AKI requiring RRT, and mortality risk of AKI among patients after lung transplantation. Pooled incidence and odds ratios (ORs) with 95% confidence interval (CI) were obtained using random-effects meta-analysis. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019134095). Results: A total of 26 cohort studies with a total of 40,592 patients after lung transplantation were enrolled. Overall, the pooled estimated incidence rates of AKI (by standard AKI definitions) and severe AKI requiring RRT following lung transplantation were 52.5% (95% CI: 45.8–59.1%) and 9.3% (95% CI: 7.6–11.4%). Meta-regression analysis demonstrated that the year of study did not significantly affect the incidence of AKI ($p = 0.22$) and severe AKI requiring RRT ($p = 0.68$). The pooled ORs of in-hospital mortality in patients after lung transplantation with AKI and severe AKI requiring RRT were 2.75 (95% CI, 1.18–6.41) and 10.89 (95% CI, 5.03–23.58). At five years, the pooled ORs of mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 1.47 (95% CI, 1.11–1.94) and 4.79 (95% CI, 3.58–6.40), respectively. Conclusion: The overall estimated incidence rates of AKI and

severe AKI requiring RRT in patients after lung transplantation are 52.5% and 9.3%, respectively. Despite advances in therapy, the incidence of AKI in patients after lung transplantation does not seem to have decreased. In addition, AKI after lung transplantation is significantly associated with reduced short-term and long-term survival.

Keywords: acute kidney injury; incidence; lung transplantation; transplantation; epidemiology; meta-analysis

1. Introduction

Acute kidney injury (AKI) is a complex clinical syndrome characterized by a sharp reduction in the glomerular filtration rate (GFR) followed by elevated serum creatinine or oliguria, and is associated with various etiologies and pathophysiological pathways. AKI is a major global health problem with a steadily increasing incidence in recent years [1–3]. The global burden of AKI is 13.3 million cases per year and is associated with significant mortality, resulting in 1.4 million deaths per year [4–6]. Mortality rates from AKI range from 16% to 50% according to the stage and vary widely according to etiology and patient comorbidities [7,8]. Those who survive the AKI are at increased risk for hypertension and progressive chronic kidney disease (CKD), including end-stage kidney disease (ESKD) [9].

Since the first human lung transplant was performed in 1963, almost 55,000 lung transplantations have been performed worldwide, now with nearly 4600 lung transplantations performed annually [10]. Up to 68% of lung transplant recipients develop AKI, which has been associated with increased one-year mortality, length of hospital stay, higher resource utilization, and related health care burden [10–22]. Though survival following lung transplantation has improved over the past few decades, morbidity and mortality related to AKI after lung transplantation and resultant progressive CKD remain relatively high and is a cause for increasing concern [16,23–25]. The incidence of AKI following lung transplantation varies widely, estimated to be as high as two-thirds of recipients, with up to 5% to 8% requiring dialysis in the initial few months post lung transplantation [11,13–15,21,24,26–29]. Differences in the definition of AKI may account for the variance of incidence of post-lung-transplant AKI [28].

Despite significant advances in lung transplantation surgical and medical practices, the epidemiology, risk factors, and mortality associated with AKI among post-lung-transplant recipients and their trends remain unclear. Therefore, we conducted a systematic review to summarize and trend the incidence of AKI (utilizing standard AKI definitions including AKIN (acute kidney injury network) [30], RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) [31], and KDIGO (kidney disease: Improving global outcomes) [32] classifications) and mortality risk of AKI in lung transplant recipients.

2. Methods

2.1. Information Sources and Search Strategy

The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews (CRD42019134095)). A systematic literature search of Ovid MEDLINE, EMBASE, and the Cochrane Database from database inceptions through June 2019 was performed to summarize the incidence and impact of AKI on mortality risk among adult patients following lung transplantation. Two investigators (P.L. and C.T.) individually performed a systematic literature search utilizing the search approach that consolidated the search terms of “lung” OR “pulmonary” AND “transplant” OR “transplantation” AND “acute kidney injury” OR “acute renal failure” OR “renal replacement therapy”. Detailed information on the search strategy from each database is provided in Online Supplementary Data 1. No language limitation was implemented. A manual review for conceivably-related studies employing references of the included studies was additionally

performed. Grey literature was also searched for further relevant information. This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [33].

2.2. Study Selection

Studies were included in this meta-analysis if they were observational studies or clinical trials that provided data on incidence of AKI (utilizing standard AKI definitions including AKIN [30], RIFLE [31], and KDIGO [32] classifications), AKI requiring renal replacement therapy (RRT), and mortality risk of AKI in adult patients after lung transplantation (age ≥ 18 years old). Eligible studies needed to provide data to assess the incidence or mortality rate of AKI with 95% confidence intervals (CIs). Retrieved articles were individually examined for eligibility by the two investigators (P.L. and C.T.). Inconsistencies were discussed with the third reviewer (W.C.) and solved by common agreement. The size of the study did not limit inclusion.

2.3. Data Collection Process

A structured data collecting form was used to collect the following data from individual studies including title, name of authors, year of the study, publication year, country where the study was conducted, patient characteristics, AKI definition, incidence of AKI, incidence of severe AKI requiring RRT, and mortality risk of AKI among patients after lung transplantation.

2.4. Statistical Analysis

Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc., Englewood, NJ, USA) was used to perform meta-analysis. Adjusted point estimates of included studies were incorporated by the generic inverse variance method of DerSimonian–Laird, which assigned the weight of an individual study based on its variance [34]. Due to the probability of between-study variance, we applied a random-effects model to pool outcomes of interest, including incidence of AKI and mortality risk. Statistical heterogeneity of studies was assessed by the Cochran's Q test ($p < 0.05$ for a statistical significance) and the I^2 statistic (≤25% represents insignificant heterogeneity, 26% to 50% represents low heterogeneity, 51% to 75% represents moderate heterogeneity, and ≥75% represents high heterogeneity) [35]. The presence of publication bias was assessed by both funnel ploy and the Egger test [36].

3. Results

The search yielded a total of 1809 articles for initial screening. After removal of 714 duplicates, the titles and abstracts of 1095 articles were screened for eligibility. A total of 922 articles were excluded (due to in vitro studies, pediatric patient population, animal studies, case reports, correspondences, or review articles). A total of 173 potentially relevant studies were included for full-length article review; 147 of them were additionally excluded from the full-text review as they did not provide the outcome of interest ($n = 77$) or were not observational studies ($n = 48$), or did not use a standard AKI definition ($n = 22$).

Thus, 26 cohort studies [10,11,13,14,19,21,24,28,29,37–53] with 40,592 patients undergoing lung transplantation were identified. Figure 1 shows a flowchart outlining identification of papers for inclusion. Table 1 presents the characteristics of the included studies. The kappa for systematic searches, selection of studies and data extraction were 0.98, 0.87, and 0.98, respectively.

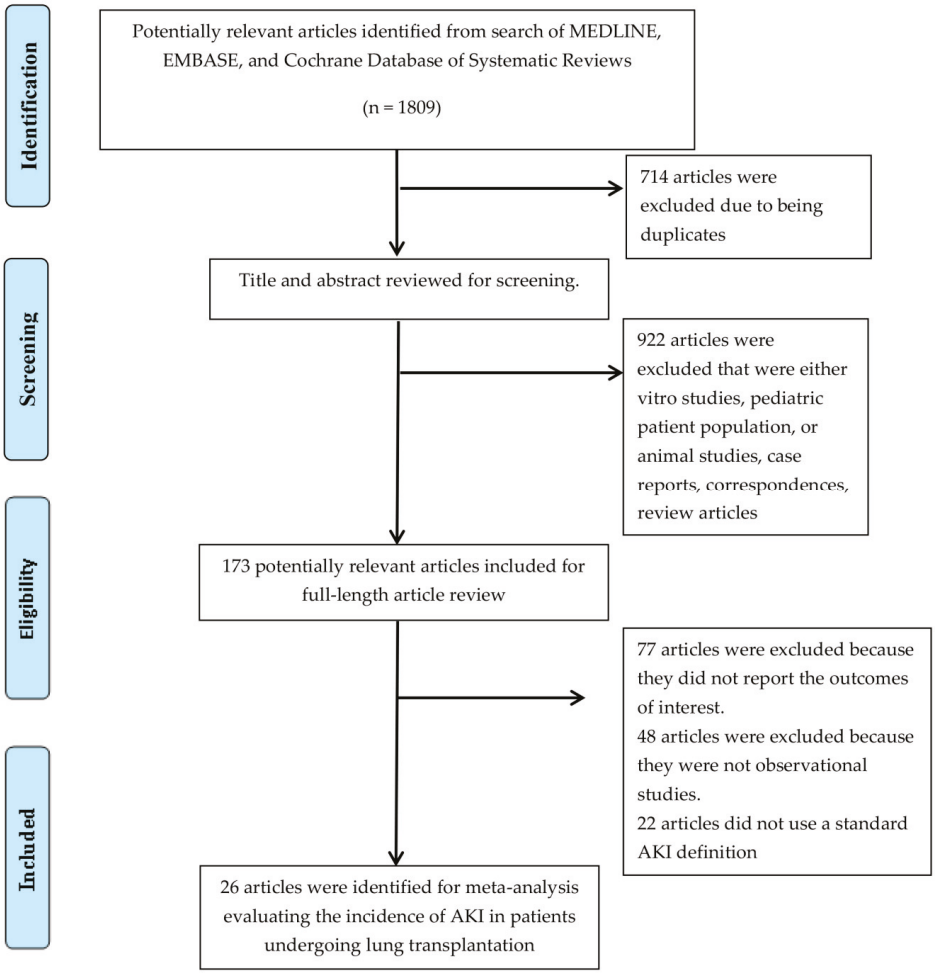

Figure 1. Outline of our search methodology. AKI, Acute kidney injury.

Table 1. Main characteristic of studies included in analysis assessing the incidence of acute kidney injury in patients after lung transplantation.

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence
Rocha et al. [13]	2005	USA	Patents underwent lung transplantation -Double 146/296 (49.3%) -COPD 134/296 (45.3%) -Cystic fibrosis 61/296 (20.6%) -Idiopathic pulmonary fibrosis 31/296 (10.5%)	296	RIFLE criteria	AKI 166/296 (56.1%) RRT 23/296 (7.8%)
Arnaoutakis et al. [11]	2011	USA	Patients underwent lung transplantation -Double 93/106 (87.7%) -COPD 33/106 (31.1%) -Idiopathic pulmonary fibrosis 22/106 (20.8%) -Cystic fibrosis 21/106 (19.8%)	106	RIFLE criteria	AKI 67/106 (63.2%) RRT 14/106 (13.2%)
Machuca et al. [37]	2011	Brazil	Patients underwent lung transplantation - Idiopathic pulmonary fibrosis 53/130 (40.8%) -COPD 52/130 (40%) -Lymphangioleiomyomatosis 8/130 (6.2%) -Cystic fibrosis 4/130 (3%)	130	Doubling of baseline serum creatinine levels	AKI 41/130 (31.5%) RRT 19/130 (14.6%)
George et al. [19]	2012	USA	Patients underwent lung transplantation from UNOS database -Double 6876/12,108 (56.8%) -COPD 4227/12,108 (34.9%) -Idiopathic pulmonary fibrosis 3369/12,108 (27.8%)	12,108	RRT	RRT 655/12,108 (5.41%)
Jacques et al. [21]	2012	Canada	Patients underwent lung transplantation -Double 85/174 (58.9%) -Emphysema 64/174 (36.8%) -Cystic fibrosis 44 /174 (25.3%) -Idiopathic pulmonary fibrosis 24/174 (13.8%)	174	RIFLE criteria	AKI 67/174 (38.5%)
Wehbe et al. [38]	2012	USA	Patients underwent lung transplantation -Double 372/657 (56.6%) -COPD 233/657 (35.5%) -Idiopathic pulmonary fibrosis 212/657 (32.3%) -Cystic fibrosis 90/657 (13.7%)	657	AKIN classification	AKI 424/657 (64.5%) RRT 40/657 (6.1%)

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence
Hennessy et al. [39]	2013	USA	Patients underwent lung transplantation -Double 98/352 (27.8%) -COPD 170/352 (48.2%) -Cystic fibrosis28/352 (8%) -Pulmonary fibrosis 53/352 (15%)	352	SCr > 3 mg/dL within 5 days after surgery	AKI 33/325 (9.4%) RRT 16/325 (4.9%)
Shigemura et al. [40]	2013	USA	-Patients underwent lobar lung transplantation. -Double 13/25 (52%) -Idiopathic pulmonary fibrosis 9/25 (36%) -Sarcoidosis 4/25 (16%) -Cystic fibrosis 2/25 (8%)	25	RRT	RRT 4/25 (16%)
Xue et al. [28]	2014	China	Patients underwent lung transplantation -Double 38/88 (43.2%) -Idiopathic pulmonary fibrosis 46/88 (52.3%) -COPD 19/88 (21.6%) -Brochiectesis7/88 (8%)	88	AKIN classification	AKI 47/88 (53.4%) RRT 3/88 (3.4%)
Ishikawa et al. [29]	2014	Canada	Patients underwent lung transplantation -Double 15/50 (30%) -Interstitial lung disease 18/50 (36%) -COPD 14/50 (28%) -Cystic fibrosis 10/50 (20%) -Alpha 1 antitrypsin deficiency 5/50 (10%)	50	RIFLE criteria	AKI during first 72 hours after transplant 27/50 (54%) AKI during hospitalization 32/50 (64%) RRT 4/50 (8%)
Fidalgo et al. [14]	2014	Canada	Patient underwent lung transplant -Double 354/445 (79.6%) -Heart-lung transplant 20/445 (4.5%) -COPD 149/445 (33.5%) -Idiopathic pulmonary fibrosis 99/445 (22.2%) -Cystic fibrosis 71/445 (16%)	445	KDIGO criteria	Total AKI 306/445 (68.8%) AKI in lung transplant only 290/425 (68.2%) RRT 36/445 (8.1%)
Silhan et al. [41]	2014	USA	Pulmonary fibrosis patients with telomerase mutation carriers underwent lung transplant -Double 5/8 (62.5%)	8	RRT	RRT 4/8 (50%)
Tokman et al. [42]	2015	USA	Pulmonary fibrosis patients underwent lung transplantation -Double 12/14 (85.7%)	14	Increase in serum creatinine of ≥ 1.5 times from baseline within seven days after transplant	AKI 8/14 (57.1%) RRT 1/14 (7.1%)

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence
Sikma et al. [44]	2017	Netherlands	Patient underwent lung transplantation -Double 148/186 (79.6%) -COPD/alpha 1 antitrypsin deficiency 80/186 (43%) -Sarcoidosis/Interstitial lung disease/usual interstitial pneumonia 14/186 (7.5%)	186	KDIGO criteria	AKI 85/186 (45.7%)
Carillo et al. [43]	2017	Italy	Patients underwent lung transplantation -Double 6/22 (27.3%) -Pulmonary fibrosis 13/22 (59%) -Emphysema 7/22(31.8%)	22	RRT	RRT 5/22 (22.7%)
Balci et al. [24]	2017	Turkey	Patients underwent lung transplantation -Idiopathic pulmonary fibrosis 10/30 (33.3%) -COPD 6/30 (20%) -Cystic fibrosis/bronchiectasis 9/30 (30%)	30	AKIN classification	AKI 16/30 (53.3%) RRT 0/30 (0%)
Nguyen et al. [10]	2017	USA	Patients underwent lung transplantation -Double 55/97 (56.7%) -COPD 11/97 (11.3%) -Idiopathic pulmonary fibrosis 50/97 (51.5%) -Cystic fibrosis 20/97 (20.6%) -Pulmonary hypertension 11/97 (11.3%)	97	RIFLE criteria	AKI 57/97 (58.8%) RRT 35/97 (38.5%)
Banga et al. [46]	2017	USA	Patients underwent lung transplantation. Data was from UNOS database from 1994–2014	24,110	RRT	RRT 1369/24,110 (5.7%)
Newton et al. [45]	2017	USA	Pulmonary fibrosis patients underwent lung transplantation. -Double 70/82 (85.4%)	82	increase in serum creatinine to ≥ 1.5 times from baseline within 7 days after transplant	AKI 54/82 (65.9%) RRT 2/82 (2.4%)
Cosgun et al. [47]	2017	USA	Patient underwent lung transplantation -Double 285/291 (97.9%) -Requiring intraoperative ECMO 134/291 (46.0%) -Cystic fibrosis 89/291 (30.6%) -COPD 88/291 (30.2%) -Idiopathic pulmonary fibrosis 63/291 (21.6%)	291	RRT	RRT 27/291 (9.3%)

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence
Ahmad et al. [48]	2018	USA	Patients underwent lung transplantation from brain death donors -Double 20/32 (62.5%) -Interstitial lung disease 24/32 (75%) -COPD 8/32 (25%)	32	RIFLE criteria	AKI at 24 hours post-transplant = 6/32 (18.8%) AKI at 72 hours post-transplant = 4/32 (12.5%)
Iyengar et al. [49]	2018	USA	Patients underwent lung transplantation -Double 267/501 (53.3%)	501	RRT	RRT 19/501 (3.8%)
Ri et al. [50]	2018	Korea	Patient underwent lung transplantation -Idiopathic pulmonary fibrosis 12/33 (36.4%) -Interstitial lung disease 20/33 (60.6%) -Primary pulmonary hypertension 1/14 (7.1%)	33	AKIN criteria	AKI 14/33 (42.4%) RRT 0/33 (0%)
Calabrese et al. [51]	2018	USA	Patient underwent lung transplantation -Double 288/321 (89.7%) -Heart-lung 6/321 (1.9%) -Idiopathic pulmonary fibrosis 210/321 (65.4%) -COPD 66/321 (20.6%) -Cystic fibrosis 31/321 (9.7%)	321	KDIGO criteria	AKI KDIGO stage 2 and 3 61/321 (19.0%)
Bennett et al. [52]	2019	Italy	Patients underwent lung transplantation -Double 66/135 (48.9%) -Pulmonary fibrosis 72/135 (53.33%) -COPD 28/135 (20.74%) -Cystic fibrosis 25/135 (18.52%)	135	KDIGO criteria	AKI 45/135 (33.3%) RRT 18/135 (13.3%)
Shashaty et al. [53]	2019	USA	Patients underwent lung transplantation -Double 180/299 (60.2%) -COPD 119/299 (39.8%) -Interstitial lung disease 123/299 (41.1%) -Cystic fibrosis 26/299 (8.70%)	299	KDIGO criteria	AKI 188/299 (62.9%) RRT 19/299 (6.4%)

Abbreviations: AKI, Acute kidney injury; AKIN, acute kidney injury network; COPD, chronic obstructive pulmonary disease; KDIGO, kidney disease improving global outcomes; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease; RRT, renal replacement therapy; UNOS, United Network for Organ Sharing; USA, United States of America; SCr, serum creatinine.

3.1. Incidence of Acute Kidney Injury among Patients after Lung Transplantation

The pooled estimated incidence rates of AKI and severe AKI requiring RRT after lung transplantation were 52.5% (95% CI: 45.8–59.1%, I^2 = 89%, Figure 2) and 9.3% (95% CI: 7.6–11.4%, I^2 = 90%, Figure 3). Subgroup analysis based on the AKI definition was performed and demonstrated a pooled estimated incidence of AKI after lung transplantation of 49% (95% CI: 38.3–59.8%, I^2 = 86%, Figure 2) by RIFLE criteria, 55.5% (95% CI: 45.2–65.4%, I^2 = 71%, Figure 2) by AKIN criteria, and 53.0% (95% CI: 38.2–67.3%, I^2 = 91%, Figure 2) by KDIGO criteria.

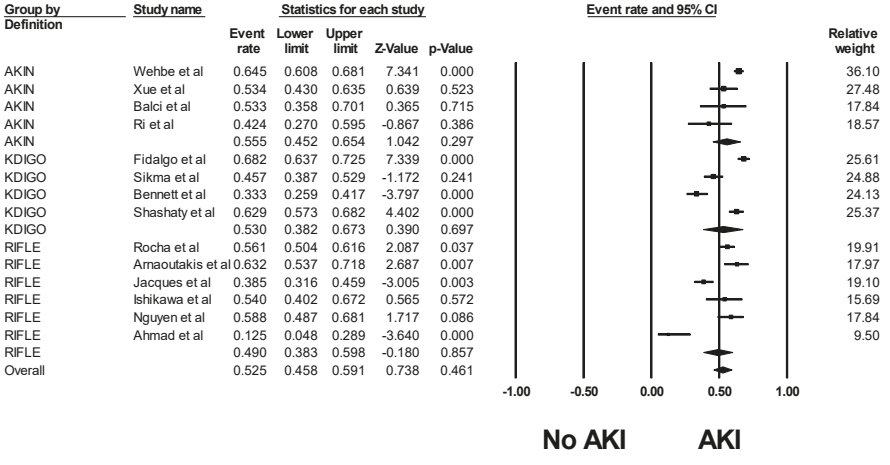

Figure 2. Forest plots of the included studies evaluating incidence rates of AKI after lung transplantation. AKI, Acute kidney injury.

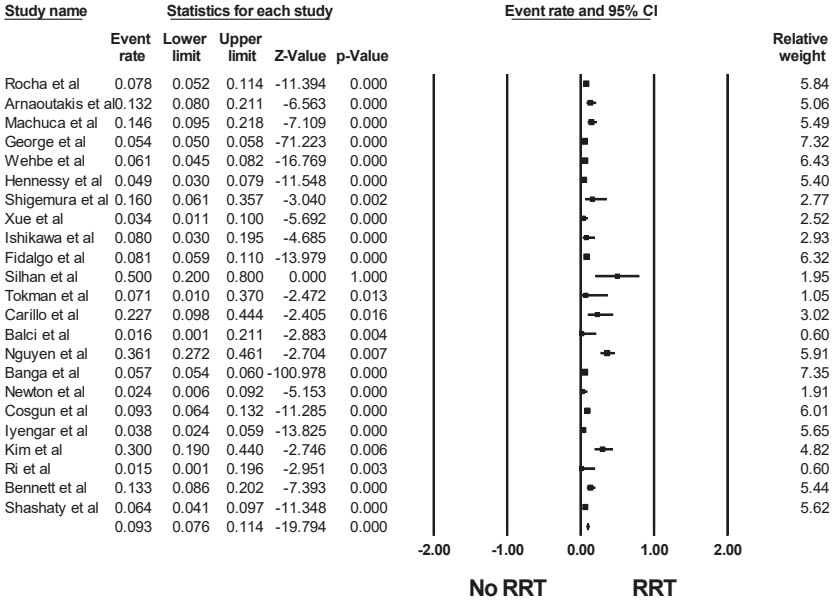

Figure 3. Forest plots of the included studies evaluating incidence rates of AKI requiring RRT after lung transplantation. AKI, Acute kidney injury; RRT, renal replacement therapy.

Meta-regression analysis demonstrated that year of study did not significantly affect the incidence of AKI ($p = 0.22$) and severe AKI requiring RRT ($p = 0.68$) among patients after lung transplantation, as shown in Figure 4.

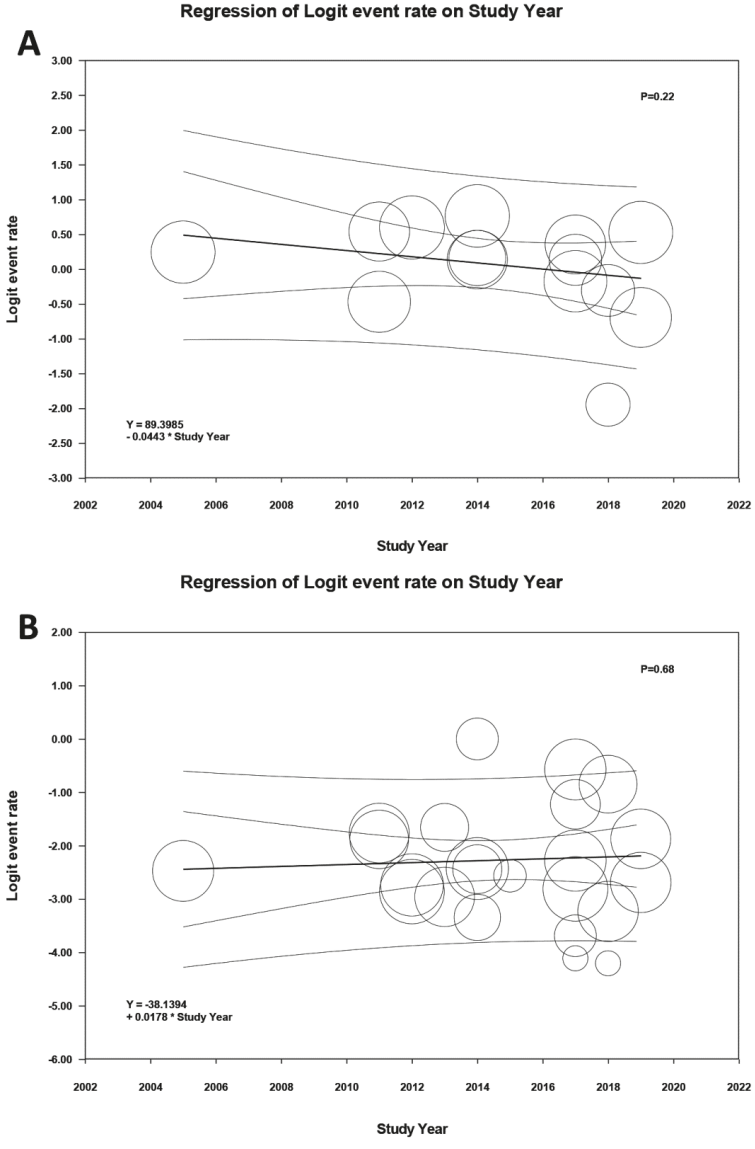

Figure 4. Meta-regression analyses showed that year of study did not significantly affect (**A**) the incidence of AKI ($p = 0.11$) and (**B**) severe AKI requiring RRT ($p = 0.54$) among patients after lung transplantation. AKI, acute kidney injury; RRT, renal replacement therapy.

3.2. Mortality Risk of Acute Kidney Injury in Patients after Lung Transplantation

Data on mortality risk from included studies are shown in Table 2. The pooled OR of hospital mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 2.75

(95% CI, 1.18–6.41, I^2 = 69%, Figure 5A) and 10.89 (95% CI, 5.03–23.58, I^2 = 82%, Figure 5B), respectively. At one year, the pooled OR of mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 2.99 (95% CI, 1.72–5.18, I^2 = 74%, Figure S1) and 8.32 (95% CI, 5.95–11.63, I^2 = 70%, Figure S2), respectively. At five years, the pooled OR of mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 1.47 (95% CI, 1.11–1.94, I^2 = 0%, Figure S3) and 4.79 (95% CI, 3.58–6.40, I^2 = 81%, Figure S4), respectively.

Table 2. Mortality risk of AKI in patients after lung transplantation.

Study	Year	Results	Confounder Adjustment
Rocha et al. [13]	2005	One-year mortality AKI: 4.33 (2.08–8.99) RRT: 23.70 (8.29–67.80) Five-year mortality AKI: 1.44 (0.90–2.30) RRT: 9.73 (2.82–33.53)	None
Arnaoutakis et al. [11]	2011	In-hospital mortality AKI: 0.48 (0.13–1.71) RRT: 28.2 (6.18–128.1) One-year mortality AKI: 0.47 (0.20–1.14) RRT: 4.97 (1.54–16.0)	Lung allocation score, pre-transplant GFR, recipient age, donor cigarette use, postoperative tracheostomy
Machuca et al. [37]	2011	Mortality AKI: 2.47 (1.13–5.39) RRT: 2.68 (1.36–5.27)	Mechanical ventilation duration, reintubation, acute rejection in the first month, coronary heart disease
George et al. [19]	2012	30-day mortality RRT: 7.87 (6.07–10.20) One-year mortality RRT: 7.89 (6.80–9.15) Five-year mortality RRT: 5.35 (4.72–6.07)	Recipient age, GFR, BMI, diagnosis, mean pulmonary artery pressure, ICU status, ECMO support, donor age, bilateral lung transplant, ischemic time, annual center volume
Jacques et al. [21]	2012	30-day mortality AKI:1.36 (0.40–4.64) Long-term mortality AKI: 1.54 (0.79–2.99)	Age, sex, indication, ICU length of stay, coronary artery disease, aprotinin use, double lung transplantation
Wehbe et al. [38]	2012	Hospital mortality AKI: 6.05 (1.83–20.00) RRT: 13.66 (6.19–30.17) One-year mortality AKI: 2.92 (1.76–4.82)	Age, sex, race, type on lung transplantation, COPD, pre-transplantation diabetes, baseline creatinine
Hennessy et al. [39]	2013	30-day mortality AKI: 10.23 (4.05–25.86) RRT: 41.41 (13.06–131.31) One-year mortality AKI: 7.01 (3.29–14.92) RRT: 43.04 (9.48–195.50)	None
Xue et al. [28]	2014	Five-year mortality AKI: 1.48 (1.04–2.11)	Age, sex, type, and cause of lung transplant, hypertension, and diabetes
Ishikawa et al. [29]	2014	Mortality AKI: 3/27 (11%) vs. 0/23 (0%)	None
Fidalgo et al. [14]	2014	Hospital mortality AKI: 22/306 (7%) vs. 0/139 (0%) One-year mortality AKI: 2.81 (1.15–6.84)	Age, sex, COPD, eGFR, LAS score, diabetes mellitus, pulmonary artery pressure, previous sternotomy, type of lung transplant, ICU length of stay
Balci et al. [24]	2017	30-day mortality AKI: 0.82 (0.18–3.74)	None
Nguyen et al. [10]	2017	One-year mortality AKI: 1.73 (0.42–7.13) RRT: 1.20 (0.32–4.60)	None

Table 2. *Cont.*

Study	Year	Results	Confounder Adjustment
Banga et al. [46]	2017	One-year mortality RRT: 7.23 (6.2–8.43) Five-year mortality RRT: 3.96 (3.43–4.56)	Age, serum albumin, type of procedure, CMV mismatch, Length of hospital stay after transplantation, recipient hospitalized at the time of transplant, history of prior cardiac surgery, acute rejection
Bennett et al. [52]	2019	One-year mortality AKI: 6.20 (2.74–14.05) RRT: 21.60 (5.75–81.11)	None
Shashaty et al. [53]	2019	One-year mortality AKI: 3.64 (1.68–7.88)	Primary graft dysfunction, age, bilateral lung transplant

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy; BMI, body mass index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HES, hydroxyethyl starch; ICU, intensive care unit; SCr, serum creatinine.

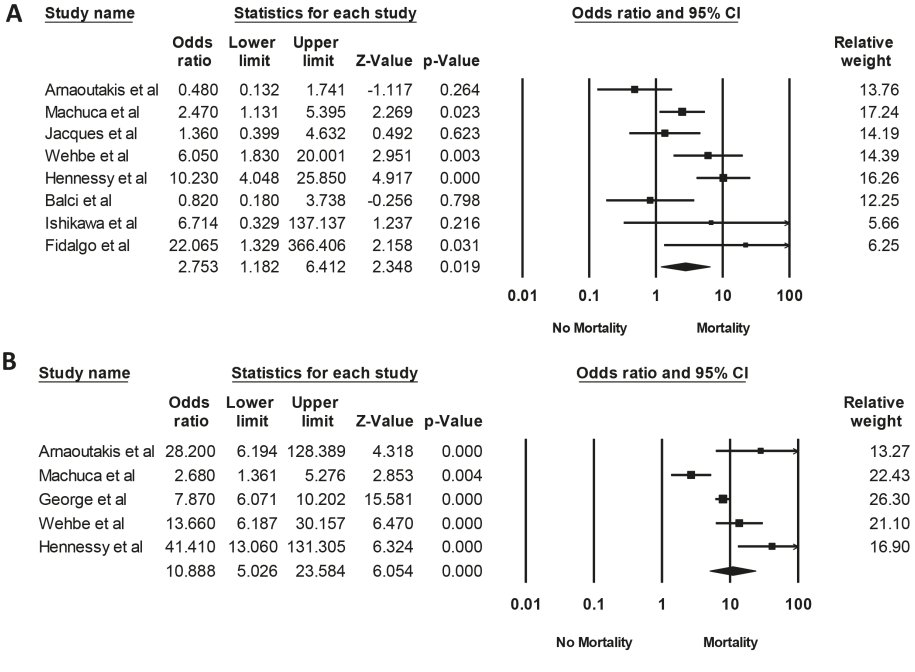

Figure 5. Forest plots of the included studies evaluating hospital mortality of (**A**) AKI and (**B**) AKI requiring RRT after lung transplantation. AKI, acute kidney injury; RRT, renal replacement therapy.

3.3. Evaluation for Publication Bias

Funnel plot (Figures S5 and S6) and Egger's regression asymmetry tests were performed to assess publication bias in analysis evaluating mortality risk of AKI in patients after lung transplant with AKI and severe AKI requiring RRT, respectively. We found no significant publication bias in meta-analysis evaluating mortality risk of patients after lung transplant with AKI ($p = 0.99$) and severe AKI requiring RRT ($p = 0.50$).

4. Discussion and Conclusions

In this systematic review, we demonstrated that AKI in patients after lung transplantation is common, with pooled incidence rates of AKI and severe AKI requiring RRT in patients after lung transplantation of 52.5% and 9.3%, respectively. We also showed that the incidence of AKI in patients after lung transplantation has not improved, despite advances in therapy. Compared to those without AKI, patients with post-lung-transplant AKI had increased short and long-term mortality.

Some specific factors related to AKI after lung transplant include hypercapnia/hypoxemia-mediated impaired renal blood flow (RBF), hemodynamics during lung transplant surgery, and the use of extracorporeal membrane oxygenation (ECMO) and cardio-pulmonary bypass (CPB) during lung transplant surgery [12,28,44,54]. Postoperative respiratory failure is common after lung transplantation; reported to be as high as 55% [55]. Hypoxemia is associated with reduced RBF in a dose-dependent relationship [56–58] thought to be related to stimulation of adrenergic neurons and alterations in nitric oxide metabolism [59]. In addition, studies have shown that hypercapnia can induce peripheral vasodilatation and decreased systemic vascular resistance, with a compensatory neurohormonal vasoconstriction response. This leads to activation of the renin-angiotensin-aldosterone system (RAAS) and direct renal vasoconstriction, resulting in a reduction in RBF and GFR [56,60–62]. Furthermore, poorly controlled hemodynamics during lung transplant surgery can result in intraoperative hypotension, one of the most significant risk factors for the development of AKI after lung transplantation [10,24]. Currently, CPB remains a standard method used in lung transplantation for intraoperative cardiorespiratory support, especially in cases of poor hemodynamic tolerance or severe pulmonary arterial hypertension [63]. However, CPB is commonly associated with inflammatory reactions and bleeding complications [64]. ECMO has more recently been used as an alternative option to CPB for intraoperative cardiopulmonary support during lung transplantation [63]. When compared to CPB, studies have demonstrated beneficial effects of intraoperative ECMO support, with lower rates of primary graft dysfunction, acute post-operative bleeding, AKI requiring RRT, and length of hospital stay [63]. However, the use of ECMO itself may also cause a renal insult related to the activation of proinflammatory mediators caused by the continuous exposure of blood to the non-biological and non-endothelialized ECMO interface [65]. Therefore, our study demonstrated that patients undergoing lung transplantation more frequently develop AKI and AKI requiring RRT than abdominal solid organ transplantation, such as liver transplantation (incidence of AKI and AKI requiring RRT of 41% and 7%, respectively) [66].

As there are currently no effective targeted pharmacotherapies available for AKI, treatment is limited to supportive strategies and RRT when indicated [4–6,8]. Patients who recover from AKI continue to have an increased risk of mortality on either short or long-term follow-up [9]. Following post-lung-transplant AKI, patients may develop CKD, with rates of progression to ESKD as high as 3.8%, 7.2%, and 7.9% at one, five, and ten years after lung transplant, respectively [17,46,67]. Therefore, prevention and early identification of AKI in patients at risk for post-lung-transplant AKI may potentially play an important role in improving patient outcomes. Important risk factors for AKI in patients after lung transplantation include bilateral lung transplantation [19,21,29,68], lower baseline estimated GFR [13,19,38,46,68], pulmonary hypertension [19,38,46], duration of mechanical ventilation requirement [13,14,24,28,46,53], the need for ECMO support [19,46,68], intraoperative hypotension, and vasopressor requirement [10,24] (Table 3).

Table 3. Reported risk factors for AKI after lung transplantation.

Reported Risk Factors for AKI after Lung Transplantation
• High baseline SCr, lower baseline eGFR [13,19,38,46,68]
• Male [52]
• Older age [19]
• Higher BMI [68]
• Carriers of the ABCB1 CGC-CGC diplotype [51]
• African American and Hispanic ethnicity [19,46,68]
• Higher mean pulmonary artery pressure, pulmonary hypertension [19,38,46]
• Intraoperative hypoxemia [29]
• Duration of mechanical ventilation requirement [13,14,24,28,46]
• Duration of ICU stay [68]
• The need of ECMO support [19,46,68]
• Bilateral lung transplantation [19,21,29,68]
• Non-COPD diagnosis [13]
• Cystic fibrosis [44,53]
• Idiopathic pulmonary fibrosis [19]
• Sarcoidosis [68]
• Intraoperative hypotension and vasopressors requirement [10,24]
• Higher HES volume [29]
• Longer cardiopulmonary bypass time [10,14,52]
• Ischemic time [19]
• Aprotinin use [21]
• Pretransplant diabetes mellitus [38,68]
• Pretransplant hypertension [28]
• Longer time on waiting list [68]
• Lower Karnofsky performance score [68]
• Supratherapeutic cyclosporine/tacrolimus trough [14,44]
• Amphotericin B use [13] and nephrotoxic medications [44]
• Infection [24,44]

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HES, hydroxyethyl starch; ICU, intensive care unit; SCr, serum creatinine.

There is experimental data that injurious ventilation strategies, such as a high tidal volume, low positive end-expiratory pressure approach can cause renal epithelial cell apoptosis and dysregulation of extracellular ligands that control renal vascular tone and endothelial integrity, resulting in AKI [69,70]. Among patients with acute respiratory distress syndrome, protective lung ventilation is associated with a reduced risk for AKI requiring dialysis and improves dialysis-free survival [71]. Therefore, future studies are needed to assess whether maintaining perioperative lung-protective ventilation helps to prevent AKI following lung transplantation [12]. Moreover, ECMO management may also play an important role in the prevention of post lung transplant AKI. High ECMO pump speed is associated with hemolysis and AKI development [65]. Future prospective studies are needed to assess the effects of ECMO pump speed on the risk of post-lung-transplantation AKI. Finally, immunosuppressive medications may also play an important role in AKI development following lung transplantation [12,72]. AKI related to calcineurin inhibitor (CNI)-induced thrombotic microangiopathy (TMA) has been reported in lung transplant recipients and is often missed or recognized late in the ICU setting [12,72]. Although TMA in lung transplant recipients is a rare condition, early recognition and management can potentially reduce post lung transplant-related morbidity and mortality [12,72,73].

Our study has some limitations. Firstly, there are statistical heterogeneities in our meta-analysis. Subgroup analyses were performed using differing AKI definitions, including RIFLE criteria AKIN criteria and KDIGO criteria. Meta-regression analysis assessing the effect of year of study on the

incidence of AKI was also performed, and we found no significant correlation between year of study and incidence of AKI post lung transplantation. Secondly, AKI diagnosis from the included studies was based on changes in serum creatinine, and data on urine output and AKI biomarkers was limited. Lastly, this systematic review is primarily based on observational studies, as the data from clinical trials or population-based studies were limited. Thus, it can, at best, demonstrate an association between AKI and increased short-term and long-term mortality post lung transplant, but not a causal relationship.

In summary, AKI and severe AKI requiring RRT are common in patients after lung transplantation, with overall estimated incidence rates of 52.5% and 9.3%, respectively. Post-lung-transplant AKI is significantly associated with reduced short-term and long-term survival. Despite advances in transplantation therapy, the incidence of AKI in patients after lung transplantation does not appear to have improved.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/10/1713/s1, Search terms for systematic review; Figure S1. Forest plots of the included studies assessing the pooled OR of mortality at one year among patients after lung transplantation with AKI; Figure S2: Forest plots of the included studies assessing the pooled OR of mortality at one year among patients after lung transplantation with severe AKI requiring RRT; Figure S3: Forest plots of the included studies assessing the pooled OR of mortality at five years among patients after lung transplantation with AKI; Figure S4: Forest plots of the included studies assessing the pooled OR of mortality at five years among patients after lung transplantation with severe AKI requiring RRT; Figure S5: Funnel plot evaluating for publication bias evaluating mortality risk of AKI in patients after lung transplant with AKI; Figure S6: Funnel plot evaluating for publication bias evaluating mortality risk of AKI in patients after lung transplant with severe AKI requiring RRT.

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References

1. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef] [PubMed]
2. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Harrison, A.M.; Erickson, S.B. Elevated admission serum calcium phosphate product as an independent risk factor for acute kidney injury in hospitalized patients. *Hosp Pract (1995)* **2019**, *47*, 73–79. [CrossRef] [PubMed]
3. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Kashani, K. U-shape association of serum albumin level and acute kidney injury risk in hospitalized patients. *PLoS ONE* **2018**, *13*, e0199153. [CrossRef]
4. Kashani, K.; Cheungpasitporn, W.; Ronco, C. Biomarkers of acute kidney injury: The pathway from discovery to clinical adoption. *Clin. Chem. Lab. Med.* **2017**, *55*, 1074–1089. [CrossRef] [PubMed]
5. Wang, Y.; Fang, Y.; Teng, J.; Ding, X. Acute Kidney Injury Epidemiology: From Recognition to Intervention. *Contrib. Nephrol.* **2016**, *187*, 1–8. [PubMed]
6. Negi, S.; Koreeda, D.; Kobayashi, S.; Yano, T.; Tatsuta, K.; Mima, T.; Shigematsu, T.; Ohya, M. Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. *Semin. Dial.* **2018**, *31*, 519–527. [CrossRef] [PubMed]
7. Hoste, E.A.J.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensiv. Care Med.* **2015**, *41*, 1411–1423. [CrossRef]
8. Cheungpasitporn, W.; Kashani, K. Electronic Data Systems and Acute Kidney Injury. *Contrib. Nephrol.* **2016**, *187*, 73–83.

9. Sawhney, S.; Marks, A.; Fluck, N.; Levin, A.; McLernon, D.; Prescott, G.; Black, C. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. *Kidney Int.* **2017**, *92*, 440–452. [CrossRef]
10. Nguyen, A.P.; Gabriel, R.A.; Golts, E.; Kistler, E.B.; Schmidt, U. Severity of Acute Kidney Injury in the Post-Lung Transplant Patient Is Associated with Higher Healthcare Resources and Cost. *J. Cardiothorac. Vasc. Anesth.* **2017**, *31*, 1361–1369. [CrossRef]
11. Arnaoutakis, G.J.; George, T.J.; Robinson, C.W.; Gibbs, K.W.; Orens, J.B.; Merlo, C.A.; Shah, A.S. Severe acute kidney injury according to the RIFLE (risk, injury, failure, loss, end stage) criteria affects mortality in lung transplantation. *J. Heart Lung Transplant.* **2011**, *30*, 1161–1168. [CrossRef] [PubMed]
12. Puttarajappa, C.M.; Bernardo, J.F.; Kellum, J.A. Renal Complications Following Lung Transplantation and Heart Transplantation. *Crit. Care Clin.* **2019**, *35*, 61–73. [CrossRef] [PubMed]
13. Rocha, P.N.; Rocha, A.T.; Palmer, S.M.; Davis, R.D.; Smith, S.R. Acute renal failure after lung transplantation: Incidence, predictors and impact on perioperative morbidity and mortality. *Am. J. Transplant.* **2005**, *5*, 1469–1476. [CrossRef] [PubMed]
14. Fidalgo, P.; Ahmed, M.; Meyer, S.R.; Lien, D.; Weinkauf, J.; Cardoso, F.S.; Jackson, K.; Bagshaw, S.M. Incidence and outcomes of acute kidney injury following orthotopic lung transplantation: A population-based cohort study. *Nephrol. Dial. Transplant.* **2014**, *29*, 1702–1709. [CrossRef]
15. Fidalgo, P.; Ahmed, M.; Meyer, S.R.; Lien, D.; Weinkauf, J.; Kapasi, A.; Cardoso, F.S.; Jackson, K.; Bagshaw, S.M. Association between transient acute kidney injury and morbidity and mortality after lung transplantation: A retrospective cohort study. *J. Crit. Care* **2014**, *29*, 1028–1034. [CrossRef]
16. Wehbe, E.; Duncan, A.E.; Dar, G.; Budev, M.; Stephany, B. Recovery from AKI and short- and long-term outcomes after lung transplantation. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 19–25. [CrossRef]
17. Chambers, D.C.; Yusen, R.D.; Cherikh, W.S.; Goldfarb, S.B.; Kucheryavaya, A.Y.; Khusch, K.; Levvey, B.J.; Lund, L.H.; Meiser, B.; Rossano, J.W.; et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung and Heart-Lung Transplantation Report—2017; Focus Theme: Allograft ischemic time. *J. Heart Lung Transplant.* **2017**, *36*, 1047–1059. [CrossRef]
18. Bloom, R.; Doyle, A. Kidney Disease after Heart and Lung Transplantation. *Arab. Archaeol. Epigr.* **2006**, *6*, 671–679. [CrossRef]
19. George, T.J.; Arnaoutakis, G.J.; Beaty, C.A.; Pipeling, M.R.; Merlo, C.A.; Conte, J.V.; Shah, A.S. Acute kidney injury increases mortality after lung transplantation. *Ann. Thorac. Surg.* **2012**, *94*, 185–192. [CrossRef]
20. Lafrance, J.P.; Miller, D.R. Acute kidney injury associates with increased long-term mortality. *J. Am. Soc. Nephrol. JASN* **2010**, *21*, 345–352. [CrossRef]
21. Jacques, F.; El-Hamamsy, I.; Fortier, A.; Maltais, S.; Perrault, L.P.; Liberman, M.; Noiseux, N.; Ferraro, P. Acute renal failure following lung transplantation: Risk factors, mortality, and long-term consequences. *Eur. J. Cardiothorac. Surg.* **2012**, *41*, 193–199. [CrossRef] [PubMed]
22. Jardel, S.; Reynaud, Q.; Durieu, I. Long-term extrapulmonary comorbidities after lung transplantation in cystic fibrosis: Update of specificities. *Clin. Transplant.* **2018**, *32*, e13269. [CrossRef] [PubMed]
23. Yusen, R.D.; Edwards, L.B.; Kucheryavaya, A.Y.; Benden, C.; Dipchand, A.I.; Goldfarb, S.B.; Levvey, B.J.; Lund, L.H.; Meiser, B.; Rossano, J.W.; et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-second Official Adult Lung and Heart-Lung Transplantation Report—2015; Focus Theme: Early Graft Failure. *J. Heart Lung Transplant.* **2015**, *34*, 1264–1277. [CrossRef] [PubMed]
24. Balci, M.; Vayvada, M.; Salturk, C.; Kutlu, C.; Ari, E. Incidence of Early Acute Kidney Injury in Lung Transplant Patients: A Single-Center Experience. *Transplant. Proc.* **2017**, *49*, 593–598. [CrossRef]
25. De La Morena, M.P.; Bravos, M.D.L.T.; Prado, R.F.; Roel, M.D.; Salcedo, J.G.; Costa, E.F.; Rivas, D.G.; Maté, J.B. Chronic Kidney Disease After Lung Transplantation: Incidence, Risk Factors, and Treatment. *Transplant. Proc.* **2010**, *42*, 3217–3219. [CrossRef]
26. Hornum, M.; Iversen, M.; Steffensen, I.; Hovind, P.; Carlsen, J.; Andersen, L.W.; Steinbrüchel, D.A.; Feldt-Rasmussen, B.; Feldt-Rasmussen, B.; Feldt-Rasmussen, B. Rapid Decline in51Cr-EDTA Measured Renal Function During the First Weeks Following Lung Transplantation. *Arab. Archaeol. Epigr.* **2009**, *9*, 1420–1426. [CrossRef]
27. Castro, A.G.; Llorca, J.; Cañas, B.S.; Fernández-Miret, B.; Zurbano, F.; Miñambres, E. Acute renal failure in lung transplantation: Incidence, correlation with subsequent kidney disease, and prognostic value. *Arch. Bronconeumol.* **2008**, *44*, 353–359. [CrossRef]

28. Xue, J.; Wang, L.; Chen, C.-M.; Chen, J.-Y.; Sun, Z.-X. Acute kidney injury influences mortality in lung transplantation. *Ren. Fail.* **2014**, *36*, 541–545. [CrossRef]
29. Ishikawa, S.; Griesdale, D.E.; Lohser, J. Acute Kidney Injury within 72 Hours After Lung Transplantation: Incidence and Perioperative Risk Factors. *J. Cardiothorac. Vasc. Anesth.* **2014**, *28*, 931–935. [CrossRef]
30. Bagshaw, S.M.; George, C.; Bellomo, R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. *Nephrol. Dial. Transplant.* **2008**, *23*, 1569–1574. [CrossRef]
31. Uchino, S.; Bellomo, R.; Goldsmith, D.; Bates, S.; Ronco, C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit. Care Med.* **2006**, *34*, 1913–1917. [CrossRef] [PubMed]
32. Palevsky, P.M.; Liu, K.D.; Brophy, P.D.; Chawla, L.S.; Parikh, C.R.; Thakar, C.V.; Tolwani, A.J.; Waikar, S.S.; Weisbord, S.D. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Am. J. Kidney Dis.* **2013**, *61*, 649–672. [CrossRef] [PubMed]
33. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
34. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
35. Higgins, J.P.T.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef]
36. Easterbrook, P.; Gopalan, R.; Berlin, J.; Matthews, D. Publication bias in clinical research. *Lancet* **1991**, *337*, 867–872. [CrossRef]
37. Machuca, T.N.; Schio, S.M.; Camargo, S.M.; Lobato, V.; Costa, C.D.O.; Felicetti, J.C.; Moreira, J.S.; Camargo, J.J. Prognostic Factors in Lung Transplantation: The Santa Casa de Porto Alegre Experience. *Transplantation* **2011**, *91*, 1297–1303. [CrossRef]
38. Wehbe, E.; Brock, R.; Budev, M.; Xu, M.; Demirjian, S.; Schreiber, M.J.; Stephany, B. Short-term and long-term outcomes of acute kidney injury after lung transplantation. *J. Heart Lung Transplant.* **2012**, *31*, 244–251. [CrossRef]
39. Hennessy, S.A.; Gillen, J.R.; Hranjec, T.; Kozower, B.D.; Jones, D.R.; Kron, I.L.; Lau, C.L. Influence of hemodialysis on clinical outcomes after lung transplantation. *J. Surg. Res.* **2013**, *183*, 916–921. [CrossRef]
40. Shigemura, N.; D'Cunha, J.; Bhama, J.K.; Shiose, A.; El Ela, A.A.; Hackmann, A.; Zaldonis, D.; Toyoda, Y.; Pilewski, J.M.; Luketich, J.D.; et al. Lobar Lung Transplantation: A Relevant Surgical Option in the Current Era of Lung Allocation Score. *Ann. Thorac. Surg.* **2013**, *96*, 451–456. [CrossRef]
41. Silhan, L.L.; Shah, P.D.; Chambers, D.C.; Snyder, L.D.; Riise, G.C.; Wagner, C.L.; Hellström-Lindberg, E.; Orens, J.B.; Mewton, J.F.; Danoff, S.K.; et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. *Eur. Respir. J.* **2014**, *44*, 178–187. [CrossRef] [PubMed]
42. Tokman, S.; Singer, J.P.; Devine, M.S.; Westall, G.P.; Aubert, J.-D.; Tamm, M.; Snell, G.I.; Lee, J.S.; Goldberg, H.J.; Kukreja, J.; et al. Clinical outcomes of lung transplant recipients with telomerase mutations. *J. Heart Lung Transplant.* **2015**, *34*, 1318–1324. [CrossRef] [PubMed]
43. Carillo, C.; Pecoraro, Y.; Anile, M.; Mantovani, S.; Oliva, A.; D'Abramo, A.; Amore, D.; Pagini, A.; De Giacomo, T.; Pugliese, F.; et al. Evaluation of Renal Function in Patients Undergoing Lung Transplantation. *Transplant. Proc.* **2017**, *49*, 699–701. [CrossRef] [PubMed]
44. Sikma, M.A.; Hunault, C.C.; Van De Graaf, E.A.; Verhaar, M.C.; Kesecioglu, J.; De Lange, D.W.; Meulenbelt, J. High tacrolimus blood concentrations early after lung transplantation and the risk of kidney injury. *Eur. J. Clin. Pharmacol.* **2017**, *73*, 573–580. [CrossRef]
45. Newton, C.A.; Kozlitina, J.; Lines, J.R.; Kaza, V.; Torres, F.; Garcia, C.K. Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post-lung transplantation survival. *J. Heart Lung Transplant.* **2017**, *36*, 845–853. [CrossRef]
46. Banga, A.; Mohanka, M.; Mullins, J.; Bollineni, S.; Kaza, V.; Tanriover, B.; Torres, F. Characteristics and outcomes among patients with need for early dialysis after lung transplantation surgery. *Clin. Transplant.* **2017**, *31*, e13106. [CrossRef]
47. Cosgun, T.; Tomaszek, S.; Opitz, I.; Wilhelm, M.; Schuurmans, M.M.; Weder, W.; Inci, I. Single-center experience with intraoperative extracorporeal membrane oxygenation use in lung transplantation. *Int. J. Artif. Organs* **2017**. [CrossRef]
48. Ahmad, O.; Shafii, A.E.; Mannino, D.M.; Choate, R.; Baz, M.A. Impact of donor lung pathogenic bacteria on patient outcomes in the immediate post-transplant period. *Transpl. Infect. Dis.* **2018**, *20*, e12986. [CrossRef]

49. Iyengar, A.; Kwon, O.J.; Sanaiha, Y.; Eisenring, C.; Biniwale, R.; Ross, D.; Ardehali, A. Lung transplantation in the Lung Allocation Score era: Medium-term analysis from a single center. *Clin. Transplant.* **2018**, *32*, e13298. [CrossRef]
50. Ri, H.S.; Son, H.J.; Oh, H.B.; Kim, S.Y.; Park, J.Y.; Kim, J.Y.; Choi, Y.J. Inhaled nitric oxide therapy was not associated with postoperative acute kidney injury in patients undergoing lung transplantation: A retrospective pilot study. *Medicine* **2018**, *97*, e10915. [CrossRef]
51. Calabrese, D.R.; Florez, R.; Dewey, K.; Hui, C.; Torgerson, D.; Chong, T.; Faust, H.; Rajalingam, R.; Hays, S.R.; Golden, J.A.; et al. Genotypes associated with tacrolimus pharmacokinetics impact clinical outcomes in lung transplant recipients. *Clin. Transplant.* **2018**, *32*, e13332. [CrossRef] [PubMed]
52. Bennett, D.; Fossi, A.; Marchetti, L.; Lanzarone, N.; Sisi, S.; Refini, R.M.; Sestini, P.; Luzzi, L.; Paladini, P.; Rottoli, P. Postoperative acute kidney injury in lung transplant recipients. *Interact. Cardiovasc. Thorac. Surg.* **2019**, *28*, 929–935. [CrossRef] [PubMed]
53. Shashaty, M.G.S.; Forker, C.M.; Miano, T.A.; Wu, Q.; Yang, W.; Oyster, M.L.; Porteous, M.K.; Cantu, E.E., III; Diamond, J.M.; Christie, J.D. The association of post-lung transplant acute kidney injury with mortality is independent of primary graft dysfunction: A cohort study. *Clin. Transplant.* **2019**, e13678. [CrossRef]
54. Sharma, P.; Welch, K.; Eikstadt, R.; Marrero, J.A.; Fontana, R.J.; Lok, A.S. Renal outcomes after liver transplantation in the model for end-stage liver disease era. *Liver Transplant.* **2009**, *15*, 1142–1148. [CrossRef] [PubMed]
55. Chatila, W.M.; Furukawa, S.; Gaughan, J.P.; Criner, G.J. Respiratory failure after lung transplantation. *Chest* **2003**, *123*, 165–173. [CrossRef] [PubMed]
56. Husain-Syed, F.; Slutsky, A.S.; Ronco, C. Lung–Kidney Cross-Talk in the Critically Ill Patient. *Am. J. Respir. Crit. Care Med.* **2016**, *194*, 402–414. [CrossRef] [PubMed]
57. Sharkey, R.; Mulloy, E.; O'Neill, S. Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. *Eur. Respir. J.* **1998**, *12*, 653–657. [CrossRef]
58. Hemlin, M.; Ljungman, S.; Carlson, J.; Maljukanovic, S.; Mobini, R.; Bech-Hanssen, O.; Skoogh, B.-E.; Skoogh, B. The effects of hypoxia and hypercapnia on renal and heart function, haemodynamics and plasma hormone levels in stable COPD patients. *Clin. Respir. J.* **2007**, *1*, 80–90. [CrossRef]
59. Sharkey, R.A.; Mulloy, E.M.; O'Neill, S.J. The Acute Effects of Oxygen and Carbon Dioxide on Renal Vascular Resistance in Patients with an Acute Exacerbation of COPD. *Chest* **1999**, *115*, 1588–1592. [CrossRef]
60. Anand, I.S.; Chandrashekhar, Y.; Ferrari, R.; Sarma, R.; Guleria, R.; Jindal, S.K.; Wahi, P.L.; Poole-Wilson, P.A.; Harris, P. Pathogenesis of congestive state in chronic obstructive pulmonary disease. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones during edema and after recovery. *Circulation* **1992**, *86*, 12–21. [CrossRef]
61. Sharkey, R.A.; Mulloy, E.M.; Kilgallen, I.A.; O'Neill, S.J. Renal functional reserve in patients with severe chronic obstructive pulmonary disease. *Thorax* **1997**, *52*, 411–415. [CrossRef] [PubMed]
62. MacNee, W. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. *Am. J. Respir. Crit. Care Med.* **1994**, *150*, 833–852. [CrossRef] [PubMed]
63. Magouliotis, D.E.; Tasiopoulou, V.S.; Svokos, A.A.; Svokos, K.A.; Zacharoulis, D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: A meta-analysis. *Gen. Thorac. Cardiovasc. Surg.* **2018**, *66*, 38–47. [CrossRef] [PubMed]
64. Cheungpasitporn, W.; Thongprayoon, C.; Kittanamongkolchai, W.; Srivali, N.; O'corragain, O.A.; Edmonds, P.J.; Ratanapo, S.; Spanuchart, I.; Erickson, S.B. Comparison of Renal Outcomes in Off-Pump Versus On-Pump Coronary Artery Bypass Grafting: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Nephrology* **2015**, *20*, 727–735. [CrossRef]
65. Thongprayoon, C.; Cheungpasitporn, W.; Lertjitbanjong, P.; Aeddula, N.R.; Bathini, T.; Watthanasuntorn, K.; Srivali, N.; Mao, M.A.; Kashani, K. Incidence and Impact of Acute Kidney Injury in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 981. [CrossRef]
66. Thongprayoon, C.; Kaewput, W.; Thamcharoen, N.; Bathini, T.; Watthanasuntorn, K.; Lertjitbanjong, P.; Sharma, K.; Salim, S.A.; Ungprasert, P.; Wijarnpreecha, K.; et al. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 372. [CrossRef]
67. Ojo, A.O.; Held, P.J.; Port, F.K.; Wolfe, R.A.; Leichtman, A.B.; Young, E.W.; Arndorfer, J.; Christensen, L.; Merion, R.M. Chronic Renal Failure after Transplantation of a Nonrenal Organ. *N. Engl. J. Med.* **2003**, *349*, 931–940. [CrossRef]

68. Grimm, J.C.; Lui, C.; Kilic, A.; Valero, V., 3rd; Sciortino, C.M.; Whitman, G.J.; Shah, A.S. A risk score to predict acute renal failure in adult patients after lung transplantation. *Ann. Thorac. Surg.* **2015**, *99*, 251–257. [CrossRef]
69. Imai, Y.; Parodo, J.; Kajikawa, O.; De Perrot, M.; Fischer, S.; Edwards, V.; Cutz, E.; Liu, M.; Keshavjee, S.; Martin, T.R.; et al. Injurious Mechanical Ventilation and End-Organ Epithelial Cell Apoptosis and Organ Dysfunction in an Experimental Model of Acute Respiratory Distress Syndrome. *JAMA* **2003**, *289*, 2104–2112. [CrossRef]
70. Koyner, J.L.; Murray, P.T. Mechanical ventilation and the kidney. *Blood Purif.* **2010**, *29*, 52–68. [CrossRef]
71. Brower, R.G.; Matthay, M.A.; Morris, A.; Schoenfeld, D.; Thompson, B.T.; Wheeler, A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N. Engl. J. Med.* **2000**, *342*, 1301–1308. [CrossRef] [PubMed]
72. Ojo, A.O. Renal Disease in Recipients of Nonrenal Solid Organ Transplantation. *Semin. Nephrol.* **2007**, *27*, 498–507. [CrossRef] [PubMed]
73. Clajus, C.; Hanke, N.; Gottlieb, J.; Stadler, M.; Weismüller, T.J.; Strassburg, C.P.; Bröcker, V.; Bara, C.; Lehner, F.; Drube, J.; et al. Renal Comorbidity After Solid Organ and Stem Cell Transplantation. *Arab. Archaeol. Epigr.* **2012**, *12*, 1691–1699. [CrossRef] [PubMed]

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Preoperative Albuminuria and Intraoperative Chloride Load: Predictors of Acute Kidney Injury Following Major Abdominal Surgery

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Abstract: Background: Postoperative Acute Kidney Injury (AKI) is a common and serious complication associated with significant morbidity and mortality. While several pre- and intra-operative risk factors for AKI have been recognized in cardiac surgery patients, relatively few data are available regarding the incidence and risk factors for perioperative AKI in other surgical operations. The aim of the present study was to determine the risk factors for perioperative AKI in patients undergoing major abdominal surgery. Methods: This was a prospective, observational study of patients undergoing major abdominal surgery in a tertiary care center. Postoperative AKI was diagnosed according to the Acute Kidney Injury Network criteria within 48 h after surgery. Patients with chronic kidney disease stage IV or V were excluded. Logistic regression analysis was used to evaluate the association between perioperative factors and the risk of developing postoperative AKI. Results: Eleven out of 61 patients developed postoperative AKI. Four intra-operative variables were identified as predictors of AKI: intra-operative blood loss ($p = 0.002$), transfusion of fresh frozen plasma ($p = 0.004$) and red blood cells ($p = 0.038$), as well as high chloride load ($p = 0.033$, cut-off value > 500 mEq). Multivariate analysis demonstrated an independent association between AKI development and preoperative albuminuria, defined as a urinary Albumin to Creatinine ratio ≥ 30 mg·g^{-1} (OR = 6.88, 95% CI: 1.43–33.04, $p = 0.016$) as well as perioperative chloride load > 500 mEq (OR = 6.87, 95% CI: 1.46–32.4, $p = 0.015$). Conclusion: Preoperative albuminuria, as well as a high intraoperative chloride load, were identified as predictors of postoperative AKI in patients undergoing major abdominal surgery.

Keywords: albuminuria; chloride; postoperative acute kidney injury

1. Introduction

Postoperative acute kidney injury (AKI) represents a common, yet under-recognized, perioperative complication, with a reported incidence varying between 1% and 36%, depending on the type of surgery and the definition of kidney failure [1–4]. AKI represents a leading cause of morbidity and mortality in surgical patients [5–7], and an increased risk for chronic kidney disease (CKD) and hemodialysis after discharge, factors associated with increased cost and resource utilization [8]. Even minor postoperative

creatinine increases not fulfilling AKI criteria are independently associated with a two-fold risk of in-hospital death and a three-day longer hospital stay [9]. Although risk factors for postoperative AKI in patients undergoing cardiac surgery have been extensively studied [10,11], there is a relative paucity of available data regarding perioperative risk factors associated with major non-cardiac surgery.

The aim of this prospective observational study was to determine the incidence and to identify the pre- and intra-operative risk factors associated with the development of postoperative AKI, using the Acute Kidney Injury Network (AKIN) criteria [12], in patients undergoing elective major abdominal surgery.

2. Methods

2.1. Study Population

This was a single-center, prospective cohort study conducted at a tertiary academic hospital. Between February 2012 and December 2016 all adult patients undergoing elective major abdominal (including vascular) surgery were enrolled. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the local institutional Ethics Committee (Approval-Nr. 5985, 14.07.2011)

On admission to hospital, the following patient variables were recorded: Age, sex, body mass index, preoperative medications, American Society of Anesthesiologists (ASA) physical status [13], and co-morbidities (arterial hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and diabetes mellitus). Perioperative evaluation of renal function included measurements of the following laboratory parameters: Serum creatinine and cystatin C, as well as urine albumin and creatinine at predefined time points. The times of measurements were: Preoperatively (Pre-op), in the recovery room (RR), and on postoperative days (POD) 1, 3, 5 and 7 (POD1, POD3, POD5, POD7). The calculated parameters were: Estimated glomerular filtration rate (eGFR), urine albumin to creatinine ratio (UACR), fractional excretion of sodium (FeNa), and fractional excretion of urea (FeUr). An eGFR < 90 mL·min·m^{-2} and a UACR value ≥ 30 mg·g^{-1} were considered abnormal. Serum and urine samples were centrifuged at 3000 rpm for 10 min and at 1500 rpm for 5 min, respectively, and stored at -80 °C until analysis. Exclusion criteria included: ASA 5 (moribund, not expected to live 24 h irrespective of procedure), chronic kidney disease (CKD) stage IV or V [14], preoperative (within the prior month) use of drugs with known nephrotoxic activity, and emergency surgery.

The recorded intra-operative surgical and anesthetic parameters were: Type of surgery, volume and type of intravenous fluids, transfusions of red blood cells, fresh frozen plasma or platelets, vasopressor administration, mean arterial blood pressure, urine output, and blood loss. The total chloride ion content of intra-operatively administered crystalloids and colloids was estimated. Patients were followed until the 7th postoperative day or hospital discharge, whatever occurred first. Preoperative patient demographics, laboratory values and intra-operative variables were evaluated for their association with perioperative AKI development.

2.2. Outcomes

The primary outcome of the study was the development of perioperative AKI, defined by the AKIN criteria using the maximal change in serum creatinine and eGFR within 48 h after surgery (Table 1). The eGFR was estimated by using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation [15].

Table 1. AKI * diagnosis based on AKIN ** creatinine criteria. (Patients receiving RRT *** are considered to have met criteria for Stage 3, irrespective of the stage they were at the commencement of RRT).

AKI Staging	Definition
Stage 1	1.5-fold increase in sCr or increase of $\geq$0.3 mg·dL^{-1}
Stage 2	2-fold increase in sCr
Stage 3	3-fold increase in sCr or sCr $\geq$ 4 mg·dL^{-1}, with acute rise of $\geq$0.5 mg·dL^{-1}

* AKI = acute kidney injury; ** AKIN = Acute Kidney Injury Network; sCr = serum creatinine; *** RRT = renal replacement therapy.

2.3. Statistical Analysis

Data were analyzed using SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as medians with range or means ± SD and were analyzed using an independent *t*-test or the Mann-Whitney test. Numerical data, expressed as counts and % proportions, were analyzed using the Pearson's chi-square or the Fisher's exact test. Simple logistic regression models were applied to determine odds ratios (ORs) and 95% confidence intervals (CIs), for the perioperative risk factors associated with postoperative AKI development. Multiple logistic regression was applied to establish a model for AKI prediction with prediction variables UACR > 30 mg·g^{-1} and intraoperative chloride load > 500 mEq.

For graphical representation, data box and whisker plots were used. For all analyses, a p value < 0.05 was considered statistically significant.

3. Results

Between February 2012 and December 2016, 61 patients (47 males and 14 females) with a mean age of 67.1 ± 10.2 years underwent major elective abdominal surgery. Eleven patients (18%) developed postoperative AKI (AKI group), while 50 did not (Non-AKI group). The baseline clinical and demographic characteristics of both groups are presented in Table 2, while preoperative laboratory values and intraoperative variables are presented in Tables 3 and 4, respectively. The two groups were comparable in terms of sex, age, body mass index, co-morbidities, major drug categories prescription, pre-operative CKD stage, and ASA score. However, a significant association between type of surgery and development of perioperative AKI was detected, with vascular surgery patients experiencing a significantly higher AKI incidence (31.8% vs. 10.3% in non-vascular surgery patients).

Table 2. Baseline clinical and demographic characteristics according to AKI status.

	Non-AKI Group (n = 50)	AKI Group (n = 11)	p Value	Odd's Ratio (95% CI)
Demographics				
Mean age, (years ± SD)	66.9 ± 10	68.2 ± 10.4	0.699	1.01 (0.95–1.08)
Male gender, (n)	33	8	0.67	1.02 (0.92–1.13)
Mean BMI, kg·m^{-2}	27.2 ± 4.2	27.7 ± 5.6	0.721	1.03 (0.89–1.19)
ASA Classification, (n)				
ASA II	27	4	0.087	1.0
ASA III	20	6	0.076	3.9 (0.73–33.80)
ASA IV	3	1	0.249	4.8 (0.33–70.40)
Comorbidities, (n)				
Hypertension	31	6	0.738	1.4 (0.20–2.75)
CKD	34	9	0.481	2.1 (0.41–10.95)
Stage I	4	2	0.226	4 (0.42–37.78)
Stage II	25	5	0.600	1.6 (0.28–9.26)
Stage III	5	2	0.301	3.2 (0.35–28.94)
CAD	14	4	0.717	1.5 (0.37–5.81)
CHF	11	5	0.067	3.8 (0.98–14.70)

Table 2. *Cont.*

	Non-AKI Group (n = 50)	AKI Group (n = 11)	p Value	Odd's Ratio (95% CI)
DM	14	5	0.137	3 (0.76–11.54)
COPD	19	6	0.174	3.1 (0.80–12.09)
Surgical Procedures, (n)				
Other abdominal Surgery	35 (89.7%)	4 (10.3%)	0.079	
Vascular surgery	15 (68.2%)	7 (31.8%)	0.035	4.1 (1.04–16.06)

Mean (SD): mean and standard deviation (in brackets), n: number of patients OR (95% CI): Odd's ratio with 95% confidence intervals (in brackets), p-values from Pearson's chi-square or Fisher's exact test. Abbreviations: AKI: Acute Kidney Injury; BMI: Body Mass Index; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease.

Table 3. Baseline laboratory values according to AKI status (expressed as mean ± SD, except UACR which is expressed in numbers of patients).

	Non-AKI Group (n = 50)	AKI Group (n = 11)	p Value	Odd's Ratio (95% CI)
Serum Creatinine, mg·dL^{-1}	0.87 (±0.23)	1.02 (±0.21)	0.063	12.6 (0.80–198.7)
Serum Cystatin C, mg·L^{-1}	0.76 (±0.19)	0.82 (±0.28)	0.319	5.20 (0.21–126.7)
eGFR, mL·min^{-1} 1.73 m^{-2}	83.92 (±15.15)	75.27 (±15.97)	0.095	0.97 (0.93–1.01)
Urine Albumin, mg·L^{-1}	24.1 (±50.7)	325 (±729.9)	0.042	1.01 (1.00–1.01)
Urine Creatinine, g·L^{-1}	1.1 (±0.6)	1.2 (±0.7)	0.344	1.66 (0.58–4.66)
UACR > 30 mg·gr^{-1}, (n)	9 (18.0)	6 (54.5)	0.011	5.47 (1.36–21.92)
FeNa, %	0.8 (±0.7)	0.8 (±0.8)	0.919	1.05 (0.40–2.75)
FeUrea, %	41.4 (±12.7)	37.2 (±10.5)	0.303	0.97 (0.92–1.03)

Mean (SD): mean and standard deviation (in brackets), n: number of patients. OR (95% CI): Odd's ratio with 95% confidence intervals (in brackets), p-values from Pearson's chi-square or Fisher's exact test. Abbreviations: AKI: Acute Kidney Injury; eGFR: estimated Glomerular Filtration Rate; UACR: Urine Albumin to Creatinine Ratio; FeNa: Fractional Excretion of Sodium; FeUrea: Fractional Excretion of Urea.

Table 4. Intraoperative variables according to AKI status (expressed as mean ± SD, except Vasopressors which are expressed in numbers of patients).

Non-AKI Group (n = 50)		AKI Group (n = 11)	p Value	Odd's Ratio (95% CI)
Intraoperative Variables(mean±SD)				
Urine output (mL·kg^{-1}·hr^{-1})	2.1 (±2.0)	1.1 (±0.8)	0.151	0.37 (0.13–1.1)
Mean Arterial Pressure (mmHg)	78.7 (±6.9)	79.6 (±10.5)	0.734	1.01 (0.93–1.10)
Vasopressor administration, (n)	32 (64.0)	8 (72.7)	0.581	1.67 (0.86–2.65)
Blood loss (mL)	479 (±508.5)	1345.5 (±1336.7)	0.002	1.06 (1.02–1.1)
Intraoperative Fluids(mean ± SD)				
Total crystalloids (mL)	2441 (±1195)	3018 (±1497)	0.171	1.00 (1.00–1.00)
Total colloids (mL)	865 (±354)	1046 (±611)	0.191	1.00 (1.00–1.00)
RBC transfusion (units)	1.1 (±1.4)	2.3 (±2.4)	0.042	1.49 (1.03–2.01)
FFP transfusion (units)	1.2 (±1.4)	2.6 (±2.1)	0.006	1.69 (1.11–2.56)
PLT transfusion (units)	0.04 (±0.28)	0.4 (±1.2)	0.088	2.04 (0.73–5.71)
Chloride load (mEq)	458.6 (±179.8)	583.9 (±191.5)	0.043	1.03 (1.01–1.05)

Mean (SD): mean and standard deviation (in brackets), n: number of patients; OR (95%CI): Odd's ratio with 95% confidence intervals (in brackets); p-values from Pearson's chi-square or Fisher's exact test. AKI: Acute Kidney Injury; RBC: Red Blood Cells; FFP: Fresh Frozen Plasma; PLT: Platelets.

There was no statistically significant difference in the preoperative eGFR between AKI and non-AKI patients (75.3 ± 16 vs. 83.9 ± 15.2 mL·min^{-1}·m^{-2}). However, in the AKI group, the eGFR was significantly lower in the recovery room (69.5 ± 18.7 vs. 85.7 ± 15.6 mL·min^{-1}·m^{-2}, p = 0.001) and remained so throughout the entire follow-up period (Figure 1).

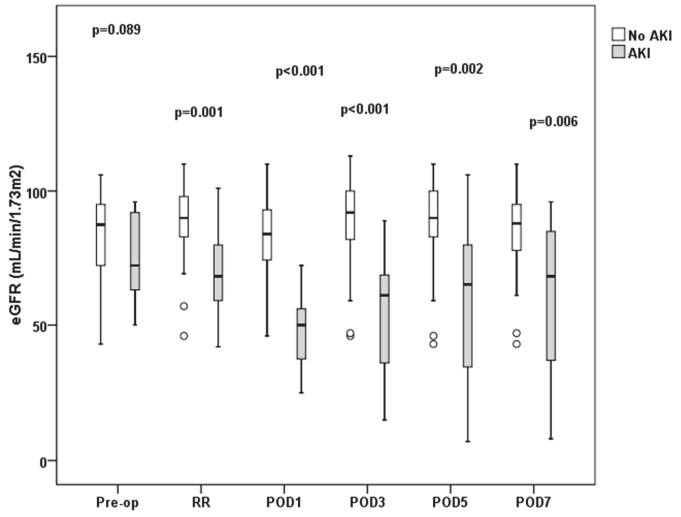

Figure 1. Estimated glomerular filtration rate (eGFR) at predefined time-points. Open boxes represent non-AKI patients, shaded boxes AKI patients. Boxes and whiskers show interquartile ranges and total observed ranges, respectively. eGFR: estimated Glomerular Filtration Rate; Pre-op: preoperatively; RR: recovery room; POD1: postoperative day 1; POD3: postoperative day 3; POD5: postoperative day 5; POD7: postoperative day 7.

Differences between AKI and non-AKI patients regarding serum creatinine and cystatin C concentrations are shown in Figures 2 and 3, respectively.

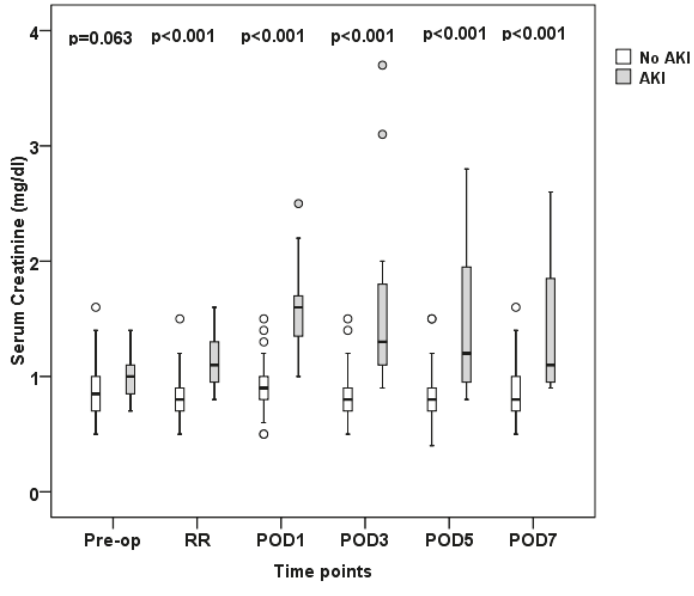

Figure 2. Serum creatinine measurements at predefined time-points. Open boxes represent non-AKI patients, shaded boxes AKI patients. Boxes and whiskers show interquartile ranges and total observed ranges, respectively. Pre-op: preoperatively; RR: recovery room; POD1: postoperative day 1; POD3: postoperative day 3; POD5: postoperative day 5; POD7: postoperative day 7.

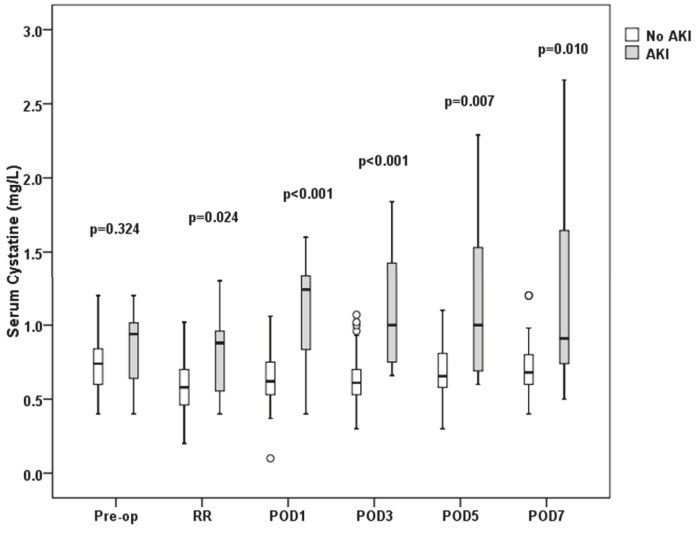

Figure 3. Serum cystatin C measurements at predefined time-points. Open boxes represent non-AKI patients, shaded boxes AKI patients. Boxes and whiskers show interquartile ranges and total observed ranges, respectively. Pre-op: preoperatively; RR: recovery room; POD1: postoperative day 1; POD3: postoperative day 3; POD5: postoperative day 5; POD7: postoperative day 7.

Univariate analysis showed that an abnormal *preoperative* UACR was strongly associated with postoperative AKI development (OR = 5.47, 95% CI: 1.36–21.92, $p = 0.019$). Four *intra-operative* variables were also identified as significant predictors of postoperative AKI (Table 4): intra-operative blood loss, transfusion of RBCs and FFP, and intraoperative chloride load. Receiver operating curve analysis showed that an intraoperative chloride load > 500 mEq (AUC 0.715 $\pm$ 0.095, $p = 0.033$) had a sensitivity of 70% and a specificity of 77% in predicting the development of AKI. There was a strong correlation between blood losses and transfusion of RBCs and FFP. Thus, due to co-linearity, only the total amount of intraoperative fluids, along with chloride load and UACR were introduced in the multivariate model. Multivariate regression analysis confirmed that a UACR $\geq$ 30 mg·g^{-1} (OR = 6.88, 95% CI: 1.43–33.04, $p = 0.016$) and chloride load > 500 mEq (OR = 6.87, 95% CI: 1.46–32.4, $p = 0.015$) were independent predictors of postoperative AKI. The remaining intra-operative variables did not differ significantly between the two groups.

4. Discussion

The present prospective study of postoperative acute kidney injury following elective major abdominal surgery showed an incidence of 18%. The development of AKI, defined by the AKIN creatinine criteria, was strongly associated with an abnormal (i.e., $\geq$30 mg·g^{-1}) preoperative urine albumin to creatinine ratio. Furthermore, four intra-operative variables were identified as independent AKI predictors: Intra-operative blood loss, transfusion of red blood cells and fresh frozen plasma, and intraoperative chloride load >500 mEq.

The incidence of postoperative AKI and its association with perioperative risk factors has been extensively studied in the cardiac surgery population [16]. In the majority of these studies, postoperative AKI was defined as deterioration in renal function requiring renal replacement therapy in patients without pre-existing kidney dysfunction. However, risk factors for AKI following major abdominal surgery have received less attention. According to a recent systematic review of risk prediction models for AKI following non-cardiac surgery, seven models were identified from six studies [17], with only two studies focusing on general surgery patients. Kheterpal et al. [18] studied

the incidence and risk factors for postoperative AKI in a general population of non-cardiac (mainly thoracic, intraperitoneal, and suprainguinal vascular) surgery patients with normal renal function (defined as a calculated preoperative creatinine clearance of $\geq$80 mL·min^{-1}). They found an AKI incidence of 0.8% and identified seven independent preoperative AKI risk factors: Age, body mass index, liver disease, peripheral vascular disease, chronic obstructive pulmonary disease, high-risk surgery, and emergent surgery. The low incidence of postoperative AKI in that study was probably related to the definition of AKI as a drop in estimated creatinine clearance below 50 mL·min^{-1}, within the first 7 postoperative days. Biteker et al. [19] studied postoperative AKI, as defined by the RIFLE [20] AKI staging criteria in elective non-cardiac major surgery patients without preoperative renal dysfunction (serum creatinine <1.6 mg·dL^{-1} for men and <1.4 mg·dL^{-1} for women, respectively). They found a postoperative AKI incidence of 6.7% and identified four independent AKI predictors (age, diabetes, Revised Cardiac Risk Index [21], and ASA physical status).

In the present study, the incidence of AKI was 18%, significantly higher compared to the aforementioned studies. This could be partly explained by the different definitions used for the diagnosis of AKI. It is well known that the AKIN classification (by "broadening" the stage I AKI criteria) increases the sensitivity of AKI diagnosis. In fact, Joannidis et al. [22] showed that by using the AKIN classification, an additional 9% of cases not fulfilling RIFLE criteria could be identified. Furthermore, the present study excluded only patients with stage IV and V chronic kidney disease and patients receiving drugs with established nephrotoxic effects [23]. In fact, 49.2% and 11.5% of the studied population had CKD stage II and III, respectively. This factor should be considered when interpreting our results, since a well-defined graded association exists between severity of reduction in baseline eGFR and progressively higher risk of AKI [24]. Furthermore, it should be noted that 22 of the total 61 patients underwent vascular surgery, mainly open abdominal aneurysm repair, a procedure known to be associated with a postoperative AKI incidence of up to 26% depending on the AKI definition [25].

It is noteworthy that in the AKI group, a significant decline in eGFR with a concomitant rise in serum creatinine and cystatin C was already evident at the recovery room, immediately following surgery. This finding is in line with previous observations in cardiac surgery patients [26], as well as surgical ICU patients [27], where an immediate postoperative elevation in serum creatinine and cystatin C has also been described. However, one should keep in mind that in the early stages of AKI, the diagnostic value of serum creatinine is limited for several well-known reasons [28]. More importantly, the various eGFR equations that have been developed are intended for diagnosing and staging CKD patients in steady-state conditions rather than estimating creatinine clearance during an AKI episode [29].

The most interesting finding of the present study was the significant association between an abnormal preoperative UACR and the development of postoperative AKI, regardless of preoperative renal function or other comorbidities. In fact, the presence of a UACR >30 mg·gr^{-1} resulted in a five-fold higher risk of AKI development. In recent years, albuminuria has been identified as a significant risk factor for AKI and adverse long-term outcomes, both in the general population [30,31] and in cardiac surgery patients [32,33]. Our findings are in line with the results of a large prospective study in the general population (the Atherosclerosis Risk in Communities (ARIC) study) [24], showing a significant risk of hospitalizations and/or death from AKI in people with increased baseline UACR. Preoperative proteinuria, independent of preoperative eGFR, was not only associated with the risk of AKI, but was also a powerful independent risk factor for long-term all-cause mortality and end stage renal disease (ESRD) after cardiac surgery [32,33]. However, to the best of our knowledge, this is the first study reporting a strong relationship between pre-operative albuminuria and postoperative AKI after non-cardiac surgery, a factor that has been overlooked in existing predictive models.

CKD is the most consistent pre-existing condition associated with a high risk of AKI in almost every relevant study. While the definition of CKD includes many parameters, with the most prevalent being albuminuria, this parameter has been largely neglected in most studies where data on urine

albumin were generally lacking [12]. Albuminuria represents a state of generalized endothelial dysfunction and is recognized as one of the most important risk factors for cardiovascular and renal events [34,35]. It is not surprising that baseline UACR was identified as an independent prognostic factor for postoperative AKI for two reasons: First, the recognition of increased UACR reclassifies patients with normal eGFR to stage I CKD, which increases the risk for AKI; and second, it unmasks an already existing renal pathology that is not detected by serum creatinine alone. In this context, angiotensin converting enzyme inhibitors (ACEi(s)), an established anti-proteinuric therapy, have been shown to reduce the incidence of postoperative AKI and all-cause mortality by 17% and 9%, respectively [36]. Thus, we can hypothesize that the protective effect of ACEi(s) may be mediated not only via the intra-renal hemodynamic effects, but also due to their anti-proteinuric properties. Nevertheless, since this is an observational study, we can only report associations and cannot claim causality.

Blood loss and the need for intraoperative transfusion of red blood cells and fresh frozen plasma were found to be associated with the development of postoperative AKI. These factors represent well-known risks for AKI [37]. A meta-analysis of 20 randomized controlled trials on perioperative hemodynamic optimization identified several interventions associated with significant reduction in the incidence of postoperative AKI [38], including optimization of intravascular volume, cardiac output, and oxygen delivery, emphasizing the importance of intraoperative preservation of renal perfusion. Furthermore, multiple studies have found an association between RBC transfusion and renal dysfunction in patients undergoing cardiac and vascular surgery. It is known that stored RBCs undergo changes known as "storage lesion", i.e., irreversible changes in RBC deformity causing stronger adherence to vascular endothelium with a resulting decreased microvascular flow [38,39].

Regarding preservation of renal perfusion, intraoperative blood pressure management is regarded as a key element. Recent observational studies identified episodes of intraoperative hypotension as an independent risk factor for AKI development [40,41]. This observation has been further strengthened by a multi-center randomized controlled trial [42], where an intraoperative strategy targeting an individualized systolic blood pressure (within 10% of patient baseline values) achieved an absolute AKI risk reduction of 16% compared to standard management, emphasizing the importance of individualized patient care. We were not able to reproduce these findings in our study population, where according to anesthetic charts, time-averaged mean arterial pressure was higher than 65 mmHg and did not differ between the two groups. However, a larger proportion of patients in the AKI group required intraoperative vasopressor support, which might be regarded as an indirect indicator of severe intraoperative hypotensive episodes.

Another intraoperative factor significantly and independently associated with development of postoperative AKI was the intraoperative infusion of a high chloride load. This finding is in line with experimental, as well as clinical data, showing that chloride infusion-induced hyperchloremia causes renal vasoconstriction resulting in cortical hypoperfusion [43,44]. A growing body of evidence from observational studies suggests that volume loading with chloride-rich solutions is associated with kidney dysfunction, as compared with the use of balanced solutions [45–47]. A recent meta-analysis including more than 6000 patients concluded that the perioperative use of chloride-rich crystalloids, as compared to the use of balanced solutions, increased the risk of AKI [48].

5. Conclusions

In conclusion, the present study showed that in patients developing postoperative AKI, a reduction of the eGFR can be detected very early in the postoperative period. An intraoperative chloride load higher than 500 mEq, as well as a pre-operative urine albumin to creatinine ratio >30 $mg \cdot g^{-1}$, were significantly and independently associated with postoperative AKI development. However, since the study patients had several comorbidities and some degree of pre-existing renal dysfunction rendering them more susceptible to future renal injury, the implications of these results might be limited to patients with similar comorbidities and not be applicable to otherwise healthy

surgical patients. Nevertheless, the presence of preoperative albuminuria seems to be a significant, yet neglected, independent risk factor for postoperative AKI. Bearing in mind that the strength of association and degree of external validity of this risk association needs further evaluation. We suggest that albuminuria should be included in the routine preoperative patient evaluation for major abdominal surgery and considered as a possible prognostic factor in future AKI risk prediction models.

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References

1. Ishani, A.; Nelson, D.; Clothier, B.; Schult, T.; Nugent, S.; Greer, N.; Slinin, Y.; Ensrud, K.E. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch. Intern. Med.* **2011**, *171*, 226–233. [CrossRef] [PubMed]
2. Bihorac, A.; Delano, M.J.; Schold, J.D.; Lopez, M.C.; Nathens, A.B.; Maier, R.V.; Layon, A.J.; Baker, H.V.; Moldawer, L.L. Incidence, clinical predictors, genomics, and outcome of acute kidney injury among trauma patients. *Ann. Surg.* **2010**, *252*, 158–165. [CrossRef] [PubMed]
3. Shaw, A. Update on acute kidney injury after cardiac surgery. *J. Thorac. Cardiovasc. Surg.* **2012**, *143*, 676–681. [CrossRef] [PubMed]
4. Grams, M.E.; Sang, Y.; Coresh, J.; Ballew, S.; Matsushita, K.; Zolnar, M.Z.; Szabo, Z.; Kalantar-Zadeh, K.; Covesdy, C.P. Acute kidney injury after major surgery: A retrospective analysis of Veterans Health Administration data. *Am. J. Kidney Dis.* **2016**, *67*, 872–880. [CrossRef] [PubMed]
5. Borthwick, E.; Ferguson, A. Perioperative acute kidney injury: Risk factors, recognition, management and outcomes. *BMJ* **2010**, *341*, c3365. [CrossRef] [PubMed]
6. Bihorac, A.; Yavas, S.; Subbiah, S.; Hobson, C.E.; Schold, J.D.; Gabrielli, A.; Layon, A.J.; Segal, M.S. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann. Surg.* **2009**, *249*, 851–858. [CrossRef] [PubMed]
7. Hobson, C.E.; Yavas, S.; Segal, M.S.; Schold, J.D.; Tribble, C.G.; Layon, A.J.; Bihorac, A. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation* **2009**, *119*, 2444–2453. [CrossRef] [PubMed]
8. Hobson, C.E.; Ozrazgat-Baslanti, T.; Kuxhausen, A.; Thottakara, P.; Efron, P.A.; Moore, F.A.; Moldawer, L.L.; Segal, M.S.; Bihorac, A. Cost and mortality associated with postoperative acute kidney injury. *Ann. Surg.* **2015**, *261*, 1207–1214. [CrossRef] [PubMed]
9. Kork, F.; Balzer, F.; Spies, C.D.; Wernecke, K.D.; Ginde, A.A.; Jankowski, J.; Eltzschik, H.K. Minor postoperative increases of creatinine are associated with higher mortality and longer hospital length of stay in surgical patients. *Anesthesiology* **2015**, *123*, 1301–1311. [CrossRef] [PubMed]
10. Thakar, C.V.; Arrigain, S.; Worley, S.; Yared, J.P.; Paganini, E.P. A clinical score to predict acute renal failure after cardiac surgery. *J. Am. Soc. Nephrol.* **2005**, *16*, 162–168. [CrossRef] [PubMed]
11. Mehta, R.H.; Grab, J.D.; O'Brien, S.M.; Bridges, C.R.; Gammie, J.S.; Haan, C.K.; Ferguson, T.B.; Peterson, E.D. Society of thoracic surgeons national cardiac surgery database investigators. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. *Circulation* **2006**, *114*, 2208–2216. [CrossRef] [PubMed]
12. Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.* **2012**, *120*, 179–184. [CrossRef] [PubMed]
13. American Society of Anesthesiologists. New classification of physical status. *Anesthesiology* **1963**, *24*, 111.
14. National kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am. J. Kidney Dis.* **2002**, *39*, S1–S266.

15. Inker, L.A.; Schmid, C.H.; Tighiouart, H.; Eckfeldt, J.H.; Feldman, H.I.; Greene, T.; Kusek, J.W.; Manzi, J.; Van Lente, F.; Zhang, Y.L.; et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N. Engl. J. Med.* **2012**, *367*, 20–29. [CrossRef] [PubMed]
16. Huen, S.C.; Parikh, C.R. Predicting acute kidney injury after cardiac surgery: A systematic review. *Ann. Thorac. Surg.* **2012**, *93*, 337–347. [CrossRef] [PubMed]
17. Wilson, T.; Quan, S.; Cheema, K.; Zarnke, K.; Quinn, R.; de Koning, L.; Dixon, E.; Pannu, N.; James, M.T. Risk prediction models for acute kidney injury following major noncardiac surgery: Systematic review. *Nephrol. Dial. Transplant.* **2016**, *31*, 231–240. [CrossRef] [PubMed]
18. Kheterpal, S.; Tremper, K.K.; Englesbe, M.J.; O'Reilly, M.; Shanks, A.M.; Fetterman, D.M.; Rosenberg, A.L.; Swartz, R.D. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. *Anesthesiology* **2007**, *107*, 892–902. [CrossRef] [PubMed]
19. Biteker, M.; Dayan, A.; Tekkesin, A.I.; Can, M.M.; Tayci, I.; Ilhan, E.; Gülizar, S. Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery. *Am. J. Surg.* **2014**, *207*, 53–59. [CrossRef] [PubMed]
20. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P. Acute renal Failure: Definition, outcome measures, animal models, fluid therapy and information technology needs. The second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, R204–R212. [CrossRef] [PubMed]
21. Lee, T.H.; Marcantonio, E.R.; Mangione, C.M.; Thomas, E.J.; Polanczyk, C.A.; Cook, E.F.; Sugarbaker, D.J.; Donaldson, M.C.; Poss, R.; Ho, K.K.; et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* **1999**, *100*, 1043–1049. [CrossRef] [PubMed]
22. Joannidis, M.; Metnitz, B.; Bauer, P.; Schusterschitz, N.; Moreno, R.; Druml, W.; Metnitz, P.G. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med.* **2009**, *35*, 1692–1702. [CrossRef] [PubMed]
23. Hosohata, K.; Ando, H.; Fujimura, A. Early detection of drug-induced kidney injury by vanin-1. *J. Pharmacol. Exp. Ther.* **2012**, *341*, 656–662. [CrossRef] [PubMed]
24. Grams, M.E.; Astor, B.C.; Bash, L.D.; Matsushita, K.; Wang, Y.; Coresh, J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J. Am. Soc. Nephrol.* **2010**, *21*, 1757–1764. [CrossRef] [PubMed]
25. Dariane, C.; Coscas, R.; Boulitrop, C.; Javerliat, I.; Vilaine, E.; Goeau-Brissonierre, O.; Coggia, M.; Massy, Z.A. Acute kidney injury after open repair of intact abdominal aortic aneurysms. *Ann. Vasc. Surg.* **2017**, *39*, 294–300. [CrossRef] [PubMed]
26. Haase-Fielitz, A.; Bellomo, R.; Devarajan, P.; Story, D.; Matalanis, G.; Dragun, D.; Haase, M. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—A prospective cohort study. *Crit. Care Med.* **2009**, *37*, 553–560. [CrossRef] [PubMed]
27. Dewitte, A.; Joannes-Boyau, O.; Sidobre, C.; Fleureau, C.; Bats, M.L.; Derarche, P.; Leuillet, S.; Ripoche, J.; Combe, C.; Ouattara, A. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 1900–1910. [CrossRef] [PubMed]
28. Wasung, M.E.; Chawla, L.S.; Madero, M. Biomarkers of renal function, which and when? *Clin. Chim. Acta* **2015**, *438*, 350–357. [CrossRef] [PubMed]
29. Levey, A.S.; Inker, L.A.; Coresh, J. GFR estimation: From physiology to public health. *Am. J. Kidney Dis.* **2014**, *63*, 820–834. [CrossRef] [PubMed]
30. Levey, A.S.; de Jongh, P.E.; Coresh, J.; El Nahas, M.; Astor, B.C.; Matsushita, K.; Gansevoort, R.T.; Kasiske, B.L.; Eckardt, K.U. The definition, classification, and prognosis of chronic kidney disease: A KDIGO controversies conference report. *Kidney Int.* **2011**, *80*, 17–28. [CrossRef] [PubMed]
31. Mikkelsen, M.; Andersen, L.; Christensen, T.; Hansen, T.K.; Eiskjaer, H.; Gjedsted, J.; Johnsen, S.P.; Hjortdal, V.E. Microalbuminuria is associated with high adverse event rate following cardiac surgery. *Eur. J. Cardiothorac. Surg.* **2011**, *39*, 932–938. [CrossRef] [PubMed]
32. Huang, T.; Wu, V.; Young, G.; Lin, Y.F.; Shiao, C.C.; Wu, P.C.; Li, W.Y.; Yu, H.Y.; Hu, F.C.; Lin, J.W.; et al. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. *J. Am. Soc. Nephrol.* **2010**, *22*, 156–163. [CrossRef] [PubMed]
33. Hobson, C.E.; Singhania, G.; Bihorac, A. Acute kidney injury in the surgical patient. *Crit. Care Clin.* **2015**, *31*, 705–723. [CrossRef] [PubMed]

34. Seliger, S.L.; Salimi, S.; Pierre, V.; Giffuni, G.; Katzel, L.; Parsa, A. Microvascular endothelial dysfunction is associated with albuminuria and CKD in older adults. *BMC Nephrol.* **2016**, *17*, 82. [CrossRef] [PubMed]
35. Brienza, N.; Giglio, M.T.; Marucci, M.; Fiore, T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit. Care Med.* **2009**, *37*, 2079–2090. [CrossRef] [PubMed]
36. Shah, M.; Jain, A.K.; Brunelli, S.M.; Coca, S.G.; Devereaux, P.J.; James, M.T.; Luo, J.; Molnar, A.O.; Mrkobrada, M.; Pannu, N.; et al. Association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use prior to major elective surgery and the risk of acute dialysis. *BMC Nephrol.* **2014**, *15*, 53. [CrossRef] [PubMed]
37. Hobson, C.; Ruchi, R.; Bihorac, A. Perioperative acute kidney injury: Risk factors and predictive strategies. *Crit. Care Clin.* **2017**, *33*, 379–396. [CrossRef] [PubMed]
38. Habib, R.H.; Zacharias, A.; Schwann, T.A.; Riordan, C.J.; Engoren, M.; Durham, S.J.; Shah, A. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome. *Crit. Care Med.* **2005**, *33*, 1749–1756. [CrossRef] [PubMed]
39. O'Keefe, S.D.; Davenport, D.L.; Minion, D.J.; Sorial, E.E.; Endean, E.D.; Xenos, E.S. Blood transfusion is associated with increased morbidity and mortality after lower extremity revascularization. *J. Vasc. Surg.* **2010**, *51*, 616–621. [CrossRef] [PubMed]
40. Salmasi, V.; Maheshwari, K.; Yang, D.; Mascha, E.J.; Singh, A.; Sessler, D.I.; Kurz, A. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery. A retrospective cohort analysis. *Anesthesiology* **2017**, *126*, 47–65. [CrossRef] [PubMed]
41. Hallqvist, L.; Granath, F.; Huldt, E.; Bell, M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery. An observational study. *Eur. J. Anaesthesiol.* **2017**, *35*, 273–279.
42. Futier, E.; Lefrant, J.Y.; Guinot, P.G.; Godet, T.; Lorne, E.; Cuvillon, P.; Bertran, S.; Leone, M.; Pastene, B.; Piriou, V.; et al. Effect of individualized vs. standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery. *JAMA* **2017**, *318*, 1346–1357. [CrossRef] [PubMed]
43. Hansen, P.B.; Jensen, B.L.; Skott, O. Chloride regulates afferent arteriolar contraction in response to depolarization. *Hypertension* **1998**, *32*, 1066–1070. [CrossRef] [PubMed]
44. Chowdhury, A.H.; Cox, E.F.; Francis, S.T.; Lobo, D.N. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasmalyte (R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann. Surg.* **2012**, *256*, 18–24. [CrossRef] [PubMed]
45. Shaw, A.D.; Bagshaw, S.M.; Goldstein SL Scherer, L.A.; Duan, M.; Schermer, C.R.; Kellum, J.A. Major complications, mortality and resource utilization after open abdominal surgery: 0.9% Saline compared to plasma-lyte. *Ann. Surg.* **2012**, *255*, 821–829. [CrossRef] [PubMed]
46. Yunos, N.M.; Bellomo, R.; Hegarty, C.; Story, D.; Ho, L.; Bailey, M. Association between a chloride-liberal vs. chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* **2012**, *308*, 1566–1572. [CrossRef] [PubMed]
47. McCluskey, S.A.; Karkouti, K.; Wijeysundera, D.; Minkovich, L.; Tait, G.; Beattie, W.S. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: A propensity-matched cohort study. *Anesth. Analg.* **2013**, *117*, 412–421. [CrossRef] [PubMed]
48. Krajewski, M.; Raghunathan, K.; Paluszkiewicz, S.M.; Schermer, C.R.; Shaw, A.D. Meta-analysis of high-versus low-chloride content in perioperative and critical care fluid resuscitation. *Br. J. Surg.* **2015**, *102*, 24–36. [CrossRef] [PubMed]

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Preadmission Statin Therapy Is Associated with a Lower Incidence of Acute Kidney Injury in Critically Ill Patients: A Retrospective Observational Study

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Abstract: This study aimed to investigate the association between preadmission statin use and acute kidney injury (AKI) incidence among critically ill patients who needed admission to the intensive care unit (ICU) for medical care. Medical records of patients admitted to the ICU were reviewed. Patients who continuously took statin for >1 month prior to ICU admission were defined as statin users. We investigated whether preadmission statin use was associated with AKI incidence within 72 h after ICU admission and whether the association differs according to preadmission estimated glomerular filtration rate (eGFR; in mL min^{-1} 1.73 m^{-2}). Among 21,236 patients examined, 5756 (27.1%) were preadmission statin users and 15,480 (72.9%) were non-statin users. Total AKI incidence within 72 h after ICU admission was 31% lower in preadmission statin users than in non-statin users [odds ratio (OR), 0.69; 95% confidence interval (CI), 0.61–0.79; $p < 0.001$]. This association was insignificant among individuals with eGFR <30 mL min^{-1} 1.73 m^{-2} ($p > 0.05$). Our results suggested that preadmission statin therapy is associated with a lower incidence of AKI among critically ill patients; however, this effect might not be applicable for patients with eGFR <30 mL min^{-1} 1.73 m^{-2}.

Keywords: acute kidney injury; statins; chronic kidney disease

1. Introduction

Acute kidney injury (AKI) is defined as a rapid worsening of renal functions [1] and affects 2–18% of inpatients and 57% of critical care patients [2–4]. AKI in critically ill patients in the intensive care unit (ICU) is an important issue because it delays recovery and increases hospital mortality [5]. Thus, appropriately preventing AKI in the ICU is currently an important task in ICU patient management [6].

Statin, known as a 3-hydroxy-3-methylglutaryl-coenzyme A inhibitor, is one of the most commonly prescribed drugs worldwide [7] that lowers the risk of cardiovascular death by reducing the serum cholesterol level [8]. Furthermore, statin has anti-inflammatory, antithrombotic,

and immunomodulating effects [9,10], also known as "pleiotropic effects" [11]. These pleiotropic effects are reported to lower the incidence of surgery-related [12,13], contrast-induced [14], and sepsis-related AKI [15]. However, some study findings show that statin failed to improve the outcomes of kidney disease, and the debate regarding the relationship between statin use and AKI is ongoing [16]. Thus, further studies are needed to substantiate the inhibitory effects of statin on AKI. Additionally, considering that statin therapy may be discontinued for many patients based on their states after ICU admission, it is important to clarify the association between preadmission statin use and AKI incidence after ICU admission.

This study aimed to investigate the association between preadmission statin use and AKI incidence after ICU admission in the general adult population. Additionally, we examined whether this association differs with respect to pre-ICU kidney function.

2. Materials and Method

This retrospective observational study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB approval number: B-1806/474-105). Because of the retrospective nature of the study, the IRB waived the need to obtain informed consent from the patients. All data for the study were collected by a medical records technician who was blinded to the purpose of this study.

2.1. Patients

The medical records of adult patients aged ≥18 years who were admitted to the ICU between January 2012 and December 2017 were analyzed. When a patient was admitted to the ICU more than once during the study period, only data from the last ICU admission case, which might be the most severe, were included in the analysis. The exclusion criteria were as follows: (1) patients with an estimated glomerular filtration rate (eGFR; in mL min^{-1} 1.73 m^{-2}) of <15 or those with end-stage renal disease (ESRD) who were undergoing renal replacement therapy (RRT) prior to admission because they usually received RRT after ICU admission regardless of AKI development; (2) patients lacking information on baseline creatinine or creatinine level within 72 h after ICU admission; and (3) patients diagnosed with AKI prior to ICU admission.

2.2. Preadmission Statin Use (Main Independent Variables)

Preadmission statin users were defined as patients who confirmed taking statins as maintenance treatment as prescribed by their physicians at least one month before ICU admission. The other cases were classified as non-statin users. Statin was classified as atorvastatin, rosuvastatin, simvastatin, pitavastatin, and other statins (pravastatin, fluvastatin, and lovastatin).

2.3. Measurements (Covariates)

Demographic information (sex, age, and body mass index) of the patients and comorbidities at ICU admission, including Acute Physiology and Chronic Health Evaluation II score and eGFR, total serum cholesterol at ICU admission (mg dL^{-1}), and data regarding admission to the emergency department and other departments (internal medicine, neurologic center, cardiothoracic surgical department, and other surgical departments) were collected. Pre-ICU admission eGFR was computed using the Modification of Diet in Renal Disease formula [17]: eGFR (mL min^{-1} 1.73 m^{-2}) = 186 × (creatinine level)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female). Using the cut-off points of total cholesterol as 160 and 200 mg/dL, which are known to be clinically meaningful, the subjects were divided into three groups (<160, 160–199, and ≥200) [18,19].

2.4. Diagnosis of AKI (Dependent Variable)

AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes criteria and grading (Appendix A) [20]. Considering the varying lengths of urinary catheters used across patients, only serum creatinine (mg dL^{-1}) was used for diagnosing AKI. Serum creatinine level measured at least within a month prior to ICU admission was defined as baseline creatinine, and AKI was diagnosed using serum creatinine levels measured within 72 h after ICU admission.

2.5. Outcomes

This study investigated how preadmission statin use is associated with the incidence of total AKI and stage ≥2 AKI after ICU admission. Additionally, we examined how this association differs according to preadmission eGFR.

2.6. Statistical Analysis

The baseline characteristics of the patients were presented as means with standard deviation or numbers with percentage. To compare preadmission statin users and non-statin users, continuous variables were tested using the two-sample t-test, while categorical variables were tested using the chi-square test. First, the individual association between each covariate and total AKI was examined with univariable logistic regression analysis. The covariates with $p < 0.1$ in the univariable logistic regression model were selected for adjustment in the final multivariable logistic regression analysis. Considering that baseline kidney function is a risk factor of AKI [21], we investigated the interaction between eGFR before ICU admission and preadmission statin use, and when there was an interaction, we performed a subgroup analysis by dividing the participants according to eGFR (≥90, 60–90, 30–60, and <30 mL min^{-1} 1.73 m^{-2}). In the subgroup analysis, the Bonferroni correction was used to prevent type I errors that resulted from multiple comparisons [22]. The same method was used for analyzing stage ≥2 AKI as the dependent variable. All analyses were performed using IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

3. Results

A total of 30,398 patients were admitted to the ICU 40,533 times between January 2012 and December 2017. These 30,398 patients were selected after excluding 10,135 cases involving the same patient being admitted to the ICU more than once. Next, we excluded 5440 patients aged <18 years, 47 ESRD patients who were undergoing RRT prior to ICU admission, 970 patients without baseline creatinine data, 2170 patients whose creatinine level was not measured within 72 h after ICU admission, and 535 patients who were diagnosed with AKI prior to ICU admission. As a result, 21,236 patients were included in the analysis, of whom 5756 (27.1%) were preadmission statin users and 15,480 (72.9%) were non-statin users (Figure 1). Their baseline characteristics are presented in Table 1. A total of 5469 (25.8%) patients developed AKI within 72 h after ICU admission, and 2216 (10.4%) of them had stage ≥2 AKI. Another 488 (2.3%) patients began postoperative RRT within 72 h after ICU admission.

3.1. Preadmission Statin Use and AKI Incidence

Table 2 shows the differences in characteristics between statin and non-statin users. The incidence of total AKI and stage ≥2 AKI among statin users was 1301/5756 (22.6%) and 439/5756 (7.6%), respectively, which was significantly lower than that in non-statin users [4168/15,480 (26.9%) and 1777/15,480 (11.5%), respectively] ($p < 0.001$). Table 3 shows the results of the multivariable logistic analysis after adjusting for the covariates selected in the univariate logistic regression analysis for total AKI incidence (Appendix B). AKI incidence within 72 h after ICU admission was 31% lower in preadmission statin users than in non-statin users [odds ratio (OR), 0.69; 95% confidence interval (CI), 0.61–0.79; $p < 0.001$]. Additionally, AKI incidence was 1.63-fold higher in patients with total cholesterol <160 mg dL^{-1} (OR: 1.63, 95% CI, 1.45–1.83; $p < 0.001$) than in those with total cholesterol

of 160–200 mg dL^{-1} at ICU admission. There was no significant difference in patients with total cholesterol >200 mg dL^{-1} ($p = 0.111$).

Table 1. Baseline characteristics of adults patients who were admitted to ICU in 2012–2017.

Variable	Total (21,236)	Mean	SD
Sex: male	12,434 (58.6%)		
Age, year		64.0	15.8
Body mass index, kg m^{-2}		23.7	3.9
APACHE II		20.0	10.0
Comorbidities at ICU admission			
eGFR [a] ≥ 90	12,993 (61.2%)		
60 ≤ eGFR [a] < 90	4527 (21.3%)		
30 ≤ eGFR [a] < 60	2364 (11.1%)		
eGFR [a] < 30	1352 (6.4%)		
Hypertension	9346 (44.0%)		
Diabetes mellitus	1969 (9.3%)		
Ischemic heart disease	538 (2.5%)		
Cerebrovascular disease	945 (4.4%)		
Chronic obstructive lung disease	921 (4.3%)		
Liver disease (LC, hepatitis, fatty liver)	683 (3.2%)		
Anemia (Hb < 10 g dL^{-1})	7569 (35.6%)		
Cancer	4308 (20.3%)		
Characteristics of ICU admission			
Admission through emergency department	12,042 (56.7%)		
Admission department			
Internal medicine	4671 (22.0%)		
Neurologic center	4975 (23.4%)		
Cardiothoracic surgical department	6875 (32.4%)		
Other surgical department	4715 (22.2%)		
Length of ICU stay, day		3.1	10.0
Length of hospital stay, day		12.9	20.1
Preadmission statin use	5756 (27.1%)		
Total serum cholesterol at ICU adm, mg dL^{-1}		138.2	47.9
<160, mg dL^{-1}	8584 (40.4%)		
160–200 mg dL^{-1}	10,751 (50.6%)		
>200 mg dL^{-1}	1901 (9.0%)		
Type of statin			
Atorvastatin	3456 (16.3%)		
Rosuvastatin	1391 (6.6%)		
Simvastatin	396 (1.9%)		
Pitavastatin	346 (1.6%)		
Other statin [b]	167 (0.8%)		
Total acute kidney injury	5469 (25.8%)		
Acute kidney injury stage ≥2	2216 (10.4%)		
RRT after ICU adm within 72 h	488 (2.3%)		

Presented as Number (percentage) or Mean value (standard deviation): [a]: eGFR (mL min^{-1} 1.73 m^{-2}): 186 × $(Creatinine)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female); [b]: Other statin: Pravastatin, Fluvastatin, and Lovastatin; ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate; LC, liver cirrhosis; Hb, hemoglobin; RRT, renal replacement therapy.

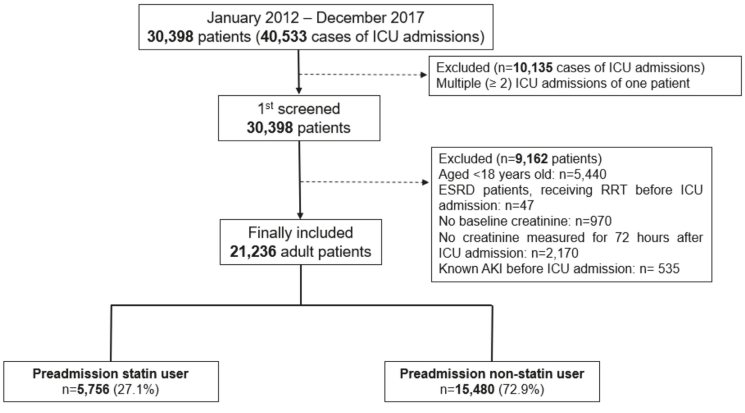

Figure 1. Flowchart of patient selection. ICU, Intensive Care Units; ESRD, End Stage Renal Disease; AKI, Acute Kidney Injury.

Table 2. Comparison of characteristics between preadmission statin user and non-statin user.

Variables		Statin Group n = 5756	Non-Statin Group n = 15,480	p-Value
Sex: male		3398 (59.0%)	9036 (58.4%)	0.384
Age, year		68.6 (12.0)	62.2 (16.6)	<0.001
Body Mass Index, kg m^{-2}		24.6 (3.8)	23.3 (3.8)	<0.001
Comorbidities at ICU admission				
	APACHE II	19.8 (9.8)	20.2 (10.1)	0.012
	eGFR [a]			<0.001
	≥90	3073 (53.4%)	9920 (64.1%)	
	60–90	1488 (25.9%)	3039 (19.6%)	
	30–60	764 (13.3%)	1.600 (10.3%)	
	<30	431 (7.5%)	921 (5.9%)	
	Hypertension	3672 (63.8%)	5674 (36.7%)	<0.001
	Diabetes mellitus	830 (14.4%)	1139 (7.4%)	<0.001
	Ischemic heart disease	314 (5.5%)	224 (1.4%)	<0.001
	Cerebrovascular disease	505 (8.8%)	440 (2.8%)	<0.001
	Chronic obstructive lung disease	229 (4.0%)	692 (4.5%)	0118
	Liver disease (LC, hepatitis, fatty liver)	87 (1.5%)	596 (3.9%)	<0.001
	Anemia (Hb < 10 g dL^{-1})	1774 (30.8%)	5795 (37.4%)	<0.001
	Cancer	875 (15.22%)	3433 (22.2%)	<0.001
Admission through ED		2640 (45.9%)	9402 (60.7%)	<0.001
Admission department				<0.001
	Internal medicine	1317 (22.9%)	3354 (21.7%)	
	Neurologic center	1252 (21.8%)	3723 (24.1%)	
	Cardiothoracic surgical department	2166 (37.6%)	4709 (30.4%)	
	Other surgical department	1021 (17.7%)	3694 (23.9%)	
Total serum cholesterol at ICU adm, mg dL^{-1}		125.2 (37.6)	143.1 (50.4)	<0.001
Length of hospital stay, day		11.3 (22.5)	13.5 (19.0)	<0.001
Length of ICU stay, day		2.5 (15.3)	3.3 (7.2)	<0.001
Total acute kidney injury		1301 (22.6%)	4168 (26.9%)	<0.001
Acute kidney injury stage ≥2		439 (7.6%)	1777 (11.5%)	<0.001
RRT after ICU adm within 72 h		140 (2.4%)	348 (2.2%)	0.426

Presented as number (percentage) or mean value (standard deviation). Two sample t-test for continuous variables and chi-square test for categorical variables were used: [a]: eGFR (mL min^{-1} 1.73 m^{-2}): 186 × $(Creatinine)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female); ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate; LC, liver cirrhosis; Hb, hemoglobin; ED, emergency department; RRT, renal replacement therapy.

Table 3. Multivariable logistic regression analysis for occurrence of acute kidney injury during 72 h after ICU admission.

Variable	Multivariable Model	
	Odds Ratio (95% CI)	p-Value
Dependent Variable: Total AKI		
Model 1: Preadmission statin use	0.69 (0.61, 0.79)	<0.001
Total serum cholesterol at ICU adm		
160–200 mg dL^{-1}	1	<0.001
<160, mg dL^{-1}	1.63 (1.45, 1.83)	<0.001
>200 mg dL^{-1}	0.86 (0.72, 1.04)	0.111
Interaction: eGFR [a] ≥ 90 × Non-statin use	1	0.001
60 ≤ eGFR [a] < 90 × Statin use	1.19 (0.95, 1.49)	0.132
30 ≤ eGFR [a] < 60 × Statin use	0.97 (0.74, 1.26)	0.801
eGFR [a] < 30 × Statin use	1.89 (1.35, 2.65)	<0.001
Dependent Variable: Stage ≥2 AKI		
Model 3: Preadmission statin use	0.69 (0.57, 0.84)	<0.001
Total serum cholesterol at ICU adm		
160–200 mg dL^{-1}	1	<0.001
<160 mg dL^{-1}	1.66 (1.38, 1.99)	<0.001
>200 mg dL^{-1}	0.85 (0.63, 1.15)	0.295
Interaction: eGFR [a] ≥ 90 × Non-statin use	1	
60 ≤ eGFR [a] < 90 × Statin use	0.95 (0.64, 1.40)	0.788
30 ≤ eGFR [a] < 90 × Statin use	1.04 (0.67, 1.61)	0.856
eGFR [a] < 30 × Statin use	1.27 (0.85, 1.91)	0.242

All covariates of $p < 0.1$ in univariable logistic regression analysis were included in multivariable logistic regression analysis. [a]: eGFR (mL min^{-1} 1.73 m^{-2}): 186 × $(Creatinine)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) ICU, intensive care unit; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

An interaction occurred between eGFR before ICU admission and total AKI after ICU admission with respect to preadmission statin use (overall $p = 0.001$, in Table 3; model 1); thus, additional subgroup analysis was performed (Table 4). When the patients were divided according to eGFR at ICU admission, total AKI incidence within 72 h after ICU admission was 28% lower among statin users with eGFR $\geq$90 mL min $^{-1}$ 1.73 m^{-2} (OR, 0.72; 95% CI, 0.63–0.82; $p < 0.001$), 26% lower among statin users with 60 $\leq$ eGFR <90 mL min $^{-1}$ 1.73 m^{-2} (OR, 0.74; 95% CI, 0.61–0.91; $p = 0.004$), and 35% lower among statin users with 30 $\leq$ eGFR <60 mL min $^{-1}$ 1.73 m^{-2} (OR, 0.65; 95% CI, 0.51–0.83; $p = 0.001$) than among non-statin users. Meanwhile, there were no significant differences in total AKI incidence between groups with eGFR <30 mL min $^{-1}$ 1.73 m^{-2} ($p = 0.095$).

Table 4. Multivariable logistic regression analysis for occurrence of acute kidney injury during 72 h after ICU admission according to eGFR at ICU admission.

Variable	Multivariable Model	
	Odds Ratio (95% CI)	***p*-Value ***
eGFR [a] $\geq$ 90 (n = 12,993)		
Preadmission statin use	0.72 (0.63, 0.82)	<0.001
60 $\leq$ eGFR [a] < 90 (n = 4527)		
Preadmission statin use	0.74 (0.61, 0.91)	0.004
30 $\leq$ eGFR [a] < 60 (n = 2364)		
Preadmission statin use	0.65 (0.51, 0.83)	0.001
eGFR [a] < 30 (n = 1340)		
Preadmission statin use	1.33 (0.95, 1.86)	0.095

p * < 0.013 was considered as statistical significance after Bonferroni correction. [a]: eGFR (mL min $^{-1}$ 1.73 m^{-2}): 186 × (Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female). ICU, intensive care unit; eGFR, estimated glomerular filtration rate.

3.2. Preadmission Statin Use and Stage $\geq$2 AKI Incidence

Table 3 also shows the results of the multivariable logistic regression analysis for stage $\geq$2 AKI incidence, including the covariates selected in the univariable logistic regression analysis (Appendix C). Stage $\geq$2 AKI incidence within 72 h after ICU admission was 31% lower among preadmission statin users than among non-statin users (OR, 0.69; 95% CI, 0.57–0.84; $p < 0.001$; model 3). Additionally, stage $\geq$2 AKI incidence was 1.66-fold higher in patients with total cholesterol <160 mg dL^{-1} (OR: 1.66, 95% CI, 1.38–1.99; $p < 0.001$) than in those with total cholesterol of 160–200 mg dL^{-1} at ICU admission. There was no significant difference in patients with total cholesterol >200 mg dL^{-1} ($p = 0.295$). Moreover, no interaction occurred between eGFR at ICU admission and stage $\geq$2 AKI with resto preadmission statin use (overall $p = 0.788$).

4. Discussion

This study showed that preadmission statin use is associated with a lower incidence of AKI after ICU admission. This association was also evident with stage $\geq$2 AKI. However, the association was not significant among patients with severe kidney dysfunction (eGFR <30 mL min^{-1} 1.73 m^{-2}) prior to ICU admission. Although the study results were derived from a retrospective observational study, it is striking because the statin group was comprised of significantly older and sicker patients and had a higher proportion of patients with renal dysfunction, more diabetes mellitus, ischemic heart disease, and cerebrovascular disease. Therefore, the study results suggested that clinicians who did not favor statin would consider prescribing statins to patients with respect to preventive effects for the development of AKI in critically ill patients.

The most interesting finding of this study was that an interaction occurred between eGFR at ICU admission and total AKI incidence with respect to preadmission statin use. In subsequent analyses, the potential benefit of preadmission statin use on AKI was not significant among patients with stage $\geq$4 chronic kidney disease (CKD). A meta-analysis, published in 2015, reported that statin

therapy does not improve the overall kidney function of CKD patients with eGFR <60 mL min^{-1} 1.73 m^{-2} and that high-dose statin therapy leads to limited improvement in kidney function [23]. Another meta-analysis, published in 2017, concluded that statin therapy was not beneficial in reducing major cardiovascular events, cardiovascular death, and all-cause mortality of patients with CKD 4 or 5 (eGFR <30 mL min^{-1} 1.73 m^{-2}) [24]. Although the primary endpoints were different from those used in our study, the previous meta-analysis suggested that statin therapy did not improve outcomes of patients with severe kidney dysfunction (CKD stage $\geq$4), which is consistent with our study finding. Patients with stage $\geq$4 CKD have worse baseline renovascular function than patients with normal kidney function and thus are more susceptible to ischemic oxidative damage, which is a major mechanism of AKI [25]. Furthermore, it was possible that treating patients with CKD stage $\geq$4 would be ineffective and the course of AKI could no longer be affected. However, it is difficult to completely explain the renal outcomes according to CKD stage solely based on this cohort study; hence, additional studies are needed.

This study suggested that preadmission statin therapy causes immunomodulatory effects, which were explained based on the pleiotropic effect of statin therapy [26]. We defined preadmission statin users as patients who confirmed taking statins as maintenance treatment as prescribed by their physicians at least one month before ICU admission. Most preadmission statin users received statin therapy for a long time, and there was some evidence that showed a clinical benefit of long-term statin therapy in patients with septic shock [27], pneumonia [28], or acute respiratory distress syndrome [29]. Although the immunomodulatory effect of statin therapy on critically ill patients remains controversial [30,31], it might affect the study results.

There is another important finding that should be carefully interpreted. The total incidence of AKI was higher in patients with <160 mg dL^{-1} of total serum cholesterol than in those with 160–200 mg dL^{-1} of total serum cholesterol, while patients with >200 mg dL^{-1} of total serum cholesterol had no association with the incidence of total AKI. In general, hyperlipidemia is an associated factor for renal damage [32]; however, hyperlipidemia was not associated with a lower incidence of AKI in this study. This can be explained based on the characteristics of ICU patients in this study. Lower cholesterol is a known factor that negatively affects the outcomes of critically ill patients [33,34], which is also coincident with our current study. Therefore, the effect of total serum cholesterol level on the incidence of AKI might be influenced by the characteristics of critically ill patients.

This study has a few limitations. First, a selection bias may have occurred due to the retrospective observational nature of the study. Second, the findings have limited generalizability because the study was conducted in a single center. For example, as previously mentioned, ethnical differences may have been involved in the effects of rosuvastatin. Lastly, because the duration of preadmission statin use differed among patients, we could not consider it in the analysis.

5. Conclusions

This study showed that preadmission statin use is associated with a lower incidence of total AKI and stage $\geq$ 2 AKI among critically ill patients after ICU admission. This association was most significantly evident among rosuvastatin users, but was absent among CKD patients with eGFR <30 mL min^{-1} 1.73 m^{-2}.

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Appendix A. Staging of Postoperative Acute Kidney Injury (KDIGO)

Stage	Serum Creatinine
1	1.5–1.9 times baseline or $\geq$0.3 mg dL^{-1} increase within 72 h after ICU admission
2	2.0–2.9 times baseline within 72 h after ICU admission
3	3.0 times baseline or increase in serum creatinine to $\geq$4.0 mg dL^{-1} or initiation of RRT within 72 h after ICU admission

KDIGO, Kidney Disease: Improving Global Outcomes; RRT, Renal Replacement Therapy.

Appendix B. Univariable Logistic Regression Analysis of Covariates for Occurrence of Total Acute Kidney Injury during 72 h after ICU Admission

Variables		Odds Ratio (95% CI)	*p*-Value
Sex: male		1.06 (1.00–1.13)	0.066
Age, year		1.02 (1.02–1.02)	<0.001
Body mass index, kg m^{-2}		0.96 (0.95–0.97)	<0.001
APACHE II		1.04 (1.04–1.04)	<0.001
Comorbidities at ICU admission			
	Hypertension	1.26 (1.18–1.34)	<0.001
	Diabetes mellitus	1.46 (1.32–1.61)	<0.001
	Ischemic heart disease	1.17 (0.97–1.42)	0.101
	Cerebrovascular disease	1.31 (1.14–1.51)	<0.001
	Chronic obstructive lung disease	1.13 (0.97–1.31)	0.109
	Liver disease (LC, hepatitis, fatty liver)	2.48 (2.13–2.89)	<0.001
	Anemia (Hb < 10 g dL^{-1})	3.82 (3.58–4.07)	<0.001
	Cancer	1.90 (1.77–2.05)	<0.001
	eGFR mL min^{-1} 1.73 m^{-2}		
	$\geq$90	1	<0.001
	60–90	0.99 (0.91–1.07)	0.731
	30–60	2.08 (1.89–2.28)	<0.001
	<30	5.18 (4.61–5.82)	<0.001
Admission through emergency department		1.52 (1.43–1.62)	<0.001
Total serum cholesterol at ICU adm			
160–200 mg dL^{-1}		1	<0.001
<160, mg dL^{-1}		2.21 (2.01, 2.43)	<0.001
>200 mg dL^{-1}		0.81 (0.69, 0.94)	<0.001
Admission department			
	Internal medicine	1	<0.001
	Neurologic center	0.25 (0.23–0.28)	<0.001
	Cardiothoracic surgical department	0.78 (0.72–0.84)	<0.001
	Other surgical department	0.83 (0.76–0.90)	<0.001
Year at ICU admission			
	2012	1	<0.001
	2013	1.31 (1.16–1.48)	<0.001
	2014	1.26 (1.12–1.42)	<0.001
	2015	1.09 (0.97–1.23)	0.150
	2016	1.02 (0.91–1.15)	0.690
	2017	0.96 (0.86–1.08)	0.535

All covariates of $p < 0.1$ in univariable logistic regression analysis were included in multivariable logistic regression analysis; ICU, intensive care unit; AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; LC, liver cirrhosis; Hb, hemoglobin.

Appendix C. Univariable Logistic Regression Analysis of Covariates for Occurrence of Stage ≥ 2 AKI Acute Kidney Injury during 72 h after ICU Admission

Variables		Odds Ratio (95% CI)	*p*-Value
Sex: male		1.04 (0.95–1.13)	0.452
Age, year		1.01 (1.01–1.02)	<0.001
Body mass index, kg m^{-2}		0.94 (0.92–0.95)	<0.001
APACHE II		1.04 (1.04–1.04)	<0.001
Comorbidities at ICU admission			
	Hypertension	1.08 (0.99–1.18)	0.106
	Diabetes mellitus	1.25 (1.09–1.44)	0.002
	Ischemic heart disease	0.94 (0.70–1.25)	0.654
	Cerebrovascular disease	1.03 (0.83–1.27)	0.795
	Chronic obstructive lung disease	0.97 (0.78–1.21)	0.816
	Liver disease (LC, hepatitis, fatty liver)	3.26 (2.73–3.88)	<0.001
	Anemia (Hb < 10 g dL^{-1})	4.86 (4.42–5.35)	<0.001
	Cancer	2.23 (2.03–2.46)	<0.001
	eGFR mL min^{-1} 1.73 m^{-2}		
	≥90	1	<0.001
	60–90	0.73 (0.64–0.82)	<0.001
	30–60	1.10 (0.96–1.27)	0.171
	<30	2.84 (2.47–3.26)	<0.001
Admission through emergency department		2.00 (1.82–2.21)	<0.001
Total serum cholesterol at ICU adm			
160–200 mg dL^{-1}		1	
<160, mg dL^{-1}		2.34 (2.02, 2.70)	<0.001
>200 mg dL^{-1}		0.81 (0.64, 1.04)	0.095
Admission department			
	Internal medicine	1	<0.001
	Neurologic center	0.20 (0.17–0.24)	<0.001
	Cardiothoracic surgical department	0.52 (0.46–0.58)	<0.001
	Other surgical department	0.67 (0.60–0.75)	<0.001
Year at ICU admission			
	2012	1	<0.001
	2013	1.52 (1.27–1.80)	<0.001
	2014	1.38 (1.16–1.63)	<0.001
	2015	1.19 (1.00–1.41)	0.053
	2016	1.05 (0.88–1.24)	0.605
	2017	1.00 (0.84–1.19)	0.999

All covariates of $p < 0.1$ in univariable logistic regression analysis were included in multivariable logistic regression analysis. ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate; LC, liver cirrhosis; Hb, hemoglobin; RRT, renal replacement therapy.

References

1. Waikar, S.S.; Bonventre, J.V. Creatinine kinetics and the definition of acute kidney injury. *J. Am. Soc. Nephrol.* **2009**, *20*, 672–679. [CrossRef] [PubMed]
2. Bellomo, R.; Kellum, J.A.; Ronco, C. Acute kidney injury. *Lancet* **2012**, *380*, 756–766. [CrossRef]
3. Lewington, A.J.; Cerda, J.; Mehta, R.L. Raising awareness of acute kidney injury: A global perspective of a silent killer. *Kidney Int.* **2013**, *84*, 457–467. [CrossRef] [PubMed]
4. Nash, K.; Hafeez, A.; Hou, S. Hospital-acquired renal insufficiency. *Am. J. Kidney Dis.* **2002**, *39*, 930–936. [CrossRef] [PubMed]
5. Thakar, C.V.; Christianson, A.; Freyberg, R.; Almenoff, P.; Render, M.L. Incidence and outcomes of acute kidney injury in intensive care units: A veterans administration study. *Crit. Care Med.* **2009**, *37*, 2552–2558. [CrossRef]
6. Macedo, E.; Mehta, R.L. Preventing acute kidney injury. *Crit. Care Clin.* **2015**, *31*, 773–784. [CrossRef] [PubMed]
7. Santodomingo-Garzon, T.; Cunha, T.M.; Verri, W.A., Jr.; Valerio, D.A.; Parada, C.A.; Poole, S.; Ferreira, S.H.; Cunha, F.Q. Atorvastatin inhibits inflammatory hypernociception. *Br. J. Pharmacol.* **2006**, *149*, 14–22. [CrossRef] [PubMed]

8. Rosenson, R.S. Low high-density lipoprotein cholesterol and cardiovascular disease: Risk reduction with statin therapy. *Am. Heart J.* **2006**, *151*, 556–563. [CrossRef]
9. Novack, V.; Terblanche, M.; Almog, Y. Do statins have a role in preventing or treating sepsis? *Crit. Care* **2006**, *10*, 113. [CrossRef]
10. Terblanche, M.; Almog, Y.; Rosenson, R.S.; Smith, T.S.; Hackam, D.G. Statins and sepsis: Multiple modifications at multiple levels. *Lancet Infect Dis.* **2007**, *7*, 358–368. [CrossRef]
11. Wang, C.Y.; Liu, P.Y.; Liao, J.K. Pleiotropic effects of statin therapy: Molecular mechanisms and clinical results. *Trends Mol. Med.* **2008**, *14*, 37–44. [CrossRef] [PubMed]
12. Molnar, A.O.; Coca, S.G.; Devereaux, P.J.; Jain, A.K.; Kitchlu, A.; Luo, J.; Parikh, C.R.; Paterson, J.M.; Siddiqui, N.; Wald, R.; et al. Statin use associates with a lower incidence of acute kidney injury after major elective surgery. *J. Am. Soc. Nephrol.* **2011**, *22*, 939–946. [CrossRef] [PubMed]
13. Campbell, J. Hmg coa reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. *J. Perioper. Pract.* **2018**, *28*, 142–143. [CrossRef] [PubMed]
14. Han, Y.; Zhu, G.; Han, L.; Hou, F.; Huang, W.; Liu, H.; Gan, J.; Jiang, T.; Li, X.; Wang, W.; et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J. Am. Coll. Cardiol.* **2014**, *63*, 62–70. [CrossRef] [PubMed]
15. Yasuda, H.; Yuen, P.S.; Hu, X.; Zhou, H.; Star, R.A. Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. *Kidney Int.* **2006**, *69*, 1535–1542. [CrossRef] [PubMed]
16. Su, X.; Zhang, L.; Lv, J.; Wang, J.; Hou, W.; Xie, X.; Zhang, H. Effect of statins on kidney disease outcomes: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **2016**, *67*, 881–892. [CrossRef] [PubMed]
17. Hallan, S.; Asberg, A.; Lindberg, M.; Johnsen, H. Validation of the modification of diet in renal disease formula for estimating gfr with special emphasis on calibration of the serum creatinine assay. *Am. J. Kidney Dis.* **2004**, *44*, 84–93. [CrossRef] [PubMed]
18. Neaton, J.D.; Blackburn, H.; Jacobs, D.; Kuller, L.; Lee, D.J.; Sherwin, R.; Shih, J.; Stamler, J.; Wentworth, D. Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. Multiple risk factor intervention trial research group. *Arch. Intern. Med.* **1992**, *152*, 1490–1500. [CrossRef] [PubMed]
19. Sempos, C.T.; Cleeman, J.I.; Carroll, M.D.; Johnson, C.L.; Bachorik, P.S.; Gordon, D.J.; Burt, V.L.; Briefel, R.R.; Brown, C.D.; Lippel, K.; et al. Prevalence of high blood cholesterol among us adults. An update based on guidelines from the second report of the national cholesterol education program adult treatment panel. *JAMA* **1993**, *269*, 3009–3014. [CrossRef] [PubMed]
20. Kellum, J.A.; Lameire, N.; Group, K.A.G.W. Diagnosis, evaluation, and management of acute kidney injury: A kdigo summary (part 1). *Crit. Care* **2013**, *17*, 204. [CrossRef] [PubMed]
21. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef]
22. Armstrong, R.A. When to use the bonferroni correction. *Ophthalmic Physiol. Opt.* **2014**, *34*, 502–508. [CrossRef]
23. Sanguankeo, A.; Upala, S.; Cheungpasitporn, W.; Ungprasert, P.; Knight, E.L. Effects of statins on renal outcome in chronic kidney disease patients: A systematic review and meta-analysis. *PLoS ONE* **2015**, *10*, e0132970. [CrossRef]
24. Messow, C.M.; Isles, C. Meta-analysis of statins in chronic kidney disease: Who benefits? *QJM* **2017**, *110*, 493–500. [CrossRef] [PubMed]
25. Basile, D.P.; Anderson, M.D.; Sutton, T.A. Pathophysiology of acute kidney injury. *Compr. Physiol.* **2012**, *2*, 1303–1353. [PubMed]
26. Liao, J.K.; Laufs, U. Pleiotropic effects of statins. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 89–118. [CrossRef] [PubMed]
27. Fuller, B.M.; Gajera, M.; Schorr, C.; Gerber, D.; Dellinger, R.P.; Zanotti, S. The association of prior statin use in septic shock treated with early goal directed therapy. *Eur. J. Emerg. Med.* **2012**, *19*, 226–230. [CrossRef] [PubMed]
28. Thomsen, R.W.; Riis, A.; Kornum, J.B.; Christensen, S.; Johnsen, S.P.; Sorensen, H.T. Preadmission use of statins and outcomes after hospitalization with pneumonia: Population-based cohort study of 29,900 patients. *Arch. Intern. Med.* **2008**, *168*, 2081–2087. [CrossRef]
29. Craig, T.; O'Kane, C.; McAuley, D. Potential mechanisms by which statins modulate the development of acute lung injury. In *Intensive Care Medicine*; Springer: Berlin, Germany, 2007; pp. 276–288.

30. Nagendran, M.; McAuley, D.F.; Kruger, P.S.; Papazian, L.; Truwit, J.D.; Laffey, J.G.; Thompson, B.T.; Clarke, M.; Gordon, A.C. Statin therapy for acute respiratory distress syndrome: An individual patient data meta-analysis of randomised clinical trials. *Intensive Care Med.* **2017**, *43*, 663–671. [CrossRef]
31. Thomas, G.; Hraiech, S.; Loundou, A.; Truwit, J.; Kruger, P.; McAuley, D.F.; Papazian, L.; Roch, A. Statin therapy in critically-ill patients with severe sepsis: A review and meta-analysis of randomized clinical trials. *Minerva Anestesiol.* **2015**, *81*, 921–930.
32. Sastre, C.; Rubio-Navarro, A.; Buendia, I.; Gomez-Guerrero, C.; Blanco, J.; Mas, S.; Egido, J.; Blanco-Colio, L.M.; Ortiz, A.; Moreno, J.A. Hyperlipidemia-associated renal damage decreases klotho expression in kidneys from apoe knockout mice. *PLoS ONE* **2013**, *8*, e83713. [CrossRef] [PubMed]
33. Wilson, R.F.; Barletta, J.F.; Tyburski, J.G. Hypocholesterolemia in sepsis and critically ill or injured patients. *Crit. Care* **2003**, *7*, 413–414. [CrossRef] [PubMed]
34. Gui, D.; Spada, P.L.; De Gaetano, A.; Pacelli, F. Hypocholesterolemia and risk of death in the critically ill surgical patient. *Intensive Care Med.* **1996**, *22*, 790–794. [CrossRef] [PubMed]

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Fluctuations in Serum Chloride and Acute Kidney Injury among Critically Ill Patients: A Retrospective Association Study

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Abstract: Exposure to dyschloremia among critically ill patients is associated with an increased risk of acute kidney injury (AKI). We aimed to investigate how fluctuations in serum chloride (Cl^-) are associated with the development of AKI in critically ill patients. We retrospectively analyzed medical records of adult patients admitted to the intensive care unit (ICU) between January 2012 and December 2017. Positive and negative fluctuations in Cl^- were defined as the difference between the baseline Cl- and maximum Cl- levels and the difference between the baseline Cl^- and minimum Cl^- levels measured within 72 h after ICU admission, respectively. In total, 19,707 patients were included. The odds of developing AKI increased 1.06-fold for every 1 mmol L^{-1} increase in the positive fluctuations in Cl^- (odds ratio: 1.06; 95% confidence interval: 1.04 to 1.08; $p < 0.001$) and 1.04-fold for every 1 mmol L^{-1} increase in the negative fluctuations in Cl^- (odds ratio: 1.04; 95% confidence interval: 1.02 to 1.06; $p < 0.001$). Increases in both the positive and negative fluctuations in Cl- after ICU admission were associated with an increased risk of AKI. Furthermore, these associations differed based on the functional status of the kidneys at ICU admission or postoperative ICU admission.

Keywords: acute kidney injury; critical care; intensive care units

1. Introduction

Acute kidney injury (AKI) is defined as an impairment of renal function [1], and is reported to occur in 2–18% of all inpatients, and 35.7–57% of all critically ill patients [2–5]. AKI that affects patients in intensive care units (ICUs) not only increases the duration of hospitalization and medical costs [6], but also increases in-hospital mortality [7]. Therefore, adequate prevention of AKI in ICUs is an important challenge in ICU patient management [8].

Serum chloride (Cl^-) is the most common anion in the human body. Dyschloremia is a collective term for hypochloremia, in which the Cl^- level is below the normal range, and hyperchloremia, in which the Cl^- level is above the normal range [9]. Increased Cl^- levels induce hyperchloremic metabolic acidosis through physiologic compensation, whereas decreased Cl^- levels induce hypochloremic metabolic alkalosis. Both conditions are associated with increased risks of AKI [10,11]. It is important to understand the association between dyschloremia and AKI in the ICU because the Cl^- level can provide important information in the planning of a fluid management strategy [12].

It is well known that increases in Cl^- levels after ICU admission are associated with the development of AKI [13–15], while the association between a decrease in Cl^- levels and the development of AKI has not been extensively studied. Critically ill patients may experience a reduction in Cl^- levels after ICU admission due to the active loss of Cl^- in the gastrointestinal tract, impaired renal Cl^- reabsorption,

hypotonic fluid infusion, excessive diuretics therapy, and malnutrition [16,17]. These conditions may be associated with the development of AKI. Thus, when studying the association between Cl^- levels and the incidence of AKI among critically ill patients, fluctuations of Cl^- levels (increases and decreases) must be considered.

Therefore, this study aimed to investigate the association between the total, positive, and negative fluctuations in Cl^- levels and the incidence of AKI.

2. Materials and Methods

2.1. Study Design and Subjects

This retrospective observational study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB approval number B-1806/474-105). The IRB exempted the need for informed consent, considering the retrospective study design. The medical records of adult patients aged ≥18 years admitted to the ICU between January 2012 and December 2017 were analyzed. For single patients admitted to the ICU twice or more during the study period, only the last ICU admission in which the patient could be in the most critical condition was included in the analysis. Patients whose medical records, regarding Cl^- and creatinine, were incomplete or missing were excluded from the analysis. Patients with an estimated glomerular filtration rate (eGFR) <15 mL min^{-1} 1.73 m^{-2}, patients with end-stage renal disease (ESRD) who underwent chronic renal replacement therapy (RRT) before ICU admission, and patients with undiagnosed AKI before ICU admission were also excluded.

This study succeeds a previous study [18] that analyzed the medical records of patients in the surgical ICU at our institution from 2011 to 2016. The previous study reported that exposure to hyperchloremia in the postoperative period in the surgical ICU was not associated with the incidence of AKI. This study differs from the previous study that analyzed the positive or negative fluctuations in Cl^- within 72 h after ICU admission; previous studies have analyzed the increases in the preoperative Cl^- to the maximum Cl^- in 0–3 days postoperatively.

2.2. Fluctuations in Cl- Levels (Independent Variables)

For the purpose of this study, the Cl- level on ICU admission (baseline Cl-) was defined as that measured within 24 h after ICU admission, and the Cl- level closest to the ICU admission time. Positive fluctuations in Cl- were defined as the difference between the baseline Cl- and the maximum Cl- levels measured within 72 h after ICU admission, while negative fluctuations in Cl- were defined as the difference between the baseline Cl- and the minimum Cl- levels measured within 72 h after ICU admission. Lastly, the total fluctuations in Cl- were defined as the difference between the minimum and maximum Cl- levels measured within 72 h after ICU admission. For example, if baseline Cl-, maximum Cl-, and minimum Cl- levels were 107 mmol L^{-1}, 111 mmol L^{-1}, and 105 mmol L^{-1}, respectively, the total positive and negative fluctuations were 6 mmol L^{-1} (111–105 mmol L^{-1}), 4 mmol L^{-1} (111–107 mmol L^{-1}), and 2 mmol L^{-1} (107–105 mmol L^{-1}), respectively. In situations where no maximum or minimum value of Cl- within 72 h after ICU admission was noted, the positive or negative fluctuation of Cl-, respectively, was considered as 0. In those cases, the total fluctuation was calculated using baseline Cl- level. For example, if baseline Cl-, maximum Cl-, and minimum Cl- levels were 105 mmol L^{-1}, 111 mmol L^{-1}, and 107 mmol L^{-1}, respectively, the total, positive, and negative fluctuations were 6 mmol L^{-1} (111–105 mmol L^{-1}), 6 mmol L^{-1} (111–105 mmol L^{-1}), and 0 mmol L^{-1} (no minimum Cl- level), respectively.

2.3. Potential Covariates

Data regarding demographics (sex, age, and body mass index), Acute Physiology, Chronic Health Evaluation II, comorbidities at ICU admission (eGFR, mL min^{-1} 1.73 m^{-2}, hypertension, diabetes mellitus, history of ischemic heart disease and cerebrovascular disease, chronic obstructive lung disease,

liver disease (liver cirrhosis, hepatitis, and fatty liver), anemia (hemoglobin <10 g dL^{-1}), cancer status regarding hospital admission through the emergency department, postoperative admission status, and the admission department (internal medicine/neurologic center/postcardiothoracic surgery/post-other surgery) at the time of ICU admission were collected. Information regarding fluid administration (i.e., NaCl 0.9%, balanced crystalloid, and hydroxyethyl starch (all in mL)) for 72 h after ICU admission was collected. Additionally, the maximum value of the cystatin c level (mg dL^{-1}) for 72 h after ICU admission was collected. Finally, the number of Cl- level measurements taken for 72 h after ICU admission were collected. The Modification of Diet in Renal Disease equation was used to calculate the eGFR before ICU admission [19]: eGFR (mL min^{-1} 1.73 m^{-2}) = 186 × (Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female).

2.4. Acute Kidney Injury within 72 h after ICU Admission (Dependent Variable)

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria and grading method were used to diagnose AKI (Appendix A) [20]. Considering the differences in the duration of urinary catheterization among the patients, only the serum creatinine (mg dL^{-1}) level was used to diagnose AKI. The serum creatinine value measured within 1 month before ICU admission closest to the time of ICU admission was used as the baseline creatinine concentration for AKI diagnosis. The serum creatinine level measured within 72 h after ICU admission was used to diagnose AKI.

2.5. Endpoint

This study investigated the associations between total, positive, and negative fluctuations in Cl- within 72 h after ICU admission and the total incidence of AKI and AKI stage ≥2. In addition, we investigated relationships between total, positive, and negative fluctuations in serum Cl^- with the maximum serum cystatin C level for 72 h after ICU admission.

2.6. Statistical Analysis

The patients' baseline characteristics were expressed as means and standard deviations (SDs) or numbers and proportions. The log odds of AKI occurrence and fluctuations in Cl^- were presented as restricted cubic splines (RCSs). After confirming a linear relationship between the fluctuation in Cl^- and log odds of developing AKI in RCSs, the fluctuation in Cl^- was included in the logistic regression model as a continuous variable. A univariable logistic regression analysis was performed to investigate the association of each covariate with the incidence of the dependent variable (AKI). Covariates with $p < 0.1$ were selected from the univariable logistic regression model, and were controlled for in the final multivariable logistic regression analysis. In the multivariable logistic regression analysis, total fluctuations in Cl^- were included in another multivariable logistic regression model with positive and negative fluctuations in Cl^- to avoid multicollinearity within variables.

Next, considering that baseline kidney function is a major risk factor of AKI [21], the interaction between fluctuations in Cl^- and eGFR and the incidence of AKI before ICU admission were investigated. After confirming that there was a significant interaction between fluctuations in Cl^- and eGFR with the incidence of AKI, we performed a subgroup analysis with four eGFR groups (eGFR ≥90, <90, <60, and <30 mL min^{-1} 1.73 m^{-2}). Lastly, the interaction between fluctuations in Cl^- and postoperative ICU admission for the incidence of AKI were investigated, and the significant interactions were also confirmed. Therefore, we performed a subgroup analysis based on postoperative ICU admission. To reduce type I errors due to multiple comparisons in the subgroup analysis, the Bonferroni correction was used [22]. The same method was used in the analysis of stage ≥2 as a dependent variable. The results of the logistic regression analysis were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Additionally, considering that the serum cystatin C was a marker of renal function in the detection of early AKI [23], we performed a generalized linear regression analysis to investigate the association between fluctuation in serum Cl^- and the maximum serum cystatin C level for 72 h after ICU admission. In this generalized linear model (GLM), gamma distribution and the log link function

were assumed for the dependent variable (maximum cystatin C level within 72 h after ICU admission). All covariates were included in the GLM. The results of GLM were expressed as the exponentiated (exp) regression coefficient (coef) with 95% CIs. All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R program (version 3.5.2 with R packages), with the level of statistical significance set at $p < 0.05$.

3. Results

There was a total of 40,533 ICU admissions between 2012 and 2017. Of these, 10,135 admission cases in which a single patient was admitted twice or more were excluded. Next, 5440 patients younger than 17 years, 44 ESRD patients who received RRT before ICU admission, 4730 patients with incomplete medical records regarding serum Cl- or creatinine levels, and 477 patients with undiagnosed AKI before admission were excluded, and the remaining 19,707 patients were finally included. There was a total of 5284 (26.8%) AKI cases within 72 h after ICU admission; 2233 (11.4%) patients had AKI stage ≥2 (Figure 1). Table 1 shows the baseline characteristics of these patients. The mean (SD) values of the total, positive, and negative fluctuations in Cl- were 7.0 (5.7), 4.4 (4.1), and 2.9 (4.6), respectively.

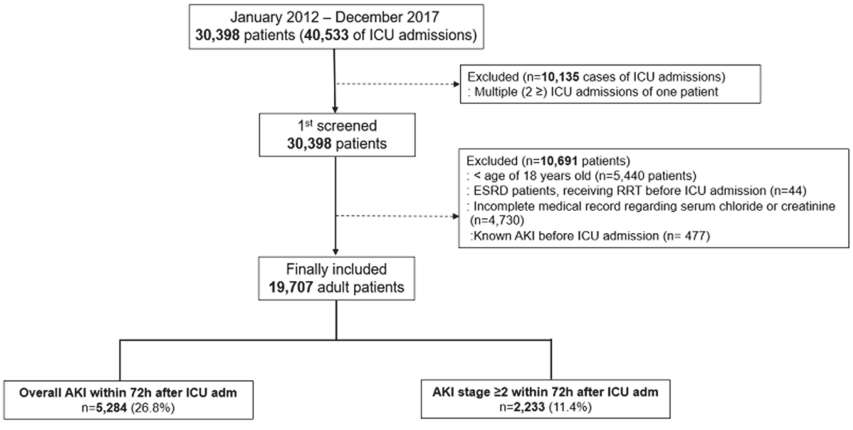


Figure 1. Flow chart of patient selection.

Table 1. Baseline characteristics of adult patients admitted to the ICU between 2012 and 2017.

Variable	Total (19,707)	Mean	SD
Sex: male	11,412 (57.9%)		
Age, year		63.8	15.9
Body mass index, kg m^{-2}		23.6	3.9
Comorbidities at ICU admission			
APACHE II		20.3	10.0
eGFR [a]: ≥90	12,164 (61.7%)		
60–90	4079 (20.7%)		
30–60	2163 (11.0%)		
<30	1301 (6.6%)		
Hypertension	8511 (43.2%)		
Diabetes mellitus	1775 (9.0%)		
Ischemic heart disease	481 (2.4%)		
Cerebrovascular disease	886 (4.5%)		
Chronic obstructive lung disease	868 (4.4%)		
Liver disease (LC, hepatitis, fatty liver)	649 (3.3%)		
Anemia (Hb <10 g dL^{-1})	7266 (36.9%)		
Cancer	4137 (21.0%)		

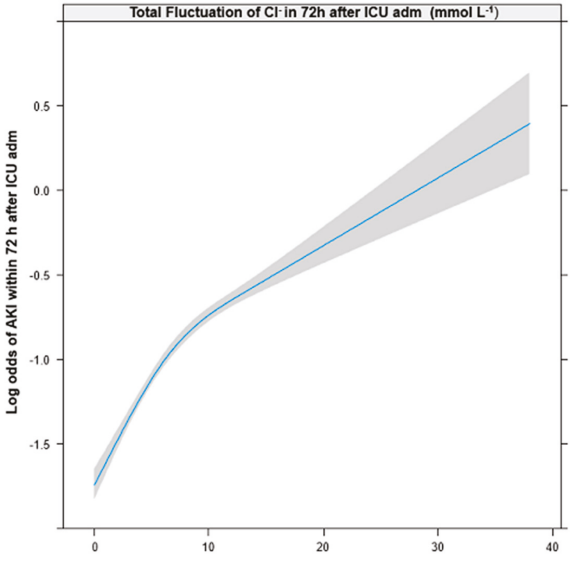
Table 1. *Cont.*

Variable	Total (19,707)	Mean	SD
Sex: male	11,412 (57.9%)		
Age, year		63.8	15.9
Body mass index, kg m^{-2}		23.6	3.9
Characteristics of ICU admission			
Admission through emergency department	11,435 (58.0%)		
Postoperative admission	8728 (44.3%)		
Admission department			
Internal medicine	4231 (21.5%)		
Neurologic center	4805 (24.4%)		
Cardiothoracic surgical department	6093 (30.9%)		
Other surgical departments	4578 (23.2%)		
Length of ICU stay, day		3.2	10.4
Length of hospital stay, day		13.3	20.5
Fluid administration for 72 h after ICU admission			
NaCl 0.9%, mL		1745.5	2124.1
Balanced crystalloid, mL		505.5	862.5
Hydroxyethyl starch, mL		79.4	270.1
Transfusion of packed RBC	8530 (43.3%)		
Serum chloride (Cl^-) in ICU, mmol L^{-1}			
Cl^- on ICU admission		106.4	6.2
The number of measurements for 72 h after ICU admission		3.2	1.0
Total fluctuation of Cl^- for 72 h after ICU admission [b]		7.0	5.7
Positive fluctuation of Cl^- for 72 h after ICU admission [c]		4.4	4.1
Negative fluctuation of Cl^- for 72 h after ICU admission [d]		2.9	4.6
Max cystatin C level mg dL^{-1} for 72 h after ICU adm (n = 2,021)		2.0	1.2
Total AKI within 72 h after ICU admission	5284 (26.8%)		
AKI stage ≥2 within 72 h after ICU admission	2233 (11.4%)		
RRT after ICU admission (within 72 h)	468 (2.4%)		

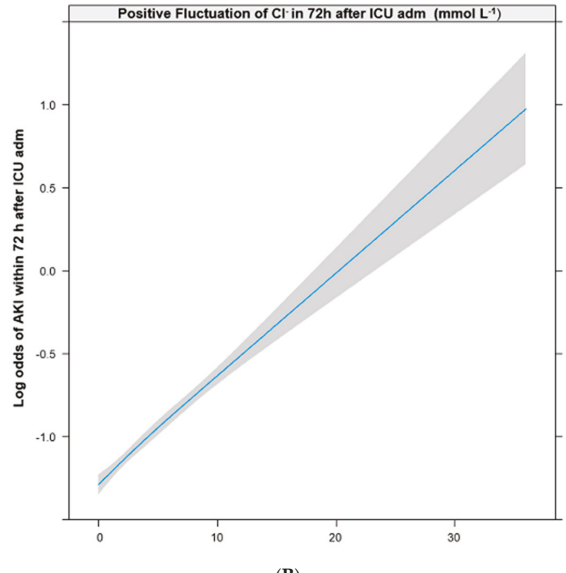
[a] eGFR (mL min^{-1} 1.73 m^{-2}): 186 × $(Creatinine)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female). [b] Total fluctuation of Cl^-: (Maximum Cl^- – Minimum Cl^-) for 72 h after ICU admission. [c] Positive fluctuation of Cl^-: (Maximum Cl^- – Preadmission Cl^-) for 72 h after ICU admission. [d] Negative fluctuation of Cl^-: (Preadmission Cl^- – Minimum Cl^-) for 72 h after ICU admission. ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate; LC, liver cirrhosis; Hb, hemoglobin; RBC, red blood cell; Max, maximum; AKI, acute kidney injury; RRT, renal replacement therapy.

3.1. AKI within 72 h after ICU Admission Based on Cl- Fluctuations

The RCSs in Figure 2 show that the log odds of developing AKI had positive and linear relationships with total (A), positive (B), and negative fluctuations (C) in Cl^- levels. Appendix B shows the results of the univariable logistic regression analysis of the associations between the individual covariates and AKI. Table 2 shows the results of the multivariable logistic regression analysis adjusted for the covariates selected from the univariable logistic regression analysis. The odds of developing AKI increased 1.05-fold for every 1 mmol L^{-1} increase in the total fluctuations in Cl^- (OR: 1.05; 95% CI: 1.03 to 1.06; $p < 0.001$), 1.06-fold for every 1 mmol L^{-1} increase in the positive fluctuations in Cl^- (OR: 1.06; 95% CI: 1.04 to 1.08; $p < 0.001$), and 1.04-fold for every 1 mmol L^{-1} increase in the negative fluctuations in Cl^- (OR: 1.04; 95% CI: 1.02 to 1.06; $p < 0.001$). The results of the subgroup analysis for total AKI based on the preadmission eGFR status and the postoperative ICU admission status are shown in Tables 3 and 4, respectively.

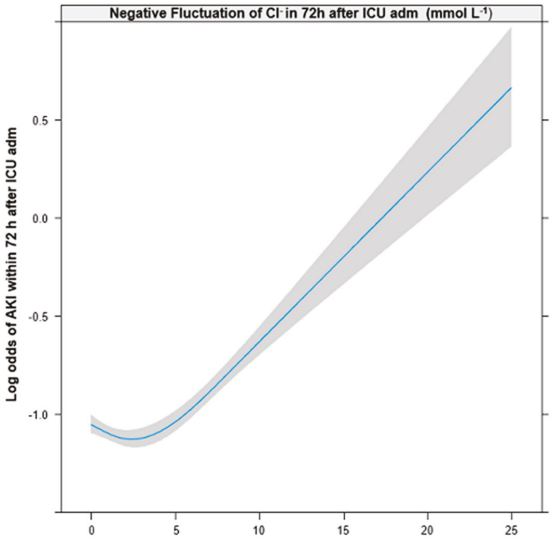


(**A**)



(**B**)

Figure 2. *Cont.*



(**C**)

Figure 2. Restricted cubic spline between total (**A**), positive (**B**), and negative (**C**) fluctuations in serum chloride within 72 h after ICU admission and occurrence of AKI. ICU, intensive care unit; AKI, acute kidney injury. RRT, renal replacement therapy.

3.2. AKI Stage ≥2 within 72 h after ICU Admission According to Cl^- Fluctuation

Appendix B shows the results of the univariable logistic regression analysis of the associations between the individual covariates and AKI stage ≥2. Table 2 shows the results of the multivariable logistic regression analysis adjusted for the covariates selected from the univariable logistic regression analysis. The odds of developing stage ≥2 AKI increased 1.08-fold for every 1 mmol L^{-1} increase in the total fluctuations in Cl^- (OR: 1.08; 95% CI: 1.06 to 1.10; $p < 0.001$), 1.09-fold for every 1 mmol L^{-1} increase in the positive fluctuations in Cl^- (OR: 1.09; 95% CI: 1.07 to 1.11; $p < 0.001$), and 1.09-fold for every 1 mmol L^{-1} increase in the negative fluctuations in Cl^- (OR: 1.09; 95% CI: 1.06 to 1.11; $p < 0.001$). The results of the subgroup analysis for AKI stage ≥2 according to preadmission eGFR grouping and postoperative ICU admission status are shown in Tables 3 and 4, respectively.

Table 2. Multivariable logistic regression analysis for total AKI and AKI stage ≥2 after ICU admission according to fluctuations of serum chloride (mmol L^{-1}).

Variables	Odds Ratio (95% CI)	*p*-Value
Dependent variables: Total AKI		
Total fluctuation of Cl^- [a] (model 1)	**1.05** (1.03, 1.06)	**<0.001**
Interaction: Total fluctuation of Cl^- [a,*] eGFR [b] ≥90	1	(<0.001)
Total fluctuation of Cl^- [a,*] eGFR [b]: 60–90	1.02 (1.00, 1.04)	0.114
Total fluctuation of Cl^- [a,*] eGFR [b]: 30–60	1.02 (1.00, 1.05)	0.153
Total fluctuation of Cl^- [a,*] eGFR [b]: <30	0.90 (0.88, 0.93)	<0.001
Interaction: Total fluctuation of Cl^- [a,*] postoperative admission	0.96 (0.95, 0.98)	<0.001
Positive fluctuation of Cl^- [c] (model 2)	**1.06** (1.04, 1.08)	**<0.001**
Interaction: Positive fluctuation of Cl^- [a,*]eGFR [b] ≥90	1	(<0.001)
Positive fluctuation of Cl^- [a,*] eGFR [b]:60–90	1.02 (0.99, 1.04)	0.259
Positive fluctuation of Cl^- [a,*] eGFR [b]:30–60	1.00 (0.97, 1.03)	0.812
Positive fluctuation of Cl^- [a,*] eGFR [b]:<30	0.87 (0.84, 0.90)	<0.001
Interaction: Positive fluctuation of Cl^- [a,*] postoperative admission	0.98 (0.96, 1.00)	0.095
Negative fluctuation of Cl^- [c] (model 2)	**1.04** (1.02, 1.06)	**<0.001**
Interaction: Negative fluctuation of Cl^- [a,*]eGFR [b] ≥90	1	(<0.001)
Negative fluctuation of Cl^- [a,*] eGFR [b]: 60–90	1.02 (0.99, 1.06)	0.145
Negative fluctuation of Cl^- [a,*] eGFR [b]: 30–60	1.05 (1.01, 1.09)	0.006
Negative fluctuation of Cl^- [a,*] eGFR [b]: <30	0.94 (0.91, 0.98)	0.003
Interaction: Negative fluctuation of Cl^- [a,*] postoperative admission	0.94 (0.92, 0.97)	<0.001
Dependent variables: AKI stage ≥2		
Total fluctuation of Cl^- [a]	**1.08** (1.06, 1.10)	**<0.001**
Interaction: Total fluctuation of Cl^- [a,*] eGFR [b]: ≥90	1	(<0.001)
Total fluctuation of Cl^- [a,*] eGFR [b]: 60–90	1.00 (0.97, 1.03)	0.853
Total fluctuation of Cl^- [a,*] eGFR [b]: 30–60	0.96 (0.92, 0.99)	0.022
Total fluctuation of Cl^- [a,*] eGFR [b]: <30	0.89 (0.86, 0.92)	<0.001
Interaction: Total fluctuation of Cl^- [a,*] postoperative admission	0.96 (0.93, 0.98)	<0.001
Positive fluctuation of Cl^- [c]	**1.09** (1.07, 1.11)	**<0.001**
Interaction: Positive fluctuation of Cl^- [a,*]eGFR [b] ≥90	1	(<0.001)
Positive fluctuation of Cl^- [a,*] eGFR [b]: 60–90	1.00 (0.96, 1.03)	0.881
Positive fluctuation of Cl^- [a,*] eGFR [b]: 30–60	0.92 (0.88, 0.96)	<0.001
Positive fluctuation of Cl^- [a,*] eGFR [b]: <30	0.87 (0.84, 0.91)	<0.001
Interaction: Positive fluctuation of Cl^- [a,*] postoperative admission		
Negative fluctuation of Cl^- [d]	**1.09** (1.06, 1.11)	**<0.001**
Interaction: Negative fluctuation of Cl^- [a,*]eGFR [b] ≥90	1	(<0.001)
Negative fluctuation of Cl^- [a,*] eGFR [b]: 60–90	0.99 (0.95, 1.04)	0.789
Negative fluctuation of Cl^- [a,*] eGFR [b]: 30–60	1.00 (0.95, 1.04)	0.853
Negative fluctuation of Cl^- [a,*] eGFR [b]: <30	0.91 (0.87, 0.95)	<0.001
Interaction: Negative fluctuation of Cl^- [a,*] postoperative admission	0.91 (0.89, 0.94)	<0.001

Covariates of $p < 0.1$ in univariable logistic regression analysis (Appendix B) were included to adjust the multivariable logistic regression model. [a] Total fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^-– Minimum Cl^-) for 72 h after ICU admission. [b] eGFR (mL min^{-1} 1.73 m^{-2}): 186 × $(Creatinine)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female). [c] Positive fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^- – Preadmission Cl^-) for 72 h after ICU admission. [d] Negative fluctuation of Cl^- (mmol L^{-1}): (Preadmission Cl^- – Minimum Cl^-) for 72 h after ICU admission. AKI, acute kidney injury; ICU, intensive care unit; eGFR, estimated glomerular filtration rate.

Table 3. Multivariable logistic regression analysis for total AKI and AKI stage ≥2 after ICU admission according to preadmission eGFR [a] group.

Variables	Odds Ratio (95% CI)	p *
Dependent variable: Total AKI		
eGFR [a] ≥90 (n = 12,164)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.04** (1.02, 1.05)	**<0.001**
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	**1.05** (1.03, 1.06)	**<0.001**
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	1.01 (0.99, 1.03)	0.204
eGFR [a] <90 (n = 7,543)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.02** (1.01, 1.04)	**0.002**
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	**1.02** (1.00, 1.04)	**0.024**
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	**1.03** (1.01, 1.05)	**0.004**
eGFR [a]: <60 (n = 3,464)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	1.01 (0.99, 1.03)	0.239
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.97, 1.01)	0.529
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	**1.03** (1.01, 1.06)	**0.004**
eGFR [a]: <30 (n = 1,301)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	0.98 (0.95, 1.01)	0.150
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.91, 1.01)	0.052
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	1.01 (0.98, 1.05)	0.469
Dependent variables: AKI stage ≥2		
eGFR [a] ≥90 (n = 12,164)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.06** (1.04, 1.08)	**<0.001**
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	**1.07** (1.05, 1.09)	**<0.001**
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	**1.04** (1.02, 1.06)	**0.001**
eGFR [a] <90 (n = 7,543)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.03** (1.01, 1.05)	**0.002**
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	1.02 (1.00, 1.04)	0.059
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	**1.04** (1.02, 1.06)	**0.001**
eGFR [a]: <60 (n = 3,464)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	1.01 (0.99, 1.03)	0.317
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.96, 1.01)	0.280
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	**1.04** (1.01, 1.07)	**0.003**
eGFR [a]: <30 (n = 1,301)		
Total fluctuation of Cl^- [b] (per 1 mmol L^{-1})	1.00 (0.97, 1.04)	0.788
Positive fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.95, 1.03)	0.489
Negative fluctuation of Cl^- [d] (per 1 mmol L^{-1})	1.02 (0.98, 1.06)	0.247

* $p < 0.013$ was considered as statistically significant after Bonferroni correction. Covariates of $p < 0.1$ in univariable logistic regression analysis (Appendix B) were included to adjust the multivariable logistic regression model. [a] eGFR (mL min $^{-1}$ 1.73m^{-2}): 186 × (Creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female). [b] Total fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^- – Minimum Cl^-) for 72 h after ICU admission. [c] Positive fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^- – Preadmission Cl^-) for 72 h after ICU admission. [d] Negative fluctuation of Cl^- (mmol L^{-1}): (Preadmission Cl^- – Minimum Cl^-) for 72 h after ICU admission.

Table 4. Multivariable logistic regression analysis for total AKI and AKI (stage ≥2) after ICU admission according to postoperative admission.

Variables	Odds ratio (95% CI)	p *
Dependent variable: Total AKI		
Postoperative admission (n = 8,728)		
Total fluctuation of Cl^- [a] (per 1 mmol L^{-1})	1.01 (1.00, 1.02)	0.170
Positive fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.03** (1.01, 1.04)	**0.002**
Negative fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.97, 1.01)	0.254
Non-postoperative admission (n = 10,992)		
Total fluctuation of Cl^- [a] (per 1 mmol L^{-1})	**1.04** (1.02, 1.05)	**<0.001**
Positive fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.04** (1.02, 1.05)	**<0.001**
Negative fluctuation of Cl^- [c] (per 1 mmol L^{-1})	**1.04** (1.02, 1.05)	**<0.001**
Dependent variables: AKI stage ≥2		
Postoperative admission (n = 8,728)		
Total fluctuation of Cl^- [a] (per 1 mmol L^{-1})	1.01 (0.99, 1.03)	0.300
Positive fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.03** (1.00, 1.05)	**0.023**
Negative fluctuation of Cl^- [c] (per 1 mmol L^{-1})	0.99 (0.96, 1.02)	0.396
Non-postoperative admission (n = 10,992)		
Total fluctuation of Cl^- [a] (per 1 mmol L^{-1})	**1.05** (1.04, 1.07)	**<0.001**
Positive fluctuation of Cl^- [b] (per 1 mmol L^{-1})	**1.05** (1.03, 1.07)	**<0.001**
Negative fluctuation of Cl^- [c] (per 1 mmol L^{-1})	**1.06** (1.04, 1.08)	**<0.001**

* $p < 0.025$ was considered as statistically significant after Bonferroni correction. Covariates of $p < 0.1$ in univariable logistic regression analysis (Appendix B) were included to adjust the multivariable logistic regression model. [a] Total fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^- – Minimum Cl^-) for 72 h after ICU admission. [b] Positive fluctuation of Cl^- (mmol L^{-1}): (Maximum Cl^- – Preadmission Cl^-) for 72 h after ICU admission. [c] Negative fluctuation of Cl^- (mmol L^{-1}): (Preadmission Cl^- – Minimum Cl^-) for 72 h after ICU admission. AKI, acute kidney injury; ICU, intensive care unit; eGFR, estimated glomerular filtration rate.

3.3. Fluctuation in Cl^- and Maximum Serum Cystatin Level during the 72 h after ICU Admission

Serum cystatin C was measured in the 2021 patients at least once within 72 h after ICU admission. In these patients, generalized linear regression analysis was performed, and the results of the GLM are presented in Table 5. A 1 mmol L^{-1} increase in the negative fluctuation in Cl^- was associated with a 1.4% increase of maximum cystatin C level (exp coef: 0.014, 95% CI: 0.002 to 0.026; $p = 0.026$), while total fluctuation of Cl^- ($p = 0.374$) and positive fluctuation of Cl^- (0.682) were not associated with the maximum cystatin C level.

Table 5. Generalized linear regression model for maximum cystatin C level within 72 h after ICU admission according to fluctuation of Cl^- (n = 2,021).

Variables	Exp Coef (95% CI)	p *
Dependent variable: maximum cystatin C level (mmol L^{-1})		
Total fluctuation of Cl^- [a] (per 1 mmol L^{-1}, model 1)	0.004 (−0.005, 0.013)	0.374
Positive fluctuation of Cl^- [b] (per 1 mmol L^{-1}, model 2)	−0.002 (−0.012, 0.008)	0.682
Negative fluctuation of Cl^- [c] (per 1 mmol L^{-1}, model 2)	**0.014** (0.002, 0.026)	0.026

* In the generalized linear model, gamma distribution and the log link function were assumed for the dependent variable (maximum cystatin C level within 72 h after ICU admission). All covariates were included in the model. [a] Total fluctuation of Cl^- (mmol L^{-1}): (maximum Cl^- – minimum Cl^-) for 72 h after ICU admission. [b] Positive fluctuation of Cl^- (mmol L^{-1}): (maximum Cl^- – preadmission Cl^-) for 72 h after ICU admission. [c] Negative fluctuation of Cl^- (mmol L^{-1}): (preadmission Cl^- – minimum Cl^-) for 72 h after ICU admission. Exp, exponentiated; Coef, coefficient; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate.

4. Discussion

This study showed that both positive and negative fluctuations in Cl^- within 72 h after ICU admission were significantly associated with the potential risk of AKI in a mixed ICU adult population. This association was also observed for AKI stage ≥2. In the subgroup analysis based on preadmission eGFR grouping, the association between positive fluctuations in Cl^- and AKI was more evident in the

eGFR ≥90 mL min^{-1} 1.73 m^{-2} group, while the association between negative fluctuations in Cl^- and AKI was more evident in the eGFR <90 or <60 mL min^{-1} 1.73 m^{-2} group. Additionally, both positive and negative fluctuations in Cl^- were associated with the risk of AKI in patients without postoperative ICU admission, while only positive fluctuations in Cl^- were significantly associated with the risk of AKI in patients with postoperative admissions.

The most novel finding of this study is that we reported that the negative fluctuations in Cl^- could also be associated with the risk of AKI in critically ill patients. While the association between positive fluctuations in Cl^- and AKI were reported in previous studies [13–15], the association regarding the negative fluctuations has yet to be reported. While positive fluctuations in Cl^- could be caused by fluid resuscitation [24], negative fluctuations in Cl^- could be caused by a loss of active Cl^- from the gastrointestinal tract, impaired renal Cl^- reabsorption, and an infusion of hypotonic fluid [16,17], which might be related to AKI [25]. Additionally, hypochloremia might be caused by negative fluctuations in Cl^-, which is a common and independent poor prognostic factor in critically ill patients [26]. Although our findings regarding positive fluctuations in CI^- were consistent with those of a meta-analysis published in 2015 [27], there was another meta-analysis, published in 2018, which concluded that the relationship between the use of chloride-rich solution and AKI remains controversial [28]. Therefore, future studies should investigate the effect of positive or negative fluctuations in Cl^- on AKI.

Another interesting finding was that the interactions related to AKI existed between the eGFR status at the time of ICU admission and total fluctuations in Cl^-. The results of the subgroup analysis based on eGFR grouping showed that the positive fluctuations in Cl^- tended to be more frequently associated with AKI in patients with normal kidney function (eGFR ≥90 mL min^{-1} 1.73 m^{-2}). In contrast, negative fluctuations in Cl^- tended to be more frequently associated with AKI in patients with CKD (eGFR <90 or 60 mL min^{-1} 1.73 m^{-2}). There are several potential explanations for our findings. First, patients with normal kidney function at ICU admission might have received more chloride-rich fluid resuscitation than CKD patients; this might have impacted the positive fluctuations in Cl^-. Secondly, since CKD patients often had disruptions in their acid–base balance [25], the negative fluctuations in Cl^- might have had a greater impact on the patients with CKD. Lastly, the impact of both positive and negative fluctuations in Cl^- was not significant in patients with CKD 4 or 5 (<30). There is a possibility that the fluctuations in Cl^- were minimized by physicians for such severe CKD patients, thus impacting these results in patients with CKD 4 or 5.

The difference in the results regarding positive fluctuations in Cl^- between this study and our previous study is also interesting [18]. In our previous study, we found that hyperchloremia (>110 mmol L^{-1}) was not associated with postoperative AKI in the surgical ICU, and there was a positive association in the increase from the preoperative Cl^- (which was measured within 1 month prior to surgery) to the maximum Cl^- measured 0–3 days postoperatively in patients with a CKD stage ≥3. The differences between two studies might be caused by the study designs. Our previous study might have been affected by fluid resuscitation or blood loss during surgery, while the present study was not affected by these factors. In general, more fluid administration is required to replace ongoing bleeding or insensible loss of fluid during surgery [29], so that the impact of the Cl^- load on AKI would be different from that in the ICU.

Although the serum cystatin C level was measured in only 2021 patients (10.2%) for 72 h after ICU admission in this study, our results regarding the relationship between Cl^- fluctuation and cystatin level were also notable. In this study, only the negative Cl^- fluctuation was associated with an increase in serum cystatin level during the 72 h after ICU admission. Considering that cystatin C is known as a marker of renal function in AKI [23], our results suggest that a decrease of Cl^- level might be an associated factor for development of AKI after ICU admission. In addition, the relationship between AKI and the increase of Cl^- could be caused by fluid administration. Furthermore, the significant relationship between the positive fluctuation and development of AKI could be related to clinical situations that require fluid administration. However, a decrease of Cl^- was more related to kidney damage via hypochloremic metabolic alkalosis [10] than to an increase in Cl^-. Considering the

relatively small sample size of patients who had their serum cystatin C measured for 72 h after ICU admission in this study, more studies should be performed in the future to confirm the relationship between dyschloremia, cystatin C levels, and AKI.

This study had a number of limitations. First, due to the retrospective cohort design, selection bias may have occurred during the data collection process. To minimize this bias, all data were collected by a medical record technician blinded from the purpose of this study. Second, this study was performed at a single center, and therefore its results may have limited generalizability. Third, Cl^- levels were not measured during the same period, using the same method for all patients included in this study. Fourth, since patients who developed AKI were much more likely to develop dyschloremia due to the inability of their kidneys to effectively regulate Cl^- levels, there is a possibility that AKI may precede changes in Cl^-, and thus might confound our study conclusions. Fifth, we could only use serum creatinine concentrations for the accurate diagnosis of AKI in accordance with the KDIGO criteria due to a lack of accurate urine output data. The exclusion of urine output data may reduce the accuracy and sensitivity of AKI diagnosis, especially for the diagnosis of more severe stages of AKI (stage 2 or 3) [30,31]. Lastly, in this study, we did not evaluate various biomarkers for AKI such as beta-2 microglobulin, liver-type fatty acid binding protein, and neutrophil gelatinase-associated lipocalin. Considering there are many biomarkers for the early detection of AKI [32], more biomarkers are needed to evaluate the direct effect of Cl^- fluctuation on AKI development.

5. Conclusions

This study showed that an increase in both the positive and negative fluctuations in Cl- after ICU admission were associated with an increased risk of AKI after ICU admission. Furthermore, these associations differed based on the kidney functionality at ICU admission or postoperative ICU admission. However, the results should be interpreted carefully considering the retrospective design, and future studies should be performed using biomarkers for AKI.

Author Contributions: T.K.O. and I.A.S. designed the study, analyzed and interpreted the data, and drafted the manuscript. Y.T.J. and Y.H.J. contributed to the acquisition of data. All authors have given approval of the final version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Staging of postoperative acute kidney injury (KDIGO).

Stage	Serum Creatinine
1	1.5–1.9 times baseline or ≥0.3 mg dL^{-1} increase within 72 h after ICU admission
2	2.0–2.9 times baseline within 72 h after ICU admission
3	3.0 times baseline or increase in serum creatinine to ≥4.0 mg dL^{-1} or initiation of RRT within 72 h after ICU admission

KDIGO, kidney disease: improving global outcomes; RRT, renal replacement therapy.

Appendix B

Table A2. Univariable logistic regression analysis of covariates for occurrence of total AKI and AKI stage ≥2 during 72 h after ICU admission.

Variables	Total AKI		AKI Stage ≥2	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Sex: male	1.09 (1.02–1.16)	0.012	1.08 (0.99–1.18)	0.093
Age, year	1.02 (1.02–1.02)	<0.001	1.01 (1.01–1.02)	<0.001
Body mass index, kg m^{-2}	0.96 (0.95–0.97)	<0.001	0.93 (0.92–0.95)	<0.001
APACHE II	1.04 (1.04–1.04)	<0.001	1.04 (1.03–1.04)	<0.001

Table A2. *Cont.*

Variables	Total AKI		AKI Stage ≥2	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Comorbidities at ICU admission				
Hypertension	1.30 (1.22–1.38)	<0.001	1.16 (1.06–1.26)	0.001
Diabetes mellitus	1.51 (1.36–1.67)	<0.001	1.42 (1.23–1.63)	<0.001
Ischemic heart disease	1.20 (0.98–1.46)	0.076	1.01 (0.76–1.34)	0.942
Cerebrovascular disease	1.31 (1.14–1.52)	<0.001	1.13 (0.92–1.38)	0.250
Chronic obstructive lung disease	1.12 (0.97–1.30)	0.131	0.96 (0.77–1.19)	0.713
Liver disease	2.46 (2.10–2.88)	<0.001	3.21 (2.68–3.83)	<0.001
Anemia (Hb <10 g dL^{-1})	3.73 (3.49–4.00)	<0.001	4.77 (4.33–5.25)	<0.001
Cancer	1.83 (1.70–1.97)	<0.001	2.06 (1.88–2.27)	<0.001
eGFR mL min^{-1} 1.73 m^{-2}				
≥90	1	(<0.001)	1	(<0.001)
60–90	1.04 (0.96–1.13)	0.343	0.77 (0.68–0.88)	<0.001
30–60	2.21 (2.01–2.44)	<0.001	1.17 (1.02–1.35)	0.029
<30	5.33 (4.73–6.00)	<0.001	3.69 (3.24–4.22)	<0.001
Admission through ED	1.51 (1.41–1.61)	<0.001	1.91 (1.73–2.10)	<0.001
Postoperative admission	0.86 (0.81, 0.92)	<0.001	0.68 (0.62, 0.74)	<0.001
Fluid administration for 72 h				
NaCl 0.9%, per 100 ml increase	1.00 (1.00, 1.00)	0.018	1.01 (1.00, 1.01)	0.001
Balanced crystalloid, per 100 mL	0.99 (0.99, 1.00)	0.014	0.98 (0.97, 0.98)	<0.001
Hydroxyethyl starch, per 100 mL	0.98 (0.97, 0.99)	0.002	0.96 (0.95, 0.98)	<0.001
Transfusion of packed RBC	2.43 (2.28, 2.60)	<0.001	2.34 (2.14, 2.57)	<0.001
The number of measurements of Cl^-	1.93 (1.86, 2.01)	<0.001	1.63 (1.54, 1.72)	<0.001
Admission department				
Internal medicine	1	(<0.001)	1	(<0.001)
Neurologic center	0.23 (0.21–0.26)	<0.001	0.19 (0.16–0.22)	<0.001
Cardiothoracic surgical department	0.79 (0.73–0.86)	<0.001	0.52 (0.47–0.59)	<0.001
Other surgical departments	0.77 (0.71–0.85)	<0.001	0.64 (0.57–0.72)	<0.001

AKI, acute kidney injury; ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; eGFR, estimated glomerular filtration rate; ED, emergency department; Hb, hemoglobin; RBC, red blood cell; RRT, renal replacement therapy.

References

1. Waikar, S.S.; Bonventre, J.V. Creatinine kinetics and the definition of acute kidney injury. *J. Am. Soc. Nephrol.* **2009**, *20*, 672–679. [CrossRef] [PubMed]
2. Bellomo, R.; Kellum, J.A.; Ronco, C. Acute kidney injury. *Lancet* **2012**, *380*, 756–766. [CrossRef]
3. Lewington, A.J.; Cerda, J.; Mehta, R.L. Raising awareness of acute kidney injury: A global perspective of a silent killer. *Kidney Int.* **2013**, *84*, 457–467. [CrossRef] [PubMed]
4. Nash, K.; Hafeez, A.; Hou, S. Hospital-acquired renal insufficiency. *Am. J. Kidney Dis.* **2002**, *39*, 930–936. [CrossRef] [PubMed]
5. Ostermann, M.; Chang, R.W. Acute kidney injury in the intensive care unit according to rifle. *Crit. Care Med.* **2007**, *35*, 1837–1843, quiz 1852. [CrossRef] [PubMed]
6. Rewa, O.; Bagshaw, S.M. Acute kidney injury-epidemiology, outcomes and economics. *Nat. Rev. Nephrol.* **2014**, *10*, 193–207. [CrossRef] [PubMed]
7. Thakar, C.V.; Christianson, A.; Freyberg, R.; Almenoff, P.; Render, M.L. Incidence and outcomes of acute kidney injury in intensive care units: A veterans administration study. *Crit. Care Med.* **2009**, *37*, 2552–2558. [CrossRef]
8. Macedo, E.; Mehta, R.L. Preventing acute kidney injury. *Crit. Care Clin.* **2015**, *31*, 773–784. [CrossRef]
9. Pfortmueller, C.A.; Uehlinger, D.; von Haehling, S.; Schefold, J.C. Serum chloride levels in critical illness-the hidden story. *Intensive Care Med. Exp.* **2018**, *6*, 10. [CrossRef]
10. Shao, M.; Li, G.; Sarvottam, K.; Wang, S.; Thongprayoon, C.; Dong, Y.; Gajic, O.; Kashani, K. Dyschloremia is a risk factor for the development of acute kidney injury in critically ill patients. *PLoS ONE* **2016**, *11*, e0160322. [CrossRef]
11. Toyonaga, Y.; Kikura, M. Hyperchloremic acidosis is associated with acute kidney injury after abdominal surgery. *Nephrology* **2017**, *22*, 720–727. [CrossRef] [PubMed]
12. Yunos, N.M.; Bellomo, R.; Glassford, N.; Sutcliffe, H.; Lam, Q.; Bailey, M. Chloride-liberal vs. Chloride-restrictive intravenous fluid administration and acute kidney injury: An extended analysis. *Intensive Care Med.* **2015**, *41*, 257–264. [CrossRef]

13. De Vasconcellos, K.; Skinner, D.L. Hyperchloraemia is associated with acute kidney injury and mortality in the critically ill: A retrospective observational study in a multidisciplinary intensive care unit. *J. Crit. Care* **2018**, *45*, 45–51. [CrossRef]
14. Jaynes, M.P.; Murphy, C.V.; Ali, N.; Krautwater, A.; Lehman, A.; Doepker, B.A. Association between chloride content of intravenous fluids and acute kidney injury in critically ill medical patients with sepsis. *J. Crit. Care* **2018**, *44*, 363–367. [CrossRef] [PubMed]
15. Sadan, O.; Singbartl, K.; Kandiah, P.A.; Martin, K.S.; Samuels, O.B. Hyperchloremia is associated with acute kidney injury in patients with subarachnoid hemorrhage. *Crit. Care Med.* **2017**, *45*, 1382–1388. [CrossRef]
16. Berend, K.; van Hulsteijn, L.H.; Gans, R.O. Chloride: The queen of electrolytes? *Eur. J. Intern. Med.* **2012**, *23*, 203–211. [CrossRef] [PubMed]
17. Yunos, N.M.; Bellomo, R.; Story, D.; Kellum, J. Bench-to-bedside review: Chloride in critical illness. *Crit. Care* **2010**, *14*, 226. [CrossRef] [PubMed]
18. Oh, T.K.; Song, I.-A.; Kim, S.J.; Lim, S.Y.; Do, S.-H.; Hwang, J.-W.; Kim, J.; Jeon, Y.-T. Hyperchloremia and postoperative acute kidney injury: A retrospective analysis of data from the surgical intensive care unit. *Crit. Care* **2018**, *22*, 277. [CrossRef] [PubMed]
19. Hallan, S.; Asberg, A.; Lindberg, M.; Johnsen, H. Validation of the modification of diet in renal disease formula for estimating gfr with special emphasis on calibration of the serum creatinine assay. *Am. J. Kidney Dis.* **2004**, *44*, 84–93. [CrossRef] [PubMed]
20. Kellum, J.A.; Lameire, N.; Group, K.A.G.W. Diagnosis, evaluation, and management of acute kidney injury: A kdigo summary (part 1). *Crit. Care* **2013**, *17*, 204. [CrossRef]
21. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef] [PubMed]
22. Armstrong, R.A. When to use the bonferroni correction. *Ophthalmic Physiol. Opt.* **2014**, *34*, 502–508. [CrossRef] [PubMed]
23. Murty, M.S.; Sharma, U.K.; Pandey, V.B.; Kankare, S.B. Serum cystatin c as a marker of renal function in detection of early acute kidney injury. *Indian J. Nephrol.* **2013**, *23*, 180–183. [CrossRef]
24. Nagami, G.T. Hyperchloremia—Why and how. *Nefrologia* **2016**, *36*, 347–353. [CrossRef] [PubMed]
25. Bank, N.; Better, O.S. Acid-base balance and acute renal failure. *Miner Electrolyte Metab.* **1991**, *17*, 116–123.
26. Tani, M.; Morimatsu, H.; Takatsu, F.; Morita, K. The incidence and prognostic value of hypochloremia in critically ill patients. *Sci. World J.* **2012**, *2012*, 474185. [CrossRef]
27. Krajewski, M.L.; Raghunathan, K.; Paluszkiewicz, S.M.; Schermer, C.R.; Shaw, A.D. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *Br. J. Surg.* **2015**, *102*, 24–36. [CrossRef] [PubMed]
28. Kawano-Dourado, L.; Zampieri, F.G.; Azevedo, L.C.P.; Correa, T.D.; Figueiro, M.; Semler, M.W.; Kellum, J.A.; Cavalcanti, A.B. Low- versus high-chloride content intravenous solutions for critically ill and perioperative adult patients: A systematic review and meta-analysis. *Anesth. Analg.* **2018**, *126*, 513–521. [CrossRef]
29. Chappell, D.; Jacob, M.; Hofmann-Kiefer, K.; Conzen, P.; Rehm, M. A rational approach to perioperative fluid management. *Anesthesiology* **2008**, *109*, 723–740. [CrossRef]
30. Bagshaw, S.M.; George, C.; Bellomo, R.; Committee, A.D.M. Changes in the incidence and outcome for early acute kidney injury in a cohort of australian intensive care units. *Crit. Care* **2007**, *11*, R68. [CrossRef]
31. Kellum, J.A.; Sileanu, F.E.; Murugan, R.; Lucko, N.; Shaw, A.D.; Clermont, G. Classifying aki by urine output versus serum creatinine level. *J. Am. Soc. Nephrol.* **2015**, *26*, 2231–2238. [CrossRef] [PubMed]
32. Vaidya, V.S.; Ferguson, M.A.; Bonventre, J.V. Biomarkers of acute kidney injury. *Annu. Rev. Pharmacol. Toxicol.* **2008**, *48*, 463–493. [CrossRef] [PubMed]

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Incidence and Cost of Acute Kidney Injury in Hospitalized Patients with Infective Endocarditis

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Abstract: Acute kidney injury (AKI) is a frequent complication of hospitalized patients with infective endocarditis (IE). Further, AKI in the setting of IE is associated with high morbidity and mortality. We aimed to examine the incidence, clinical parameters, and hospital costs associated with AKI in hospitalized patients with IE in an endemic area with an increasing prevalence of opioid use. This retrospective cohort study included 269 patients admitted to a major referral center in Kentucky with a primary diagnosis of IE from January 2013 to December 2015. Of these, 178 (66.2%) patients had AKI by Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria: 74 (41.6%) had AKI stage 1 and 104 (58.4%) had AKI stage ≥2. In multivariable analysis, higher comorbidity scores and the need for diuretics were independently associated with AKI, while the involvement of the tricuspid valve and the need for vasopressor/inotrope support were independently associated with severe AKI (stage ≥2). The median total direct cost of hospitalization was progressively higher according to each stage of AKI ($17,069 for no AKI; $37,111 for AKI stage 1; and $61,357 for AKI stage ≥2; $p < 0.001$). In conclusion, two-thirds of patients admitted to the hospital due to IE had incident AKI. The occurrence of AKI significantly increased healthcare costs. The higher level of comorbidity, the affection of the tricuspid valve, and the need for diuretics and/or vasoactive drugs were associated with severe AKI in this susceptible population.

Keywords: acute kidney injury; infective endocarditis; healthcare costs; opioid use

1. Introduction

Infective endocarditis (IE) is a severe infectious process that carries high morbidity and mortality [1–3]. Reports indicate that the incidence of IE in the United States has been increasing steadily in recent years [4,5]. The crude incidence has increased from 7.6 to 9.3 cases per 100,000 persons annually from 1998–2013 [5]. Moreover, healthcare costs for patients with IE increased eighteen-fold, from $1.1 million in 2010 to $22.2 million in 2015 [6].

In the United States, some areas such as the Midwest and West have exhibited a steady increase in the incidence of IE in relation to the growing incidence of opioid dependence [7]. According to the National Survey on Drug Use and Health, persons with opioid and other substance use disorder

who inject drugs are at higher risk of blood-borne infections and IE [8]. Infectious complications are common and constitute a major cause of hospitalizations [9].

Acute kidney injury (AKI) is a syndrome that occurs in about 20% of hospitalized patients [10,11]. AKI is also associated with high morbidity and mortality and affects hospital resource utilization and healthcare costs [12,13]. Patients with IE can develop distinct forms of acute or subacute kidney disease such as glomerulonephritis, infarction or cortical necrosis [14,15], manifesting as AKI [16]. Prior studies have shown that older age and the degree of thrombocytopenia were associated with an increased risk of AKI in patients with IE [17]. Moreover, some antibiotics commonly used to treat IE (e.g., aminoglycosides, vancomycin, etc.) can exert toxicity to the kidneys under specific circumstances [18].

The main objective of this study was to examine the incidence and clinical parameters associated with AKI in hospitalized patients with IE in Kentucky, a state highly impacted by the opioid epidemic. We also examined hospital costs associated with the occurrence of AKI and major adverse kidney events (MAKE) in this susceptible population.

2. Materials and Methods

2.1. Study Design and Participants

Single-center, retrospective cohort study. The study population included adult patients 18 years or older who were admitted to the University of Kentucky Albert B. Chandler Hospital with IE as the primary diagnosis. Patients were excluded if they had a history of end-stage kidney disease (ESKD), baseline estimated glomerular filtration rate (eGFR) less than 15 mL/min/1.73 m^2, were recipients of a kidney transplant, or if they had a prior episode of IE that required hospitalization. The study period was from January 2013–December 2015. The study was approved by the University of Kentucky Institutional Review Board.

2.2. Study Variables and Definitions

Data were gathered through automated and manual extraction from electronic health records (EHRs) and validated through comprehensive individual review of all records. The presence of comorbidities at the time of index hospitalization was assessed using the Elixhauser score [19], with individual comorbidities identified using ICD-9/10-CM codes. IE as the primary diagnosis was defined by the modified Duke Criteria [20]. IE characteristics including the location, type and number of affected cardiac valves were obtained by individual review of EHRs (consult notes, echocardiography reports, etc.). Baseline eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21], and baseline serum creatinine (SCr) was assessed as follows: (1) Outpatient SCr value closest to index admission within 1 year of hospitalization; if unavailable, (2) last inpatient SCr value from prior hospitalization within 1 year of index admission; if unavailable, (3) lowest SCr value throughout the index hospitalization. We gathered data of substance use disorder specific for opioid and IV drug use with the following ICD-9-CM codes: 292.0–9, 304.00–93, 305.20–93, 648.30–34, 655.50–53, 760.72–75, 779.5, 965.00–09, and V654.2. We extracted medication exposure, procedure data, and total costs related to the index hospitalization from the hospital billing system. The University of Kentucky Albert B. Chandler Hospital utilizes Allscripts Sunrise Clinical Manager™ EHR software (Allscripts, Chicago, IL, USA). Microbiologic data were obtained from blood, valve, abscess fluid, pleural fluid and bone biopsy.

2.3. Study Outcomes

2.3.1. Clinical Outcomes

The primary outcome was incident in-hospital AKI defined and graded by the Kidney Disease Improving Global Outcomes (KDIGO) SCr-criteria. [22] We grouped AKI stages 2 and 3 due to the low numbers in each category in relation to AKI stage 1 and no AKI. A secondary outcome was MAKE,

a composite of all-cause mortality, dependence on renal replacement therapy (RRT), or inability to recover at least 50% (MAKE50) or 25% (MAKE25) of baseline eGFR (if not on RRT) up to 90 days after hospital discharge [23]. Other secondary outcomes included hospital mortality and hospital readmission due to recurrent or a new episode of IE [24,25].

2.3.2. Healthcare Cost Outcomes

The healthcare cost outcome was the median total direct cost of hospitalization in dollars. Other outcomes included hospital length of stay (days) and total days in a telemetry or intensive care unit (ICU) bed.

2.4. Statistical Analysis

Categorical data were reported as number of observations (percentages) and continuous variables as mean ± standard deviation (SD), or median (1st quartile (IQ1)—3rd quartile (IQ3)) as appropriate. Comparisons between groups for categorical variables were made using chi-squared test or Fisher's exact test. Continuous variables were compared using the ANOVA or Kruskal-Wallis test as appropriate.

Multivariable logistic regression modeling was used for AKI stage 1 (vs. no AKI), AKI stage ≥2 (vs. no AKI or AKI stage 1), and MAKE (50% or 25%) as dependent variables and included candidate independent variables that were statistically significant in the bivariate analysis and/or carried clinical significance for the association with the dependent variables. The model section was performed using stepwise regression with a cutoff of 0.1 for variables to enter the model and 0.05 to be removed. All statistical analyses were performed using SAS 9.3 (SAS Institute, Charlotte, NC, USA) with an alpha level set at $p < 0.05$ (two-tailed) for all comparisons.

3. Results

3.1. Clinical Characteristics

A total of 269 patients were included in the study. The cohort derivation algorithm is detailed in Figure 1. The mean (SD) age was 45.4 (16.2) years, 59.5% were male, and 95.5% white. The overall incidence of AKI was 66.2%, 74 (41.6%) patients had AKI stage 1 and 104 (58.4%) patients had AKI stage ≥2. The frequency of substance use disorder was not significantly different according to AKI status (54.5% in patients with AKI vs. 50.5% in patients without AKI, $p = 0.540$). Patient's clinical characteristics according to AKI status are detailed in Table 1.

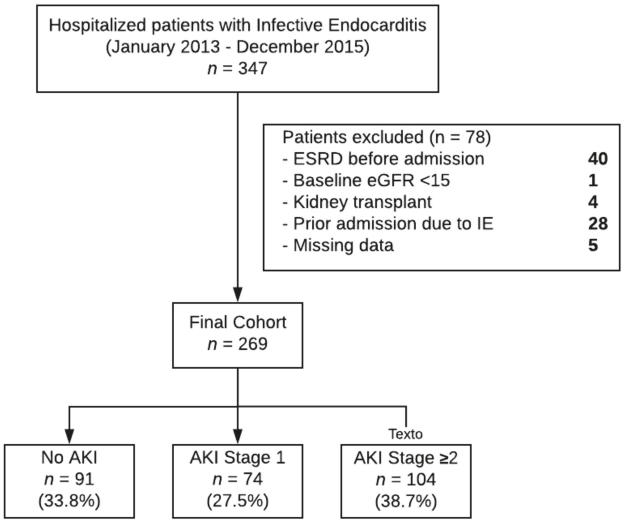

Figure 1. Cohort derivation. Abbreviations: AKI (acute kidney injury), eGFR (estimated glomerular filtration rate), ESRD (end-stage renal disease), IE (infective endocarditis).

Table 1. Patient characteristics according to acute kidney injury status.

	No AKI	AKI Stage 1	AKI Stage ≥2	*p*
	n = 91	*n* = 74	*n* = 104	
Demographics				
Age, years, mean ± SD	44.6 ± 15.6	45.5 ± 16.5	45.8 ± 16.8	0.860
Gender, male, n (%)	62 (68.1)	34 (46.0)	64 (61.5)	0.013
Ethnic group, white, *n* (%)	86 (94.5)	71 (96.0)	99 (95.2)	0.939
BMI, kg/m^2, mean ± SD	27.9 ± 10.9	29.8 ± 11.0	26.9 ± 7.1	0.140
Comorbidity				
Elixhauser Score, median (IQ1-IQ3)	4.0 (3.0–6.0)	6.0 (4.0–7.0)	7.0 (5.0–8.0)	<0.001
Diabetes, *n* (%)	23 (25.3)	14 (18.9)	18 (17.3)	0.361
Hypertension, *n* (%)	55 (60.4)	41 (55.4)	69 (66.4)	0.328
Hepatitis B, *n* (%)	1 (1.1)	9 (12.2)	7 (6.7)	0.011
Hepatitis C, *n* (%)	27 (29.7)	38 (51.4)	51 (49.0)	0.006
Congenital heart defect, *n* (%)	6 (6.6)	8 (10.8)	9 (8.7)	0.628
Current substance use disorder, *n* (%)	46 (50.5)	42 (56.8)	55 (52.9)	0.672
Baseline eGFR, mL/min/1.73 m^2, median (IQ1-IQ3)	105.3 (69.1–127.6)	96.8 (45.5–123.9)	103.2 (71.4–122.9)	0.220
Medications During Hospitalization				
Opiods, *n* (%)	3 (3.3)	6 (8.1)	9 (8.7)	0.279
ACEI or ARB, *n* (%)	36 (39.6)	12 (16.2)	21 (20.2)	<0.001
Aminoglycosides, *n* (%)	36 (39.6)	31 (41.9)	52 (50.0)	0.305
Diuretic, *n* (%)	38 (41.8)	51 (68.9)	83 (79.8)	<0.001
NSAIDs, *n* (%)	54 (59.3)	51 (68.9)	77 (74.0)	0.088
Pressor or inotrope, *n* (%)	0 (0.0)	5 (6.8)	19 (18.3)	<0.001
Vancomycin, *n* (%)	76 (83.5)	69 (93.2)	89 (85.6)	0.142
Piperacillin/tazobactam, *n* (%)	30 (33.0)	23 (31.1)	38 (36.5)	0.733
Cefepime, *n* (%)	25 (27.5)	30 (40.5)	39 (37.5)	0.169
Vancomycin + Pip/Tazo, *n* (%)	30 (33.0)	24 (32.4)	36 (34.6)	0.948
Vancomycin + Cefepime, *n* (%)	26 (28.6)	32 (43.2)	37 (35.6)	0.146
Infective endocarditis characteristics				
ICU care, *n* (%)	38 (41.8)	39 (52.7)	46 (44.2)	0.346
Sepsis, *n* (%)	32 (35.2)	36 (48.7)	66 (63.5)	<0.001
Osteomyelitis, *n* (%)	14 (15.4)	7 (9.5)	18 (17.3)	0.327

Table 1. *Cont.*

	No AKI	AKI Stage 1	AKI Stage ≥2	*p*
	***n* = 91**	***n* = 74**	***n* = 104**	
Number of affected cardiac valves,				
0, *n* (%)	45 (49.5)	26 (35.1)	29 (27.9)	0.006
1, *n* (%)	40 (44.0)	42 (56.8)	56 (53.8)	
≥2, *n* (%)	6 (6.5)	6 (8.1)	19 (18.3)	
Affected valve,				
Mitral, *n* (%)	31 (34.1)	27 (37.0)	34 (32.7)	0.837
Aortic, *n* (%)	38 (41.8)	24 (32.9)	35 (33.7)	0.395
Tricuspid, *n* (%)	20 (22.0)	18 (24.7)	47 (45.2)	<0.001
Pulmonic, *n* (%)	1 (1.1)	2 (2.7)	2 (1.9)	0.856
Type of valve, prosthetic, *n* (%)	23 (25.3)	20 (27.0)	33 (31.7)	0.585
Procedures,				
Valve replacement, *n* (%)	16 (17.6)	14 (18.9)	33 (31.7)	0.037
Valve repair, *n* (%)	11 (12.1)	12 (16.2)	16 (15.4)	0.716
Other, *n* (%)	8 (8.8)	3 (4.1)	13 (12.5)	0.165
Microbiologic data				
MRSA, *n* (%)	23 (25.3)	20 (27.0)	37 (35.6)	0.286
MSSA, *n* (%)	16 (17.6)	12 (16.2)	27 (26.0)	0.227
MSSE, *n* (%)	0 (0.0)	0 (0.0)	1 (1.0)	0.458
Other *Staphylococcus*, *n* (%)	11 (12.1)	12 (16.2)	8 (7.7)	0.197
Streptococcus, *n* (%)	24 (26.4)	13 (17.6)	17 (16.3)	0.155
Enterococcus, *n* (%)	12 (13.2)	15 (20.3)	16 (15.4)	0.460
Gram-negative rods, *n* (%)	10 (11.0)	13 (17.6)	15 (14.4)	0.492
Rothia, *n* (%)	2 (2.2)	2 (2.7)	1 (1.0)	0.659
Candida sp., *n* (%)	1 (1.1)	5 (6.8)	9 (8.7)	0.068
Negative culture, *n* (%)	4 (4.4)	4 (5.4)	2 (1.9)	0.428

Abbreviations: ACEI (angiotensin-converting-enzyme inhibitor), AKI (acute kidney injury), ARB (angiotensin receptor blocker), BMI (body mass index), eGFR (estimated glomerular filtration rate), ICU (intensive care unit), IQ (interquartile), MRSA (methicillin-resistant *Staphylococcus aureus*), MSSA (methicillin-susceptible *Staphylococcus aureus*), MSSE (methicillin-susceptible *Staphylococcus epidermidis*), NSAID (nonsteroidal anti-inflammatory drug), Pip/Tazo (piperacillin/tazobactam), SD (standard deviation).

3.2. Clinical Parameters Associated with AKI

When compared with patients without AKI, patients with AKI had higher Elixhauser comorbidity scores (median (IQ1-IQ3) 4.0 (3.0–6.0) for no AKI, 6.0 (4.0–7.0) for AKI stage 1 and 7.0 (5.0–8.0) for AKI stage ≥2, $p < 0.001$), more likely to have hepatitis B and C coinfection, sepsis, and tricuspid valve involvement (21.9% for no AKI, 24.7% for AKI stage 1 and 45.2% for AKI stage ≥2, $p < 0.001$), and required more frequently diuretics and vasopressor/inotrope support. Patients with AKI more frequently had valve replacement interventions (17.6% for no AKI, 18.9% for AKI stage 1 and 31.7% for AKI stage ≥2, $p = 0.037$) (Table 1). Patients with AKI were less likely to receive angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) (39.6% for no AKI, 16.2% for AKI stage 1 and 20.2% for AKI stage ≥2, $p < 0.001$). There was no difference among the IE causative organisms between patients with and without AKI (Table 1).

In multivariable analysis, higher Elixhauser comorbidity score, more frequent exposure to diuretics and non-steroidal anti-inflammatory drugs (NSAIDs), and less frequent exposure to an ACEI/ARB were independently associated with AKI. Further, requiring vasopressor/inotrope support and having tricuspid valve involvement independently associated with AKI stage ≥2 (adjusted OR of 4.94, 95% CI: 1.52–16.01, $p = 0.008$ and 2.97, 95% CI: 1.59–5.51, $p < 0.001$, respectively) (Table 2).

Table 2. Multivariable logistic regression models of AKI stage ≥1 and AKI stage ≥2 as the dependent variables and relevant clinical parameters as the independent variables.

	AKI Stage ≥1 vs. No AKI		AKI Stage ≥2 vs. AKI Stage 1 or No AKI	
	OR	95% CI	OR	95% CI
ACEI or ARB, Yes vs. No	0.28 **	0.13–0.57	0.66	0.33–1.32
Tricuspid valve affected, Yes vs. No	1.71	0.84–3.46	2.97 **	1.59–5.51
Use of diuretic, Yes Vs. No	3.18 **	1.63–6.23	2.04 *	1.04–4.01
Hepatitis B coinfection, Yes vs. No	6.57	0.78–55.16	0.61	0.19–1.97
Use of NSAID, Yes vs. No	1.95 *	1.01–3.76	1.72	0.90–3.25
Pressor or Inotrope need, Yes vs. No	-	-	4.94 *	1.52–16.01
Diabetes, Yes vs. No	0.47	0.21–1.06	0.55	0.26–1.19
Elixhauser score, per 1-unit score	1.35 **	1.16–1.56	1.35 **	1.17–1.55

Candidate variables for the multivariable models included age, baseline eGFR, hepatitis B or C coinfection, use of diuretic, use of ACEI or ARB, affection of the tricuspid valve, use of NSAID, need of pressor or inotrope, Elixhauser comorbidity score, history of diabetes, and zip code with the highest percentage of population below poverty level. C-statistic: 0.830, 0.788 for AKI stage ≥1 vs. no AKI and AKI stage ≥2 vs. AKI stage 1 or no AKI, respectively. * $p < 0.05$; ** $p < 0.01$. Abbreviations: ACEI (angiotensin-converting enzyme inhibitor), ARB (angiotensin-receptor blocker), NSAID (nonstereoidal anti-inflammatory drug).

3.3. Clinical Outcomes Associated with AKI

Patients with AKI stage ≥2 had slightly higher hospital mortality rates than those without AKI or AKI stage 1 (19.2% vs. 13.3%, $p = 0.194$). The frequency of MAKE50 was significantly higher in patients with AKI vs. those without AKI (38.5% for no AKI, 54.1% for AKI Stage 1, and 59.6% for AKI Stage ≥2, $p = 0.011$) (Table 3). Patients with AKI had also a slightly higher frequency of MAKE25 than those without AKI (71.9% vs. 60.4%, $p = 0.125$). There was no difference in hospital readmission rates due to IE according to AKI classification (Table 3).

Table 3. Study outcomes in hospitalized patients with infective endocarditis according to acute kidney injury status.

	No AKI $n = 91$	AKI Stage 1 $n = 74$	AKI Stage ≥2 $n = 104$	p Value
Clinical outcomes				
Hospital mortality, *n* (%)	14 (15.4)	8 (10.8)	20 (19.2)	0.312
Readmission due to IE, (%)	4 (4.4)	4 (5.4)	3 (2.9)	0.687
MAKE50 *, *n* (%)	35 (38.5)	40 (54.1)	62 (59.6)	0.011
MAKE25 #, *n* (%)	55 (60.4)	51 (68.9)	77 (74.0)	0.125
Healthcare cost outcomes				
Total direct hospitalization cost, dollars, median (IQ1-IQ3)	17,069 (6722–31,910)	37,111 (20,100–58,258)	61,357 (34,164–88,495)	<0.001
Hospital length of stay, days, median (IQ1-IQ3)	9.0 (5.0–17.5)	23.0 (12.0–43.8)	34.5 (16.8–48.0)	<0.001
Telemetry bed days, median (IQ1-IQ3)	3.0 (0.0–10.0)	8.0 (2.0–17.0)	9.5 (1.0–20.0)	<0.001
ICU length of stay, median (IQ1-IQ3)	0.0 (0.0–2.0)	1.5 (0.0–5.0)	6.0 (1.5–14.5)	<0.001

* MAKE50 = Major Adverse Kidney Event, which includes mortality at or within 90 days of hospital discharge, continued RRT-dependence at 90 days after hospital discharge, or recovery of at least 50% of baseline eGFR within 90 days of discharge.# MAKE25 = Major Adverse Kidney Event, which includes mortality at or within 90 days of hospital discharge, continued RRT-dependence at 90 days after hospital discharge, or recovery of at least 25% of baseline eGFR within 90 days of discharge. Abbreviations: AKI (acute kidney injury), ICU (intensive care unit), IQ (interquartile range), MAKE (major adverse kidney event).

In multivariable analysis, the occurrence of sepsis as a complication of IE was independently associated with MAKE50 (adjusted OR 2.03, 95% CI: 1.23–3.36, $p = 0.006$). Further, AKI stage ≥2 had a borderline significant association with MAKE50 (adjusted OR 1.97, 95% CI: 1.09–3.58, $p = 0.126$) (Table 4).

Table 4. Multivariable logistic regression models of major adverse kidney events as the dependent variable and relevant clinical parameters as the independent variables.

	MAKE50		MAKE25	
	OR	**95% CI**	**OR**	**95% CI**
Sepsis, Yes vs. No	2.03 **	1.23–3.36	1.56	0.91–2.66
AKI Severity				
Stage ≥2 vs. No AKI	1.97	1.09–3.58	1.66	0.89–3.10
Stage 1 vs. No AKI	1.74	0.92–3.28	1.37	0.71–2.64

Candidate variables for the multivariable models included age, gender, history of hypertension, sepsis during indexed admission, affection of tricuspid valve, use of NSAID, use of ACEI or ARB, and AKI severity. C-statistic: 0.641, 0.590 for MAKE50 and MAKE25 respectively. ** $p < 0.01$. MAKE50 = Major Adverse Kidney Event, which includes mortality at or within 90 days of hospital discharge, continued RRT-dependence at 90 days after hospital discharge, or no recovery of at least 50% of baseline eGFR within 90 days of discharge. MAKE25 = Major Adverse Kidney Event, which includes mortality at or within 90 days of hospital discharge, continued RRT-dependence at 90 days after hospital discharge, or no recovery of at least 25% of baseline eGFR within 90 days of discharge. Abbreviations: AKI (acute kidney injury), KDIGO (kidney disease improving global outcomes), MAKE (major adverse kidney event).

3.4. Healthcare Costs Outcomes

The median cost of hospitalization was $35,552. The median cost of hospitalization in the AKI group was three times higher than in the no AKI group ($52,654 (25,846–73,946) vs. 17,069 (6722–31,910), $p < 0.001$) and increased accordingly to AKI severity (Figure 2 and Table 3). Patients with AKI had a longer length of hospital stay (median (IQ1–IQ3) 9.0 (5.0–17.5) days for no AKI, 23.0 (12.0–43.8) for AKI stage 1 and 34.5 (16.8–48.0) for AKI stage ≥2, $p < 0.001$). Similarly, patients with AKI had a longer length of ICU stay and more days on telemetry beds when compared with those without AKI (Table 3).

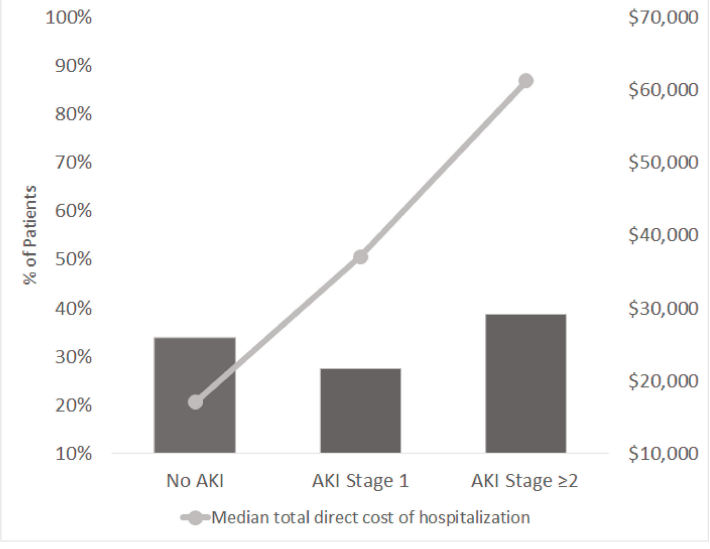

Figure 2. Incidence of acute kidney injury and median total hospitalization direct cost in hospitalized patients with a primary diagnosis of infective endocarditis.

4. Discussion

The main finding of our study is the high incidence of AKI in a large cohort of hospitalized patients with IE. About 2 out of 3 patients (66.2%) suffered from an episode of AKI while in the hospital, which translated into higher resource utilization and healthcare costs. The median cost of hospitalization

was 3.6 times higher in patients with severe AKI (stage ≥2) vs. those without AKI. We also found that tricuspid valve involvement, the need for vasopressor/inotrope support and diuretics, and a higher level of comorbidity were associated with severe AKI (stage ≥2).

Other studies have also reported the incidence of AKI in patients with IE. Ritchie et al., [18] studied a cohort of 211 patients diagnosed with bacterial endocarditis at the Brigham and Women's Hospital between January 2009 and October 2013. They reported a lower incidence of AKI of 38.9% (only 15.2% of patients in their cohort had substance use disorder vs. 53.2% in our cohort). In contrast, our study used the KDIGO SCr-criteria to define AKI, while they used the Acute Kidney Injury Network's (AKIN) SCr and urine output criteria [26]. Furthermore, in our cohort, patients had overall higher comorbidity scores in comparison to the referred study. In addition, Boils et al., [16] reported a biopsy-based pathologic series of 49 patients who had kidney function impairment in the setting of IE. The most common presentation of kidney disease in this population was AKI (79% of the cases) and the most common kidney biopsy findings were necrotizing and crescentic glomerulonephritis (53%) and endocapillary proliferative glomerulonephritis (37%). In addition, acute tubular injury was present in 86% of the cases.

Patients with severe AKI (stage ≥2) had slightly higher hospital mortality rates than those without AKI or AKI stage 1. Further, patients with severe AKI (stage ≥2) had significantly higher rates of major adverse kidney events than patients without AKI. Emerging evidence suggests that not only those patients with clinical evidence of AKI but also approximately 20% of patients that do not meet SCr-criteria of AKI still have increased risk of developing acute kidney disease (persistent alterations in kidney function or structure within the next 3 months following an episode of AKI), which is associated with incident or progression of CKD, ESKD, and death [27,28]. It is possible that some patients in the no AKI group may have had subclinical AKI [29] not detected by SCr changes precluding a more pronounced differentiation in clinical outcomes among those with vs. without AKI. In addition, the observed absence of mortality differentiation according to incident AKI or AKI severity stages may be due to the low event rate and lack of power. Overall rates of hospital mortality in patients with IE reported in other studies range between 18% and 24% [30–32], similar to the hospital mortality rate reported in our study (15.6%). Further, Wallace et al., [32] studied a cohort of 208 patients with IE and reported that mortality at discharge was 18% and at 6 months post-discharge was 27%, demonstrating that after discharge these patients are still at high risk of death.

Our study showed that higher comorbidity scores, exposure to NSAIDs, and the need for diuretics were associated with AKI. Diuretics are commonly used in patients with AKI since fluid overload is one of the major complications of decreased kidney function, and diuretics are also used for risk-stratification of AKI progression (furosemide stress test) [33]. Therefore, the association of diuretic use with AKI may be a reflection of more severe forms of AKI (e.g., oliguric/anuric AKI) and not necessarily thought to be contributory to the development or progression of AKI. Few studies have reported clinical parameters associated with AKI in the setting of IE. In multivariable analysis, Ritchie et al., [18] identified independent clinical parameters associated with AKI such as CKD, treatment with nafcillin or oxacillin, treatment with aminoglycoside and vancomycin, and similarly to our study, need of or exposure to loop diuretics. In contrast, we did not find major differences in relation to antibiotic exposure in those with vs. without AKI.

Our study also found that patients with severe AKI (stage ≥2) were more likely to have tricuspid valve involvement and required vasopressor/inotrope support more frequently than patients without AKI. Right-side IE (RSIE) occurs more commonly in persons with substance use disorder, especially persons who inject drugs [34]. In our cohort, patients with tricuspid valve affection (vs. other valves) had more substance use disorder, hepatitis C coinfection and sepsis (74.1% vs. 44.3%; 61.2% vs. 35%; 70.6% vs. 40.4%, respectively, $p < 0.001$ for all), which may have influenced the higher frequency of severe AKI. Lemaire et al., [35] studied 6264 patients with IE who underwent valvular surgery, 809 (12.9%) with a diagnosis of substance use disorder. They found that patients with a substance use disorder were more likely to have post-operative complications, especially infectious complications

such as pneumonia (OR 1.4, 95% CI 1.14–1.74), sepsis (OR 1.4, 95% CI 1.16–1.63), and renal complications (OR 1.5, 95% CI 1.23–1.77), defined based on ICD-9-CM diagnosis codes.

We also found that healthcare resource utilization and costs were higher in IE patients with AKI vs. those without AKI. In a different cohort study of 25,495 hospitalized patients who had AKI, Collister et al., reported that AKI was associated with longer length of hospital stay and increased hospital total cost [36]. They also found that incident AKI Stage 1 and 2 resulted in 1.2–1.3 times higher hospital total cost than no AKI while AKI Stage 3 and the need of dialysis were associated with 1.8–2.5 times higher cost. Fleischauer et al., [6] gathered data from 128 hospitals in North Carolina (n = 505 patients) and reported healthcare costs related to IE. They found that hospital admissions for drug dependence-associated IE increased twelve-fold from 2010 to 2015 (0.2 to 2.7 cases per 100,000 persons per year). Similarly, the total cost of hospitalization of IE patients increased eighteen-fold in the same period of time (from 1.1 to ~22.2 million). The major limitation of this study is that they only included hospitalizations with drug dependence-related IE listed as an ICD-9/10 CM diagnosis.

Our study has limitations. First, our study is a retrospective, single-center, cohort study of relatively small sample size and therefore the results may not be generalizable to other populations, particularly those with a low prevalence of substance use disorder or more diverse racial backgrounds (>90% of our study population was white). Second, we did not use urine output criteria as part of the AKI definition or examined the clinical etiology of AKI due to lack of data availability. Third, the time point at which antibiotics or other drugs were administered during the course of AKI was not characterized. Therefore, exposure to these drugs may have occurred before, during or after AKI, which can introduce confounding by indication to the interpretation of the results (e.g., more or less exposure in the context of clinically evident AKI rather than a drug-related attributable risk for the AKI event).

Our study has several strengths. First, we examined a large cohort of hospitalized patients with a primary diagnosis of IE compared to other studies examining AKI in the setting of IE [16,18]. Second, we examined distinct clinical parameters (patient-specific, IE-specific and medication exposure) associated with AKI as well as resource utilization and healthcare cost associated with the occurrence of AKI. Our study therefore further contributes to identifying patients with IE at high risk of AKI. Third, our cohort is unique in that is from an area with a high prevalence of opioid use disorder. Finally, our study highlights the need to identify clinical parameters that may inform risk-stratification of AKI and adverse outcomes in this susceptible population.

5. Conclusions

Two out of three patients admitted to the hospital with a primary diagnosis of IE had AKI. A higher level of comorbidity was independently associated with AKI. Patients with AKI more frequently received diuretics and patients with severe AKI (stage ≥2) more frequently required pressor/inotrope support. The affection of the tricuspid valve was independently associated with severe AKI (stage ≥2). Patients with severe AKI (stage ≥2) had more frequently major adverse kidney events up to 90 days post-discharge. Further, resource utilization and healthcare cost were significantly higher in patients with AKI vs. those without AKI. Future studies should aim to develop risk-stratification tools for AKI and adverse outcomes in hospitalized patients with IE and therefore guide preventive strategies that ameliorate the burden of complications in this susceptible population.

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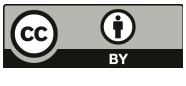
References

1. Murdoch, D.R.; Corey, G.R.; Hoen, B.; Miro, J.M.; Fowler, V.G., Jr.; Bayer, A.S.; Karchmer, A.W.; Olaison, L.; Pappas, P.A.; Moreillon, P.; et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch. Intern. Med.* **2009**, *169*, 463–473. [CrossRef] [PubMed]
2. Thuny, F.; Grisoli, D.; Cautela, J.; Riberi, A.; Raoult, D.; Habib, G. Infective endocarditis: Prevention, diagnosis, and management. *Can. J. Cardiol.* **2014**, *30*, 1046–1057. [CrossRef] [PubMed]
3. Baddour, L.M.; Wilson, W.R.; Bayer, A.S.; Fowler, V.G., Jr.; Bolger, A.F.; Levison, M.E.; Ferrieri, P.; Gerber, M.A.; Tani, L.Y.; Gewitz, M.H.; et al. Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation* **2005**, *111*, e394–e434. [CrossRef] [PubMed]
4. Pant, S.; Patel, N.J.; Deshmukh, A.; Golwala, H.; Patel, N.; Badheka, A.; Hirsch, G.A.; Mehta, J.L. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J. Am. Coll. Cardiol.* **2015**, *65*, 2070–2076. [CrossRef] [PubMed]
5. Toyoda, N.; Chikwe, J.; Itagaki, S.; Gelijns, A.C.; Adams, D.H.; Egorova, N.N. Trends in Infective Endocarditis in California and New York State, 1998–2013. *JAMA* **2017**, *317*, 1652–1660. [CrossRef] [PubMed]
6. Fleischauer, A.T.; Ruhl, L.; Rhea, S.; Barnes, E. Hospitalizations for Endocarditis and Associated Health Care Costs Among Persons with Diagnosed Drug Dependence—North Carolina, 2010–2015. *MMWR Morb. Mortal. Wkly. Rep.* **2017**, *66*, 569–573. [CrossRef]
7. Vivolo-Kantor, A.M.; Seth, P.; Gladden, R.M.; Mattson, C.L.; Baldwin, G.T.; Kite-Powell, A.; Coletta, M.A. Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses—United States, July 2016–September 2017. *MMWR Morb. Mortal. Wkly. Rep.* **2018**, *67*, 279–285. [CrossRef]
8. Jones, C.M. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010. *Drug Alcohol Depend.* **2013**, *132*, 95–100. [CrossRef]
9. Scheidegger, C.; Zimmerli, W. Incidence and spectrum of severe medical complications among hospitalized HIV-seronegative and HIV-seropositive narcotic drug users. *AIDS* **1996**, *10*, 1407–1414. [CrossRef]
10. Susantitaphong, P.; Cruz, D.N.; Cerda, J.; Abulfaraj, M.; Alqahtani, F.; Koulouridis, I.; Jaber, B.L. World incidence of AKI: A meta-analysis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1482–1493. [CrossRef]
11. Szczech, L.A.; Harmon, W.; Hostetter, T.H.; Klotman, P.E.; Powe, N.R.; Sedor, J.R.; Smedberg, P.; Himmelfarb, J. World Kidney Day 2009: Problems and challenges in the emerging epidemic of kidney disease. *J. Am. Soc. Nephrol.* **2009**, *20*, 453–455. [CrossRef] [PubMed]
12. Silver, S.A.; Long, J.; Zheng, Y.; Chertow, G.M. Cost of Acute Kidney Injury in Hospitalized Patients. *J. Hosp. Med.* **2017**, *12*, 70–76. [CrossRef] [PubMed]
13. Rewa, O.; Bagshaw, S.M. Acute kidney injury—Epidemiology, outcomes and economics. *Nat. Rev. Nephrol.* **2014**, *10*, 193–207. [CrossRef] [PubMed]
14. Neugarten, J.; Gallo, G.R.; Baldwin, D.S. Glomerulonephritis in bacterial endocarditis. *Am. J. Kidney. Dis.* **1984**, *3*, 371–379. [CrossRef]
15. Majumdar, A.; Chowdhary, S.; Ferreira, M.A.; Hammond, L.A.; Howie, A.J.; Lipkin, G.W.; Littler, W.A. Renal pathological findings in infective endocarditis. *Nephrol. Dial. Transplant.* **2000**, *15*, 1782–1787. [CrossRef]
16. Boils, C.L.; Nasr, S.H.; Walker, P.D.; Couser, W.G.; Larsen, C.P. Update on endocarditis-associated glomerulonephritis. *Kidney Int.* **2015**, *87*, 1241–1249. [CrossRef]
17. Conlon, P.J.; Jefferies, F.; Krigman, H.R.; Corey, G.R.; Sexton, D.J.; Abramson, M.A. Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. *Clin. Nephrol.* **1998**, *49*, 96–101.
18. Ritchie, B.M.; Hirning, B.A.; Stevens, C.A.; Cohen, S.A.; DeGrado, J.R. Risk factors for acute kidney injury associated with the treatment of bacterial endocarditis at a tertiary academic medical center. *J. Chemother.* **2017**, *29*, 292–298. [CrossRef]

19. Elixhauser, A.; Steiner, C.; Harris, D.R.; Coffey, R.M. Comorbidity measures for use with administrative data. *Med. Care* **1998**, *36*, 8–27. [CrossRef]
20. Durack, D.T.; Lukes, A.S.; Bright, D.K. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am. J. Med.* **1994**, *96*, 200–209. [CrossRef]
21. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Castro, A.F., 3rd; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **2009**, *150*, 604–612. [CrossRef] [PubMed]
22. Keslin, M.H.; Messner, R.P.; Williams, R.C., Jr. Glomerulonephritis with subacute bacterial endocarditis. Immunofluorescent studies. *Arch. Intern. Med.* **1973**, *132*, 578–581. [CrossRef] [PubMed]
23. Kellum, J.A.; Zarbock, A.; Nadim, M.K. What endpoints should be used for clinical studies in acute kidney injury? *Intensive Care Med.* **2017**, *43*, 901–903. [CrossRef] [PubMed]
24. Leaf, D.E.; Jacob, K.A.; Srivastava, A.; Chen, M.E.; Christov, M.; Juppner, H.; Sabbisetti, V.S.; Martin, A.; Wolf, M.; Waikar, S.S. Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness. *J. Am. Soc. Nephrol.* **2017**, *28*, 1877–1885. [CrossRef] [PubMed]
25. Rubenfeld, G.D.; Angus, D.C.; Pinsky, M.R.; Curtis, J.R.; Connors, A.F., Jr.; Bernard, G.R. Outcomes research in critical care: Results of the American Thoracic Society Critical Care Assembly Workshop on Outcomes Research. The Members of the Outcomes Research Workshop. *Am. J. Resp. Crit. Care.* **1999**, *160*, 358–367. [CrossRef] [PubMed]
26. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef] [PubMed]
27. James, M.T.; Levey, A.S.; Tonelli, M.; Tan, Z.; Barry, R.; Pannu, N.; Ravani, P.; Klarenbach, S.W.; Manns, B.J.; Hemmelgarn, B.R. Incidence and Prognosis of Acute Kidney Diseases and Disorders Using an Integrated Approach to Laboratory Measurements in a Universal Health Care. *JAMA Netw. Open* **2019**, *2*, e191795. [CrossRef] [PubMed]
28. Haase, M.; Kellum, J.A.; Ronco, C. Subclinical AKI—An emerging syndrome with important consequences. *Nat. Rev. Nephrol.* **2012**, *8*, 735–739. [CrossRef]
29. Ronco, C.; Kellum, J.A.; Haase, M. Subclinical AKI is still AKI. *Crit. Care* **2012**, *16*, 313. [CrossRef]
30. Cresti, A.; Chiavarelli, M.; Scalese, M.; Nencioni, C.; Valentini, S.; Guerrini, F.; D'Aiello, I.; Picchi, A.; De Sensi, F.; Habib, G. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. *Cardiovasc. Diagn. Ther.* **2017**, *7*, 27–35. [CrossRef]
31. Alkhawam, H.; Sogomonian, R.; Zaiem, F.; Vyas, N.; El-Hunjul, M.; Jolly, J.; Al-Khazraji, A.; Ashraf, A. Morbidity and mortality of infective endocarditis in a hospital system in New York City serving a diverse urban population. *J. Invest. Med.* **2016**, *64*, 1118–1123. [CrossRef] [PubMed]
32. Wallace, S.M.; Walton, B.I.; Kharbanda, R.K.; Hardy, R.; Wilson, A.P.; Swanton, R.H. Mortality from infective endocarditis: Clinical predictors of outcome. *Heart* **2002**, *88*, 53–60. [CrossRef]
33. Koyner, J.L.; Davison, D.L.; Brasha-Mitchell, E.; Chalikonda, D.M.; Arthur, J.M.; Shaw, A.D.; Tumlin, J.A.; Trevino, S.A.; Bennett, M.R.; Kimmel, P.L.; et al. Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity. *J. Am. Soc. Nephrol.* **2015**, *26*, 2023–2031. [CrossRef] [PubMed]
34. Hussain, S.T.; Witten, J.; Shrestha, N.K.; Blackstone, E.H.; Pettersson, G.B. Tricuspid valve endocarditis. *Ann. Cardiothorac. Surg.* **2017**, *6*, 255–261. [CrossRef] [PubMed]
35. Lemaire, A.; Dombrovskiy, V.; Saadat, S.; Batsides, G.; Ghaly, A.; Spotnitz, A.; Lee, L.Y. Patients with Infectious Endocarditis and Drug Dependence Have Worse Clinical Outcomes after Valvular Surgery. *Surg. Infect.* **2017**, *18*, 299–302. [CrossRef] [PubMed]
36. Collister, D.; Pannu, N.; Ye, F.; James, M.; Hemmelgarn, B.; Chui, B.; Manns, B.; Klarenbach, S.; Alberta Kidney Disease Network. Health Care Costs Associated with AKI. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1733–1743. [CrossRef]



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The Incidence of Chronic Kidney Disease Three Years after Non-Severe Acute Kidney Injury in Critically Ill Patients: A Single-Center Cohort Study

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Abstract: The risk of chronic kidney disease (CKD) following severe acute kidney injury (AKI) in critically ill patients is well documented, but not after less severe AKI. The main objective of this study was to evaluate the long-term incidence of CKD after non-severe AKI in critically ill patients. This prospective single-center observational three-years follow-up study was conducted in the medical intensive care unit in Bordeaux's hospital (France). From 2013 to 2015, all patients with severe (kidney disease improving global outcomes (KDIGO) stage 3) and non-severe AKI (KDIGO stages 1, 2) were enrolled. Patients with prior eGFR < 90 mL/min/1.73 m^2 were excluded. Primary outcome was the three-year incidence of CKD stages 3 to 5 in the non-severe AKI group. We enrolled 232 patients. Non-severe AKI was observed in 112 and severe AKI in 120. In the non-severe AKI group, 71 (63%) were male, age was 62 ± 16 years. The reason for admission was sepsis for 56/112 (50%). Sixty-two (55%) patients died and nine (8%) were lost to follow-up. At the end of the follow-up the incidence of CKD was 22% (9/41); Confidence Interval (CI) $_{95\%}$ (9.3–33.60)% in the non-severe AKI group, tending to be significantly lower than in the severe AKI group (44% (14/30); CI $_{95\%}$ (28.8–64.5)%; $p = 0.052$). The development of CKD three years after non-severe AKI, despite it being lower than after severe AKI, appears to be a frequent event highlighting the need for prolonged follow-up.

Keywords: acute kidney injury; critically ill patients; renal recovery; chronic kidney disease; end stage renal disease

1. Introduction

Acute kidney injury (AKI) is very common in Intensive Care Unit (ICU) patients since it is estimated to develop in up to 50% of them [1]. The short-term implications have been studied extensively and include an increase in mortality [2], hospitalization length, rehospitalizations [3], and impaired quality of life [4]. The long-term implications in critically-ill patients are still not well known, except for severe AKI (defined most of the time by AKI-requiring renal replacement therapy (RRT)). In that category of patients, Schiffl et al. (2008) found that five years after RRT, 14% of them developed chronic kidney disease (CKD) [5]. Gammelager et al. (2013) demonstrated that among surviving patients requiring RRT, the incidence of end-stage renal disease (ESRD) at five years was 4% [6].

To date, non-severe AKI outcomes were predominantly studied in non-critically ill patients, using large administrative data sets [7], e.g., veterans' health administration data [8]. These analyses

are known to have low sensibility [9] and to underestimate the less severe form of AKI [10]. Another big cohort including non-severe AKI in non-critically ill patients is the 5-year prospective case-control 'AKI Risk in Derby' study. Patients were divided into two groups according to the kidney disease improving global outcomes (KDIGO) classification (severe AKI corresponding to KDIGO 3 and non-severe AKI corresponding to KDIGO 1 or 2) [11]. Preliminary results after a 12-month follow-up showed that patients with severe AKI had worse kidney function than patients with non-severe AKI, but kidney function declined in both groups compared to control patients [12]. These studies did not enroll many critically ill patients who typically present with a different spectrum of AKI etiologies [13]. These patients are often exposed to multiple nephrotoxic agents (antibiotics, iodine contrast products, etc.), severe hemodynamic variations, and inflammatory state ("sepsis"), each being able to worsen the long-term renal prognosis.

To date, it is difficult to determine the real risk of developing CKD in critically ill patients with non-severe AKI. The incidence of CKD many years after a non-severe AKI in ICU could be thus underestimated. The main objective of this study was to evaluate the long-term incidence of CKD after non-severe AKI in critically ill patients. This would be the first study to address this issue. Secondary objectives were to compare CKD incidence after non-severe vs. severe AKI episodes, to evaluate risk factors for developing CKD, and to identify the proportion among CKD patients followed by a nephrologist.

2. Materials and Methods

2.1. Study Design

This prospective three-year follow-up observational study was carried out in Bordeaux, France, from September 2013 to May 2015. Our center participated in the artificial kidney initiation in kidney injury (AKIKI) study [14], during which all patients with AKI from stage 1 of the KDIGO classification were prospectively and carefully screened. Data were collected during the period of hospitalization. After discharge, the follow-up was carried out three years after enrollment. A direct contact with the general practitioner (GP) and/or the patient was achieved. According to French law, the database was declared to the French data protection authority (declaration number 2168624). The study obtained the approval of the ethics commission of the French society of intensive care medicine and was assigned as CE SRLF 18-20.

2.2. Participants

Patients were enrolled if they were 18 years of age or older, received invasive mechanical ventilation, catecholamine infusion, or both, and developed AKI assessed by an increase of serum creatinine (SCr) of >26.5 μmol/L within 48 h or an increase of >1.5 times the baseline value, according to KDIGO guidelines [11]. Patients with an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2 prior to ICU admission, using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula, were excluded. Serum creatinine assays were standardized (IDMS calibration). Enrollment and collection of hospitalization data were recorded prospectively. Follow-up outcomes were collected prospectively three years after enrollment for each patient, in order to limit memorization bias or loss of data, using medical records and phone calls with GPs and patients.

2.3. Acute Kidney Injury Classification

The KDIGO staging of AKI was used to define non-severe AKI (AKI stages 1 and 2) and severe AKI (AKI stage 3) [11]. Only SCr was considered because of inconsistent urine output data. Baseline SCr were SCr at admission in the case of normal renal function or SCr less than 1 year in the case of abnormal SCr at admission. All baseline SCr were obtained by previous blood tests.

2.4. Exposure Variables

Information relative to smoker status, past medical history of hypertension, diabetes, chronic heart failure, ischemic heart disease (IHD), stroke, peripheral arterial disease (PAD), prior CKD, reason of admission, simplified acute physiology score II (SAPS II), length of hospitalization, catecholamine, aminoglycoside, contrast agent use, or death were collected using prospectively recorded data and patient questioning if applicable.

Because some patients were treated both with continuous veno-venous hemodialysis (CVVHD) and intermittent hemodialysis (IHD), we only recorded the first RRT modality that was used during the ICU stay.

2.5. Long-Term Incidence of CKD at Three Years

We defined CKD as eGFR <60 mL/min/1.73 m^2, using the chronic kidney disease epidemiology collaboration (CKD-EPI) corresponding to CKD stage 3 or more according to the KDIGO classification. Creatinine level were collected by family calls or GP calls. In the case of abnormal creatinine level, absence of AKI was checked using an anteriority blood test.

2.6. Other Outcomes

Recovery from AKI was determined at ICU discharge. It was defined as a return of SCr to <26.5 µmol/L (<0.3 mg/dL) above baseline for alive and non-dependent RRT patients. These data were collected using hospital records or using data from blood tests performed outside the hospital, with prior consent of the patient. We called CKD patients to ask if they were followed by a nephrologist. The survival state and date of death if applicable were collected using hospital records, GP, and family phone calls.

2.7. Statistical Analysis

Statistical analysis was carried out using JMP® Version 14, SAS Institute Inc., Cary, NC, USA, 1989–2007. Descriptive statistics included mean ± standard deviation (SD) or median (Quartile 1-Quartile 3). Quantitative variables were compared using a *t*-test, and qualitative variables using Chi^2 Pearson test. The multivariate analysis was carried out using logistic regression. To choose independent variables included in the model, we allowed one independent variable for every 20 patients analyzed. Interactions between independent variables were checked using the Pearson correlation test for quantitative variables and the Chi^2 test for ordinal or binomial variables using Yates' correction if the sample size was <10. Quantitative variables were stratified into a range when a constant magnitude of association was not consistent. Renal survival was studied using the Kaplan–Meier curve. Survival curves were compared using a log-rank test. A value of $p < 0.05$ was considered statistically significant (double-sided).

3. Results

3.1. Participants

From 2013–2015, 304 patients with AKI were admitted to the ICU (Figure 1). Among them, 72 had prior CKD and were excluded and 232 patients were enrolled. No patients had missing baseline creatinine value. Non-severe AKI was present in 112 (AKI stage 1, 62; stage 2, 50) and severe AKI in 120 (AKI stage 3). In the non-severe AKI group, 71/112 (63%) were male with a mean age of 62 ± 16 years. In 56/112 (50%), the reason for admission was sepsis, 89/112 (79%) required catecholamines, and 92/112 (79%) were intubated. The simplified acute physiology score II (SAPS II) was 59 ± 17. The duration of hospitalization was 9 ± 10 days. All descriptive characteristics and the comparison between non-severe AKI vs. severe AKI are presented in Table 1. In severe AKI, patients had a higher SAPS II (65 ± 20 vs. 59 ± 17; $p = 0.01$). The ICU mortality rate was also higher in the severe patients

group (57/120 (48%) vs. 34/112 (30%); $p = 0.01$). Renal replacement therapy was performed in 73/120 (61%) of patients with severe AKI, and CVVHD was used in 57/73 (78%) of these patients. One hundred and seven patients died in hospital (40 in the non-severe group and 67 in the severe group). Cause of death was multiple organ failure (35 patients), withholding or withdrawing of life-prolonging therapy (16), neurologic disorder (15), septic shock (11), acute respiratory distress syndrome (10), hemorrhagic shock (3), cardiac arrest (4), or others (13). Among the 78/112 (69%) patients with non-severe AKI who survived at ICU discharge, renal recovery was observed in 68/78 (87%) patients compared to 22/63 (35%) patients with severe AKI ($p < 0.001$).

Table 1. Descriptive characteristics of patients enrolled in the cohort and comparative descriptive characteristics of patients with non-severe AKI and severe AKI.

Characteristics of Patients	Patients Enrolled $n = 232$ (%)	Non-Severe AKI $n = 112$ (%)	Severe AKI $n = 120$ (%)	p Value
Males	142 (63)	71 (63)	71 (59)	0.5
Age	62 ± 16	62 ± 16	62 ± 16	0.8
Smoker	97 (42)	50 (45)	47 (39)	0.4
Hypertension	115 (50)	62 (55)	53 (44)	0.1
Diabetes	55 (24)	31 (28)	24 (20)	0.2
Heart failure	42 (18)	20 (18)	22 (18)	0.9
Stroke	21 (9)	12 (11)	9 (8)	0.4
PAD	17 (7)	6 (5)	11 (9)	0.3
IHD	33 (14)	19 (17)	14 (11)	0.2
Basal SCr	78 ± 18	78 ± 19	77 ± 17	0.6
Sepsis	118 (51)	56 (50)	62 (52)	0.8
Contrast agent	55 (24)	26 (23)	29 (24)	0.9
Aminosid use	84 (36)	43 (38)	42 (35)	0.6
NIV or HFNC	192 (83)	6 (5)	5 (4)	0.7
Orotracheal intubation	192 (83)	92 (82)	100 (83)	0.8
Catecholamine use	191 (82)	89 (79)	102 (85)	0.3
SAPS II	62 ± 19	59 ± 17	65 ± 20	0.01
Maximal SCr (μmol/L)	266 ± 181	153 ± 56	371 ± 195	<0.001
AKI stage:				
1	62 (27)	62 (55)	0 (0)	
2	50 (21)	50 (45)	0 (0)	
3	120 (52)		120 (100)	
RRT		0	73 (61)	
CVVHD		0	57 (48)	
IHH		0	16 (13)	
Renal recovery	90/141 (64)	68/78 (87)	22/63 (35)	<0.001
ICU length of stay (days)	9 ± 10	9 ± 10	9 ± 11	0.9
Intra-ICU deaths	91 (39)	34 (30)	57 (48)	0.01
Hospital length of stay (days)	36 ± 100	37 ± 109	34 ± 91	0.8

PAD: Peripheral arterial disease; IHD: Ischemic heart disease; HFNC: High-flow nasal cannula; NIV: Non-invasive ventilation; AKI: Acute kidney injury; SAPS II: Simplified acute physiology score II; SCr: Serum creatinine; ICU: Intensive care unit; RRT: renal replacement therapy; CVVHD: Continuous venovenous hemodialysis; IH: Intermittent hemodialysis.

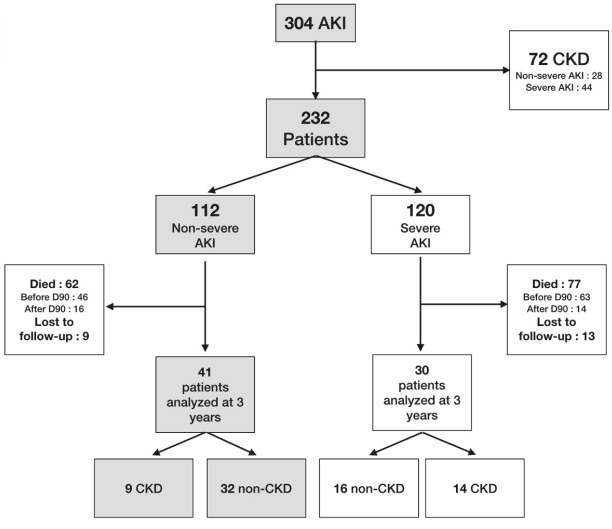


Figure 1. Flow chart. CKD: chronic kidney disease; AKI: acute kidney injury.

Descriptive characteristics of all patients enrolled (patients enrolled) and comparative descriptive characteristics between non-severe AKI and severe AKI. Statistical analysis was carried out to compare these two subgroups.

3.2. Follow-Up

A flow diagram is presented in Figure 1. In non-severe AKI, 34/112 (30%) died in the ICU and 28/112 (25%) during the follow-up. We lost 9/112 (8%) patients to follow-up. In this group, 41 patients completed the study.

3.3. Primary Outcome: Long-Term Incidence of CKD at Three Years

In non-severe AKI, the incidence of CKD during a three years follow-up amongst patients who survived was 9/41 (22% CI $_{95\%}$ (9.3–33.6)). It tended to be lower than in in the severe AKI group (14/30 (44% CI $_{95\%}$ (28.8–64.5)) $p = 0.052$). Among the 23 patients who developed CKD, whatever the group, 8 had recovered from AKI (6 in the non-severe group) and 9 had eGFR < 60 mL/min/1.73 m^2 (4 in the non-severe group) at ICU discharge. CKD stages at three years are summarized in Table 2.

Table 2. Chronic kidney disease stage at three years follow-up (eGFR (mL/min/1.73 m^2)).

CKD Stages At 3 Years	Non-Severe AKI at Inclusion $n = 41$ (%)	Severe AKI at Inclusion $n = 30$ (%)	Total $n = 71$ (%)
CKD3 (60 < eGFR < 30)	7 (17)	10 (33)	17 (24)
CKD4 (30 < eGFR < 15)	2 (5)	1 (3)	3 (4)
CKD5 (eGFR < 15))	0	3 (10)	3 (4)

AKI: acute kidney injury; CKD: chronic kidney disease.

3.4. Secondary Outcomes

3.4.1. Risk Factors for CKD at Three Years

In the univariate analysis, hypertension (Odd Ratio (OR) = 3.5 (1.2–10.5)), diabetes (OR = 3.6 (1.2–10.3)), SCr (OR = 1.007 (1.002–1.011)), and severe AKI (OR = 3 (1.1–8.5)) were significantly associated with CKD at three years.

In the multivariate analysis, hypertension and diabetes presented interactions (Chi^2 $p = 0.004$), as well as Scr and severe AKI. Diabetes and severe AKI were the variables maintained in the analysis. In this model, only diabetes (OR = 3.3 (1.3–8.3)) was significantly associated with CKD at three years. Conversely, the severity of AKI was not associated with CKD (severe vs. non-severe) (OR = 1.96 (0.8–5)) (Table 3).

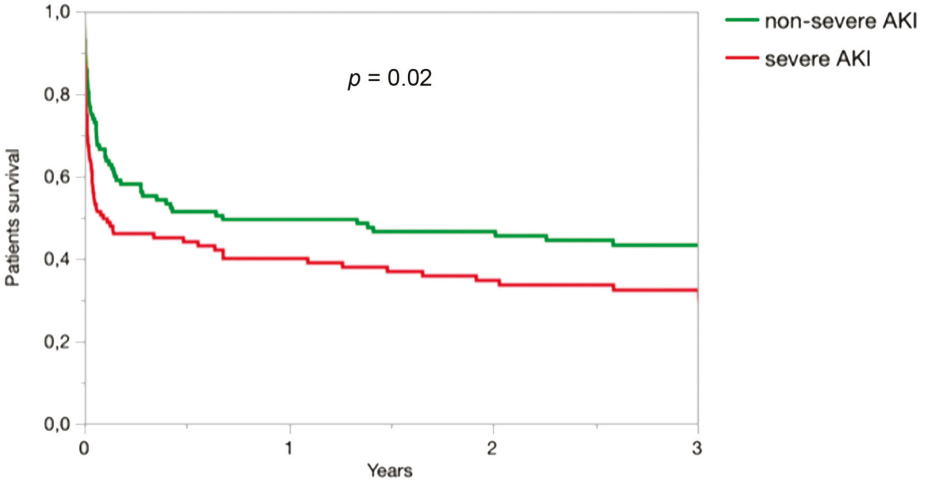
Table 3. Risk factors for developing CKD at three years.

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio eGFR < 60 (mL/min/1.73 m^2)	**Confidence Interval 5%**	**Odds Ratio eGFR < 60 (mL/min/1.73 m^2)**	**Confidence Interval 5%**
Male	0.5	(0.2–1.4)		
Age	1.1	(0.99–1.2)		
Smoker	1.8	(0.6–4.8)		
Hypertension	3.5	(1.2–10.5)		
Diabetes	3.6	(1.2–10.3)	3.3	(1.3–8.3)
Heart failure	2.3	(0.6–9.1)		
Stroke	0.3	(0.04–2.7)		
PAD	2.1	(0.3–16.3)		
IHD	1.8	(0.4–7.3)		
Sepsis	1.7	(0.6–4.6)		
Contrast agent	1.3	(0.4–3.8)		
Aminosid use	2.1	(0.8–5.8)		
Orotracheal intubation	0.7	(0.2–2.1)		
Vasopressor	1.6	(0.4–6.5)		
SAPS II	1.5	(0.2–12.9)		
Length of hospitalization in ICU (days)	0.97	(0.94–1.04)		
Hospital length of stay (days)	0.99	(0.98–1.01)		
Maximum SCr	1.007	(1.002–1.01)		
Non-severe AKI	1		1	
Severe AKI	3	(1.1–8.5)	1.96	(0.8–5)
AKI stage 1	0.2	(0.05–0.4)		
AKI stage 2	0.5	(0.2–1.5)		
AKI stage 3	1			
RRT	2.7	(0.9–8.2)		
CVVHD	0.8	(0.2–3.1)		
Readmission at hospital during follow-up	1.5	(0.5–4.3)		

Multivariate analysis was proceeded using logistic regression. PAD: Peripheral arterial disease; IHD: Ischemic heart disease; HFNC: High-flow nasal cannula; NIV: Non-invasive ventilation; AKI: Acute kidney injury; SAPS II: Simplified Acute physiology score; SCr: Serum creatinine; CVVHD: Continuous veno-venous hemodialysis; RRT: Renal replacement therapy; ICU: Intensive care unit.

3.4.2. Patients Survival

Patients survival was assessed in the set of 232 included patients. At three years, survival was 38% in our series. The three years survival was 43% in the non-severe AKI group and 32% in the severe AKI group with statistical difference ($p = 0.02$) (Figure 2).



Time	0	90 days	1 year	2 years	3 years
Non-severe AKI	*n* = 112	63	52	46	27
Severe AKI	*n* = 120	49	41	33	21

Figure 2. Patients' survival rate. Renal survival was assessed in 232 patients. The three years renal survival was 43% in the non-severe AKI group and 32% in the severe AKI group with statistical difference. Comparison of renal survival rate using log-rank test.

3.4.3. Renal Specialist Following

Eleven out of twenty-three (48%) patients who developed CKD were followed by a nephrologist.

4. Discussion

This study is the first in the literature to estimate the incidence of CKD three years after non-severe AKI in critically ill patients. At three years, an eGFR of <60 mL/min1.73 m^2 (defining CKD) was present in 22% CI $_{95\%}$ (9.3–33.6) in the non-severe AKI group, half of whom were not followed by a nephrologist.

Our study is original. The incidence of CKD only three years after non-severe AKI is high (22%). No study has focused on stage 1 and 2 AKI in critically ill patients while only a few studies have studied stage 1 and 2 AKI in non-critically ill patients. In the recent analysis of U.S. veterans' health administration data, incidence of CKD (eGFR < 60 mL/min/1.73 m^2) at 1 year was 31% in AKI stage 1-patients and 27% in AKI stage 2-patients [15]. However, patients had more risk factor to develop CKD than ours; they were male (95%), older than ours, and basal eGFR was 84 mL/min/1.73 m^2. We excluded patients with an eGFR of <90 mL/min/1.73 m^2 prior to AKI Many similar studies excluded patients with prior eGFR < 60 mL/min/1.73 m^2. Indeed, patients with an eGFR of 60–90 mL/min/1.73 m^2 do not have normal renal function and it has been very well demonstrated that even a slight degree of chronic renal failure promotes future alteration of eGFR [16]. By excluding patients with DFG < 90 mL/min/1.73 m^2 at inclusion, we ensure a decrease of 30 mL/min in three years, which is clinically very significant.

Nevertheless, many factors may influence CKD development three years after an AKI in ICU and we cannot conclude whether non-severe AKI itself was independently implicated in the high CKD incidence at three years. First, AKI itself: in vitro studies have highlighted different mechanisms linking AKI and CKD, such as persistent interstitial inflammation or tubular's vascular damages [16]. Secondly, individual factor can lead to the development of CKD at long-term. For example, diabetes is associated

with a decrease in kidney function in many studies. In the multivariate analysis, diabetes was a risk factor for a decline in kidney function in AKI patients without prior CKD. These results were already demonstrated in non-critically ill patients. However, many other clinical conditions are associated with the risk of developing CKD such as age, sex, diabetes, hypertension, albuminuria, initial eGFR, high triglyceride levels, and low HDL cholesterol levels [17,18]. In a future study, the Kidneyfailurerisk.com Canadian score, which estimates the risk to develop CKD at 2 or 5 years and is well validated in a variety of populations [19], could be used to compare the expected incidence assessed by this score with the observed increased incidence of CKD.

One third of surviving patients had apparent complete renal recovery at ICU discharge but later developed CKD. However, for the other patients, we could not determine if they recovered later or if they kept low eGFR over the three years. These findings are in accordance with studies performed in non-critically ill patients, which found an increased risk of CKD following non-dialysis-dependent AKI, even after biological renal recovery [20,21]. Absence of renal recovery at ICU discharge remains common in our study (about a third of the cases). Kellum et al. studied 17,000 ICU patients with stage 2–3 AKI and showed that early relapse of AKI occurred in 37% of cases. Late sustained reversal (after 7 days and sustained through hospital discharge) and relapse were two risk factors for a decreased age-adjusted one-year renal survival [22].

One of the strength of our study comes from the recording of anterior SCr rather than MDRD estimated SCr. The main limitation of our study is its single-center characteristic with a consecutive low number of surviving patients at three years, which favors a risk of type 2 error. We have screened more than 300 patients in three years. The enrollment was exhaustive because it was integrated in a clinical trial in which the medical team was very involved. Only 22 patients were lost to follow-up (<10%), a satisfactory proportion for this type of study. Despite this, because of CKD occurring before AKI accounted for many exclusions but also because of many deaths, few patients (23%) could be analyzed at the three-year follow-up. This lack of power probably explains the absence of significant association between AKI severity and CKD. This association was already suggested by many studies showing that severe AKI remains the main prognostic factor of CKD after a long follow-up period. We could not determine whether CKD developed before death in the patients who died. However, 109/139 patients (78%) died before day 90, which is the time limit after which CKD can be defined. Our hypothesis is that less severe patients with a longer outcome need a specific follow-up to detect and to prevent CKD. This pragmatic view led us to identify incidence of CKD only in patients who survived at three years.

It is clear that AKI survivors require a long-term follow-up [23]. First, they are at high risk of developing CKD even in cases of non-severe AKI, including if their kidney function has recovered at ICU discharge. Second, this risk is probably underestimated both by the patient and the general practitioner because less than 50% of patients with CKD were followed by a nephrologist in our study. Third, it was already shown that the risk of mortality and cardiovascular complications is very high in patients with an eGFR of <60 mL/min/1.73 m^2 and the long-term consequences concern other organs and persist despite renal recovery [24,25].

The risk of developing CKD at three years after non-severe AKI, despite it being lower than after a severe AKI, remains high. These findings have to be confirmed by larger studies. A long-term follow up is required and all physicians involved in the patient's follow-up, including intensivists, should pay attention to that phenomenon.

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References

1. Hoste, E.A.J.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef] [PubMed]
2. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Beginning and Ending Supportive Therapy for the Kidney, I. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA J. Am. Med Assoc.* **2005**, *294*, 813–818. [CrossRef] [PubMed]
3. Horkan, C.M.; Purtle, S.W.; Mendu, M.L.; Moromizato, T.; Gibbons, F.K.; Christopher, K.B. The Association of Acute Kidney Injury in the Critically Ill and Postdischarge Outcomes. *Crit. Care Med.* **2015**, *43*, 354–364. [CrossRef] [PubMed]
4. Delannoy, B.; Floccard, B.; Thiolliere, F.; Kaaki, M.; Badet, M.; Rosselli, S.; Ber, C.E.; Saez, A.; Flandreau, G.; Guérin, C. Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: A multicentre prospective study. *Intensive Care Med.* **2009**, *35*, 1907–1915. [CrossRef]
5. Schiffl, H.; Fischer, R. Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. Eur. Ren. Assoc.* **2008**, *23*, 2235–2241. [CrossRef]
6. Gammelager, H.; Christiansen, C.F.; Johansen, M.B.; Tønnesen, E.; Jespersen, B.; Sørensen, H.T. Five-year risk of end-stage renal disease among intensive care patients surviving dialysis-requiring acute kidney injury: A nationwide cohort study. *Crit. Care* **2013**, *17*, R145. [CrossRef]
7. Lafrance, J.-P.; Miller, D.R. Acute kidney injury associates with increased long-term mortality. *J. Am. Soc. Nephrol. JASN* **2010**, *21*, 345–352. [CrossRef]
8. Heung, M.; Steffick, D.E.; Zivin, K.; Gillespie, B.W.; Banerjee, T.; Hsu, C.-Y.; Powe, N.R.; Pavkov, M.E.; Williams, D.E.; Saran, R.; et al. Centers for Disease Control and Prevention CKD Surveillance Team Acute Kidney Injury Recovery Pattern and Subsequent Risk of CKD: An Analysis of Veterans Health Administration Data. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2016**, *67*, 742–752. [CrossRef]
9. Tomlinson, L.A.; Riding, A.M.; Payne, R.A.; Abel, G.A.; Tomson, C.R.; Wilkinson, I.B.; Roland, M.O.; Chaudhry, A.N. The accuracy of diagnostic coding for acute kidney injury in England—A single centre study. *BMC Nephrol.* **2013**, *14*, 58. [CrossRef]
10. Sawhney, S.; Fraser, S.D. Epidemiology of AKI: Utilizing Large Databases to Determine the Burden of AKI. *Adv. Chronic Kidney Dis.* **2017**, *24*, 194–204. [CrossRef]
11. Palevsky, P.M.; Liu, K.D.; Brophy, P.D.; Chawla, L.S.; Parikh, C.R.; Thakar, C.V.; Tolwani, A.J.; Waikar, S.S.; Weisbord, S.D. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2013**, *61*, 649–672. [CrossRef] [PubMed]
12. Horne, K.L.; Shardlow, A.; Taal, M.W.; Selby, N.M. Long Term Outcomes after Acute Kidney Injury: Lessons from the ARID Study. *Nephron* **2015**, *131*, 102–106. [CrossRef] [PubMed]
13. Rewa, O.; Bagshaw, S.M. Acute kidney injury-epidemiology, outcomes and economics. *Nat. Publ. Group* **2014**, *10*, 193–207. [CrossRef] [PubMed]
14. Gaudry, S.; Hajage, D.; Schortgen, F.; Martin-Lefevre, L.; Pons, B.; Boulet, E.; Boyer, A.; Chevrel, G.; Lerolle, N.; Carpentier, D.; et al. AKIKI Study Group Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N. Engl. J. Med.* **2016**, *375*, 122–133. [CrossRef] [PubMed]
15. Gansevoort, R.T.; Matsushita, K.; van der Velde, M.; Astor, B.C.; Woodward, M.; Levey, A.S.; de Jong, P.E.; Coresh, J. Chronic Kidney Disease Prognosis Consortium Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int.* **2011**, *80*, 93–104. [CrossRef]
16. Heung, M.; Chawla, L.S. Acute kidney injury: Gateway to chronic kidney disease. *Nephron Clin. Pract.* **2014**, *127*, 30–34. [CrossRef]
17. O'Seaghdha, C.M.; Lyass, A.; Massaro, J.M.; Meigs, J.B.; Coresh, J.; D'Agostino, R.B.; Astor, B.C.; Fox, C.S. A risk score for chronic kidney disease in the general population. *Am. J. Med.* **2012**, *125*, 270–277. [CrossRef]
18. McMahon, G.M.; Preis, S.R.; Hwang, S.-J.; Fox, C.S. Mid-adulthood risk factor profiles for CKD. *J. Am. Soc. Nephrol. JASN* **2014**, *25*, 2633–2641. [CrossRef]

19. Tangri, N.; Grams, M.E.; Levey, A.S.; Coresh, J.; Appel, L.J.; Astor, B.C.; Chodick, G.; Collins, A.J.; Djurdjev, O.; Elley, C.R.; et al. CKD Prognosis Consortium Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *JAMA J. Am. Med Assoc.* **2016**, *315*, 164–174. [CrossRef]
20. Jones, J.; Holmen, J.; De Graauw, J.; Jovanovich, A.; Thornton, S.; Chonchol, M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2012**, *60*, 402–408. [CrossRef]
21. Bucaloiu, I.D.; Kirchner, H.L.; Norfolk, E.R.; Hartle, J.E.; Perkins, R.M. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int.* **2012**, *81*, 477–485. [CrossRef] [PubMed]
22. Kellum, J.A.; Sileanu, F.E.; Bihorac, A.; Hoste, E.A.J.; Chawla, L.S. Recovery after Acute Kidney Injury. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 784–791. [CrossRef] [PubMed]
23. Vandenberghe, W.; Hoste, E.A.J. Acute kidney injury survivors should have long-term follow-up. *Crit. Care* **2014**, *18*, 703. [CrossRef] [PubMed]
24. Tonelli, M.; Muntner, P.; Lloyd, A.; Manns, B.J.; Klarenbach, S.; Pannu, N.; James, M.T.; Hemmelgarn, B.R. Alberta Kidney Disease Network Risk of coronary events in people with chronic kidney disease compared with those with diabetes: A population-level cohort study. *Lancet* **2012**, *380*, 807–814. [CrossRef]
25. Shiao, C.-C.; Wu, P.-C.; Huang, T.-M.; Lai, T.-S.; Yang, W.-S.; Wu, C.-H.; Lai, C.-F.; Wu, V.-C.; Chu, T.-S.; Wu, K.-D. National Taiwan University Hospital Study Group on Acute Renal Failure (NSARF) and the Taiwan Consortium for Acute Kidney Injury and Renal Diseases (CAKs) Long-term remote organ consequences following acute kidney injury. *Crit. Care* **2015**, *19*, 438. [CrossRef]

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Review

Utilizing the Patient Care Process to Minimize the Risk of Vancomycin-Associated Nephrotoxicity

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Abstract: Vancomycin-associated acute kidney injury (AKI) is a popular topic in the medical literature with few clear answers. While many studies evaluate the risk of AKI associated with vancomycin, few data are high quality and/or long in duration of follow-up. This review takes the clinician through an approach to evaluate a patient for risk of AKI. This evaluation should include patient assessment, antibiotic prescription, duration, and monitoring. Patient assessment involves evaluating severity of illness, baseline renal function, hypotension/vasopressor use, and concomitant nephrotoxins. Evaluation of antibiotic prescription includes evaluating the need for methicillin-resistant *Staphylococcus aureus* (MRSA) coverage and/or vancomycin use. Duration of therapy has been shown to increase the risk of AKI. Efforts to de-escalate vancomycin from the antimicrobial regimen, including MRSA nasal swabs and rapid diagnostics, should be used to lessen the likelihood of AKI. Adequate monitoring includes therapeutic drug monitoring, ongoing fluid status evaluations, and a continual reassessment of AKI risk. The issues with serum creatinine make the timely evaluation of renal function and diagnosis of the cause of AKI problematic. Most notably, concomitant piperacillin-tazobactam can increase serum creatinine via tubular secretion, resulting in higher rates of AKI being reported. The few studies evaluating the long-term prognosis of AKI in patients receiving vancomycin have found that few patients require renal replacement therapy and that the long-term risk of death is unaffected for patients surviving after the initial 28-day period.

Keywords: vancomycin; MRSA; nephrotoxicity; acute kidney injury; piperacillin-tazobactam; creatinine; KIM-1; AKIN; KDIGO; RIFLE

1. Introduction

Vancomycin has been a mainstay of empiric therapy for gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), for over 50 years. The history of vancomycin has also been littered with safety concerns since the days of "Mississippi Mud", which the impure formulations of vancomycin were affectionately called. In the 1980s, nephrotoxicity concerns rose again. These concerns largely went away as studies found that this nephrotoxicity was generally reversible and randomized; controlled trials of one gram of vancomycin every 12 h reported nephrotoxicity rates of 0–5% [1–3].

Efficacy concerns prompted the development of the vancomycin consensus document. The 2009 consensus statement recommended trough concentrations of 15–20 mg/L for severe infections in an attempt to overcome increasing vancomycin minimum inhibitory concentrations (MICs) in MRSA [4]. The unintended consequence of this recommendation was a significant increase in the rate of nephrotoxicity reported in the literature. However, it is unclear how much of this increase was

due to increased trough concentrations versus the more stringent nephrotoxicity definitions that were being adopted into routine use for research.

Vancomycin use rose by 32% from 2006 to 2012 in the US despite increasing fears regarding nephrotoxicity [5]. Therefore, many clinicians still have faith in vancomycin as a relatively safe antimicrobial despite multiple observational reports and one randomized, controlled trial suggesting otherwise [1,4,5].

The discordance between the data associating vancomycin with nephrotoxicity (including unclear dosing and monitoring requirements) and routine antibiotic prescribing patterns for MRSA infections leave the reasonable clinician debating the best course of action regarding how to incorporate this literature into practice. This review aims to walk the reader through the patient care process (Table 1), analyzing potential factors associated with the development of vancomycin-associated nephrotoxicity or its outcomes during each step.

Table 1. Summary of the patient care process to assess the risk of nephrotoxicity in patients being considered for vancomycin therapy.

Stage of Patient Care Process	Characteristic	Measures	Notes
Patient assessment	Severity of illness	APACHE II Pitt bacteremia score ICU residence	Increased severity of illness has been associated with nephrotoxicity
	Concomitant disease states	Renal dysfunction	Nephrotoxicity increased whether as a cutpoint for serum creatinine or creatinine clearance. Also serum creatinine as a continuous variable.
		Increased creatinine clearance	Only found as a risk factor in one cohort to date.
	Concomitant nephrotoxins	Hypotension and/or vasopressor use	No data regarding the impact of the duration of hypotension.
		ACE inhibitor, amphotericin B, tacrolimus, loop diuretics, and tenofovir	Information regarding the impact of dose and/or duration is lacking
		Piperacillin/tazobactam	Increases diagnosis of nephrotoxicity, but may be renal-protective
Antibiotic prescription	Patient need for an antibiotic	Clinical and microbiologic assessment	Tension exists between the need for rapid adequate empiric therapy and providing antibiotics to patients with non-infectious diseases
	Patient need for vancomycin	Clinical and microbiologic assessment	Assess for risk of MRSA. Further advances in risk scores for assessing risk are needed.
Duration of therapy	Vancomycin duration	Days of vancomycin therapy	Nephrotoxicity risk increases with longer durations of therapy. Most clinical guidelines recommend seven days of vancomycin. Notable exceptions include endocarditis and osteomyelitis.
	Vancomycin discontinuation	Microbiologic assessment	Use of rapid diagnostics, nasal PCR swabs can help aid in discontinuation of vancomycin.
Monitoring	Therapeutic drug monitoring	Vancomycin concentrations	AUC goal should be 400–650 mg·h/L If a trough approach is utilized, please hold at least one dose for a trough ≥25 mg/L
	Fluid status	Intake and output reporting	Both fluid overload and hypovolemia are associated with nephrotoxicity. Accurate intake and output charting can be difficult in some practice environments.
	Reassessment of nephrotoxicity risk	See patient assessment section	

ICU: intensive care unit; ACE: angiotensin converting enzyme; MRSA: methicillin-resistant *Staphylococcus aureus*; PCR: polymerase chain reaction; AUC: area under the curve.

2. Patient Assessment

Every patient that receives vancomycin is not the same. The baseline risk of nephrotoxicity varies based on several factors. These factors include the patient's baseline severity of illness, concomitant disease states, and concomitant nephrotoxins. This means that the patients are likely to have a higher or lower baseline risk of nephrotoxicity based on the presence or absence of the factors that will be discussed in this section.

Several patient characteristics can be utilized to indicate a patient's severity of illness. These variables are not routinely evaluated together in a multivariable model due to concerns regarding collinearity. Multiple studies have found that the risk of nephrotoxicity increases as the baseline APACHE II score increases [6,7]. We have also found that an increased Pitt bacteremia score was associated with nephrotoxicity in patients with MRSA bacteremia [8]. The impact of increasing Sequential Organ Failure Assessmentscores on nephrotoxicity has not been studied, to our knowledge. Intensive care unit residence has also been associated with vancomycin-associated nephrotoxicity in two retrospective studies by Lodise and colleagues [9,10].

Renal dysfunction at baseline has also been associated with nephrotoxicity in multiple studies. Baseline serum creatinine levels ≥1.7 or 2.0 mg/dL were found to be independent predictors of nephrotoxicity in retrospective analyses [11,12]. We have also found that evaluating baseline serum creatinine as a continuous variable (1 mg/dL increments) is also associated with nephrotoxicity [13]. A computer-guided cutpoint of an estimated CrCl ≤ 86.6 mL/min was also associated with time to nephrotoxicity (adjusted odds ratio (OR) 3.7; 95% confidence interval (CI) 1.2–11.5) [9]. The mechanism of why impaired renal function would play a role in the development of nephrotoxicity has yet to be fully elucidated. Some potential reasons would include increased drug exposure through decreased baseline renal function as well the pre-existing kidney damage noted by an increased serum creatinine (and possible diagnosis of chronic kidney disease). The finding by Rutter and colleagues of increased creatinine clearance being associated with nephrotoxicity further adds to the uncertainty regarding this potential factor [14].

Several studies have also reported the association between vasopressor use and nephrotoxicity. These studies do not report information regarding the duration of hypotension prior to vasopressor use [6,12,15,16]. This means that vasopressor use is sometimes used as a surrogate marker of hypotension. It is unknown whether the hypotensive episode or vasopressor use has a greater impact on the development of nephrotoxicity. The majority of studies that have evaluated the impact of hypotensive events on nephrotoxicity have had limited numbers of patients having hypotensive events [17–19]. Rutter and colleagues found hypotensive events to be significantly associated with nephrotoxicity in the largest study to evaluate the impact of hypotensive events in patients receiving vancomycin [14].

Receipt of other nephrotoxic agents may also contribute to nephrotoxicity. A systematic review demonstrated that patients receiving concomitant nephrotoxins were more likely to develop nephrotoxicity (OR 3.30; 95% CI 1.30–8.39) [20]. The role of individual agents, including dose and/or duration, is more difficult to ascertain given that most currently available data have very few events and only allow for the evaluation of a few select covariates. Models that attempt to evaluate too many variables compared to the number of events in the study suffer from overfitting issues, compromising their external validity.

Nephrotoxicity is a known risk associated with the use of aminoglycosides and amphotericin B [21,22]. The use of concomitant aminoglycoside or amphotericin B in addition to vancomycin was the only factor independently associated with nephrotoxicity in one multivariate analysis [23]. Aminoglycosides were also the only concomitant medication associated with nephrotoxicity in a study specifically evaluating critically ill patients [24].

Two large, retrospective cohort studies of hospitalized patients suggest that nephrotoxicity is associated with concomitant angiotensin converting enzyme inhibitor, amphotericin B, tacrolimus, loop diuretics, and tenofovir [14,25]. The concomitant use of a loop diuretic in patients receiving

vancomycin and an antipseudomonal beta-lactam was associated with nephrotoxicity in a multicenter observational study (OR 3.27; 95% CI 1.42–7.53) [16].

The concomitant receipt of piperacillin-tazobactam has been the focus of most recent studies regarding vancomycin-associated nephrotoxicity. Several studies have highlighted the increased risk of acute kidney injury (AKI) associated with concomitant receipt of piperacillin-tazobactam with vancomycin [16,26–28]. Some studies focused on patients admitted to the intensive care unit have not found this association [29,30]. Schreier and colleagues demonstrated that the empiric use of this combination is not associated with nephrotoxicity when de-escalation occurs within the first 48–72 h [31].

The mechanisms for the increased rates of nephrotoxicity with piperacillin-tazobactam have been unclear. Data suggest that the association is not due to the beta-lactamase inhibitor or the infusion strategy [32]. Some have even suggested that the increase in serum creatinine with piperacillin-tazobactam does not represent nephrotoxicity in these patients. Piperacillin-tazobactam is known to increase serum creatinine through inhibition of creatinine tubular secretion without decreasing glomerular filtration rate [33]. There are also clinical data suggesting that the addition of piperacillin-tazobactam to vancomycin lowers dialysis rates even in the face of increased rates of AKI as measured by increases in serum creatinine [29]. Data from a benchtop animal study suggest that the concomitant use of piperacillin/tazobactam may delay the increase in kidney injury molecule-1 (KIM-1) in animals receiving vancomycin [34]. Therefore, piperacillin-tazobactam may be renal-protective even though it increases serum creatinine.

3. Antibiotic Prescription

Up to 50% of inpatient antimicrobial use has been shown to be inappropriate [35]. A recent study has also shown that vancomycin remains one of the most commonly used antimicrobials in hospitals [5]. This is in part due to the high prevalence of methicillin-resistance amongst *S. aureus* isolates as well as the pressures to ensure adequate empiric coverage for the suspected infection. Adding to the concern are diagnostic dilemmas including inconclusive radiographic evidence of infection and the era of health-care associated pneumonia that dramatically increased vancomycin use. A patient-by-patient assessment MRSA risk is needed to avoid the overprescribing of empiric MRSA coverage, which will hopefully be aided in the future by better risk scores and/or rapid diagnostics beyond nasal swabs.

Given the high prevalence of methicillin-resistance amongst *S. aureus* isolates, empiric therapy with vancomycin is common. This is in part due to its inclusion as a first-line option for MRSA in Infectious Diseases Society of America (IDSA) guidelines for skin and soft-tissue infections, diabetic foot infections, endocarditis, febrile neutropenia, meningitis, pneumonia, and surgical prophylaxis [36–43].

However, there are clinical scenarios where vancomycin is not the optimal agent for definitive therapy. There are currently seven oral and 11 intravenous agents that are approved by the U.S. Food and Drug Administration that are active against MRSA. Vancomycin should be evaluated against these other options to determine the optimal agent for a particular patient. Vancomycin is not the optimal agent for a patient that is eligible for oral antimicrobial therapy, as multiple studies have shown the non-inferiority of oral antimicrobials for serious infections [44,45].

4. Duration of Therapy

Several studies have demonstrated that the risk of nephrotoxicity is associated with the duration of vancomycin therapy [27]. Multiple studies have shown that the risk of nephrotoxicity increases after four days of therapy [9,10,15,19,20]. Others have found that a duration of therapy of seven or 14–15 days is associated with nephrotoxicity [6,8,11]. Another study found that the rates of nephrotoxicity increased when the duration was extended from seven or fewer days (6%) to 8–14 days (21%), and to 30% when extended >14 days [23]. Most patients should not require vancomycin for more than seven days [36,39,41–43]. Some notable exceptions include osteomyelitis and endocarditis [37,38].

De-escalation is a sound antimicrobial strategy for several reasons, including reducing vancomycin duration and possibly the risk of nephrotoxicity. A retrospective study found that the de-escalation of anti-MRSA agents in culture-negative nosocomial pneumonia within the first four days of empiric therapy was associated with a lower rate of AKI (36% vs. 50%; difference, −13.8%; 95% CI −26.9 to −0.4) [46]. Rapid diagnostic tests may further assist with de-escalation due to their strong negative predictive value [47,48]. The use of MRSA polymerase chain reaction (PCR) testing shortened the duration of anti-MRSA coverage in a small retrospective study by approximately two days and was associated with decreased rates of AKI (26% vs. 3%; $p = 0.02$) [49].

5. Monitoring

5.1. Vancomycin Concentrations

The IDSA/Society for Healthcare Epidemiology of America (SHEA) antimicrobial stewardship guidelines provide a weak recommendation for the therapeutic drug monitoring of vancomycin based on low-quality evidence [50]. To date, only one randomized controlled trial has evaluated the impact of vancomycin therapeutic drug monitoring on the development of nephrotoxicity (serum creatinine increase of 0.5 mg/dL or more) [51]. This trial did observe that vancomycin therapeutic drug monitoring was independently inversely associated with nephrotoxicity (adjusted OR 0.04; 95% CI 0.01–0.30) in 70 patients with hematologic malignancies. However, the generalizability of this study is somewhat limited given the patient population and routine concomitant administration of amikacin (~80%) and amphotericin B (~30%).

The 2009 version of the vancomycin consensus guidelines recommended using 30–45 mg/kg/day based on total body weight to achieve vancomycin serum trough concentrations of 15–20 mg/L [4]. The authors stated that this approach should extrapolate to an area under the curve (AUC) of ~400 mg·h/L. There were several reports of increased nephrotoxicity associated with the implementation of these guideline recommendations. The vast majority of these reports discussed the increased risk of nephrotoxicity being associated with vancomycin trough concentrations (either 15 or 20 mg/L or greater). A meta-analysis of these studies documented that a vancomycin trough of 15 mg/L or greater was associated with nephrotoxicity (OR 2.67; 95% CI 1.95–3.65) [20]. However, the authors note that nephrotoxicity was reversible in the majority of cases and that short-term dialysis was only required in 3% of nephrotoxic episodes. A case series of nine patients found obstructive tubular casts containing vancomycin in the presence of elevated serum vancomycin concentrations [52]. Eight of the nine patients had serum vancomycin concentrations of at least 35 mg/L. The authors confirmed the clinical observations by administrating vancomycin to four mice. The vancomycin-containing casts also occurred in the mice in the presence of elevated vancomycin concentrations. Vancomycin therapy should be held for at least one dosing interval if the true vancomycin trough is greater than 25 mg/L.

There was more variance in AUC with trough-based monitoring than anticipated by the original guideline authors. Neely et al. evaluated three data sets through modeling and simulation to compare obtained trough values to AUC estimations. The simulation results suggest that an AUC/MIC ≥ 400 mg·h/L can be achieved with a trough <15 mg/L in 60% of patients [53]. A retrospective study by Ghosh et al. reported that 61% of patients achieving an AUC/MIC ≥ 400 mg·h/L had a vancomycin trough <15 mg/L [54]. A prospective trial of 252 patients found that 31% of patients with an AUC/MICs ≥ 400 mg·h/L had a trough concentration <10 mg/L and 68% had a trough concentration <15 mg/L [55]. Therefore, multiple studies have shown that AUC provides a better estimate of vancomycin exposure than a single trough concentration.

A recent meta-analysis of eight observational studies ($n = 2491$) suggested a cutpoint of 650 mg·h/L for the risk of vancomycin-associated nephrotoxicity. Patients with an AUC/MIC < 650 mg·h/L were less likely to develop nephrotoxicity whether the AUC was calculated in the first 24 h period (OR 0.36; 95% CI 0.23–0.56) or second 24 h period (OR 0.45; 95% CI 0.27–0.75) [56]. Using an AUC monitoring strategy was associated with significantly lower rates of nephrotoxicity than trough-guided monitoring

(OR 0.68; 95% CI 0.46–0.99). However, this finding is based on only two studies, with one retrospective study representing 90% of the total sample in the analysis.

The primary issue with all of these analyses is that they all fail to identify if increased vancomycin concentrations are the cause of nephrotoxicity or if they are increased as a result of nephrotoxicity. In addition, the reliance upon retrospective analyses and computer-generated cutpoints brings the stability of the values generated into question. The lack of randomized, controlled trials targeting different trough or AUC values is particularly concerning in that we may be continuously creating risk factors for nephrotoxicity that are never validated prospectively in a randomized trial.

5.2. Fluid Status

The European Society of Intensive Care Medicine issued strong recommendations (lower-level evidence) regarding the use of controlled fluid resuscitation with crystalloids and avoiding fluid overload to prevent the development of nephrotoxicity [57]. To our knowledge, no data exist assessing the association between hypovolemia and nephrotoxicity specifically related to vancomycin therapy. However, we believe continuous reassessment of volume status should take place throughout the course of treatment as part of the patient and drug monitoring process, as the detrimental effects of either hypovolemia or fluid overload have been reviewed elsewhere [58].

5.3. Reassessment of Nephrotoxicity Risk

We are unaware of literature that documents the clinical benefit of re-assessing the patient's risk of nephrotoxicity. However, we feel that this should be a routine part of clinical care, as it makes common sense that assessing for the risk of adverse events should be a continual process.

6. Diagnosis of AKI

More than 35 definitions of acute renal dysfunction have previously been identified in the literature [59]. The most commonly utilized definitions of vancomycin-associated nephrotoxicity are consistent with the Acute Kidney Injury Network (AKIN), Kidney Disease Improving Global Outcomes (KDIGO), and Risk, Injury, Failure, Loss, End stage renal disease (RIFLE) criteria but vary between studies [60–62]. The 2009 version of the vancomycin consensus guidelines defines vancomycin-induced nephrotoxicity based on an increase in serum creatinine of 0.5 mg/dL or a ≥50% increase from baseline [4]. Most of these definitions allow for classification based on serum creatinine or urine output as a surrogate for the diagnosis of kidney injury. The vast majority of studies evaluating vancomycin and nephrotoxicity have focused on serum creatinine changes due to their retrospective nature. Data regarding urine output has typically not been evaluated in these retrospective evaluations due to the lack of information regarding the urine volume and/or the accuracy of the data for timing and volume charted.

Clinicians have used serum creatinine as a diagnostic criterion for AKI for decades. This surrogate measure is plagued by several issues. The accuracy of serum creatinine in estimating renal function in patients with extremes of weight (e.g., anorexics, weight lifters) or decreased muscle mass (e.g., elderly, long-term spinal cord injury patients) may be less accurate, since creatinine is a product of muscle catabolism [63–65]. Additionally, the kinetics of creatinine often result in a delay between kidney injury and the subsequent rise in serum creatinine. This may lead to delays in recognition and diagnosis of nephrotoxicity [66].

Various medications have also been associated with increases in serum creatinine without changes to renal function. Similar to piperacillin-tazobactam, there are several agents including trimethoprim, cimetidine, pyrimethamine, and various antiretroviral agents that have been found to increase serum creatinine through inhibition of creatinine tubular secretion without decreasing glomerular filtration rate [67–71].

More sensitive urinary biomarkers have been evaluated recently as potential replacement(s) to serum creatine, given its issues in estimating glomerular filtration rate and/or diagnosing

AKI. These candidates to serve as next-generation biomarkers include urinary KIM-1, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), cystatin C, clusterin, fatty acid binding protein-liver type (L-FABP), and osteopontin [72]. Animal studies have suggested that KIM-1 and/or clusterin monitoring may identify nephrotoxicity in the setting of vancomycin exposure more quickly [73,74]. Continuous monitoring of renal function is also being explored as an alternative to conventional methods. The optimal molecule to facilitate the continuous monitoring has not been identified in the last ten years [75]. Additional research is needed to assess the feasibility and utility of these monitoring methods in clinical practice.

7. Prognosis of AKI

In general, patient outcomes after AKI are poorly described in current literature. The rate of in-hospital death associated with AKI ranges from 15–60% depending upon the patient population studied and the degree of renal impairment reached [76,77]. The presence of any KDIGO stage of AKI has been associated with death up to 10 years (OR 1.30; 95% CI 1.1–1.6) from being admitted to an intensive care unit (ICU) [78]. This effect was not observed when only patients who survived the first 28 days were evaluated (OR 1.26; 95% CI 1.0–1.6).

Nephrotoxicity in the setting of vancomycin therapy appears to be reversible in most cases. Jeffres and colleagues observed that 73% of patients with nephrotoxicity had reductions in serum creatinine levels to near baseline by hospital discharge [6]. A larger study found that 81% of cases of nephrotoxicity resolved [11]. A meta-analysis found that short-term dialysis was only required in 3% (6/192) of all patients who developed nephrotoxicity [20]. None of these patients required long-term dialysis. A retrospective study evaluating the timing of serum creatinine lowering in patients with AKI observed that serum creatinine remained 50% above baseline for a median duration of seven days (interquartile range (IQR0 3, 20 days) [10]. While vancomycin had higher rates of nephrotoxicity (18.2% vs. 8.4%) compared to linezolid in a randomized, controlled trial of patients with MRSA nosocomial pneumonia, its use was not associated with 60-day mortality (26.6% vs. 28.1%) [79].

8. Conclusions

Vancomycin remains a first-line agent for the treatment of MRSA infections despite different generations questioning its nephrotoxic potential. The lack of prospective randomized, controlled trials evaluating various vancomycin dosing strategies and/or combination empiric therapy regimens has left clinicians to depend on data from cohorts (primarily retrospective) to evaluate vancomycin's nephrotoxic potential. These gold standard trials could have a dramatic impact by informing which dosing strategies and vancomycin-based combinations are safest to use, particularly in patients at risk of nephrotoxicity.

Clinicians should not fear using vancomycin in the absence of these data. Patients who develop AKI while receiving vancomycin infrequently require acute renal replacement therapy and even fewer chronic therapy The short-term mortality increase associated with AKI may be an indicator of more acute illness, or it could even be a result of more aggressive/risky interventions being used in these patients. We would advise to evaluate the patient in addition to the serum creatinine instead of basing treatment decisions solely on laboratory values.

We are hopeful that the novel biomarkers for kidney injury will help clear the issues regarding the timing of renal injury and better elucidate the potential causes. Several medications can compete with creatinine via tubular secretion. This competition creates uncertainty regarding whether serum creatinine increases represent damage to the kidneys or not. The most frequent instance is piperacillin-tazobactam being prescribed along with vancomycin to provide empiric gram-negative and anaerobic coverage. Having a more accurate marker of kidney function could potentially help clinicians from unnecessarily avoiding this combination. In addition, some clinicians are choosing alternatives that may result in other safety issues in select patients (e.g., cefepime and neurotoxicity) [80].

Antimicrobial stewardship efforts can be conducted in the meantime to decrease the duration of combination empiric therapy. This approach has additional benefits outside of the AKI prevention.

We recognize that some clinicians may seek to avoid vancomycin in patients with multiple risk factors for nephrotoxicity. This makes common sense even though there are no data to validate this approach. One study that sought to evaluate the random assignment of other anti-MRSA agents versus vancomycin in patients at risk of nephrotoxicity failed to observe a difference between these approaches [81]. However, another study has shown improvements in clinical outcomes by avoiding nephrotoxins [82]. This is why we advocate using a patient-specific approach that evaluates the patient, severity of illness, and concomitant medications in order to make an informed decision that takes the specific patient's baseline (and ongoing) risk into account.

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References

1. Hazlewood, K.A.; Brouse, S.D.; Pitcher, W.D.; Hall, R.G. Vancomycin-associated nephrotoxicity: Grave concern or death by character assassination? *Am. J. Med.* **2010**, *123*, 182. [CrossRef]
2. Farber, B.F.; Moellering, R.C., Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob. Agents Chemother.* **1983**, *23*, 138–141. [CrossRef]
3. Downs, N.J.; Neihart, R.E.; Dolezal, J.M.; Hodges, G.R. Mild nephrotoxicity associated with vancomycin use. *Arch. Intern. Med.* **1989**, *149*, 1777–1781. [CrossRef]
4. Rybak, M.J.; Lomaestro, B.M.; Rotschafer, J.C.; Moellering, R.C.; Craig, W.A.; Billeter, M.; Dalovisio, J.R.; Levine, D.P. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin. Infect. Dis.* **2009**, *49*, 325–327. [CrossRef]
5. Baggs, J.; Fridkin, S.K.; Pollack, L.A.; Srinivasan, A.; Jernigan, J.A. Estimating national trends in inpatient antibiotic use among us hospitals from 2006 to 2012. *JAMA Intern. Med.* **2016**, *176*, 1639–1648. [CrossRef]
6. Jeffres, M.N.; Isakow, W.; Doherty, J.A.; Micek, S.T.; Kollef, M.H. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. *Clin. Ther.* **2007**, *29*, 1107–1115. [CrossRef]
7. Davies, S.W.; Guidry, C.A.; Petroze, R.T.; Hranjec, T.; Sawyer, R.G. Vancomycin and nephrotoxicity; just another myth? *J. Trauma Acute Care Surg.* **2013**, *75*, 830–835. [CrossRef]
8. Hall, R.G., II; Hazlewood, K.A.; Brouse, S.D.; Giuliano, C.A.; Haase, K.K.; Frei, C.R.; Forcade, N.A.; Bell, T.; Bedimo, R.J.; Alvarez, C.A. Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant Staphylococcus aureus bacteremia: A retrospective cohort study. *BMC Pharmacol. Toxicol.* **2013**, *14*, 1–6. [CrossRef]
9. Lodise, T.P.; Lomaestro, B.; Graves, L.; Drusano, G.L. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob. Agents Chemother.* **2008**, *52*, 1330–1336. [CrossRef]
10. Lodise, T.P.; Patel, N.; Lomaestro, B.M.; Rodvold, K.A.; Drusano, G.L. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin. Infect. Dis.* **2009**, *49*, 507–514. [CrossRef]
11. Pritchard, L.; Baker, C.; Leggett, J.; Sehdev, P.; Brown, A.; Bayley, K.B. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. *Am. J. Med.* **2010**, *123*, 1143–1149. [CrossRef] [PubMed]
12. Hall, R.G., II; Yoo, E.; Faust, A.; Smith, T.; Goodman, E.; Mortensen, E.M.; Felder, V.; Alvarez, C.A. Impact of total body weight on acute kidney injury in patients with gram-negative bacteremia. *Expert Rev. Clin. Pharmacol.* **2018**, *11*, 651–654. [CrossRef]
13. Hall, R.G., II; Yoo, E.; Faust, A.; Smith, T.; Goodman, E.; Mortensen, E.M.; Raza, J.; Dehmami, F.; Alvarez, C.A. Impact of piperacillin/tazobactam on nephrotoxicity in patients with Gram-negative bacteraemia. *Int. J. Antimicrob. Agents* **2019**, *53*, 343–346. [CrossRef] [PubMed]

14. Rutter, W.C.; Burgess, D.R.; Talbert, J.C.; Burgess, D.S. Acute kidney injury in patients treated with vancomycin and piperacillin-tazobactam: A retrospective cohort analysis. *J. Hosp. Med.* **2017**, *12*, 77–82. [CrossRef]
15. Minejima, E.; Choi, J.; Beringer, P.; Lou, M.; Tse, E.; Wong-Beringer, A. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. *Antimicrob. Agents Chemother.* **2011**, *55*, 3278–3283. [CrossRef]
16. Mullins, B.P.; Kramer, C.J.; Bartel, B.J.; Catlin, J.S.; Gilder, R.E. Comparison of the nephrotoxicity of vancomycin in combination with cefepime, meropenem, or piperacillin/tazobactam: A prospective, multicenter study. *Ann. Pharmacother.* **2018**, *52*, 639–644. [CrossRef] [PubMed]
17. Bosso, J.A.; Nappi, J.; Rudisill, C.; Wellein, M.; Bookstaver, P.B.; Swindler, J.; Mauldin, P.D. Relationship between vancomycin trough concentrations and nephrotoxicity: A prospective multicenter trial. *Antimicrob. Agents Chemother.* **2011**, *55*, 5475–5479. [CrossRef] [PubMed]
18. Horey, A.; Mergenhagen, K.A.; Mattappallil, A. The relationship of nephrotoxicity to vancomycin trough serum concentrations in a veteran's population: A retrospective analysis. *Ann. Pharmacother.* **2012**, *46*, 1477–1483. [CrossRef]
19. Meaney, C.J.; Hynicka, L.M.; Tsoukleris, M.G. Vancomycin-associated nephrotoxicity in adult medicine patients: Incidence, outcomes, and risk factors. *Pharmacotherapy* **2014**, *34*, 653–661. [CrossRef]
20. van Hal, S.J.; Paterson, D.L.; Lodise, T.P. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob. Agents Chemother.* **2013**, *57*, 734–744. [CrossRef] [PubMed]
21. Mingeot-Leclercq, M.P.; Tulkens, P.M. Aminoglycosides: Nephrotoxicity. *Antimicrob. Agents Chemother.* **1999**, *43*, 1003–1012. [CrossRef]
22. Fanos, V.; Cataldi, L. Amphotericin B-induced nephrotoxicity: A review. *J. Chemother.* **2000**, *12*, 463–470. [CrossRef] [PubMed]
23. Hidayat, L.K.; Hsu, D.I.; Quist, R.; Shriner, K.A.; Wong-Beringer, A. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: Efficacy and toxicity. *Arch. Intern. Med.* **2006**, *166*, 2138–2144. [CrossRef] [PubMed]
24. Hanrahan, T.P.; Kotapati, C.; Roberts, M.J.; Rowland, J.; Lipman, J.; Roberts, J.A.; Udy, A. Factors associated with vancomycin nephrotoxicity in the critically ill. *Anaesth. Intensive Care* **2015**, *43*, 594–599. [CrossRef]
25. Rutter, W.C.; Cox, J.N.; Martin, C.A.; Burgess, D.R.; Burgess, D.S. Nephrotoxicity during vancomycin therapy in combination with piperacillin-tazobactam or cefepime. *Antimicrob. Agents Chemother.* **2017**, *62*, e02089-16. [CrossRef] [PubMed]
26. Hammond, D.A.; Smith, M.N.; Li, C.; Hayes, S.M.; Lusardi, K.; Bookstaver, P.B. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. *Clin. Infect. Dis.* **2017**, *64*, 666–674. [CrossRef]
27. Luther, M.K.; Timbrook, T.T.; Caffrey, A.R.; Dosa, D.; Lodise, T.P.; LePlant, K.L. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: A systematic review and meta-analysis. *Crit. Care Med.* **2018**, *46*, 12–20. [CrossRef] [PubMed]
28. Carreno, J.; Smiraglia, T.; Hunter, C.; Tobin, E.; Lomaestro, B. Comparative incidence and excess risk of acute kidney injury in hospitalised patients receiving vancomycin and piperacillin/tazobactam in combination or as monotherapy. *Int. J. Antimicrob. Agents* **2018**, *52*, 643–650. [CrossRef]
29. Hammond, D.A.; Smith, M.N.; Painter, J.T.; Meena, N.K.; Lusardi, K. Comparative incidence of acute kidney injury in critically ill patients receiving vancomycin with concomitant piperacillin-tazobactam or cefepime: A retrospective cohort study. *Pharmacotherapy* **2016**, *36*, 463–571. [CrossRef]
30. Buckley, M.S.; Hartsock, N.C.; Berry, A.J.; Bikin, D.S.; Richards, E.C.; Yerondopoulos, M.J.; Kobic, E.; Wicks, L.M.; Hammond, D.A. Comparison of acute kidney injury risk associated with vancomycin and concomitant piperacillin/tazobactam or cefepime in the intensive care unit. *J. Crit. Care* **2018**, *48*, 32–38. [CrossRef]
31. Schreier, D.J.; Kashani, K.B.; Sakhuja, A.; Mara, K.C.; Toottooni, M.S.; Personett, M.S.; Nelson, S.; Rule, A.D.; Steckelberg, J.M.; Tande, A.J.; et al. Incidence of acute kidney injury among critically ill patients with brief empiric use of antipseudomonal β-lactams with vancomycin. *Clin. Infect. Dis.* **2018**. Epub ahead of print. [CrossRef] [PubMed]
32. Rutter, W.C.; Burgess, D.S. Acute kidney injury in patients treated with iv beta-lactam/beta-lactamase inhibitor combinations. *Pharmacotherapy* **2017**, *37*, 593–598. [CrossRef] [PubMed]

33. Choudhury, D.; Ahmed, Z. Drug-associated renal dysfunction and injury. *Nat. Clin. Pract. Nephrol.* **2006**, *2*, 80–91. [CrossRef] [PubMed]
34. Pais, G.M.; Liu, J.; Avedissian, S.N.; Xanthos, T.; Chalkias, A.; d'Aloja, E.; Locci, E.; Gilchrist, A.; Prozialeck, W.C.; Rhodes, N.J.; et al. Urinary Biomarker and Histopathological Evaluation of Vancomycin and Piperacillin Tazobactam Nephrotoxicity in Comparison with Vancomycin in a Rat Model and a Confirmatory Cellular Model. *bioRxiv* **2019**. Epub ahead of print. [CrossRef]
35. Dellit, T.H.; Owens, R.C.; McGowan, J.E., Jr.; Gerding, D.N.; Weinstein, R.A.; Burke, J.P.; Huskins, W.C.; Paterson, D.L.; Fishman, N.O.; Carpenter, C.F.; et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin. Infect. Dis.* **2007**, *44*, 159–177. [CrossRef]
36. Stevens, D.L.; Bisno, A.L.; Chambers, H.F.; Dellinger, E.P.; Goldstein, E.J.; Gorbach, S.L.; Hirschmann, J.V.; Kaplan, S.L.; Montoya, J.G.; Wade, J.C. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* **2014**, *59*, e10–e52. [CrossRef] [PubMed]
37. Lipsky, B.A.; Berendt, A.R.; Cornia, P.B.; Pile, J.C.; Peters, E.J.; Armstrong, D.G.; Deery, H.G.; Embil, J.M.; Joseph, W.S.; Karchmer, A.W.; et al. 2012 infectious diseases society of america clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *J. Am. Podiatr. Med. Assoc.* **2013**, *103*, 2–7. [CrossRef]
38. Baddour, L.M.; Wilson, W.R.; Bayer, A.S.; Fowler, V.G., Jr.; Tleyjeh, I.M.; Rybak, M.J.; Barsic, B.; Lockhart, P.B.; Gewitz, M.H.; Levison, M.E.; et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. *Circulation* **2015**, *132*, 1435–1486. [CrossRef] [PubMed]
39. Freifeld, A.G.; Bow, E.J.; Sepkowitz, K.A.; Boeckh, M.J.; Ito, J.I.; Mullen, C.A.; Raad, I.I.; Rolston, K.V.; Young, J.A.; Wingard, J.R. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* **2011**, *52*, 56–93. [CrossRef] [PubMed]
40. Tunkel, A.R.; Hartman, B.J.; Kaplan, S.L.; Kaufman, B.A.; Roos, K.L.; Scheld, W.M.; Whitley, R.J. Practice guidelines for the management of bacterial meningitis. *Clin. Infect. Dis.* **2004**, *39*, 1267–1284. [CrossRef]
41. Mandell, L.A.; Wunderink, R.G.; Anzueto, A.; Bartlett, J.G.; Campbell, G.D.; Dean, N.C.; Dowell, S.F.; File, T.M., Jr.; Musher, D.M.; Niederman, M.S.; et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin. Infect. Dis.* **2007**, *44* (Suppl. 2), 27–72. [CrossRef] [PubMed]
42. Kalil, A.C.; Metersky, M.L.; Klompas, M.; Muscedere, J.; Sweeney, D.A.; Palmer, L.B.; Napolitano, L.M.; O'Grady, N.P.; Bartlett, J.G.; Carratalà, J.; et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin. Infect. Dis.* **2016**, *63*, 61–111. [CrossRef] [PubMed]
43. Bratzler, D.W.; Dellinger, E.P.; Olsen, K.M.; Perl, T.M.; Auwaerter, P.G.; Bolon, M.K.; Fish, D.N.; Napolitano, L.M.; Sawyer, R.G.; Slain, D.; et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg. Infect. (Larchmt)* **2013**, *14*, 73–156. [CrossRef] [PubMed]
44. Iversen, K.; Ihlemann, N.; Gill, S.U.; Madsen, T.; Elming, H.; Jensen, K.T.; Bruun, N.E.; Høfsten, D.E.; Fursted, K.; Christensen, J.J.; et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N. Engl. J. Med.* **2019**, *380*, 415–424. [CrossRef] [PubMed]
45. Li, H.K.; Rombach, I.; Zambellas, R.; Walker, A.S.; McNally, M.A.; Atkins, B.L.; Lipsky, B.A.; Hughes, H.C.; Bose, D.; Kümin, M.; et al. Oral versus intravenous antibiotics for bone and joint infection. *N. Engl. J. Med.* **2019**, *380*, 425–436. [CrossRef] [PubMed]
46. Cowley, M.C.; Ritchie, D.J.; Hampton, N.; Kollef, M.H.; Micek, S.T. Outcomes associated with de-escalating therapy for methicillin-resistant Staphylococcus aureus in culture-negative nosocomial pneumonia. *Chest* **2019**, *155*, 53–59. [CrossRef]
47. Dangerfield, B.; Chung, A.; Webb, B.; Seville, M.T. Predictive value of methicillin-resistant Staphylococcus aureus (MRSA) nasal swab PCR assay for MRSA pneumonia. *Antimicrob. Agents Chemother.* **2014**, *58*, 859–864. [CrossRef]
48. Parente, D.M.; Cunha, C.B.; Mylonakis, E.; Timbrook, T.T. The clinical utility of methicillin-resistant Staphylococcus aureus (MRSA) nasal screening to rule out MRSA pneumonia: A diagnostic meta-analysis with antimicrobial stewardship implications. *Clin. Infect. Dis.* **2018**, *67*, 1–7. [CrossRef] [PubMed]

49. Baby, N.; Faust, A.C.; Smith, T.; Sheperd, L.A.; Knoll, L.; Goodman, E.L. Nasal methicillin-resistant Staphylococcus aureus (MRSA) PCR testing reduces the duration of MRSA-targeted therapy in patients with suspected MRSA pneumonia. *Antimicrob. Agents Chemother.* **2017**, *61*, e02432-16. [CrossRef]
50. Barlam, T.F.; Cosgrove, S.E.; Abbo, L.M.; MacDougall, C.; Schuetz, A.N.; Septimus, E.J.; Srinivasan, A.; Dellit, T.H.; Falck-Ytter, Y.T.; Fishman, N.O.; et al. Implementing an antibiotic stewardship program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin. Infect. Dis.* **2016**, *62*, 51–77. [CrossRef]
51. Fernández de Gatta, M.D.; Calvo, M.V.; Hernández, J.M.; Caballero, D.; San Miguel, J.F.; Domínguez-Gil, A. Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies. *Clin. Pharmacol. Ther.* **1996**, *60*, 332–340. [PubMed]
52. Luque, Y.; Louis, K.; Jouanneau, C.; Placier, S.; Esteve, E.; Bazin, D.; Rondeau, E.; Letavernier, E.; Wolfromm, A.; Gosset, C.; et al. Vancomycin-Associated Cast Nephropathy. *J. Am. Soc. Nephrol.* **2017**, *28*, 1723–1728. [CrossRef]
53. Neely, M.N.; Youn, G.; Jones, B.; Jelliffe, R.W.; Drusano, G.L.; Rodvold, K.A.; Lodise, T.P. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob. Agents. Chemother.* **2014**, *58*, 309–316. [CrossRef]
54. Ghosh, N.; Chavada, R.; Maley, M.; van Hal, S.J. Impact of source of infection and vancomycin $AUC_{0\text{-}24}/MIC_{BMD}$ targets on treatment failure in patients with methicillin-resistant Staphylococcus aureus bacteraemia. *Clin. Microbiol. Infect.* **2014**, *20*, 1098–1105. [CrossRef] [PubMed]
55. Neely, M.N.; Kato, L.; Youn, G.; Kraler, L.; Bayard, D.; van Guilder, M.; Schumitzky, A.; Yamada, W.; Jones, B.; Minejima, E. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. *Antimicrob. Agents Chemother.* **2018**, *62*, e02042-17. [CrossRef] [PubMed]
56. Aljefri, D.M.; Avedissian, S.N.; Rhodes, N.J.; Postelnick, M.J.; Nguyen, K.; Scheetz, M.H. Vancomycin Area under the Curve and Acute Kidney Injury: A Meta-analysis. *Clin. Infect. Dis.* **2019**. Epub ahead of print. [CrossRef] [PubMed]
57. Joannidis, M.; Druml, W.; Forni, L.G.; Groeneveld, A.B.J.; Honore, P.M.; Hoste, E.; Ostermann, M.; Oudemans-van Straaten, H.M.; Schetz, M. Prevention of acute kidney injury and protection of renal function in the intensive care unit: Update 2017: Expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine. *Intensive Care Med.* **2017**, *43*, 730–749. [CrossRef]
58. Ostermann, M.; Straaten, H.M.; Forni, L.G. Fluid overload and acute kidney injury: Cause or consequence? *Crit. Care* **2015**, *19*, 443. [CrossRef]
59. Kellum, J.A.; Levin, N.; Bouman, C.; Lameire, N. Developing a consensus classification system for acute renal failure. *Curr. Opin. Crit. Care* **2002**, *8*, 509–514. [CrossRef]
60. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L.; Palevsky, P.; Acute Dialysis Quality Initiative workgroup. Acute renal failure—Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, 204–212. [CrossRef]
61. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute Kidney Injury Network. cute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef]
62. Kidney Disease: Improving Global Outcomes (KDIGO); Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int. Suppl.* **2012**, *2*. [CrossRef]
63. Perrone, R.D.; Madias, N.E.; Levey, A.S. Serum creatinine as an index of renal function: New insights into old concepts. *Clin. Chem.* **1992**, *38*, 1933–1953.
64. Spencer, K. Analytical reviews in clinical biochemistry: The estimation of creatinine. *Ann. Clin. Biochem.* **1986**, *23*, 1–25. [CrossRef]
65. Heymsfield, S.B.; Arteaga, C.; McManus, C.; Smith, J.; Moffitt, S. Measurement of muscle mass in humans: Validity of the 24-hour urinary creatinine method. *Am. J. Clin. Nutr.* **1983**, *37*, 478–494. [CrossRef] [PubMed]
66. Waikar, S.S.; Bonventre, J.V. Creatinine kinetics and the definition of acute kidney injury. *Am. Soc. Nephrol.* **2009**, *20*, 672–679. [CrossRef]
67. Delanaye, P.; Mariat, C.; Cavalier, E.; Maillard, N.; Krzesinski, J.M.; White, C.A. Trimethoprim, creatinine and creatinine-based equations. *Nephron Clin. Pract.* **2011**, *119*, 187–194. [CrossRef]

68. van Acker, B.A.; Koomen, G.C.; Koopman, M.G.; de Waart, D.R.; Arisz, L. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* **1992**, *340*, 1326–1329. [CrossRef]
69. Opravil, M.; Keusch, G.; Luthy, R. Pyrimethamine inhibits renal secretion of creatinine. *Antimicrob. Agents Chemother.* **1993**, *37*, 1056–1060. [CrossRef]
70. German, P.; Liu, H.C.; Szwarcberg, J.; Hepner, M.; Andrews, J.; Kearney, B.P.; Mathias, A. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J. Acquir. Immune Defic. Syndr.* **2012**, *61*, 32–40. [CrossRef]
71. Maggi, P.; Montinaro, V.; Mussini, C.; Di Biagio, A.; Bellagamba, R.; Bonfanti, P.; Calza, L.; Cherubini, C.; Corsi, P.; Gargiulo, M.; et al. Novel antiretroviral drugs and renal function monitoring of HIV patients. *AIDS Rev.* **2014**, *16*, 144–151.
72. Bonventre, J.V.; Vaidya, V.S.; Schmouder, R.; Feig, P.; Dieterie, F. Next-generation biomarkers for detecting kidney toxicity. *Nat. Biotechnol.* **2010**, *28*, 436–440. [CrossRef]
73. O'Donnell, J.N.; Rhodes, N.J.; Lodise, T.P.; Prozialeck, W.C.; Miglis, C.M.; Joshi, M.D.; Venkatesan, N.; Pais, G.; Cluff, C.; Lamar, P.C.; et al. 24-Hour pharmacokinetic relationships for vancomycin and novel urinary biomarkers of acute kidney injury. *Antimicrob. Agents Chemother.* **2017**, *61*, e00416-17. [CrossRef]
74. Pais, G.M.; Avedissian, S.N.; O'Donnell, J.N.; Rhodes, N.J.; Lodise, T.P.; Prozialeck, W.C.; Lamar, P.C.; Cluff, C.; Gulati, A.; Fitzgerald, J.C.; et al. Comparative performance of urinary biomarkers for vancomycin induced kidney injury according to timeline of injury. *Antimicrob. Agents Chemother.* **2019**. Epub ahead of print. [CrossRef] [PubMed]
75. Dorshow, R.B.; Asmelash, B.; Chinen, L.K.; Debreczeny, M.P.; Fitch, R.M.; Freskos, J.K.; Galen, K.P.; Gaston, K.R.; Marzan, T.A.; Poreddy, A.R.; et al. *New Optical Probes for the Continuous Monitoring of Renal Function*; Proceedings of SPIE; SPIE: Bellingham, WA, USA, 2008; Volume 6867, pp. 1–11.
76. Uchino, S.; Kellum, J.A.; Bellomo, R.; Doig, G.S.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; et al. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* **2005**, *294*, 813–818. [CrossRef]
77. Xue, J.L.; Daniels, F.; Star, R.A.; Kimmel, P.L.; Eggers, P.W.; Molitoris, B.A.; Himmelfarb., J.; Collins, A.J. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J. Am. Soc. Nephrol.* **2006**, *17*, 1135–1142. [CrossRef] [PubMed]
78. Linder, A.; Fjell, C.; Levin, A.; Walley, K.R.; Russell, J.A.; Boyd, J.H. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. *Am. J. Respir. Crit. Care Med.* **2014**, *189*, 1075–1081. [CrossRef]
79. Chavanet, P. The ZEPHyR study: A randomized comparison of linezolid and vancomycin for MRSA pneumonia. *Med. Mal. Infect.* **2013**, *43*, 451–455. [CrossRef]
80. Payne, L.E.; Gagnon, D.J.; Riker, R.R.; Seder, D.B.; Glisic, E.K.; Morris, J.G.; Fraser, G.L. Cefepime-induced neurotoxicity: A systematic review. *Crit. Care* **2017**, *21*, 276. [CrossRef]
81. Carreno, J.J.; Kenney, R.M.; Divine, G.; Vazquez, J.A.; Davis, S. Randomized controlled trial to determine the efficacy of early switch from vancomycin to vancomycin alternatives as a strategy to prevent nephrotoxicity in patients with multiple risk factors for adverse renal outcomes (STOP-NT). *Ann. Pharmacother.* **2017**, *51*, 185–193. [CrossRef]
82. Meersch, M.; Schmidt, C.; Hoffmeier, A.; Van Aken, H.; Wempe, C.; Gerss, J.; Zarbock, A. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: The PrevAKI randomized controlled trial. *Intensive Care Med.* **2017**, *43*, 1551–1561. [CrossRef] [PubMed]

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Risk of Incident Non-Valvular Atrial Fibrillation after Dialysis-Requiring Acute Kidney Injury

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Abstract: The influence of acute kidney injury (AKI) on subsequent incident atrial fibrillation (AF) has not yet been fully addressed. This retrospective nationwide cohort study was conducted using Taiwan's National Health Insurance Research Database from 1 January 2000 to 31 December 2010. A total of 41,463 patients without a previous AF, mitral valve disease, and hyperthyroidism who developed de novo dialysis-requiring AKI (AKI-D) during their index hospitalization were enrolled. After propensity score matching, "non-recovery group" (n = 2895), "AKI-recovery group" (n = 2895) and "non-AKI group" (control group, n = 5790) were categorized. Within a follow-up period of 6.52 $\pm$ 3.88 years (median, 6.87 years), we found that the adjusted risks for subsequent incident AF were increased in both AKI-recovery group (adjusted hazard ratio (aHR) = 1.30; 95% confidence intervals (CI), 1.07–1.58; $p \leq 0.01$) and non-recovery group (aHR = 1.62; 95% CI, 1.36–1.94) compared to the non-AKI group. Furthermore, the development of AF carried elevated risks for major adverse cardiac events (aHR = 2.11; 95% CI, 1.83–2.43), ischemic stroke (aHR = 1.33; 95% CI, 1.19–1.49), and all stroke (aHR = 1.28; 95% CI, 1.15–1.43). (all $p \leq 0.001$, except otherwise expressed) The authors concluded that AKI-D, even in those who withdrew from temporary dialysis, independently increases the subsequent risk of de novo AF.

Keywords: acute kidney injury; adverse cardiovascular events; atrial fibrillation; dialysis

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an increasing trend of prevalence following widespread population aging [1]. It is estimated that AF currently affects around 2.3 million adults in the United States, and the number of affected people is projected to increase to 5.6–15.9 million by 2050 [1]. AF has a significant effect on cardiovascular events including stroke, peripheral embolization, and associated morbidities and mortalities [1]. The existence of AF is independently associated with the risk of the development and severity of acute kidney injury (AKI) in both surgical and medical settings [2].

Recent studies suggest that AKI episodes are associated with a higher risk of developing cardiovascular events and overall mortality [3–5]. Nevertheless, the influence of AKI on subsequent incident AF has not been fully addressed in previous research. Most investigations only evaluate the concurrent occurrence of AKI and AF in a limited number of patients undergoing cardiac surgeries within a relatively short follow-up period [6,7]. In these studies, the development of postoperative AKI was found as an independent factor associated with the new-onset postoperative AF [6,7]. In line with these interpretations, new-onset AF after AKI in a nationwide survey for an extended followed-up period is necessary [7–10]. In particular, the National Institute for Health and Clinical Excellence (NICE) guideline raises an ultimate critical point: if the development of AF occurs, the assessment to evaluate the risk of having a stroke is necessary. However, little information is available regarding cardiovascular events and outcomes after new-onset AF in this subset.

A proper understanding of the risk factors associated with kidney disease and AF development may allow primary care physicians to initiate preventive strategies and thereby potentially decrease the risk of AF. Thus, we conducted this study aiming to test the hypothesis that the occurrence of dialysis-requiring AKI (AKI-D), as well as the "recovery pattern" of the AKI, would increase the subsequent risk of subsequent AF and result in worse cardiovascular injury.

2. Materials and Methods

2.1. Data Source

This retrospective population-based cohort study was conducted using the data of Taiwan's National Health Insurance Research Database (NHIRD) in the period from 1 January 2000 to 3 December 2010. The NHIRD is an encrypted database released by the National Health Research Institutes (NHRI) for research purposes. The NHIRD includes all information on outpatient visits, hospital admissions, prescriptions, interventional procedures, disease profiles, and vital status of the National Health Insurance (NHI) program which provides comprehensive medical care covering more than 99% of the country's population of 23 million people. The baseline comorbidities were identified from at least three outpatient visits or one inpatient claim within one year preceding the index hospitalization with the first dialysis. This identification method has been well validated with adequate predictive power [3]. The Charlson Comorbidity Index (CCI) was calculated by weighting baseline comorbidities.

For confidentiality purposes, identification numbers were encrypted before being released for research, but the uniqueness of the encrypted identification is retained to ensure valid internal linkage. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the institutional review board of the National Taiwan University Hospital (201212021RINC), and informed consent was waived since all personal data were de-identified in the database to protect privacy.

2.2. Study Cohort and Design

This study included patients aged 18 to 100 years without a history of AF, mitral valve disease, and hyperthyroidism for at least one year preceding study enrollment, and who developed de novo AKI-D during their index hospitalization and survived to at least 30 days after discharge.

Disease diagnoses were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). AKI-D was defined by ICD-9 codes for AKI (584.3, 634.3, 635.3, 636.3, 637.3, 638.3, 639.3, 669.3, or 958.5) along with procedure codes for acute dialysis. CKD was defined by ICD-9 codes for CKD (580, 580.x, 584.x, 586, 399.5). Advanced CKD was defined as CKD patients with concomitant erythropoiesis-stimulating agents [3]. The diagnosis accuracy of AKI and chronic kidney disease (CKD) by ICD-9-CM, as well as the definition of advanced CKD, were detailed in Supplementary File 1.

Renal function recovery was defined by withdrawal from dialysis before the 31st day after discharge. The patients who had successfully withdrawn from dialysis within hospitalization or within the 30-day period after hospital discharge were categorized into "AKI-recovery" group, while those had not withdrawn from dialysis within the 30-day period were categorized in "non-recovery" group. In an attempt to make a less biased comparison, we further constructed a control group which contained patients without AKI and who survived to discharge from the remaining hospitalized patients (non-AKI group).

2.3. Research Variables

The demographic data including age, gender, monthly income, hospital levels, baseline comorbidities, CHA2DS2-VASc scores before discharge, the frequency of outpatient visits and medications within one year following discharge, and the patients' outcomes were identified and analyzed.

2.4. Outcome Variables

Our primary outcome was de novo AF development (ICD-9-CM code 427.31) after hospital discharge. To ensure the accuracy of the AF identification, the diagnosis of AF needed to be confirmed by a doctor, or doctors, and recorded in the diagnosis list of the chart more than twice in outpatient visits, or recorded in the discharge diagnosis list more than once in an inpatient setting. The diagnostic accuracy of AF based on the ICD-9-CM codes has been previously validated [11–13]. The secondary outcomes included major adverse cardiac event (MACE), ischemic stroke (ICD-9-CM code 433.x, 434.x, or 436), and hemorrhage stroke (ICD-9-CM code 431 or 432). MACE was defined as coronary artery disease-related death, nonfatal myocardial infarction, angina, and revascularizations.

We evaluated the influences of AKI-D on the risk of subsequent incident AF in the whole study population as well as in different subgroups. Furthermore, besides testing the association between AKI-D and these outcomes, we also evaluated the association between AF and the above-mentioned secondary outcomes. All enrolled patients were followed from the date of index hospital discharge to the first diagnosed outcomes and were censored at death unrelated to coronary artery disease, or at the end of the study (31 December 2010).

2.5. Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). A two-sided p-value of ≤ 0.05 was considered statistically significant. Continuous variables were presented as the mean $\pm$ standard deviation (SD), and categorical variables were described as counts (percentages). The propensity scores were determined by multivariate logistic regression analysis. The Cox proportional hazard model was applied to examine the effect of non-recovery and AKI-recovery groups on subsequent AF development, as well as the influence of AF on other major adverse events. Because withdrawal from dialysis is likely to adhere to the condition of acute kidney disease, advanced CKD was identified to be a time-varying covariate [3,14].

By using the propensity score matching method, we proposed three matched groups (non-recovery group: AKI-recovery group: non-AKI group) on a 1:1:2 ratio. The propensity scores, containing the baseline characteristics and risk factors listed in Table 1, were calculated by multivariate logistic regression.

Table 1. Comparisons of the baseline characteristics among the three groups.

Variables	Before Matching n = 20,540				After Matching n = 11,680			
	Non-Recovery n = 4807	AKI-Recovery n = 5283	Non-AKI n = 10,450	p	Non-Recovery n = 2895	AKI-Recovery n = 2895	Non-AKI n = 5790	p
Age, years	59.7 ± 15.2	60.3 ± 17.7	59.8 ± 16.1	<0.001	59.6 ± 15.7	60.2 ± 17.2	60.6 ± 15.7	0.01
Gender, men	2390 (49.7%)	3172 (60.0%)	5540 (53.0%)	<0.001	1542 (53.3%)	1535 (53.0%)	3178 (54.9%)	0.68
Monthly income, NTD				<0.001				0.21
<19,100	1700 (35.4%)	2103 (39.8%)	3649 (34.9%)		1064 (36.8%)	1099 (38.0%)	2203 (38.1%)	
19,100–41,999	2449 (51.0%)	2434 (46.1%)	5285 (50.6%)		1443 (49.8%)	1378 (47.6%)	2925 (50.5%)	
≥42,000	658 (13.7%)	746 (14.1%)	1516 (14.5%)		388 (13.4%)	418 (14.4%)	762 (13.2%)	
Hospital level *				<0.001				<0.001
Level 1	1916 (39.9%)	2648 (50.1%)	4046 (38.7%)		1218 (42.1%)	1184 (40.9%)	2641 (45.6%)	
Level 2	2092 (43.5%)	2158 (40.84%)	3972 (38.0%)		1249 (43.1%)	1340 (46.3%)	2282 (39.4%)	
Levels 3 + 4	799 (16.6%)	477 (9.0%)	2,432 (23.3%)		428 (14.8%)	371 (12.8%)	967 (16.7%)	
Baseline Comorbidities								
CCI	2.8 ± 1.6	2.1 ± 1.5	2.4 ± 1.6	<0.001	2.4 ± 1.6	2.4 ± 1.6	2.4 ± 1.6	0.29
Myocardial infarction	22 (0.5%)	27 (0.5%)	37 (0.4%)	0.31	12 (0.4%)	10 (0.4%)	22 (0.4%)	0.91
Congestive heart failure	287 (6.0%)	215 (4.1%)	457 (4.4%)	<0.001	131 (4.5%)	136 (4.7%)	279 (4.8%)	0.91
Peripheral vascular disease	26 (0.5%)	34 (0.6%)	54 (0.5%)	0.59	13 (0.5%)	17 (0.6%)	39 (0.7%)	0.47
Cerebrovascular disease	284 (5.9%)	335 (6.3%)	629 (6.0%)	0.62	175 (6.0%)	173 (6.0%)	345 (6.0%)	0.94
Dementia	24 (0.5%)	74 (1.4%)	68 (0.7%)	<0.001	20 (0.7%)	19 (0.7%)	35 (0.6%)	0.85
COPD	333 (6.9%)	362 (6.9%)	640 (6.1%)	0.08	179 (6.2%)	209 (7.2%)	414 (7.2%)	0.23
Rheumatologic disease	47 (1.0%)	61 (1.2%)	103 (1.0%)	0.57	30 (1.0%)	28 (1.0%)	69 (1.2%)	0.66
Peptic ulcer disease	403 (8.4%)	350 (6.6%)	691 (6.6%)	<0.001	205 (7.1%)	207 (7.2%)	450 (7.8%)	0.55
Hemiplegia or paraplegia	10 (0.2%)	20 (0.4%)	25 (0.2%)	0.18	8 (0.3%)	9 (0.3%)	13 (0.2%)	0.71
CKD	2396 (49.8%)	1063 (20.1%)	3225 (30.9%)	<0.001	1005 (34.7%)	932 (32.2%)	1910 (33.0%)	0.06
Liver disease [a]	178 (3.7%)	204 (3.9%)	355 (3.4%)	0.30	96 (3.3%)	99 (3.4%)	192 (3.3%)	0.93
Tumor	86 (1.8%)	137 (2.6%)	195 (1.9%)	0.004	62 (2.1%)	56 (1.9%)	113 (2.0%)	0.77
Diabetes	1254 (26.1%)	1186 (22.5%)	2653 (25.4%)	<0.001	687 (23.7%)	708 (24.5%)	1504 (26.0%)	0.16

Table 1. *Cont.*

Variables	Before Matching n = 20,540				After Matching n = 11,680			
	Non-Recovery n = 4807	AKI-Recovery n = 5283	Non-AKI n = 10,450	p	Non-Recovery n = 2895	AKI-Recovery n = 2895	Non-AKI n = 5790	p
CHA2DS2-VASc †				<0.001				<0.001
0	211 (4.4%)	706 (13.4%)	1018 (9.7%)		204 (7.1%)	200 (6.9%)	400 (6.9%)	
1	890 (18.5%)	996 (18.9%)	1979 (18.9%)		636 (22.0%)	631 (21.8%)	1125 (19.4%)	
2	1268 (26.4%)	976 (18.5%)	1908 (18.3%)		834 (28.8%)	613 (21.2%)	1144 (19.8%)	
3	885 (18.4%)	858 (16.2%)	1896 (18.1%)		534 (18.5%)	505 (17.4%)	1124 (19.4%)	
4	706 (14.7%)	683 (12.9%)	1462 (14.0%)		438 (15.1%)	410 (14.2%)	894 (15.4%)	
5	456 (9.5%)	483 (9.1%)	1123 (10.8%)		279 (9.6%)	307 (10.6%)	691 (11.9%)	
6	245 (5.1%)	350 (6.6%)	660 (6.3%)		194 (6.7%)	158 (5.5%)	306 (5.3%)	
7	120 (2.5%)	174 (3.3%)	296 (2.8%)		98 (3.4%)	91 (3.1%)	155 (2.7%)	
8	24 (0.5%)	50 (1.0%)	99 (1.0%)		23 (0.8%)	27 (0.9%)	45 (0.8%)	
9	2 (0.04%)	7 (0.1%)	9 (0.1%)		2 (0.1%)	3 (0.1%)	6 (0.1%)	

Note: Continuous variables were presented as a mean ± standard deviation, and statistically analyzed using one-way analysis of variance, while categorical variables were described as counts (percentages) and analyzed using Chi-squared tests. † denotes "before discharge"; [a] moderate or severe liver disease. * Level 1, 2, 3 and 4 denote medical center, regional hospital, district hospital and local medical clinic, respectively; Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; Gr, group; MACE, major adverse cardiac event; NSAID, non-steroid anti-inflammatory drug; NTD, new Taiwan Dollar.

Several demographic factors were adjusted in the hazard models to evaluate the impact of AKI on AF, as well as the influence of incident AF to other adverse events. Variable selection was performed using stepwise multiple regression methods, with both *p*-to-enter and *p*-to-leave equal to 0.15. Final results of multivariate analyses were presented by hazard ratio (HR) and adjusted HR (aHR) with 95% confidence interval (CI). To exclude the confounding effect of subsequent impaired renal function and the influence of chronic dialysis, we additionally took "advanced CKD" as a "time-varying covariate" in the Cox proportional hazard model determining the adjusted risk for subsequent AF.

3. Results

3.1. Characteristics of the Three Groups

From the period of 1 January 2000, to 31 December 2010, a total of 10,091 AKI-D patients were eligible for inclusion. Among them, 5284 patients withdrew from dialysis for at least 30 days, but 4807 patients did not. After the exclusion and sampling processes, a total of 10,450 patients without AKI and who survived to hospital discharge were enrolled as control group. After propensity score matching on a 1:1:2 ratio, we categorized these patients into non-recovery (n = 2895), AKI-recovery (n = 2895) and non-AKI (n = 5790) groups (Figure 1).

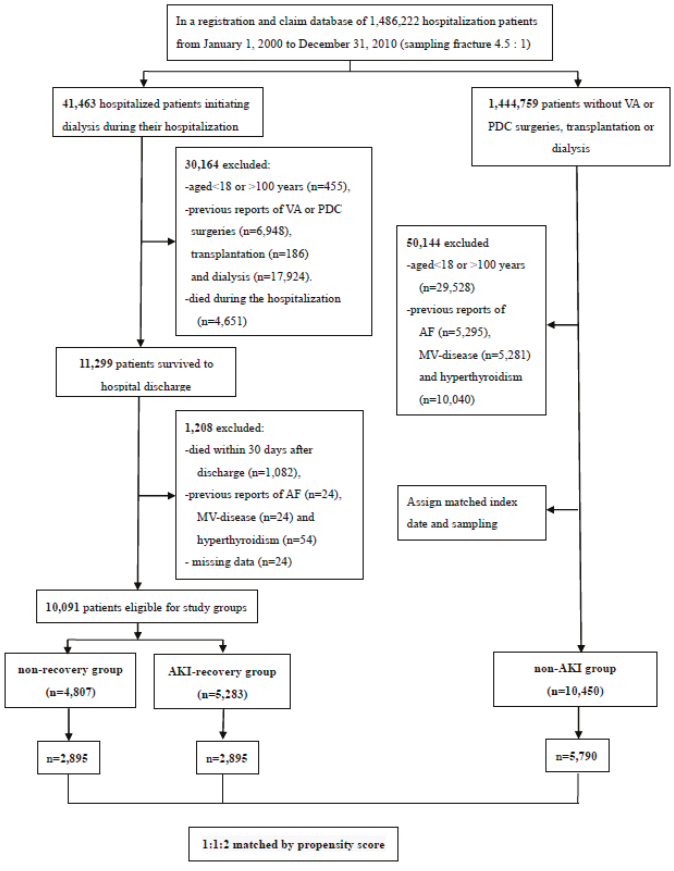

Figure 1. Study flow diagram. Abbreviations: AF, atrial fibrillation; MV, mitral valve; PDC, peritoneal dialysis catheter; VA, vascular access.

The follow-up period of the whole post-matching cohort was 6.38 ± 3.83 years (median, 6.68 years; range, 0.02–10.99 years). Among the three groups, the non-AKI group was the oldest. While the gender, socioeconomic status, baseline comorbidities, as well as outpatient follow-up visits and medication status were not statistically different among the three groups (Table 1). All primary outcome (AF, $p = 0.002$) and secondary outcomes (MACE, ischemic stroke, hemorrhage stroke and all stroke, all $p \leq 0.001$) were of statistical significance among the three groups (Table 2).

3.2. Risk of Incident Atrial Fibrillation

The occurrence time of AF since discharge was 3.24 ± 2.94 years (median, 0.24 years; range, 0.02–10.94 years). The incidence rates of AF were 0.94%, 1.14%, and 1.34% before propensity score matching in "non-AKI group", "AKI-recovery group", and "non-recovery group", respectively.

After propensity score matching, the adjusted risks for subsequent de novo AF development were significantly higher in both the "non-recovery group" (aHR = 1.62; 95% CI, 1.36–1.94; $p \leq 0.001$) and the "AKI-recovery group" (aHR = 1.30; 95% CI, 1.07–1.58; $p \leq 0.01$) compared to the "Non-AKI group" (Table 3 and Figure 2). When compared with "non-recovery group", the "AKI-recovery group" had a significantly lower risk of subsequent AF (aHR = 0.80; 95% CI, 0.616–0.933; $p \leq 0.01$).

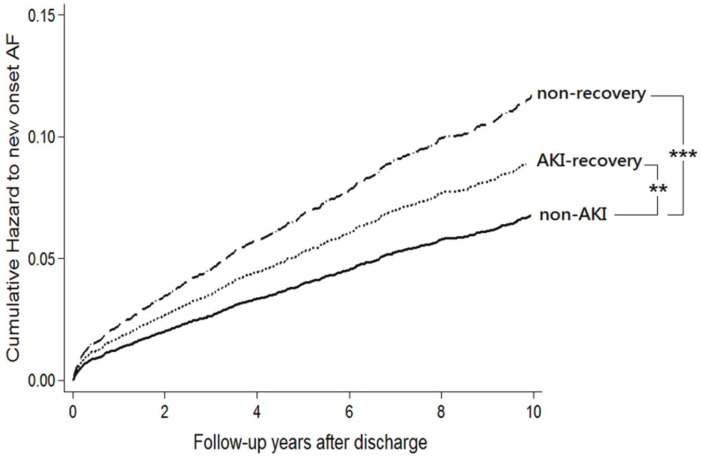

Figure 2. Cumulative incidences of atrial fibrillation among the three groups. Note: The analysis was performed using the Cox proportional hazard method with adjustment to the Charlson Comorbidity Index, age, gender and advanced chronic kidney disease (time-varying covariate). *** denotes $p < 0.001$, ** denotes $p < 0.01$. Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury.

Table 2. Comparisons of the variables within one year following hospital discharge and outcomes among the three groups.

Variables	Before Matching n = 20,540				After Matching n = 11,680			
	Non-Recovery n = 4807	AKI-Recovery n = 5283	Non-AKI n = 10,450	p	Non-Recovery n = 2895	AKI-Recovery n = 2895	Non-AKI n = 5790	p
Outpatient visits, times ‡				< 0.001				0.09
0–5 visits	4596 (95.6%)	4932 (93.3%)	9297 (89.0%)		2763 (95.4%)	2747 (94.9%)	5530 (95.5%)	
6–10 visits	121 (2.5%)	151 (2.9%)	450 (4.3%)		67 (2.3%)	74 (2.6%)	190 (3.3%)	
11–15 visits	66 (1.4%)	123 (2.3%)	479 (4.6%)		47 (1.6%)	50 (1.7%)	123 (2.1%)	
>15 visits	24 (0.5%)	77 (1.5%)	224 (2.1%)		18 (0.6%)	24 (0.8%)	47 (0.8%)	
Medication for hypertension ‡								
Alpha-Blocker	571 (11.9%)	629 (11.9%)	1000 (9.6%)	<0.001	358 (12.4%)	341 (11.8%)	698 (12.1%)	0.74
Beta-Blocker	2000 (41.6%)	1898 (35.9%)	3904 (37.4%)	<0.001	1129 (39.0%)	1143 (39.5%)	2369 (40.9%)	0.52
Calcium-Channel Blocker	3006 (62.5%)	2610 (49.4%)	4986 (47.7%)	<0.001	1614 (55.8%)	1630 (56.3%)	3360 (58.0%)	0.49
Diuretic	1707 (35.5%)	2485 (47.0%)	4168 (39.9%)	<0.001	1193 (41.2%)	1231 (42.5%)	2522 (43.6%)	0.35
ACEI/ARB	1725 (35.9%)	1791 (33.9%)	4176 (40.0%)	<0.001	1057 (36.5%)	1073 (37.1%)	2231 (38.5%)	0.44
Other Medication ‡								
Anti-diabetic drugs	1468 (30.5%)	1595 (30.2%)	3230 (30.9%)	0.57	849 (29.3%)	887 (30.6%)	1846 (31.9%)	0.16
Aspirin	411 (8.6%)	396 (7.5%)	1259 (12.1%)	<0.001	246 (8.5%)	247 (8.5%)	517 (8.9%)	0.88
Clopidogrel	143 (3.0%)	291 (5.5%)	443 (4.2%)	<0.001	104 (3.6%)	114 (3.9%)	212 (3.7%)	0.70
Ticlopidine	208 (4.33%)	117 (2.2%)	370 (3.5%)	<0.001	85 (2.9%)	86 (3.0%)	194 (3.4%)	0.57
Dipyridamole	1059 (22.0%)	792 (15.0%)	2224 (21.3%)	<0.001	538 (18.6%)	555 (19.2%)	1147 (19.8%)	0.61
Nitrate	868 (18.1%)	1050 (19.9%)	1262 (12.1%)	<0.001	501 (17.3%)	524 (18.1%)	1053 (18.2%)	0.71
Statin	519 (10.8%)	628 (11.9%)	1524 (15.6%)	<0.001	334 (11.5%)	355 (12.3%)	743 (12.8%)	0.35
Proton pump inhibitor	26 (0.5%)	57 (1.1%)	64 (0.6%)	0.001	24 (0.8%)	22 (0.8%)	42 (0.7%)	0.84
NSAID	3062 (63.7%)	2832 (53.6%)	7863 (75.2%)	<0.001	1811 (65.6%)	1833 (63.3%)	3707 (64.0%)	0.84
H2-blocker	1173 (24.4%)	1232 (23.3%)	2718 (26.0%)	<0.001	692 (23.9%)	739 (25.5%)	1535 (26.5%)	0.09

Table 2. *Cont.*

Variables	Before Matching n = 20,540				After Matching n = 11,680			
	Non-Recovery n = 4807	AKI-Recovery n = 5283	Non-AKI n = 10,450	p	Non-Recovery n = 2895	AKI-Recovery n = 2895	Non-AKI n = 5790	p
Outcome ‡‡								
Atrial fibrillation	384 (8.0%)	274 (5.2%)	759 (7.3%)	<0.001	214 (7.4%)	149 (5.2%)	383 (6.6%)	0.002
MACE	830 (17.3%)	617 (11.7%)	1449 (13.9%)	<0.001	467 (16.1%)	333 (11.5%)	772 (13.3%)	<0.001
Ischemia Stroke	1226 (25.5%)	824 (15.6%)	4195 (40.1%)	<0.001	696 (24.0%)	481 (16.6%)	2286 (39.5%)	<0.001
Hemorrhage Stroke	367 (7.6%)	229 (4.3%)	1176 (11.3%)	<0.001	222 (7.7%)	140 (4.8%)	719 (13.7%)	<0.001
All stroke	1399 (29.1%)	944 (17.9%)	4748 (45.4%)	<0.001	802 (27.7%)	555 (19.2%)	2617 (45.2%)	<0.001
Advanced CKD	988 (20.6%)	723 (13.7%)	702 (6.8%)	<0.001	822 (28.4%)	482 (16.6%)	423 (7.3%)	<0.001
Mortality	2486 (51.7%)	2204 (41.7%)	3025 (29.0%)	<0.001	1482 (51.2%)	1188 (41.0 %)	1890 (32.6%)	<0.001

Note: Continuous variables were presented as a mean ± standard deviation, and statistically analyzed using one-way analysis of variance, while categorical variables were described as counts (percentages) and analyzed using Chi-squared tests. † denotes "before discharge"; ‡ denotes "within one year following hospital discharge"; ‡‡ denotes "follow-up until death or the end of the study (31 December 2010)"; Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Gr, group; MACE, major adverse cardiac event; NSAID, non-steroid anti-inflammatory drug; NTD, new Taiwan dollar.

Table 3. Incidences and risks of atrial fibrillation development among the three groups.

	Atrial Fibrillation			Crude Risk	Adjusted Risk ‡	Adjusted Risk ‡‡
	Events	Person-Years	Incidence Rate §	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Before propensity score-matching						
non-AKI	759	81,186.67	0.94	ref	ref	ref
AKI-recovery	274	24,007.06	1.14	1.08 (0.94–1.24)	1.16 (1.00–1.33)	1.15 (1.10–1.32)
non-recovery	384	28,726.82	1.34	1.36 *** (1.20–1.54)	1.62 *** (1.43–1.83)	1.58 *** (1.39–1.80)
After propensity score-matching						
non-AKI	383	45,562.79	0.84	ref	ref	ref
AKI-recovery	149	13,462.42	1.11	1.18 (0.98–1.43)	1.33 ** (1.10–1.61)	1.30 ** (1.07–1.58)
non-recovery	214	17,088.48	1.25	1.42 *** (1.20–1.68)	1.72 *** (1.45–2.03)	1.62 *** (1.36–1.94)

Note: Cox proportional hazard model was applied to exam the effect of dialysis-requiring AKI on subsequent atrial fibrillation development. § presented as "100 person-year". ‡ Adjusted for Charlson Comorbidity Index, age, and gender. ‡‡ Adjusted for Charlson Comorbidity Index, age, gender, and advanced chronic kidney disease (time-varying covariate). ** denotes p-value ≤ 0.01; *** denotes p-value ≤ 0.001. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; Gr, group; HR, hazard ratio.

3.3. Risk of Incident Atrial Fibrillation in Subgroups

In the subgroup comparison, we found that "AKI-recovery group" has a significantly higher risk of incident AF than the "non-AKI group" in some subgroups. These subgroups included the patients without congestive heart failure (CHF) (aHR = 1.23; 95% CI, 1.06–1.42) and chronic obstructive pulmonary disease (aHR = 1.18; 95% CI, 1.01–1.36), those with CKD (aHR = 1.37; 95% CI, 1.05–1.80) and diabetes mellitus (aHR = 1.37; 95% CI, 1.05–1.79), as well as those receiving angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) (aHR = 1.27; 95% CI, 1.04–1.54) and beta-blocker (aHR = 1.49; 95% CI, 1.24–1.80). Additionally, the subgroups who received anticoagulants (aHR = 1.23; 95% CI, 1.00–1.51) had marginally significant increased risks of AF (Figure 3).

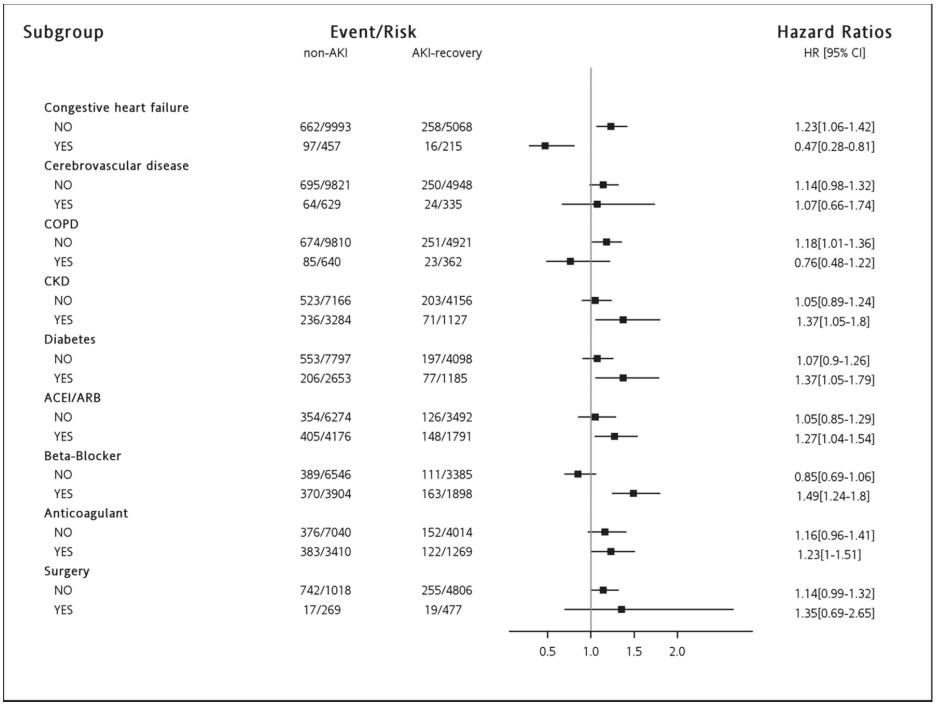

Figure 3. Subgroup comparisons for the risk of atrial fibrillation. Note: The forest plot for the comparison of AKI-recovery group versus non-AKI group was drawn using the before-matching population with adjustment to the Charlson Comorbidity Index, age, and gender. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AF, atrial fibrillation; AKI, acute kidney injury; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

3.4. Risk of Major Adverse Events between Patients with and without Incident Atrial Fibrillation

After propensity score matching, the patients with de novo AF augmented risks for MACE (aHR = 2.11; 95% CI, 1.83–2.43), ischemic stroke (aHR = 1.33; 95% CI, 1.19–1.49) and all stroke (aHR = 1.28; 95% CI, 1.15–1.43) (all $p \leq 0.001$) (Table 4).

Table 4. Incidences and risks of major adverse events between patients with and without atrial fibrillation.

	AF			Non-AF			Crude Risk	Adjusted Risk ‡
	Event	Person-Year	Incidence Rate §	Event	Person-Year	Incidence Rate §	HR (95% CI)	HR (95% CI)
Before propensity score-matching								
MACE	987	9230.59	10.69	2466	117,959.62	2.09	2.25 ** (2.03–2.49)	1.88 ** (1.70–2.09)
Hemorrhagic stroke	161	10,381.48	1.55	1611	121,543.88	1.33	1.20 * (1.02–1.41)	1.24 * (1.05–1.46)
Ischemic stroke	667	7077.34	9.42	5578	96,917.20	5.76	1.62 ** (1.49–1.75)	1.31 ** (1.21–1.42)
Total stroke	714	6867.78	10.40	6377	93,540.77	6.82	1.50 ** (1.39–1.62)	1.26 ** (1.17–1.36)
After propensity score-matching								
MACE	511	4729.33	10.80	1337	67,595.80	1.98	2.49 ** (2.17–2.86)	2.11 ** (1.83–2.43)
Hemorrhagic stroke	89	5321.74	1.67	992	68,827.18	1.44	1.20 (0.97–1.49)	1.23 (0.99–1.53)
Ischemic stroke	333	3766.11	8.84	3130	55,361.13	5.65	1.57 ** (1.40–1.75)	1.33 ** (1.19–1.49)
All Stroke	362	3654.72	9.90	3612	53,357.19	6.77	1.46 ** (1.31–1.63)	1.28 ** (1.15–1.43)

Note: Cox proportional hazard model was applied to exam the effect of dialysis-requiring AKI on subsequent atrial fibrillation development. § presented as "100 person-year". ‡ Adjusted to Charlson Comorbidity Index, age, and gender. * denotes p-value ≤ 0.05; ** denotes p-value ≤ 0.001; Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; MACE, major adverse cardiac event.

4. Discussion

This study is the first to demonstrate a long-term association between AKI and the subsequent incident AF in critically ill patients using a large nationwide cohort. We found that the experience of severe AKI necessitating dialysis, even in the patients who only required temporary dialysis, was associated with increased risk of subsequent incident AF. Moreover, the experience of incident AF further carried a higher risk of MACE, and ischemic stroke in these patients. Since AKI carries an increased risk of coronary events [3], the increased AF following AKI could at least partially explain the elevated probability of MACE after AKI. Since the current study was designed using a selected population set from a nationwide database to evaluate the influence of AKI-D on the incident AF, the incidence rate of AF in this study was not comparable to other investigations [15,16] for an epidemiological purpose.

Most of the previous studies evaluating the association between AF and AKI were designed with a relatively short study period using patients who underwent cardiac surgeries [6,7]. One such study enrolled 446 cardiac surgical patients and found that the development of postoperative AKI was an independent factor associated with new-onset AF [6]. Another prospective study including 2572 cardiac surgical patients disclosed that the occurrence of postoperative AKI carried the 1.7-fold increased risk of developing postoperative AF [7]. In the subgroup comparison of the current study, although insufficient case numbers made the results not statistically significant, we also observed a tendency that patients receiving cardiac surgeries had a higher risk of incident AF than those without (aHR, 1.35 versus 1.14) (Figure 3). Nevertheless, the results from post-cardiac surgical patients probably could not be extensively applied to other patient settings, because the cardiac surgical patient is a special population with a higher risk of AF due to the relevant involvement of heart structurally and electrically [8,17]. Furthermore, the temporal association between AKI and AF was difficult to be clarified by these studies because of a short period of observation [7,9,10]. Compared to the previous studies, the clarified temporal association between in-hospital AKI and new-onset AF after hospital discharge, along with the long-term follow-up period in the current study, provides more strengthened evidence in this field.

In particular, we provide an important outcome estimate: that is, even after being adjusted with progression to subsequent advanced CKD or ESRD, in the worst of circumstances, AKI still independently contributes to subsequent incident AF or all-cause mortality. Therefore, the risk factors of the kidney injury that had engendered an AKI event may persist and eventually lead to future AF without direct causal association to the subsequent CKD.

4.1. Acute Kidney Injury and Atrial Fibrillation

An increasing body of evidence has shown that AKI is independently associated with the occurrence of AF [18]. AKI causes "remote organ injury" in the heart by the "classical" acute uremic effect, the inflammatory state and the modulating effect of the underlying morbidities associated with the injured kidneys, as well as the health care dilemma [5].

Several mechanisms are proposed for explaining the association between AKI and the elevated risk of AF: (1) The increased preload because of the AKI-induced salt and water retention at the acute stage could increase the cardiac structural change [19–22]. (2) The myocardial damage and impaired left ventricular function secondary to the enhanced neutrophil trafficking, endothelial dysfunction, myocyte apoptosis, as well as an increased level of inflammatory cytokines [19–22]. Additionally, fibroblast growth factor 23 (FGF-23), a biomarker for predicting early AKI presentation and cardiovascular morbidity and mortality [23], is disclosed to have markedly elevated serum level in patients with AKI. Higher FGF-23 levels were also found to be associated with elevated risk of AF development in both patients with and without clinical cardiovascular disease [24]. Thus, the enhanced AF incidence might be attributed to the atrial remodeling related to increased FGF-23 levels [25]. Taken together, these results provide a new perspective on the pathogenesis of sinoatrial dysfunction after AKI and open new avenues for treatment of the disease. (3) The activation of the sympathetic

nervous system: previous studies have demonstrated that ischemia-reperfusion injury related AKI would activate a sympathetic reflex [26]. The activating sympathetic activation of the atrium would subsequently cause remodeling of the cardiac autonomic neural tissue and promote further persistence and recurrence of AF [27].

Of note, in the subgroup of "patients without CHF", the finding that "recovery AKI-D patients had a higher risk of subsequent AF than non-AKI patients" was consistent with the results from our whole study population. This was reasonable when we considered this finding as a result without the confounding the effect of CHF. Nevertheless, diverse observations were disclosed in patients with CHF. In these patients, the indication of dialysis could more likely be "fluid overload", which was associated with a more favorable prognosis than other indications. On the contrary, the mortality risk might be higher in patients with more severe AKI-D and CHF than those who only had AKI-D. Owing to the lack of the etiology and severity of congestive heart failure, and the indication of dialysis in the database for further analysis, the observation among patients with CHF should be inconclusive (Figure 3).

Additionally, the results among the subgroups of "hypertensive patients taking beta-blocker and ACEI/ARB" were also consistent with the findings from the whole population. These findings could be interpreted as the beneficial effects of the aforementioned anti-hypertensive medications minimizing the other confounding effects of the underlying cardiovascular disease. In contrast, the influences of AKI-D on AF were blunted in the patients not taking beta-blockers and ACEI/ARB. In fact, this subgroup contains two patient groups (patients without hypertension, and hypertensive patients not taking beta-blocker or ACEI/ARB for treatment) with different prognostic characteristics. Without doing further analysis, we could not draw any conclusions regarding this issue (Figure 3).

4.2. Major Adverse Events Associated with Atrial Fibrillation

In the current study, incident AF was associated with several major adverse events (Table 4). Similar findings were also demonstrated that the development of AKI-D was associated with increased risk of in-hospital mortality and adverse events among patients with AF [2]. Following our results, patients who have AF and AKI will have a high incidence of cardiovascular events, especially coronary events and ischemic stroke. Distant organ injury, a direct consequence of deleterious systemic effects following AKI, is an important issue for clinical care [5].

The association between AF and abnormal renal function is also an interesting and essential issue to be discussed. Among stable anticoagulated patients with AF, the presence of impaired baseline renal function was reported as an independent risk factor of the occurrence of thrombotic/vascular events, stroke, bleeding, and mortality [28,29]. During the two-year follow-up period, about 21% to 32% of patients had a rapid renal function deterioration (decline of estimated Glomerular filtration rate (eGFR) > 5–10 mL/min/1.73 m^2) [28,30]. More renal function deterioration in absolute levels (decreases of eGFR $\geq$ 15–25 mL/min/1.73 m^2 within two years) or relative percentage (decline of $\geq$25% eGFR) within 2 years was independently associated with the occurrence of stroke or death in these patients [29]. The independent risk factors for the development of severe kidney disease include diabetes, CHF, coronary artery disease and impaired baseline renal function [28]. However, normal or near-normal baseline renal function did not exclude the subsequent development of severe renal impairment over time [28].

Regarding the therapeutic strategy for AF, the old drug "Warfarin" is thought to be associated with higher risk for AKI, which is probably due to a higher risk of glomerular hemorrhage known as anticoagulation-related nephropathy [31]. In a randomized study enrolling 18,113 patients, Bohm et al. [32] found that patients receiving warfarin, as opposed to those receiving direct oral anticoagulants (DOAC), have more rapid eGFR decline after an average follow-up period of 30 months. Patients with poor international normalized ratio control (i.e., time in the therapeutic range <65%) tend to have a faster decline in eGFR. Similarly, Chan et al. [33] found that DOAC users had an overall 21%

lower risk of AKI compared with warfarin users among Asians with nonvalvular AF. The beneficial effect was especially disclosed in among patients with eGFR > 60 mL/min/1.73 m^2.

As to the association between AF and MACE, some information should be addressed. In a prospective cohort of 23,928 participants without coronary artery disease conducted by Soliman et al. [34], AF was associated with around two-fold elevated the risk of myocardial infarction within a 6.9 year (median 4.5 years) follow-up. Consistent findings were found in the study enrolling 4,608 participants by O'Neal et al. [35]. Within the median follow-up period of 12.2 years, 17.3% participants developed myocardial infarction, and AF independently carried 1.7 folds increase the risk of myocardial infarction. The increased cardiovascular risk of AF was further confirmed by a systemic review and meta-analysis including 15 cohort studies. Another work also found that AF is associated with an elevated risk of CHF and all-cause mortality in patients regardless of having coronary artery disease, and additionally with an elevated risk of subsequent myocardial infarction in those without coronary artery disease [36]. Of note, the influences of AF on increasing risk of cardiovascular events were more prominent in women than men and African-Americans than Caucasians [34,35,37].

Despite receiving oral warfarin treatment, patients with AF still have a high rate of cardiovascular events, including fatal/nonfatal myocardial infarction, cardiac revascularization, and cardiovascular death. The independent predictors of cardiovascular events included age, smoking, history of cerebrovascular and cardiac events, metabolic syndrome, CHF, and male gender [38].

The cardiovascular safety of oral anticoagulants has long been debated. By using a systemic review and meta-analysis, Tornyos et al., [39] disclosed that most of the DOACs were of safer than warfarin regarding the risk of subsequent myocardial infarction. A very recent work by Lee et al. [40] further exhibited a favorable effect of DOACs as compared to warfarin in reducing cardiac complications in AF. In the analysis using 31,739 patients, all DOACs were associated with lower risk of myocardial infarction than warfarin.

AKI is now considered a growing global health alert [41]. These findings are noteworthy from the perspective of a clinician caring for an individual with dialysis-requiring AKI. Considerable growth in AKI epidemiology and improvements in post-hospitalization resource utilization [42] allowed us to examine the impact of AKI on AF and identify a large vulnerable population with increased risk of cardiovascular events and all-cause mortality [3,4].

4.3. Limitations

Several limitations are worth mentioning. First, the nature of the observational study is subject to bias. Second, the study using administrative data is potentially limited by unmeasured confounding. The epidemiological data, the etiology, and severity of AKI, the indication of dialysis initiation, as well as some known risk factors including alcohol abuse and body mass index, which may further provide meaningful information regarding the association with subsequent AF, are not available in such a nationwide insurance research database. Third, the primary outcome of the current study is "non-valvular AF". The observations accrued here might not be extrapolated to patients with "valvular AF". Fourth, the precision of the disease diagnoses based on ICD-9-CM may be a concern. Fifth, although we have taken "advanced CKD" as a covariate in the Cox model when evaluating the adjusted risk for subsequent AF, the confounding effect of subsequent impaired renal function and chronic dialysis could not be completely excluded. Sixth, the start point of the follow-up period is indeed arguable. Some confounding effect from acute dialysis may exist, which probably increases the risk of AF in "AKI-recovery group", if immediate period after discharge is included in the observation period. Nevertheless, changing the start point from "after discharge" to "the 31st day after discharge" decreases 11% AF events without changing the results of the current study.

However, despite widespread interest and extensive research on AF, our understanding of the etiology and pathogenesis of this disease process is still incomplete. As a result, there are no set primary preventive strategies in a place apart from general cardiac risk factor prevention goals. Our result

seems intuitive that a better understanding of acute dialysis as the risk factors for AF would better prepare medical professionals to initially prevent or subsequently treat these patients and follow up with groups who could not wean from acute dialysis.

5. Conclusions

In this current nationwide cohort study, we found that the experience of severe AKI necessitating dialysis carries an increased risk of subsequent AF, even in those weaned from acute dialysis. Further study is needed to determine the mechanisms which link AKI and subsequent AF and to identify potentially modifiable risk factors to decrease the burden of AF and subsequent risk of major adverse events.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/9/248/s1, Supplementary File 1. Validation of AKI code by NSARF; Validation of CKD code by NSARF; Definition of advanced CKD.

Author Contributions: Formal analysis: C.-C.S., Y.-T.H., and V.-C.W.; Investigation: V.-C.W.; supervision: V.-C.W.; validation: C.-C.S., J.-J.W., Y.-F.L., L.C., E.C., W.-P.C., L.-J.T., C.-H.W., and Y.-T.H.; writing—original draft: C.-C.S., W.C.K., and Y.-T.H.; writing—review and editing: C.-C.S., J.-J.W., Y.-F.L., L.C., E.C., W.-P.C., L.-J.T., C.-H.W., and V.-C.W.

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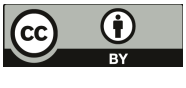
Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rahman, F.; Kwan, G.F.; Benjamin, E.J. Global epidemiology of atrial fibrillation. *Nat. Rev. Cardiol.* **2014**, *11*, 639–654. [CrossRef] [PubMed]
2. Chan, L.; Mehta, S.; Chauhan, K.; Poojary, P.; Patel, S.; Pawar, S.; Patel, A.; Correa, A.; Patel, S.; Garimella, P.S.; et al. National trends and impact of acute kidney injury requiring hemodialysis in hospitalizations with atrial fibrillation. *J. Am. Hear. Assoc.* **2016**, *5*, e004509. [CrossRef] [PubMed]
3. Wu, V.C.; Wu, C.H.; Huang, T.M.; Wang, C.Y.; Lai, C.F.; Shiao, C.C.; Chang, C.H.; Lin, S.L.; Chen, Y.Y.; Chen, Y.M.; et al. Long-term risk of coronary events after AKI. *J. Am. Soc. Nephrol.* **2014**, *25*, 595–605. [CrossRef] [PubMed]
4. Wu, V.C.; Wu, P.C.; Wu, C.H.; Huang, T.M.; Chang, C.H.; Tsai, P.R.; Ko, W.J.; Chen, L.; Wang, C.Y.; Chu, T.S.; et al. The impact of acute kidney injury on the long-term risk of stroke. *J. Am. Heart Assoc.* **2014**, *3*, e000933. [CrossRef] [PubMed]
5. Shiao, C.C.; Wu, P.C.; Huang, T.M.; Lai, T.S.; Yang, W.S.; Wu, C.H.; Lai, C.F.; Wu, V.C.; Chu, T.S.; Wu, K.D.; et al. Long-term remote organ consequences following acute kidney injury. *Crit. Care* **2015**, *19*, 438. [CrossRef] [PubMed]
6. Diplaris, K.; Ampatzidou, F.; Karagounnis, L.; Drossos, G.; Vlahou, A. The role of blood transfusion in the development of atrial fibrillation after coronary artery bypass grafting. *Thorac. Cardiovasc. Surg.* **2016**, *64*, 688–692. [CrossRef] [PubMed]
7. Ng, R.R.G.; Tan, G.H.J.; Liu, W.; Ti, L.K.; Chew, S.T.H. The association of acute kidney injury and atrial fibrillation after cardiac surgery in an asian prospective cohort study. *Medicine* **2016**, *95*, e3005. [CrossRef] [PubMed]
8. Maesen, B.; Nijs, J.; Maessen, J.; Allessie, M.; Schotten, U. Post-operative atrial fibrillation: A maze of mechanisms. *Europace* **2011**, *14*, 159–174. [CrossRef] [PubMed]

9. Ommen, S.R.; Odell, J.A.; Stanton, M.S. Atrial arrhythmias after cardiothoracic surgery. *New Engl. J. Med.* **1997**, *336*, 1429–1434. [CrossRef] [PubMed]
10. Auer, J.; Lamm, G.; Weber, T.; Berent, R.; Ng, C.-K.; Porodko, M.; Eber, B. Renal function is associated with risk of atrial fibrillation after cardiac surgery. *Can. J. Cardiol.* **2007**, *23*, 859–863. [CrossRef]
11. Lin, L.-J.; Cheng, M.-H.; Lee, C.-H.; Wung, D.-C.; Cheng, C.-L.; Kao Yang, Y.-H. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation—A nationwide descriptive study in taiwan. *Clin. Ther.* **2008**, *30*, 1726–1736. [CrossRef] [PubMed]
12. Chao, T.-F.; Huang, Y.-C.; Liu, C.-J.; Chen, S.-J.; Wang, K.-L.; Lin, Y.-J.; Chang, S.-L.; Lo, L.-W.; Hu, Y.-F.; Tuan, T.-C.; et al. Acute myocardial infarction in patients with atrial fibrillation with a cha2ds2-vasc score of 0 or 1: A nationwide cohort study. *Hear. Rhythm.* **2014**, *11*, 1941–1947. [CrossRef] [PubMed]
13. Jensen, P.N.; Johnson, K.; Floyd, J.; Heckbert, S.R.; Carnahan, R.; Dublin, S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol. Drug Saf.* **2012**, *21*, 141–147. [CrossRef] [PubMed]
14. Wang, W.J.; Chao, C.T.; Huang, Y.C.; Wang, C.Y.; Chang, C.H.; Huang, T.M.; Lai, C.F.; Huang, H.Y.; Shiao, C.C.; Chu, T.S.; et al. The impact of acute kidney injury with temporary dialysis on the risk of fracture. *J. Bone Miner. Res.* **2013**, *29*, 676–684. [CrossRef] [PubMed]
15. Chao, T.-F.; Liu, C.-J.; Tuan, T.-C.; Chen, T.-J.; Hsieh, M.-H.; Lip, G.Y.H.; Chen, S.-A. Lifetime Risks, Projected Numbers, and Adverse Outcomes in Asian Patients With Atrial Fibrillation: A Report From the Taiwan Nationwide AF Cohort Study. *Chest* **2018**, *153*, 453–466. [CrossRef] [PubMed]
16. Chien, K.-L.; Su, T.-C.; Hsu, H.-C.; Chang, W.-T.; Chen, P.-C.; Chen, M.-F.; Lee, Y.-T. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. *Int. J. Cardiol.* **2010**, *139*, 173–180. [CrossRef] [PubMed]
17. January, C.T.; Wann, L.S.; Alpert, J.S.; Calkins, H.; Cigarroa, J.E.; Cleveland, J.C., Jr.; Conti, J.B.; Ellinor, P.T.; Ezekowitz, M.D.; Field, M.E.; et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J. Am. Coll. Cardiol.* **2014**, *64*, e1–e76. [CrossRef] [PubMed]
18. Ologunde, R.; Zhao, H.; Lu, K.; Ma, D. Organ cross talk and remote organ damage following acute kidney injury. *Int. Urol. Nephrol.* **2014**, *46*, 2337–2345. [CrossRef] [PubMed]
19. Grams, M.E.; Rabb, H. The distant organ effects of acute kidney injury. *Kidney Int.* **2012**, *81*, 942–948. [CrossRef] [PubMed]
20. Kelly, K.J. Distant effects of experimental renal ischemia/reperfusion injury. *J. Am. Soc. Nephrol.* **2003**, *14*, 1549–1558. [CrossRef] [PubMed]
21. Bhalodia, Y.S.; Sheth, N.R.; Vaghasiya, J.D.; Jivani, N.P. Homocysteine-dependent endothelial dysfunction induced by renal ischemia/reperfusion injury. *J. Nephrol.* **2011**, *24*, 631–635. [CrossRef] [PubMed]
22. Kelly, K.J.; Meehan, S.M.; Colvin, R.B.; Williams, W.W.; Bonventre, J.V. Protection from toxicant-mediated renal injury in the rat with anti-cd54 antibody. *Kidney Int.* **1999**, *56*, 922–931. [CrossRef] [PubMed]
23. Leaf, D.E.; Christov, M.; Jüppner, H.; Siew, E.; Ikizler, T.A.; Bian, A.; Chen, G.; Sabbisetti, V.S.; Bonventre, J.V.; Cai, X.; et al. Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. *Kidney Int.* **2016**, *89*, 939–948. [CrossRef] [PubMed]
24. Mathew, J.S.; Sachs, M.C.; Katz, R.; Patton, K.K.; Heckbert, S.R.; Hoofnagle, A.N.; Alonso, A.; Chonchol, M.; Deo, R.; Ix, J.H.; et al. Fibroblast growth factor-23 and incident atrial fibrillation: the multi-ethnic study of atherosclerosis (mesa) and the cardiovascular health study (chs). *Circulation* **2014**, *130*, 298–307. [CrossRef] [PubMed]
25. Sciacqua, A.; Perticone, M.; Tripepi, G.; Miceli, S.; Tassone, E.J.; Grillo, N.; Carullo, G.; Sesti, G.; Perticone, F. Renal disease and left atrial remodeling predict atrial fibrillation in patients with cardiovascular risk factors. *Int. J. Cardiol.* **2014**, *175*, 90–95. [CrossRef] [PubMed]
26. Cao, W.; Li, A.; Li, J.; Wu, C.; Cui, S.; Zhou, Z.; Liu, Y.; Wilcox, C.S.; Hou, F.F. Reno-cerebral reflex activates the renin-angiotensin system, promoting oxidative stress and renal damage after ischemia-reperfusion injury. *Antioxid. Redox Signal* **2017**, *27*, 415–432. [CrossRef] [PubMed]
27. Lane, K.; Dixon, J.J.; MacPhee, I.A.M.; Philips, B.J. Renohepatic crosstalk: Does acute kidney injury cause liver dysfunction? *Nephrol. Dial. Transplant.* **2013**, *28*, 1634–1647. [CrossRef] [PubMed]

28. Roldan, V.; Marin, F.; Fernandez, H.; Manzano-Fernandez, S.; Gallego, P.; Valdes, M.; Vicente, V.; Lip, G.Y. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *Am. J. Cardiol.* **2013**, *111*, 1159–1164. [CrossRef] [PubMed]
29. Peng, X.S.; Meng, G.W.; Zhang, J.; Wang, X.F.; Zhao, L.X.; Wang, Y.W.; Zhang, L.D. Electrochemical fabrication of ordered Ag2S nanowire arrays. *Mater. Res. Bull.* **2002**, *37*, 1369–1375. [CrossRef]
30. Violi, F.; Pastori, D.; Perticone, F.; Hiatt, W.R.; Sciacqua, A.; Basili, S.; Proietti, M.; Corazza, G.R.; Lip, G.Y.H.; Pignatelli, P. Relationship between low ankle-brachial index and rapid renal function decline in patients with atrial fibrillation: A prospective multicentre cohort study. *BMJ Open* **2015**, *5*, e008026. [CrossRef] [PubMed]
31. Brodsky, S.V.; Hebert, L.A. Anticoagulant-Related Nephropathy: Is an AKI Elephant Hiding in Plain View? *J. Am. Coll. Cardiol.* **2016**, *68*, 2284–2286. [CrossRef] [PubMed]
32. Bohm, M.; Ezekowitz, M.D.; Connolly, S.J.; Eikelboom, J.W.; Hohnloser, S.H.; Reilly, P.A.; Schumacher, H.; Brueckmann, M.; Schirmer, S.H.; Kratz, M.T.; et al. Changes in renal function in patients with Atrial Fibrillation: An analysis from the RE-LY Trial. *J. Am. Coll. Cardiol.* **2015**, *65*, 2481–2493. [CrossRef] [PubMed]
33. Chan, Y.H.; Yeh, Y.H.; See, L.C.; Wang, C.L.; Chang, S.H.; Lee, H.F.; Wu, L.S.; Tu, H.T.; Kuo, C.T. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. *J. Am. Coll. Cardiol.* **2016**, *68*, 2272–2283. [CrossRef] [PubMed]
34. Soliman, E.Z.; Safford, M.M.; Muntner, P.; Khodneva, Y.; Dawood, F.Z.; Zakai, N.A.; Thacker, E.L.; Judd, S.; Howard, V.J.; Howard, G.; et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern. Med.* **2014**, *174*, 107–114. [CrossRef] [PubMed]
35. O'Neal, W.T.; Sangal, K.; Zhang, Z.-M.; Soliman, E.Z. Atrial fibrillation and incident myocardial infarction in the elderly. *Clin. Cardiol.* **2014**, *37*, 750–755. [CrossRef] [PubMed]
36. Ruddox, V.; Sandven, I.; Munkhaugen, J.; Skattebu, J.; Edvardsen, T.; Otterstad, J.E. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. *Eur. J. Prev. Cardiol.* **2017**, *24*, 1555–1566. [CrossRef] [PubMed]
37. Emdin, C.A.; Wong, C.X.; Hsiao, A.J.; Altman, D.G.; Peters, S.A.; Woodward, M.; Odutayo, A.A. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: Systematic review and meta-analysis of cohort studies. *BMJ* **2016**, *352*, h7013. [CrossRef] [PubMed]
38. Pastori, D.; Pignatelli, P.; Angelico, F.; Farcomeni, A.; Del Ben, M.; Vicario, T.; Bucci, T.; Raparelli, V.; Cangemi, R.; Tanzilli, G.; Lip, G.Y.H.; Violi, F. Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants. *Chest* **2015**, *147*, 1644–1650. [CrossRef] [PubMed]
39. Tornyos, A.; Kehl, D.; D'Ascenzo, F.; Komócsi, A. Risk of myocardial infarction in patients with long-term non-vitamin k antagonist oral anticoagulant treatment. *Prog. Cardiovasc. Dis.* **2016**, *58*, 483–494. [CrossRef] [PubMed]
40. Lee, C.J.; Gerds, T.A.; Carlson, N.; Bonde, A.N.; Gislason, G.H.; Lamberts, M.; Olesen, J.B.; Pallisgaard, J.L.; Hansen, M.L.; Torp-Pedersen, C. Risk of myocardial infarction in anticoagulated patients with atrial fibrillation. *J. Am. Coll. Cardiol.* **2018**, *72*, 17–26. [CrossRef] [PubMed]
41. Li, P.K.T.; Burdmann, E.A.; Mehta, R.L. World kidney day 2013: Acute kidney injury—global health alert. *Am. J. Kidney Dis.* **2013**, *61*, 359–363. [CrossRef] [PubMed]
42. Liangos, O.; Wald, R.; O'Bell, J.W.; Price, L.; Pereira, B.J.; Jaber, B.L. Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. *Clin. J. Am. Soc. Nephrol.* **2006**, *1*, 43–51. [CrossRef] [PubMed]



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Incidence and Impact of Acute Kidney Injury in Patients Receiving Extracorporeal Membrane Oxygenation: A Meta-Analysis

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Abstract: Background: Although acute kidney injury (AKI) is a frequent complication in patients receiving extracorporeal membrane oxygenation (ECMO), the incidence and impact of AKI on mortality among patients on ECMO remain unclear. We conducted this systematic review to summarize the incidence and impact of AKI on mortality risk among adult patients on ECMO. Methods: A literature search was performed using EMBASE, Ovid MEDLINE, and Cochrane Databases from inception until March 2019 to identify studies assessing the incidence of AKI (using a standard AKI definition), severe AKI requiring renal replacement therapy (RRT), and the impact of AKI among adult patients on ECMO. Effect estimates from the individual studies were obtained and combined utilizing random-effects, generic inverse variance method of DerSimonian-Laird. The protocol for this systematic review is registered with PROSPERO (no. CRD42018103527). Results: 41 cohort studies with a total of 10,282 adult patients receiving ECMO were enrolled. Overall, the pooled estimated incidence of AKI and severe AKI requiring RRT were 62.8% (95%CI: 52.1%–72.4%) and 44.9% (95%CI: 40.8%–49.0%), respectively. Meta-regression showed that the year of study did not significantly affect the incidence of AKI ($p = 0.67$) or AKI requiring RRT ($p = 0.83$). The pooled odds ratio (OR) of hospital mortality among patients receiving ECMO with AKI on RRT was 3.73 (95% CI, 2.87–4.85). When the analysis was limited to studies with confounder-adjusted analysis, increased hospital mortality remained significant among patients receiving ECMO with AKI requiring RRT with pooled OR of 3.32 (95% CI, 2.21–4.99). There was no publication bias as evaluated by the funnel plot and Egger's regression asymmetry test with $p = 0.62$ and $p = 0.17$ for the incidence of AKI and severe AKI requiring RRT, respectively. Conclusion: Among patients receiving ECMO, the incidence rates of AKI and severe AKI requiring RRT are high, which has not changed over time. Patients who develop AKI requiring RRT while on ECMO carry 3.7-fold higher hospital mortality.

Keywords: acute kidney injury; AKI; extracorporeal membrane oxygenation; ECMO; epidemiology; meta-analysis

1. Introduction

Extracorporeal membrane oxygenation (ECMO), as a mechanical circulatory support system, is utilized as a treatment for cardiovascular or respiratory failure [1–3]. There are two main types of ECMO, including venovenous (VV)-ECMO for patients with isolated respiratory failure and venoarterial (VA)-ECMO for combined severe cardiac and respiratory failure [4]. Over the past 40 years, the clinical applications and feasibility of ECMO have expanded in patients with refractory cardiorespiratory failure, and there has been an exponential increase in the number of centers utilizing ECMO globally [3,5–9]. Studies have demonstrated survival benefits of ECMO ranging from 20% to 50% in patients with cardiac arrest, severe adult respiratory distress syndrome (ARDS), and refractory cardiogenic shock [5,10–16].

Despite these benefits, there have been a number of reports to highlight the concomitant occurrence of organ failures and complications including acute kidney injury (AKI), infections, thrombosis, bleeding and coagulopathy, and neurological events [17,18]. The underlying mechanisms for AKI among patients requiring ECMO appear to be complex and include hemodynamic instabilities, inflammatory responses, coagulation-platelet abnormalities, and immune-mediated injury that arise from the primary underlying disease, premorbid conditions and the ECMO circuit [18–28]. Due to previously non-uniform definitions of AKI, the reported incidences of AKI among patients requiring ECMO therapy ranged widely from 8% up to 85% [4,7,15,18–70]. In addition, the incidence and mortality associated with AKI in patients requiring ECMO and their trends remain unclear.

This systematic review was conducted with the aim to summarize the incidence (using standard AKI definitions) and the impact of AKI on mortality risk among adult patients on ECMO.

2. Methods

2.1. Information Sources and Search Strategy

The protocol for this systematic review and meta-analysis is registered with International Prospective Register of Systematic Reviews (PROSPERO no. CRD42018103527). A systematic literature review of EMBASE, Ovid MEDLINE, and the Cochrane Database of Systematic Reviews from database inception through March 2019 was conducted to summarize the incidence and impact of AKI on mortality risk among adult patients on ECMO. Two authors (C.T. and W.C.) independently performed a systematic literature search utilizing a search approach that consolidated the search terms "extracorporeal membrane oxygenation" OR "ECMO" AND "acute kidney injury" OR "acute renal failure." Further details regarding the search strategy utilized for each database are provided in Online Supplementary Data 1. No language restriction was implemented. A manual search for conceivably related articles utilizing references of the included studies was additionally performed. This systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [71].

2.2. Study Selection

Studies were included in this systematic review if they were clinical trials or observational studies that reported the incidence of AKI (using standard AKI definitions including RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) [72], AKIN (Acute Kidney Injury Network) [73], and KDIGO (Kidney Disease: Improving Global Outcomes) classifications) [74], severe AKI requiring renal replacement therapy (RRT), and mortality risk of AKI among adult patients (age ≥ 18 years old) on ECMO. Eligible studies needed to provide the data to evaluate the incidence or mortality rate of AKI with 95% confidence intervals (CI). Retrieved articles were independently examined for eligibility by the two authors (C.T. and W.C.). Inconsistencies were discussed and resolved by shared agreement. The size of the study did not limit inclusion.

2.3. Data Collection Process

A structured data collecting form was adopted to gather the following data from individual study including title, name of authors, publication year, year of the study, country where the study was conveyed, type of ECMO, AKI definition, incidence of AKI, incidence of severe AKI requiring RRT, and mortality risk of AKI among patients on ECMO.

2.4. Statistical Analysis

We used the Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc, Englewood, NJ, USA) to conduct the meta-analysis. Adjusted point estimates of included studies were consolidated by the generic inverse variance method of DerSimonian-Laird, which assigned the weight of individual study based on its variance [75]. Due to the probability of between-study variance, we applied a random-effects model to pool outcomes of interest, including the incidence of AKI and mortality risk. Statistical heterogeneity of studies was assessed by the Cochran's Q test ($p < 0.05$ for a statistical significance) and the I^2 statistic (≤25%: insignificant heterogeneity, 26%–50%: low heterogeneity, 51%–75%: moderate heterogeneity and ≥75%: high heterogeneity) [76]. The presence of publication bias was evaluated by both the funnel plot and the Egger test [77].

3. Results

A total of 1,632 potentially eligible articles were identified with our search approach. After excluding 644 articles that were either in-vitro studies, focused on pediatric patient population, animal studies, case reports, correspondences, or review articles, and 831 articles due to being duplicates, 157 articles remained for full-length article review. Seventy-three articles were subsequently excluded as they did not provide data on the incidence of AKI or mortality of AKI, while 33 articles were excluded because they were not clinical trials or observational studies. Ten studies [19–28] were additionally excluded because they did not use a standard AKI definition or did not report the incidence of severe AKI requiring RRT. Therefore, 41 cohort studies [7,15,29–67] with a total of 10,282 adult patients receiving ECMO were enrolled. The systematic review of the literature flowchart is demonstrated in Figure 1. The characteristics of the included studies are shown in Table 1.

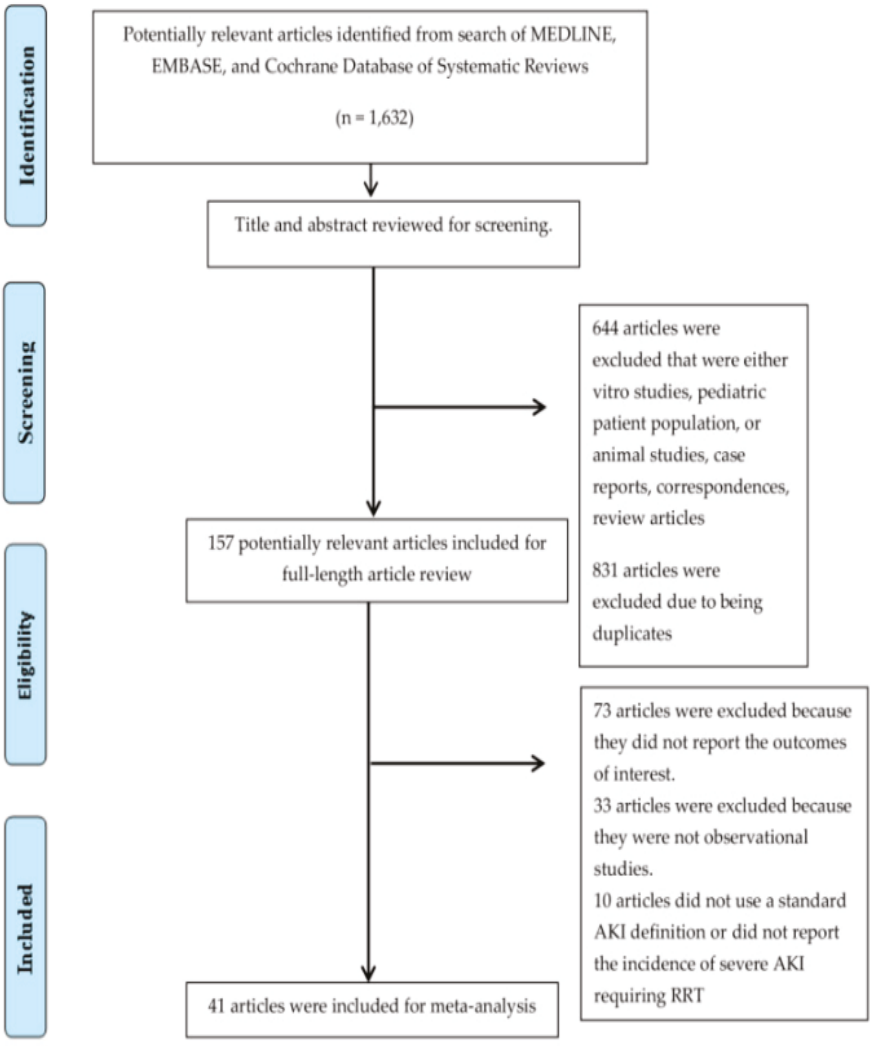

Figure 1. The flowchart for the systematic review.

Table 1. Main characteristic of studies included in this meta-analysis of AKI incidence and mortality among patients requiring ECMO [7,15,29–67].

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence	Mortality
Pagani et al. [15]	2001	USA	ECMO for cardiogenic shock or arrest	33	RRT	RRT 10/33 (30.3%)	Hospital mortality 9/10 (90%)
Yap et al. [29]	2003	Taiwan	ECMO for cardiogenic shock	10	RRT	RRT 5/10 (50%)	Mortality 5/5 (100%)
Lin et al. [30]	2006	Taiwan	ECMO	46	AKI; RIFLE criteria	AKI 36/46 (78.3%) CRRT 16/46 (34.8%)	AKI: Hospital mortality 28/36 (78%) CRRT: Hospital mortality 16/16 (100%)
Tsai et al. [31]	2008	Taiwan	ECMO	288	CRRT	CRRT 104/288 (36.1%)	Hospital mortality 79/104 (76%)
Bakhtiary et al. [32]	2008	Germany	VA-ECMO for refractory cardiogenic shock	45	CRRT	CRRT 39/45 (86.7%)	N/A
Luo et al. [33]	2009	China	VA-ECMO in severe heart failure	45	CRRT	CRRT 12/45 (26.6%)	Hospital mortality 7/9 (78%)
Brogan et al. [34]	2009	USA	ECMO in severe respiratory failure	1473	RRT	RRT 648/1473 (44%)	Hospital mortality RRT 390/648 (60%)
Wang et al. [35]	2009	China	VA ECMO for refractory cardiogenic shock after cardiac surgery	62	CRRT	CRRT 23/62 (37.0%)	N/A
Yan et al. [36]	2010	China	ECMO after cardiac surgery	67	AKI; RIFLE and AKIN criteria	RIFLE AKI 54/67 (80.6%) AKIN AKI 57/67 (85.1%) RRT 30/67 (44.8%)	Hospital mortality RIFLE AKI 32/54 (59%) AKIN AKI 33/57 (58%) RRT 22/30 (73%)
Elsharkawy et al. [37]	2010	USA	VA-ECMO after cardiac surgery	233	RRT	RRT 101/233 (43.3%)	Hospital mortality 79/101 (78%)
Hsu et al. [38]	2010	Taiwan	VA-ECMO for cardiogenic shock after cardiac surgery	51	CRRT	CRRT 38/51 (74.5%)	N/A

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence	Mortality
Lan et al. [39]	2010	Taiwan	ECMO	607	RRT	RRT 301/607 (49.6%)	Hospital mortality 259/301 (86%)
Rastan et al. [40]	2010	Germany	VA-ECMO for cardiogenic shock after cardiac surgery	517	RRT	RRT 336/517 (65.0%)	N/A
Wu et al. [41]	2010	Taiwan	ECMO	346	RRT	RRT 187/346 (54%)	RRT 72/102 (71%)
Chen et al. [42]	2011	Taiwan	ECMO	102	AKI; AKIN criteria	AKI 62/102 (60.8%) CRRT 26/102 (25.5%)	Hospital mortality AKI 51/62 (82%) CRRT 22/26 (85%)
Bermudez et al. [43]	2011	USA	ECMO for refractory cardiogenic shock; VA (88%)	42	RRT	RRT 17/42 (40.5%)	N/A
Chang et al. [44]	2012	Taiwan	Successfully weaned from ECMO	113	AKI; AKIN criteria at 48 h post-ECMO removal	AKI 51/113 (45.1%)	Hospital mortality AKI 23/51 (45%)
Kim et al. [45]	2012	Korea	ECMO; VA-ECMO (85%), VV-ECMO (15%)	26	AKI; AKIN criteria	AKI 10/26 (38.5%)	N/A
Lee et al. [46]	2012	Korea	ECMO; VA-ECMO (74%), VV-ECMO (26%)	185	CRRT	CRRT 76/185 (41.1%)	N/A
Loforte et al. [47]	2012	Italy	VA-ECMO	73	CRRT	CRRT 38/73 (52.1%)	N/A
Wu et al. [48]	2012	Taiwan	ECMO for non-post cardiotomy cardiogenic shock or cardiac arrest	60	RRT	RRT 19/60 (31.7%)	Hospital mortality 13/19 (68%)

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence	Mortality
Aubron et al. [49]	2013	Australia	ECMO; VA-ECMO (67%), VV-ECMO (33%)	158	RRT	VA-ECMO RRT 61/105 (58.1%) VV-ECMO RRT 27/53 (50.9%)	Hospital mortality VA-ECMO RRT 27/61 (44%) VV-ECMO RRT 13/27 (48%)
Kielstein et al. [50]	2013	Germany	ECMO; VA-ECMO (45%), VV-ECMO (55%)	200	RRT	RRT 117/200 (58.5%) RRT after ECMO 92/175 (52.6%)	90-day mortality 97/117 (83%)
Wu et al. [51]	2013	Taiwan	ECMO for acute myocardial infarction-induced cardiac arrest	35	RRT	RRT 16/35 (45.7%)	Hospital mortality 14/16 (88%)
Lazzeri et al. [52]	2013	Italy	ECMO for refractory cardiac arrest	25	RRT	RRT 16/24 (66.7%)	Mortality 9/16 (56%)
Unosawa et al. [53]	2013	Japan	VA-ECMO for refractory cardiogenic shock after cardiac surgery	47	RRT	RRT 15/47 (31.9%)	Mortality on ECMO 7/15 (46.7%)
Xue et al. [54]	2014	China	ECMO in lung transplantation	45	AKI; AKIN criteria	AKI 17/45 (37.8%)	N/A
Schmidt et al. [7]	2014	Australia	ECMO for refractory cardiogenic shock or acute respiratory failure	172	AKI; RIFLE criteria	AKI at ECMO day 1 98/172 (57.0%) CRRT during ECMO 103/172 (59.9%)	90-day mortality CRRT 34/103 (33%)
Hsiao et al. [55]	2014	Taiwan	ECMO for ARDS	81	CRRT	CRRT 33/81 (40.7%)	Hospital mortality CRRT 22/33 (67%)
Lee et al. [56]	2015	Korea	ECMO; VA-ECMO (71%), VV-ECMO (29%)	322	AKI; KDIGO criteria	AKI 265/322 (82.3%)	Hospital mortality 151/265 (57%)
Haneya [57]	2015	Germany	VV-ECMO for ARDS	262	AKI; KDIGO criteria	AKI 109/262 (41.6%) RRT during ECMO 52/262 (19.8%)	Mortality AKI 56/109 (51%) RRT during ECMO 23/52 (44%)

Table 1. *Cont.*

Study	Year	Country	Patients	Number	AKI Definition	AKI Incidence	Mortality
Huang et al. [58]	2016	China	ECMO for acute respiratory distress syndrome; VA-ECMO (17%), VV-ECMO (83%)	23	AKI; AKIN criteria	AKI 13/23 (56.5%)	Mortality 9/13 (69%)
Antonucci et al. [59]	2016	Belgium	ECMO; VA-ECMO (59%), VV-ECMO (41%)	135	AKI; AKIN criteria	AKI 95/135 (70.4%) CRRT 63/135 (46.7%)	ICU mortality AKI 55/95 (58%) CRRT 38/63 (60%)
Tsai et al. [60]	2017	Taiwan	ECMO	167	AKI; RIFLE, AKIN and KDIGO on ECMO day 1	RIFLE AKI 126/167 (75.4%) AKIN AKI 141/167 (84.4%) KDIGO AKI 142/167 (85.0%)	Hospital mortality RIFLE AKI 85/126 (67%) AKIN AKI 90/126 (71%) RIFLE AKI 90/126 (71%)
Panholzer et al. [61]	2017	Germany	VV-ECMO for ARDS	46	RRT	RRT 31/46 (67.4%)	Mortality RRT 23/31 (74%)
Chong et al. [62]	2018	Taiwan	VA-ECMO for acute fulminant myocarditis and cardiogenic shock	35	AKI; not specified	AKI 26/35 (74.3%) RRT 15/35 (42.9%)	Hospital mortality AKI 14/26 (54%) RRT 11/15 (73%)
Devasagayaraj et al. [63]	2018	USA	VV-ECMO for ARDS	54	CRRT	CRRT 16/54 (29.6%)	Hospital mortality 9/16 (56%)
Liao et al. [64]	2018	China	ECMO; VA-ECMO (93%), VV-ECMO (7%)	170	AKI; KDIGO criteria	AKI 91/170 (53.5%)	N/A
Paek et al. [65]	2018	Korea	ECMO	538	CRRT	CRRT 296/838 (35.3%)	30-day mortality 195/296 (66%)
He et al. [66]	2018	China	ECMO	92	CRRT	CRRT 32/92 (34.8%)	Hospital mortality 19/32 (59%)
Chen et al. [67]	2019	Taiwan	ECMO	3251	RRT	RRT 1759/3251 (54.1%)	Hospital mortality 1298/1759 (74%)

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AKIN, Acute Kidney Injury Network; CRRT, continuous renal replacement therapy; ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; N/A, not available; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, Renal replacement therapy; USA, United States of America; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

3.1. Incidence of AKI in Patients Requiring ECMO

Overall, the pooled estimated incidence of AKI and severe AKI requiring RRT while on ECMO were 62.8% (95%CI: 52.1%–72.4%, I^2 = 94%, Figure 2A) and 44.9% (95%CI: 40.8%-49.0%, I^2 = 91%, Figure 2B), respectively. Subgroup analyses were performed according to AKI definitions. The pooled estimated incidence rates of AKI by RIFLE, AKIN, and KDIGO criteria were 67.5% (95%CI: 43.9%–84.6%, I^2 = 85%), 57.8% (95%CI: 44.6%–70.0%, I^2 = 86%), and 68.2% (95%CI: 43.8%–85.55%, I^2 = 98%), respectively.

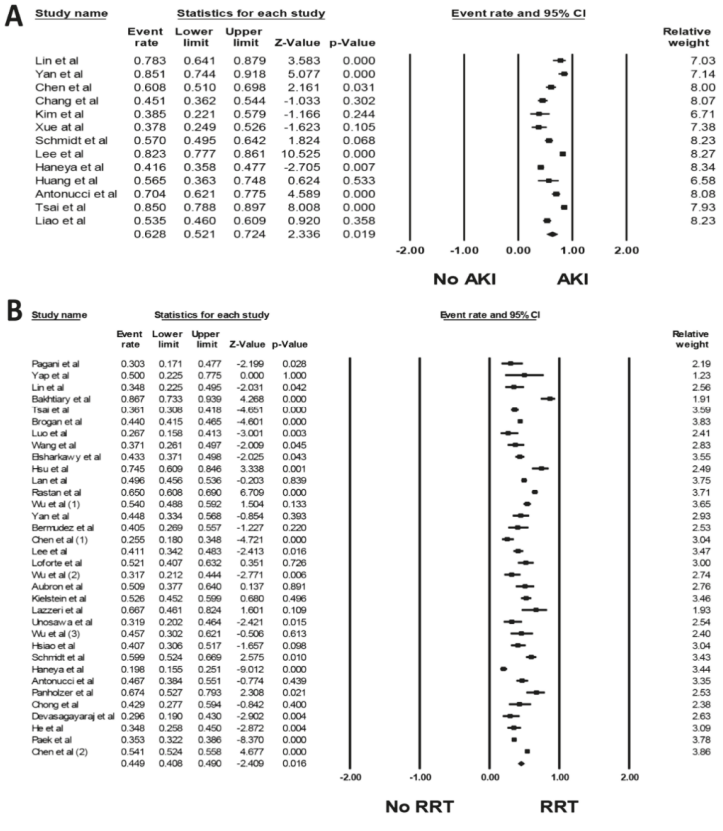

Figure 2. Forest plots of the included studies assessing (**A**) incidence rates of AKI while on ECMO and (**B**) incidence rate of severe AKI requiring RRT while on ECMO. A diamond data marker depicts the overall rate from each included study (square data marker) and 95%CI.

Subgroup analysis based on the type of ECMO was also performed. Pooled estimated incidence of AKI and severe AKI requiring RRT while on venoarterial (VA)-ECMO were 60.8% (95%CI: 32.9%–83.1%, I^2 = 96%) and 49.5% (95%CI: 39.6%–59.4%, I^2 = 90%), respectively. Pooled estimated incidence of AKI and severe AKI requiring RRT while on venovenous (VV)-ECMO were 45.7% (95%CI: 33.2%–58.8%, I^2 = 47%) and 37.0% (95%CI: 14.8%–66.5%, I^2 = 95%), respectively. Meta-regression showed that year of the study did not significantly affect the incidence of AKI (p = 0.67) or AKI requiring RRT (p = 0.83), as shown in Figure 3.

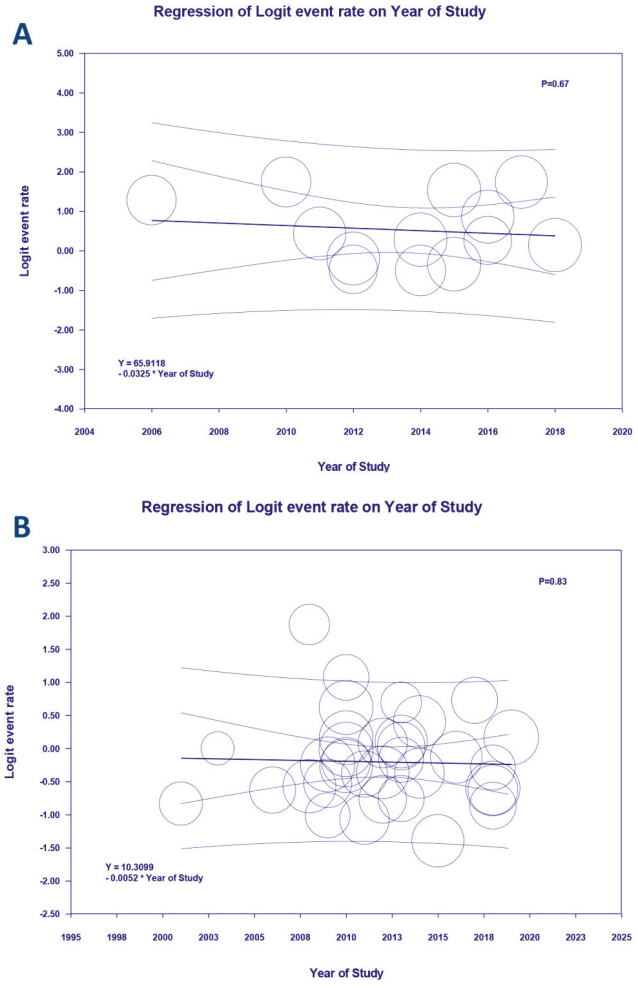

Figure 3. Meta-regression analyses showed that year of the study did not significantly affect (**A**) the incidence of AKI ($p = 0.67$) or (**B**) AKI requiring RRT ($p = 0.83$). The solid black line depicts the weighted regression line based on variance-weighted least squares. The inner and outer lines represent the 95%CI and prediction interval encompassing the regression line. The circles indicate log event rates in individual study.

3.2. AKI associated Mortality in Patients Requiring ECMO

Mortality rate and mortality risk associated with AKI in patients requiring ECMO are demonstrated in Tables 1 and 2, respectively. The pooled estimated hospital and/or 90-day mortality rates of patients with AKI and severe AKI requiring RRT while on ECMO were 62.0% (95%CI: 54.7%–68.8%, $I^2 = 73\%$, Figure 4A) and 68.4% (95%CI: 62.6%–73.6%, $I^2 = 87\%$, Figure 4B), respectively.

Table 2. Characteristics of studies included in this meta-analysis of AKI associated mortality risk among patients requiring ECMO.

Study.	Year	Number	Outcomes	Confounder Adjustment
Pagani et al. [15]	2001	33	Hospital mortality 8.25 (0.89–76.12)	None
Lin et al. [30]	2006	46	Hospital mortality AKI: 14.0 (2.46–79.55) CRRT: 16/16 vs. 14/30	None
Luo et al. [33]	2009	45	Hospital mortality CRRT: 7.0 (1.26–38.99)	None
Brogan et al. [34]	2009	1473	Hospital mortality Renal insufficiency/failure: 2.13 (1.69–2.72) RRT: 2.13 (1.73–2.63)	Age, duration of mechanical ventilation, weight, pre-ECMO pH, race, diagnosis, ECMO mode, post-ECMO complication
Elsharkawy et al. [37]	2010	233	Hospital mortality RRT: 3.18 (1.77–5.70)	None
Yan et al. [36]	2010	67	Hospital mortality RIFLE AKI: 8.0 (1.61–39.68) AKIN AKI: 12.38 (1.47–104.33) CRRT: 5.73 (1.98–16.58)	None
Lan et al. [39]	2010	607	Hospital mortality RRT: 6.49 (4.12–10.23)	Age, stroke, pre-ECMO infection, hypoglycemia, alkalosis
Chen et al. [67]	2011	102	Hospital mortality AKI: 4.32 (1.65–11.30) CRRT: 5.80 (1.82–18.43)	Age, GCS
Chang et al. [44]	2012	113	Hospital mortality AKI: 2.1 (1.48–3.00)	None
Wu et al. [48]	2012	60	Hospital mortality RRT: 3.76 (1.18–11.95)	None
Kielstein et al. [50]	2013	200	90-day mortality RRT: 5.47(2.87–10.44)	None

Table 2. *Cont.*

Study.	Year	Number	Outcomes	Confounder Adjustment
Aubron et al. [49]	2013	158	VA ECMO RRT: 2.12 (0.92–4.88) VV ECMO RRT: 2.52 (0.80–7.95)	None
Wu et al. [51]	2013	35	Hospital mortality RRT: 12 (2.08–69.09)	None
Slottosch et al. [23]	2013	77	30-day mortality Renal failure: 2.20 (0.78–6.12)	None
Unosawa et al. [53]	2013	47	Mortality during ECMO RRT: 1.67 (0.48–5.83)	None
Lazzeri et al. [52]	2013	25	Mortality RRT: 2.14 (0.38–12.20)	None
Hsiao et al. [55]	2014	81	Hospital mortality CRRT: 2.17 (0.87–5.45)	None
Schmidt et al. [7]	2014	172	Hospital mortality CRRT at ECMO day 1–3: 4.1 (1.71–9.82) 90-day mortality CRRT at ECMO day 1–3: 3.17 (1.32–7.61)	APACHE, fluid balance, major bleeding, propensity score
Lee et al. [56]	2015	322	Hospital mortality AKI: 3.71 (1.96–7.02)	None
Haneya et al. [57]	2015	262	Mortality AKI: 2.18 (1.31–3.61) RRT during ECMO: 1.72 (0.53–5.59)	Age, SOFA score, minute volume, pH, lactate, RRT prior to ECMO, RBC, and FFP transfusion
Huang et al. [58]	2016	23	Mortality AKI: 20.25 (1.88–218.39)	None

Table 2. *Cont.*

Study.	Year	Number	Outcomes	Confounder Adjustment
Lyu et al. [27]	2016	84	Mortality ARF: 23.90 (7.00–81.60)	None
Antonucci et al. [59]	2016	135	ICU mortality AKI: 1.86 (0.88–3.93) CRRT: 1.70 (0.85–3.37)	None
Tsai et al. [60]	2017	167	Hospital mortality RIFLE AKI: 8.55 (3.63–20.16) AKIN AKI: 13.53 (3.87–47.28) KDIGO AKI: 12.69 (3.62–44.46)	None
Panholzer et al. [61]	2017	46	Mortality RRT: 40.25 (4.54–356.93)	None
Martucci et al. [28]	2017	82	Mortality on ECMO AKI stage 3: 4.55 (1.37–15.17)	None
Chong et al. [62]	2018	35	Hospital mortality AKI: 9.33 (1.02–85.70) RRT: 11.0 (2.26–53.64)	None
Devasagayaraj et al. [63]	2018	54	Hospital mortality RRT: 5.69 (1.58–20.56)	None
Chen et al. [67]	2019	3,251	Hospital mortality RRT: 3.92 (3.36–4.57)	Age, sex, ECMO indication, comorbid conditions, hospital level, study year

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AKIN, Acute Kidney Injury Network; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; ECMO, Extracorporeal membrane oxygenation; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale/Score; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; N/A, not available; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RBC, red blood cells; RRT, Renal replacement therapy; pH, potential hydrogen; SOFA, Sequential Organ Failure Assessment; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

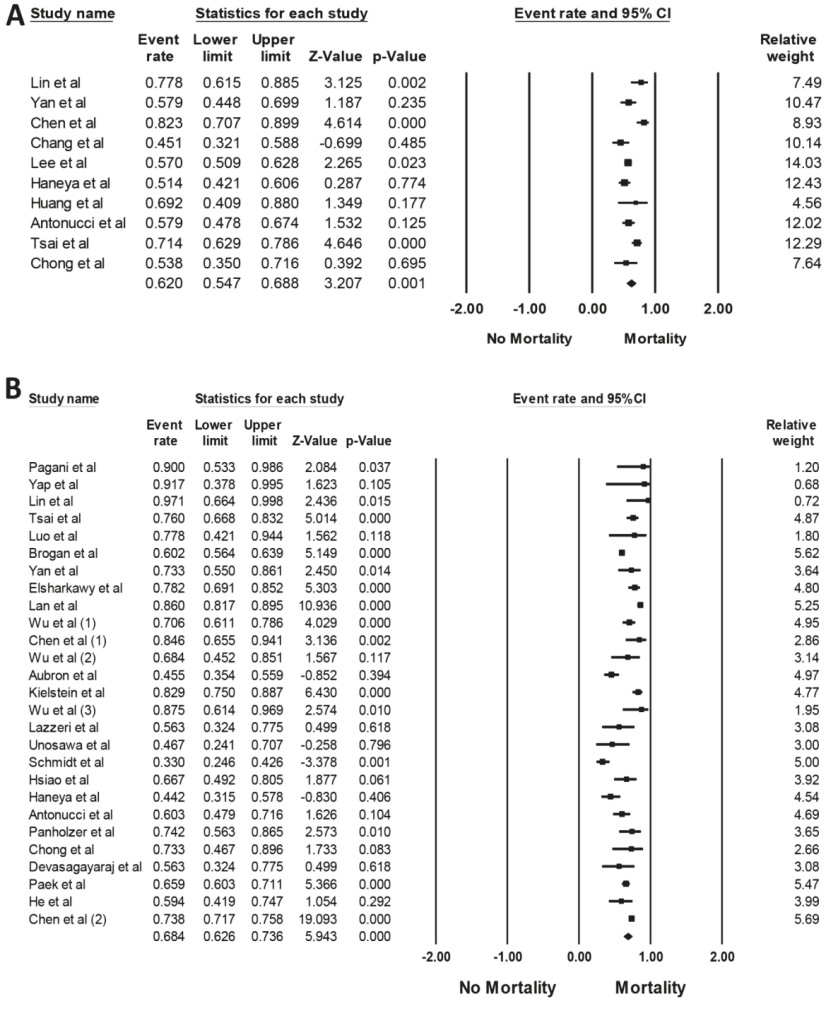

Figure 4. Forest plots of the included studies assessing (**A**) mortality rate of patients with AKI while on ECMO and (**B**) mortality rate of patients with severe AKI requiring RRT while on ECMO. A diamond data label serves as the overall rate from each study (square data marker) and 95%CI.

The pooled OR of hospital mortality among patients receiving ECMO with AKI on RRT was 3.73 (95% CI, 2.87–4.85, I^2 = 62%, Figure 5A). When the analysis was limited to studies with confounder-adjusted analysis, the increased hospital mortality remained significant among patients receiving ECMO with AKI requiring RRT with pooled OR of 3.32 (95% CI, 2.21–4.99, I^2 = 82%, Figure 5B).

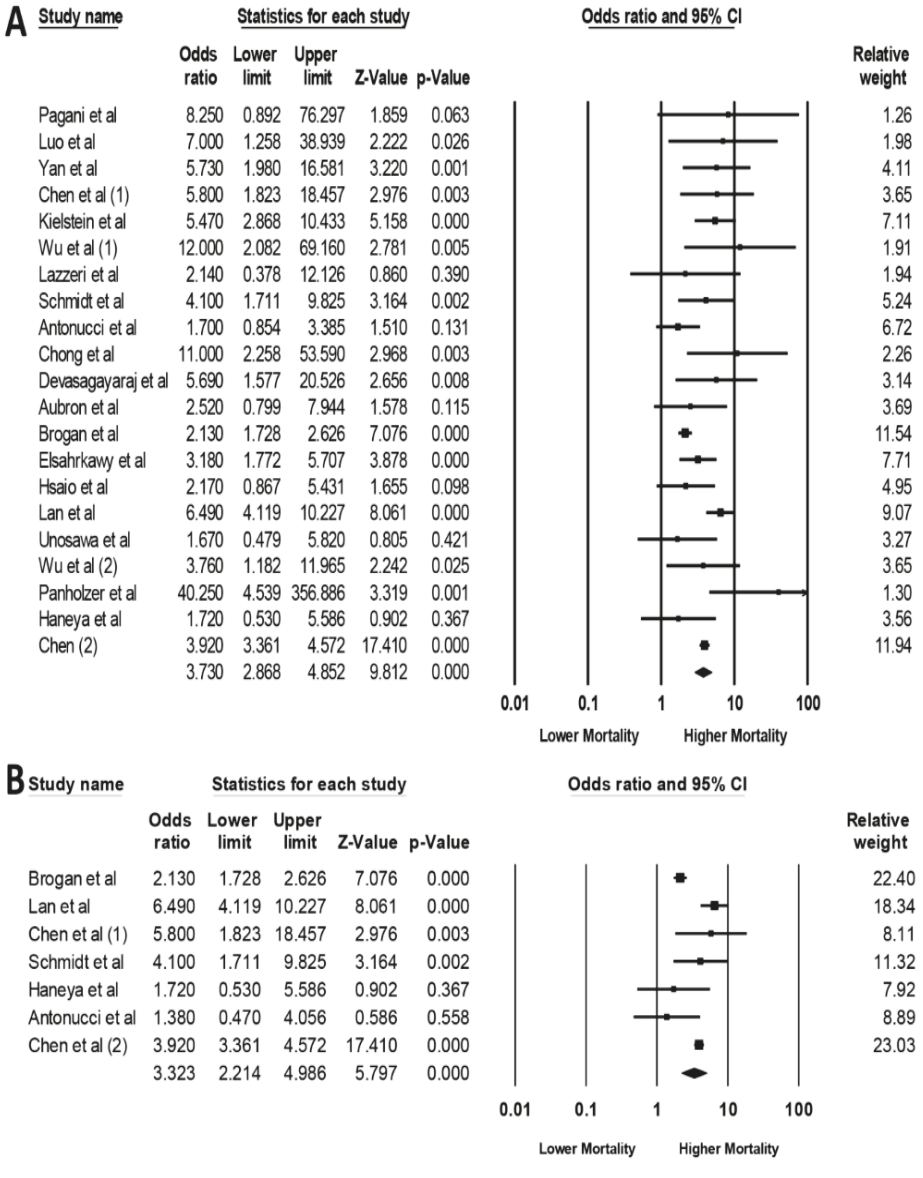

Figure 5. Forest plots of the included studies assessing (**A**) hospital mortality among patients receiving ECMO with AKI on RRT and (**B**) hospital mortality among patients receiving ECMO with AKI on RRT limited to studies with confounder-adjusted analysis. A diamond data label serves as the overall rate from each included study (square data marker) and 95%CI.

Meta-regression showed that year of the study did not significantly affect hospital mortality among patients receiving ECMO with AKI requiring RRT ($p = 0.86$), as shown in Figure 6.

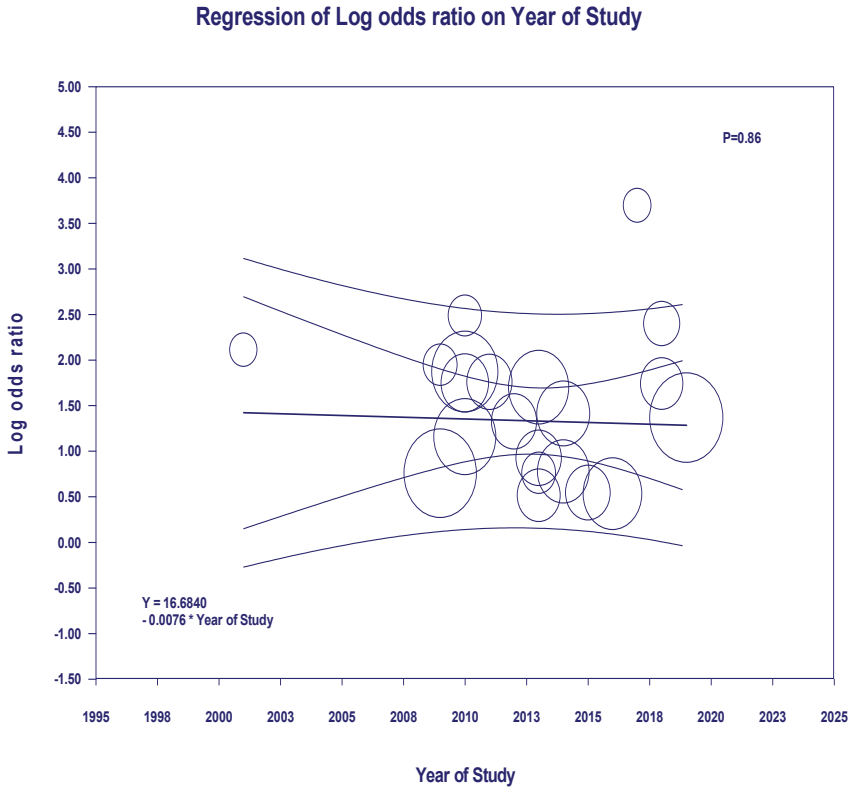

Figure 6. Meta-regression analyses showed that year of the study did not significantly affect hospital mortality among patients receiving ECMO with AKI requiring RRT ($p = 0.86$). The solid black line depicts the weighted regression line based on variance-weighted least squares. The inner and outer lines represent the 95%CI and prediction interval encompassing the regression line. The circles indicate log event rates in an individual study.

3.3. Evaluation for Publication Bias

Funnel plots (Figure 7) and Egger's regression asymmetry tests were utilized to assess for publication bias in our meta-analyses evaluating the incidence of AKI and severe AKI requiring RRT while on ECMO. There was no publication bias as determined by the funnel plot and Egger's regression asymmetry test with $p = 0.62$ and $p = 0.17$ for the incidence of AKI and severe AKI requiring RRT, respectively.

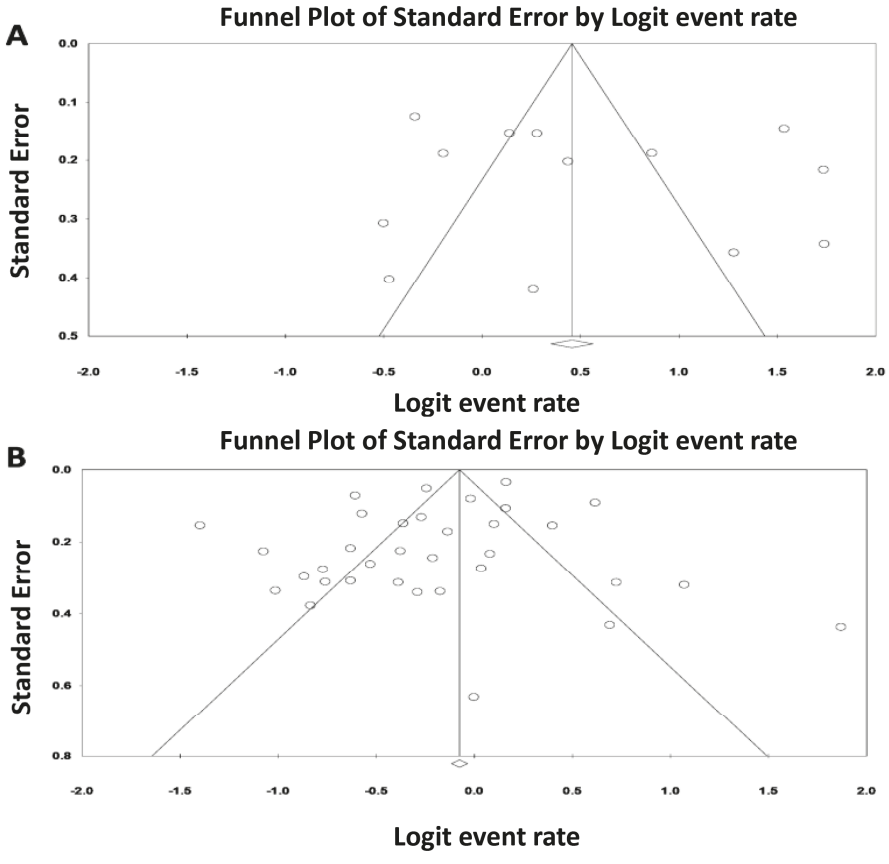

Figure 7. Funnel plot demonstrated no publication bias in analyses evaluating (**A**) incidence of AKI in patients requiring ECMO and (**B**) severe AKI requiring RRT.

4. Discussion

The findings of our meta-analysis demonstrate that patients who required ECMO had incidence rates of AKI (using standard AKI definitions) and severe AKI requiring RRT of 62.8% and 44.9%, respectively. Moreover, patients with AKI and severe AKI requiring RRT had high associated mortality rates of 62.0% and 68.4%, respectively.

Although the mechanisms underlying ECMO associated-AKI remains unclear, it is likely complex and multifactorial, including contributing factors such as primary disease progression, altered hemodynamics, low cardiac output syndrome, exposure to nephrotoxic agents (for management of underlying diseases), new-onset sepsis, high intrathoracic pressures, fluid overload, ischemia-reperfusion injury, release of proinflammatory mediators and oxidative stress, hemolysis and iron-mediated (hemoglobin-induced) renal injury, and hypercoagulable state resulting in renal microembolisms [4,8,68,78,79]. Studies have demonstrated the activation of proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukins (e.g., IL-1β, IL-6, IL-8) and other cytokine signaling cascades due to the continuous exposure of blood to non-biological and non-endothelialized ECMO interface [68,80,81]. Activation of the inflammatory cascades can result in hyperdynamic vasodilated hypotensive states, leading to AKI [68,78].

Following the initiation of ECMO treatment, there are improvements in oxygenation and oxygen consumption as well as hemodynamics [3,5–9]. However, ischemia-reperfusion injury can also occur after the restoration of circulation to previously hypoxic cells and hypoperfused organs, leading to the production of reactive oxygen species (ROS) and oxidative stress-mediated injury [68,78]. In addition, ECMO-associated complications or adverse effects such as hemolysis, hemorrhage or thrombosis also can play important roles in the development of AKI [29,68,82–84]. Despite the advance of a new miniaturized ECMO system, hemolysis due to shear stress from the ECMO circuit has been reported among ECMO patients with incidences between 5% and 18% [17,85–87]. This can contribute to heme pigment-induced AKI [83,84]. Although improvements in the ECMO technology have led to less thrombus development in its circuit with an improved capacity of the circuit to remove large emboli [68,82], smaller thrombi can still develop and result in renal microembolism [68,82], particularly with VA-ECMO [82].

The type of ECMO may also differently affect AKI risk. Our study demonstrated a higher incidence of AKI among patients requiring VA-ECMO (60.8%) than those requiring VV-ECMO (45.7%). While VV-ECMO is typically utilized for patients with isolated respiratory failure, VA-ECMO is used for combined severe cardiac and respiratory failure [4]. In VA-ECMO, there is a mixture of pulsatile arterial flow from the native heart and non-pulsatile arterial flow from the ECMO pump. Conversely, VV-ECMO maintains pulsatile cardiac output, and alterations in renal perfusion may conceivably be smaller [4]. Recent studies have shown that pulsatile flow may provide beneficial effects over non-pulsatile flow, especially protective effects on microcirculation and renal perfusion [88–90]. The differences in patient population and pulsatility between the two types of ECMO are likely explanations underlying the higher AKI incidence among patients requiring VA-ECMO.

As there is no treatment available for AKI, management of AKI is limited to appropriate secondary preventive measures and supportive strategies [91–96]. RRT in the form of continuous renal replacement therapy (CRRT) is often required among patients requiring ECMO with severe AKI [42,55,97]. Our study demonstrated no significant correlation between the year of study and the incidence of AKI and/or severe AKI requiring RRT despite considerable changes in technology and practice of ECMO among adult patients. Furthermore, we showed a 3.7-fold increased risk of hospital mortality among ECMO patients with severe AKI requiring RRT. Thus, prevention and early identification of AKI among patients at-risk of ECMO-associated AKI could potentially play a crucial role in improved survival. Studies have shown several important AKI risk factors among patients requiring ECMO including older age, elevated lactate levels before ECMO initiation, high dose of inotropic drugs, severely reduced left ventricular ejection fraction, cirrhosis, postcardiotomy shock as an indication for ECMO, and finally ECMO pump speed and its duration [56,64,67]. Lee et al. recently observed a lower AKI association with a higher ECMO pump speed [56]. Although the underlying pathophysiology remains unclear, excessive ECMO pump speed has been shown to induce hemolysis and complement activation in vitro and animal model [98,99]. In pediatric patients receiving ECMO, Lou et al. also demonstrated higher pump speeds are associated with hemolysis and a number of other adverse clinical outcomes [100]. To prevent hemolysis-mediated kidney injury, it is suggested to limit pump revolutions/min (RPM) to safe levels (i.e., 3000 to 3500 RPM) in order to avoid excessive negative pressures generated within the pump [101]. Future prospective studies are required to assess the effects of ECMO pump speed on AKI risk in ECMO patients. In addition, future studies creating risk prediction models for ECMO-associated AKI are needed to assist with the prevention of AKI in a timely manner, which could potentially lead to an improvement in patient survival.

Our study has several limitations. Firstly, there are statistical heterogeneities in our meta-analysis. Potential sources for heterogeneities were the variations in patient characteristics among the included studies. However, we performed subgroup analysis to assess the AKI incidence based on types of ECMO and a separate meta-analysis that only included studies with confounder-adjusted analysis for mortality risk. Another limitation was that AKI diagnosis was mainly based on serum creatinine [102–104] while the data on urine output and novel biomarkers for AKI [105–108] were limited. Lastly, this systematic

review is primarily based on observational studies, as the data from clinical trials or population-based studies were limited. Therefore, it can at best, demonstrate an association but not a causal relationship.

5. Conclusions

In conclusion, there is an overall high incidence of AKI and severe AKI requiring RRT in ECMO patients of 62.8% and 44.9%, respectively. The incidence of ECMO-associated AKI has not changed over time. AKI requiring RRT while on ECMO is associated with 3.7-fold increased risk of hospital mortality. Future studies should focus on strategies for prediction, detection, and prevention of AKI among patients who receive ECMO.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/7/981/s1.

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Conflicts of Interest: The authors deny any conflict of interest.

References

1. Guru, P.K.; Singh, T.D.; Passe, M.; Kashani, K.B.; Schears, G.J.; Kashyap, R. Derivation and Validation of a Search Algorithm to Retrospectively Identify CRRT Initiation in the ECMO Patients. *Appl. Clin. Inform.* **2016**, *7*, 596–603. [CrossRef] [PubMed]
2. Hill, J.D.; O'Brien, T.G.; Murray, J.J.; Dontigny, L.; Bramson, M.L.; Osborn, J.J.; Gerbode, F. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N. Engl. J. Med.* **1972**, *286*, 629–634. [CrossRef] [PubMed]
3. Peek, G.J.; Mugford, M.; Tiruvoipati, R.; Wilson, A.; Allen, E.; Thalanany, M.M.; Hibbert, C.L.; Truesdale, A.; Clemens, F.; Cooper, N.; et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* **2009**, *374*, 1351–1363. [CrossRef]
4. Chen, Y.C.; Tsai, F.C.; Fang, J.T.; Yang, C.W. Acute kidney injury in adults receiving extracorporeal membrane oxygenation. *J. Formos. Med. Assoc.* **2014**, *113*, 778–785. [CrossRef] [PubMed]
5. Thiagarajan, R.R.; Barbaro, R.P.; Rycus, P.T.; Mcmullan, D.M.; Conrad, S.A.; Fortenberry, J.D.; Paden, M.L. Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J.* **2017**, *63*, 60–67. [CrossRef] [PubMed]
6. Paden, M.L.; Conrad, S.A.; Rycus, P.T.; Thiagarajan, R.R. Extracorporeal Life Support Organization Registry Report 2012. *ASAIO J.* **2013**, *59*, 202–210. [CrossRef]
7. Schmidt, M.; Bailey, M.; Kelly, J.; Hodgson, C.; Cooper, D.J.; Scheinkestel, C.; Pellegrino, V.; Bellomo, R.; Pilcher, D. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med.* **2014**, *40*, 1256–1266. [CrossRef]
8. Hamdi, T.; Palmer, B.F. Review of Extracorporeal Membrane Oxygenation and Dialysis-Based Liver Support Devices for the Use of Nephrologists. *Am. J. Nephrol.* **2017**, *46*, 139–149. [CrossRef]
9. Husain-Syed, F.; Ricci, Z.; Brodie, D.; Vincent, J.L.; Ranieri, V.M.; Slutsky, A.S.; Taccone, F.S.; Gattinoni, L.; Ronco, C. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: From native to artificial organ crosstalk. *Intensive Care Med.* **2018**, *44*, 1447–1459. [CrossRef]
10. Bosarge, P.L.; Raff, L.A.; McGwin, G., Jr.; Carroll, S.L.; Bellot, S.C.; Diaz-Guzman, E.; Kerby, J.D. Early initiation of extracorporeal membrane oxygenation improves survival in adult trauma patients with severe adult respiratory distress syndrome. *J. Trauma Acute Care Surg.* **2016**, *81*, 236–243. [CrossRef]
11. Combes, A.; Leprince, P.; Luyt, C.E.; Bonnet, N.; Trouillet, J.L.; Léger, P.; Pavie, A.; Chastre, J. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit. Care Med.* **2008**, *36*, 1404–1411. [CrossRef] [PubMed]

12. Massetti, M.; Tasle, M.; Le Page, O.; Deredec, R.; Babatasi, G.; Buklas, D.; Thuaudet, S.; Charbonneau, P.; Hamon, M.; Grollier, G.; et al. Back from irreversibility: Extracorporeal life support for prolonged cardiac arrest. *Ann. Thorac. Surg.* **2005**, *79*, 178–183. [CrossRef] [PubMed]
13. Shin, T.G.; Choi, J.H.; Jo, I.J.; Sim, M.S.; Song, H.G.; Jeong, Y.K.; Song, Y.B.; Hahn, J.Y.; Choi, S.H.; Gwon, H.C.; et al. Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation. *Crit. Care Med.* **2011**, *39*, 1–7. [CrossRef] [PubMed]
14. Bednarczyk, J.M.; White, C.W.; Ducas, R.A.; Golian, M.; Nepomuceno, R.; Hiebert, B.; Bueddefeld, D.; Manji, R.A.; Singal, R.K.; Hussain, F.; et al. Resuscitative extracorporeal membrane oxygenation for in hospital cardiac arrest: A Canadian observational experience. *Resuscitation* **2014**, *85*, 1713–1719. [CrossRef] [PubMed]
15. Pagani, F.D.; Aaronson, K.D.; Swaniker, F.; Bartlett, R.H. The use of extracorporeal life support in adult patients with primary cardiac failure as a bridge to implantable left ventricular assist device. *Ann. Thorac. Surg.* **2001**, *71* (Suppl. 3), S77–S81. [CrossRef]
16. Kagawa, E.; Dote, K.; Kato, M.; Sasaki, S.; Nakano, Y.; Kajikawa, M.; Higashi, A.; Itakura, K.; Sera, A.; Inoue, I.; et al. Should we emergently revascularize occluded coronaries for cardiac arrest?: Rapid-response extracorporeal membrane oxygenation and intra-arrest percutaneous coronary intervention. *Circulation* **2012**, *126*, 1605–1613. [CrossRef]
17. Zangrillo, A.; Landoni, G.; Biondi-Zoccai, G.; Greco, M.; Greco, T.; Frati, G.; Patroniti, N.; Antonelli, M.; Pesenti, A.; Pappalardo, F. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit. Care Resusc.* **2013**, *15*, 172–178.
18. Ostermann, M.; Connor, M.; Jr Kashani, K. Continuous renal replacement therapy during extracorporeal membrane oxygenation: Why, when and how? *Curr. Opin. Crit. Care* **2018**, *24*, 493–503. [CrossRef]
19. Kagawa, E.; Inoue, I.; Kawagoe, T.; Ishihara, M.; Shimatani, Y.; Kurisu, S.; Nakama, Y.; Dai, K.; Takayuki, O.; Ikenaga, H.; et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. *Resuscitation* **2010**, *81*, 968–973. [CrossRef]
20. Hei, F.; Lou, S.; Li, J.; Yu, K.; Liu, J.; Feng, Z.; Zhao, J.; Hu, S.; Xu, J.; Chang, Q.; et al. Five-year results of 121 consecutive patients treated with extracorporeal membrane oxygenation at Fu Wai Hospital. *Artif. Organs* **2011**, *35*, 572–578. [CrossRef]
21. Tsai, T.Y.; Tsai, F.C.; Chang, C.H.; Jenq, C.C.; Hsu, H.H.; Chang, M.Y.; Tian, Y.C.; Hung, C.C.; Fang, J.T.; Yang, C.W.; et al. Prognosis of patients on extracorporeal membrane oxygenation plus continuous arteriovenous hemofiltration. *Chang. Gung Med. J.* **2011**, *34*, 636–643. [PubMed]
22. Belle, L.; Mangin, L.; Bonnet, H.; Fol, S.; Santre, C.; Delavenat, L.; Savary, D.; Bougon, D.; Vialle, E.; Dompnier, A.; et al. Emergency extracorporeal membrane oxygenation in a hospital without on-site cardiac surgical facilities. *EuroIntervention* **2012**, *8*, 375–382. [CrossRef] [PubMed]
23. Slottosch, I.; Liakopoulos, O.; Kuhn, E.; Deppe, A.C.; Scherner, M.; Madershahian, N.; Choi, Y.H.; Wahlers, T. Outcomes after peripheral extracorporeal membrane oxygenation therapy for postcardiotomy cardiogenic shock: A single-center experience. *J. Surg. Res.* **2013**, *181*, e47–e55. [CrossRef] [PubMed]
24. Seco, M.; Forrest, P.; Jackson, S.A.; Martinez, G.; Andvik, S.; Bannon, P.G.; Ng, M.; Fraser, J.F.; Wilson, M.K.; Vallely, M.P. Extracorporeal membrane oxygenation for very high-risk transcatheter aortic valve implantation. *Heart Lung Circ.* **2014**, *23*, 957–962. [CrossRef] [PubMed]
25. Saxena, P.; Neal, J.; Joyce, L.D.; Greason, K.L.; Schaff, H.V.; Guru, P.; Shi, W.Y.; Burkhart, H.; Li, Z.; Oliver, W.C.; et al. Extracorporeal Membrane Oxygenation Support in Postcardiotomy Elderly Patients: The Mayo Clinic Experience. *Ann. Thorac. Surg.* **2015**, *99*, 2053–2060. [CrossRef] [PubMed]
26. Thajudeen, B.; Kamel, M.; Arumugam, C.; Ali, S.A.; John, S.G.; Meister, E.E.; Mosier, J.M.; Raz, Y.; Madhrira, M.; Thompson, J.; et al. Outcome of patients on combined extracorporeal membrane oxygenation and continuous renal replacement therapy: A retrospective study. *Int. J. Artif. Organs* **2015**, *38*, 133–137. [CrossRef] [PubMed]
27. Lyu, L.; Long, C.; Hei, F.; Ji, B.; Liu, J.; Yu, K.; Chen, L.; Yao, J.; Hu, Q.; Hu, J.; et al. Plasma Free Hemoglobin Is a Predictor of Acute Renal Failure During Adult Venous-Arterial Extracorporeal Membrane Oxygenation Support. *J. Cardiothorac. Vasc. Anesth.* **2016**, *30*, 891–895. [CrossRef]
28. Martucci, G.; Panarello, G.; Occhipinti, G. Anticoagulation and Transfusions Management in Veno-Venous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: Assessment of Factors Associated With Transfusion Requirements and Mortality. *J. Intensive Care Med.* **2017**, *34*, 630–639. [CrossRef]

29. Yap, H.J.; Chen, Y.C.; Fang, J.T.; Huang, C.C. Combination of continuous renal replacement therapies (CRRT) and extracorporeal membrane oxygenation (ECMO) for advanced cardiac patients. *Ren. Fail.* **2003**, *25*, 183–193. [CrossRef]
30. Lin, C.Y.; Chen, Y.C.; Tsai, F.C.; Tian, Y.C.; Jenq, C.C.; Fang, J.T.; Yang, C.W. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. *Nephrol. Dial. Transplant.* **2006**, *21*, 2867–2873. [CrossRef]
31. Tsai, C.W.; Lin, Y.F.; Wu, V.C.; Chu, T.S.; Chen, Y.M.; Hu, F.C.; Wu, K.D.; Ko, W.J. SAPS 3 at dialysis commencement is predictive of hospital mortality in patients supported by extracorporeal membrane oxygenation and acute dialysis. *Eur. J. Cardiothorac. Surg.* **2008**, *34*, 1158–1164. [CrossRef]
32. Bakhtiary, F.; Keller, H.; Dogan, S.; Dzemali, O.; Oezaslan, F.; Meininger, D.; Ackermann, H.; Zwissler, B.; Kleine, P.; Moritz, A. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: Clinical experiences in 45 adult patients. *J. Thorac. Cardiovasc. Surg.* **2008**, *135*, 382–388. [CrossRef] [PubMed]
33. Luo, X.J.; Wang, W.; Hu, S.S.; Sun, H.S.; Gao, H.W.; Long, C.; Song, Y.H.; Xu, J.P. Extracorporeal membrane oxygenation for treatment of cardiac failure in adult patients. *Interact. Cardiovasc. Thorac. Surg.* **2009**, *9*, 296–300. [CrossRef] [PubMed]
34. Brogan, T.V.; Thiagarajan, R.R.; Rycus, P.T.; Bartlett, R.H.; Bratton, S.L. Extracorporeal membrane oxygenation in adults with severe respiratory failure: A multi-center database. *Intensive Care Med.* **2009**, *35*, 2105–2114. [CrossRef]
35. Wang, J.; Han, J.; Jia, Y.; Zeng, W.; Shi, J.; Hou, X.; Meng, X. Early and intermediate results of rescue extracorporeal membrane oxygenation in adult cardiogenic shock. *Ann. Thorac. Surg.* **2009**, *88*, 1897–1903. [CrossRef] [PubMed]
36. Yan, X.; Jia, S.; Meng, X.; Dong, P.; Jia, M.; Wan, J.; Hou, X. Acute kidney injury in adult postcardiotomy patients with extracorporeal membrane oxygenation: Evaluation of the RIFLE classification and the Acute Kidney Injury Network criteria. *Eur. J. Cardiothorac. Surg.* **2010**, *37*, 334–338. [CrossRef]
37. Elsharkawy, H.A.; Li, L.; Esa, W.A.; Sessler, D.I.; Bashour, C.A. Outcome in patients who require venoarterial extracorporeal membrane oxygenation support after cardiac surgery. *J. Cardiothorac. Vasc. Anesth.* **2010**, *24*, 946–951. [CrossRef]
38. Hsu, P.S.; Chen, J.L.; Hong, G.J.; Tsai, Y.T.; Lin, C.Y.; Lee, C.Y.; Chen, Y.G.; Tsai, C.S. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: Predictors of early mortality and outcome from 51 adult patients. *Eur. J. Cardiothorac. Surg.* **2010**, *37*, 328–333. [CrossRef]
39. Lan, C.; Tsai, P.R.; Chen, Y.S.; Ko, W.J. Prognostic factors for adult patients receiving extracorporeal membrane oxygenation as mechanical circulatory support—A 14-year experience at a medical center. *Artif. Organs* **2010**, *34*, E59–E64. [CrossRef]
40. Rastan, A.J.; Dege, A.; Mohr, M.; Doll, N.; Falk, V.; Walther, T.; Mohr, F.W. Early and late outcomes of 517 consecutive adult patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *J. Thorac. Cardiovasc. Surg.* **2010**, *139*, 302–311. [CrossRef]
41. Wu, V.C.; Tsai, H.B.; Yeh, Y.C.; Huang, T.M.; Lin, Y.F.; Chou, N.K.; Chen, Y.S.; Han, Y.Y.; Chou, A.; Lin, Y.H.; et al. Patients supported by extracorporeal membrane oxygenation and acute dialysis: Acute physiology and chronic health evaluation score in predicting hospital mortality. *Artif. Organs* **2010**, *34*, 828–835. [CrossRef] [PubMed]
42. Chen, Y.C.; Tsai, F.C.; Chang, C.H.; Lin, C.Y.; Jenq, C.C.; Juan, K.C.; Hsu, H.H.; Chang, M.Y.; Tian, Y.C.; Hung, C.C.; et al. Prognosis of patients on extracorporeal membrane oxygenation: The impact of acute kidney injury on mortality. *Ann. Thorac. Surg.* **2011**, *91*, 137–142. [CrossRef] [PubMed]
43. Bermudez, C.A.; Rocha, R.V.; Toyoda, Y.; Zaldonis, D.; Sappington, P.L.; Mulukutla, S.; Marroquin, O.C.; Toma, C.; Bhama, J.K.; Kormos, R.L. Extracorporeal membrane oxygenation for advanced refractory shock in acute and chronic cardiomyopathy. *Ann. Thorac. Surg.* **2011**, *92*, 2125–2131. [CrossRef] [PubMed]
44. Chang, W.W.; Tsai, F.C.; Tsai, T.Y.; Chang, C.H.; Jenq, C.C.; Chang, M.Y.; Tian, Y.C.; Hung, C.C.; Fang, J.T.; Yang, C.W.; et al. Predictors of mortality in patients successfully weaned from extracorporeal membrane oxygenation. *PLoS ONE* **2012**, *7*, e42687. [CrossRef] [PubMed]
45. Kim, T.H.; Lim, C.; Park, I.; Kim, D.J.; Jung, Y.; Park, K.H. Prognosis in the patients with prolonged extracorporeal membrane oxygenation. *Korea J. Thorac. Cardiovasc. Surg.* **2012**, *45*, 236–241. [CrossRef] [PubMed]

46. Lee, S.H.; Chung, C.H.; Won Lee, J.; Ho Jung, S.; Choo, S.J. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation (ECMO). *J. Card. Surg.* **2012**, *27*, 255–263. [CrossRef] [PubMed]
47. Loforte, A.; Montalto, A.; Ranocchi, F.; Della Monica, P.L.; Casali, G.; Lappa, A.; Menichetti, A.; Contento, C.; Musumeci, F. Peripheral extracorporeal membrane oxygenation system as salvage treatment of patients with refractory cardiogenic shock: Preliminary outcome evaluation. *Artif. Organs* **2012**, *36*, E53–E61. [CrossRef] [PubMed]
48. Wu, M.Y.; Lee, M.Y.; Lin, C.C.; Chang, Y.S.; Tsai, F.C.; Lin, P.J. Resuscitation of non-postcardiotomy cardiogenic shock or cardiac arrest with extracorporeal life support: The role of bridging to intervention. *Resuscitation* **2012**, *83*, 976–981. [CrossRef]
49. Aubron, C.; Cheng, A.C.; Pilcher, D.; Leong, T.; Magrin, G.; Cooper, D.J.; Scheinkestel, C.; Pellegrino, V. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: A 5-year cohort study. *Crit. Care* **2013**, *17*, R73. [CrossRef]
50. Kielstein, J.T.; Heiden, A.M.; Beutel, G.; Gottlieb, J.; Wiesner, O.; Hafer, C.; Hadem, J.; Reising, A.; Haverich, A.; Kühn, C.; et al. Renal function and survival in 200 patients undergoing ECMO therapy. *Nephrol. Dial. Transplant.* **2013**, *28*, 86–90. [CrossRef]
51. Wu, M.Y.; Tseng, Y.H.; Chang, Y.S.; Tsai, F.C.; Lin, P.J. Using extracorporeal membrane oxygenation to rescue acute myocardial infarction with cardiopulmonary collapse: The impact of early coronary revascularization. *Resuscitation* **2013**, *84*, 940–945. [CrossRef] [PubMed]
52. Lazzeri, C.; Bernardo, P.; Sori, A.; Innocenti, L.; Passantino, S.; Chiostri, M.; Gensini, G.F.; Valente, S. Renal replacement therapy in patients with refractory cardiac arrest undergoing extracorporeal membrane oxygenation. *Resuscitation* **2013**, *84*, e121–e122. [CrossRef] [PubMed]
53. Unosawa, S.; Sezai, A.; Hata, M.; Nakata, K.; Yoshitake, I.; Wakui, S.; Kimura, H.; Takahashi, K.; Hata, H.; Shiono, M. Long-term outcomes of patients undergoing extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. *Surg. Today* **2013**, *43*, 264–270. [CrossRef] [PubMed]
54. Xue, J.; Wang, L.; Chen, C.M.; Chen, J.Y.; Sun, Z.X. Acute kidney injury influences mortality in lung transplantation. *Ren. Fail.* **2014**, *36*, 541–545. [CrossRef] [PubMed]
55. Hsiao, C.C.; Chang, C.H.; Fan, P.C.; Ho, H.T.; Jenq, C.C.; Kao, K.C.; Chiu, L.C.; Lee, S.Y.; Hsu, H.H.; Tian, Y.C.; et al. Prognosis of patients with acute respiratory distress syndrome on extracorporeal membrane oxygenation: The impact of urine output on mortality. *Ann. Thorac. Surg.* **2014**, *97*, 1939–1944. [CrossRef] [PubMed]
56. Lee, S.W.; Yu, M.Y.; Lee, H.; Ahn, S.Y.; Kim, S.; Chin, H.J.; Na, K.Y. Risk Factors for Acute Kidney Injury and In-Hospital Mortality in Patients Receiving Extracorporeal Membrane Oxygenation. *PLoS ONE* **2015**, *10*, e0140674. [CrossRef] [PubMed]
57. Haneya, A.; Diez, C.; Philipp, A.; Bein, T.; Mueller, T.; Schmid, C.; Lubnow, M. Impact of Acute Kidney Injury on Outcome in Patients With Severe Acute Respiratory Failure Receiving Extracorporeal Membrane Oxygenation. *Crit. Care Med.* **2015**, *43*, 1898–1906. [CrossRef]
58. Huang, L.; Li, T.; Xu, L.; Hu, X.M.; Duan, D.W.; Li, Z.B.; Gao, X.J.; Li, J.; Wu, P.; Liu, Y.W. Extracorporeal Membrane Oxygenation Outcomes in Acute Respiratory Distress Treatment: Case Study in a Chinese Referral Center. *Med. Sci. Monit.* **2017**, *23*, 741–750. [CrossRef]
59. Antonucci, E.; Lamanna, I.; Fagnoul, D.; Vincent, J.L.; De Backer, D.; Silvio Taccone, F. The Impact of Renal Failure and Renal Replacement Therapy on Outcome During Extracorporeal Membrane Oxygenation Therapy. *Artif. Organs* **2016**, *40*, 746–754. [CrossRef]
60. Tsai, T.Y.; Chien, H.; Tsai, F.C.; Pan, H.C.; Yang, H.Y.; Lee, S.Y.; Hsu, H.H.; Fang, J.T.; Yang, C.W.; Chen, Y.C. Comparison of, R.I.F.L.E.; AKIN, and KDIGO classifications for assessing prognosis of patients on extracorporeal membrane oxygenation. *J. Formos. Med. Assoc.* **2017**, *116*, 844–851. [CrossRef]
61. Panholzer, B.; Meckelburg, K.; Huenges, K.; Hoffmann, G.; von der Brelie, M.; Haake, N.; Pilarczyk, K.; Cremer, J.; Haneya, A. Extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: An analysis of differences between survivors and non-survivors. *Perfusion* **2017**, *32*, 495–500. [CrossRef] [PubMed]
62. Chong, S.Z.; Fang, C.Y.; Fang, H.Y.; Chen, H.C.; Chen, C.J.; Yang, C.H.; Hang, C.L.; Yip, H.K.; Wu, C.J.; Lee, W.C. Associations with the In-Hospital Survival Following Extracorporeal Membrane Oxygenation in Adult Acute Fulminant Myocarditis. *J. Clin. Med.* **2018**, *7*, 452. [CrossRef] [PubMed]

63. Devasagayaraj, R.; Cavarocchi, N.C.; Hirose, H. Does acute kidney injury affect survival in adults with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation? *Perfusion* **2018**, *33*, 375–382. [CrossRef] [PubMed]
64. Liao, X.; Cheng, Z.; Wang, L.; Li, B. Analysis of the risk factors of acute kidney injury in patients receiving extracorporeal membrane oxygenation. *Clin. Nephrol.* **2018**, *90*, 270–275. [CrossRef] [PubMed]
65. Paek, J.H.; Park, S.; Lee, A.; Park, S.; Chin, H.J.; Na, K.Y.; Lee, H.; Park, J.T.; Kim, S. Timing for initiation of sequential continuous renal replacement therapy in patients on extracorporeal membrane oxygenation. *Kidney Res. Clin. Pract.* **2018**, *37*, 239–247. [CrossRef]
66. He, P.; Zhang, S.; Hu, B.; Wu, W. Retrospective study on the effects of the prognosis of patients treated with extracorporeal membrane oxygenation combined with continuous renal replacement therapy. *Ann. Transl. Med.* **2018**, *6*, 455. [CrossRef] [PubMed]
67. Zhang, H.; Wu, J.; Zou, D.; Xiao, X.; Yan, H.; Li, X.C.; Chen, W. Ablation of interferon regulatory factor 4 in T cells induces "memory" of transplant tolerance that is irreversible by immune checkpoint blockade. *Am. J. Transplant.* **2019**, *19*, 884–893. [CrossRef]
68. Kilburn, D.J.; Shekar, K.; Fraser, J.F. The Complex Relationship of Extracorporeal Membrane Oxygenation and Acute Kidney Injury: Causation or Association? *BioMed Res. Int.* **2016**, *2016*, 1094296. [CrossRef]
69. Cheng, R.; Hachamovitch, R.; Kittleson, M.; Patel, J.; Arabia, F.; Moriguchi, J.; Esmailian, F.; Azarbal, B. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann. Thorac.Surg.* **2014**, *97*, 610–616. [CrossRef]
70. Lin, C.Y.; Tsai, F.C.; Tian, Y.C.; Jenq, C.C.; Chen, Y.C.; Fang, J.T.; Yang, C.W. Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation. *Ann. Thorac. Surg.* **2007**, *84*, 1256–1262. [CrossRef]
71. Moher, D.; Liberati, A.; Tetzlaff JAltman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
72. Bellomo, R.; Ronco, C.; Kellum, J.A.; Mehta, R.L. Palevsky PAcute renal failure—Definition outcome measures animal, m.o.d.e.l.s., fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **2004**, *8*, R204–R212. [CrossRef] [PubMed]
73. Mehta, R.L.; Kellum, J.A.; Shah, S.V.; Molitoris, B.A.; Ronco, C.; Warnock, D.G.; Levin, A. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Crit. Care* **2007**, *11*, R31. [CrossRef] [PubMed]
74. Section 2: AKI Definition. *Kidney Int.* **2012**, *2*, 19–36. [CrossRef] [PubMed]
75. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
76. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef] [PubMed]
77. Easterbrook, P.J.; Gopalan, R.; Berlin, J.A.; Matthews, D.R. Publication bias in clinical research. *Lancet* **1991**, *337*, 867–872. [CrossRef]
78. McDonald, C.I.; Fraser, J.F.; Coombes, J.S.; Fung, Y.L. Oxidative stress during extracorporeal circulation. *Eur. J. Cardiothorac. Surg.* **2014**, *46*, 937–943. [CrossRef] [PubMed]
79. Ikeda, M.; Prachasilchai, W.; Burne-Taney, M.J.; Rabb, H.; Yokota-Ikeda, N. Ischemic acute tubular necrosis models and drug discovery: A focus on cellular inflammation. *Drug Discov. Today* **2006**, *11*, 364–370. [CrossRef] [PubMed]
80. Yimin, H.; Wenkui, Y.; Jialiang, S.; Qiyi, C.; Juanhong, S.; Zhiliang, L.; Changsheng, H.; Ning, L.; Jieshou, L. Effects of continuous renal replacement therapy on renal inflammatory cytokines during extracorporeal membrane oxygenation in a porcine model. *J. Cardiothorac. Surg.* **2013**, *8*, 113. [CrossRef] [PubMed]
81. McILwain, R.B.; Timpa, J.G.; Kurundkar, A.R.; Holt, D.W.; Kelly, D.R.; Hartman, Y.E.; Neel, M.L.; Karnatak, R.K.; Schelonka, R.L.; Anantharamaiah, G.M.; et al. Plasma concentrations of inflammatory cytokines rise rapidly during ECMO-related SIRS due to the release of preformed stores in the intestine. *Lab. Investig.* **2010**, *90*, 128–139. [CrossRef] [PubMed]
82. Reed, R.C.; Rutledge, J.C. Laboratory and clinical predictors of thrombosis and hemorrhage in 29 pediatric extracorporeal membrane oxygenation nonsurvivors. *Pediatr. Dev. Pathol.* **2010**, *13*, 385–392. [CrossRef] [PubMed]

83. Williams, D.C.; Turi, J.L.; Hornik, C.P.; Bonnadonna, D.K.; Williford, W.L.; Walczak, R.J.; Watt, K.M.; Cheifetz, I.M. Circuit oxygenator contributes to extracorporeal membrane oxygenation-induced hemolysis. *ASAIO J.* **2015**, *61*, 190–195. [CrossRef] [PubMed]
84. Askenazi, D.J.; Selewski, D.T.; Paden, M.L.; Cooper, D.S.; Bridges, B.C.; Zappitelli, M.; Fleming, G.M. Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1328–1336. [CrossRef] [PubMed]
85. Lubnow, M.; Philipp, A.; Foltan, M.; Enger, T.B.; Lunz, D.; Bein, T.; Haneya, A.; Schmid, C.; Riegger, G.; Müller, T.; et al. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange—Retrospective analysis of 265 cases. *PLoS ONE* **2014**, *9*, e112316. [CrossRef] [PubMed]
86. Murphy, D.A.; Hockings, L.E.; Andrews, R.K.; Aubron, C.; Gardiner, E.E.; Pellegrino, V.A.; Davis, A.K. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus. Med. Rev.* **2015**, *29*, 90–101. [CrossRef]
87. Lehle, K.; Philipp, A.; Zeman, F.; Lunz, D.; Lubnow, M.; Wendel, H.P.; Göbölös, L.; Schmid, C.; Müller, T. Technical-Induced Hemolysis in Patients with Respiratory Failure Supported with Veno-Venous ECMO—Prevalence and Risk Factors. *PLoS ONE* **2015**, *10*, e0143527. [CrossRef] [PubMed]
88. Ademir, T.; Ak, K.; Aljodi, M.; Elçi, M.E.; Arsan, S.; Isbir, S. The effects of pulsatile cardiopulmonary bypass on acute kidney injury. *Int. J. Artif. Organs* **2012**, *35*, 511–519. [CrossRef]
89. Abu-Omar, Y.; Ratnatunga, C. Cardiopulmonary bypass and renal injury. *Perfusion* **2006**, *21*, 209–213. [CrossRef]
90. Santana-Santos, E.; Marcusso, M.E.; Rodrigues, A.O.; Queiroz, F.G.; Oliveira, L.B.; Rodrigues, A.R.; Palomo, J.D. Strategies for prevention of acute kidney injury in cardiac surgery: An integrative review. *Revista Brasileira Terpia Intensiva* **2014**, *26*, 183–192. [CrossRef]
91. Thongprayoon, C.; Kaewput, W.; Thamcharoen, N.; Bathini, T.; Watthanasuntorn, K.; Lertjitbanjong, P.; Sharma, K.; Salim, S.A.; Ungprasert, P.; Wijarnpreecha, K.; et al. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 372. [CrossRef] [PubMed]
92. Thongprayoon, C.; Kaewput, W.; Thamcharoen, N.; Bathini, T.; Watthanasuntorn, K.; Salim, S.A.; Ungprasert, P.; Lertjitbanjong, P.; Aeddula, N.R.; Torres-Ortiz, A.; et al. Acute Kidney Injury in Patients Undergoing Total Hip Arthroplasty: A Systematic Review and Meta-Analysis. *J. Clin. Med.* **2019**, *8*, 66. [CrossRef] [PubMed]
93. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Harrison, A.M.; Erickson, S.B. Elevated admission serum calcium phosphate product as an independent risk factor for acute kidney injury in hospitalized patients. *Hosp. Pract. (1995)* **2019**, *47*, 73–79. [CrossRef] [PubMed]
94. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Kashani, K. U-shape association of serum albumin level and acute kidney injury risk in hospitalized patients. *PLoS ONE* **2018**, *13*, e0199153. [CrossRef] [PubMed]
95. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Erickson, S.B. Admission calcium levels and risk of acute kidney injury in hospitalised patients. *Int. J. Clin. Pract.* **2018**, *72*, e13057. [CrossRef] [PubMed]
96. Thongprayoon, C.; Cheungpasitporn, W.; Mao, M.A.; Sakhuja, A.; Erickson, S.B. Admission hyperphosphatemia increases the risk of acute kidney injury in hospitalized patients. *J. Nephrol.* **2018**, *31*, 241–247. [CrossRef] [PubMed]
97. Razo-Vazquez, A.O.; Thornton, K. Extracorporeal Membrane Oxygenation-What the Nephrologist Needs to Know. *Adv. Chronic Kidney Dis.* **2016**, *23*, 146–151. [CrossRef]
98. Pedersen, T.H.; Videm, V.; Svennevig, J.L.; Karlsen, H.; Østbakk, R.W.; Jensen, Ø.; Mollnes, T.E. Extracorporeal membrane oxygenation using a centrifugal pump and a servo regulator to prevent negative inlet pressure. *Ann. Thorac. Surg.* **1997**, *63*, 1333–1339. [CrossRef]
99. Kress, D.C.; Cohen, D.J.; Swanson, D.K.; Hegge, J.O.; Young, J.W.; Watson, K.M.; Rasmussen, P.W.; Berkoff, H.A. Pump-induced hemolysis in a rabbit model of neonatal ECMO. *ASAIO Trans.* **1987**, *33*, 446–452.
100. Lou, S.; MacLaren, G.; Best, D.; Delzoppo, C.; Butt, W. Hemolysis in pediatric patients receiving centrifugal-pump extracorporeal membrane oxygenation: Prevalence, risk factors, and outcomes. *Crit. Care Med.* **2014**, *42*, 1213–1220. [CrossRef]

101. Toomasian, J.M.; Bartlett, R.H. Hemolysis and ECMO pumps in the 21st Century. *Perfusion* **2011**, *26*, 5–6. [CrossRef] [PubMed]
102. Thongprayoon, C.; Cheungpasitporn, W.; Kittanamongkolchai, W.; Harrison, A.M.; Kashani, K. Prognostic Importance of Low Admission Serum Creatinine Concentration for Mortality in Hospitalized Patients. *Am. J. Med.* **2017**, *130*, 545–554. [CrossRef] [PubMed]
103. Thongprayoon, C.; Cheungpasitporn, W.; Kashani, K. Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients. *J. Thorac. Dis.* **2016**, *8*, E305–E311. [CrossRef] [PubMed]
104. Thongprayoon, C.; Cheungpasitporn, W.; Kittanamongkolchai, W.; Srivali, N.; Ungprasert, P.; Kashani, K. Optimum methodology for estimating baseline serum creatinine for the acute kidney injury classification. *Nephrology (Carlton)* **2015**, *20*, 881–886. [CrossRef] [PubMed]
105. Vaidya, V.S.; Ramirez, V.; Ichimura, T.; Bobadilla, N.A.; Bonventre, J.V. Urinary kidney injury molecule-1: A sensitive quantitative biomarker for early detection of kidney tubular injury. *Am. J. Physiol. Renal Physiol.* **2006**, *290*, F517–F529. [CrossRef]
106. Mishra, J.; Ma, Q.; Prada, A.; Mitsnefes, M.; Zahedi, K.; Yang, J.; Barasch, J.; Devarajan, P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J. Am. Soc. Nephrol.* **2003**, *14*, 2534–2543. [CrossRef]
107. Hosohata, K.; Ando, H.; Fujimura, A. Urinary vanin-1 as a novel biomarker for early detection of drug-induced acute kidney injury. *J. Pharmacol. Exp. Ther.* **2012**, *341*, 656–662. [CrossRef]
108. Kashani, K.; Cheungpasitporn, W.; Ronco, C. Biomarkers of acute kidney injury: The pathway from discovery to clinical adoption. *Clin. Chem. Lab. Med.* **2017**, *55*, 1074–1089. [CrossRef]

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Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis

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Abstract: Background: The study's aim was to summarize the incidence and impacts of post-liver transplant (LTx) acute kidney injury (AKI) on outcomes after LTx. Methods: A literature search was performed using the MEDLINE, EMBASE and Cochrane Databases from inception until December 2018 to identify studies assessing the incidence of AKI (using a standard AKI definition) in adult patients undergoing LTx. Effect estimates from the individual studies were derived and consolidated utilizing random-effect, the generic inverse variance approach of DerSimonian and Laird. The protocol for this systematic review is registered with PROSPERO (no. CRD42018100664). Results: Thirty-eight cohort studies, with a total of 13,422 LTx patients, were enrolled. Overall, the pooled estimated incidence rates of post-LTx AKI and severe AKI requiring renal replacement therapy (RRT) were 40.7% (95% CI: 35.4%–46.2%) and 7.7% (95% CI: 5.1%–11.4%), respectively. Meta-regression showed that the year of study did not significantly affect the incidence of post-LTx AKI ($p = 0.81$). The pooled estimated in-hospital or 30-day mortality, and 1-year mortality rates of patients with post-LTx AKI were 16.5% (95% CI: 10.8%–24.3%) and 31.1% (95% CI: 22.4%–41.5%), respectively. Post-LTx AKI and severe AKI requiring RRT were associated with significantly higher mortality with pooled ORs of 2.96 (95% CI: 2.32–3.77) and 8.15 (95%CI: 4.52–14.69), respectively. Compared to those without post-LTx AKI, recipients with post-LTx AKI had significantly increased risk of liver graft failure and chronic kidney disease with pooled ORs of 3.76 (95% CI: 1.56–9.03) and 2.35 (95% CI: 1.53–3.61), respectively. Conclusion: The overall estimated incidence rates of post-LTx AKI and severe AKI requiring RRT are 40.8% and 7.0%, respectively. There are significant associations of post-LTx AKI with increased mortality and graft failure after transplantation. Furthermore, the incidence of post-LTx AKI has remained stable over the ten years of the study.

Keywords: Acute renal failure; Acute kidney injury; Epidemiology; Incidence; Meta-analysis; Liver Transplantation; Transplantation; Systematic reviews

1. Introduction

Acute kidney injury (AKI) is associated with high mortality worldwide (1.7 million deaths per year) [1–4]. Patients who survive AKI are at increased risk for significant morbidities such as hypertension and progressive chronic kidney disease (CKD) [5]. The incidence of AKI has steadily increased in recent years [2]. It has been suggested that AKI's global burden is 13.3 million cases a year [6]. In the United States, hospitalizations for AKI have been steeply rising, and data from national inpatient sample shows that the number of hospitalizations due to AKI increased from 953,926 in 2000 to 1,823,054 in 2006 and 3,959,560 in 2014, which accounts for one hospitalization associated with AKI every 7.5 minutes [7,8].

AKI is a common and significant complication after liver transplantation (LTx), and is associated with increased mortality, hospital length of stay, utilization of resources, and health care costs [9–27]. Although the survival of LTx recipients has improved substantially over the past five decades, mortality rates related to post-LTx AKI and subsequent progressive CKD remain high and are of increasing concern [14,15,28–31]. The underlying mechanisms for post-LTx AKI appear to be complex and differ from other medical or surgery-associated AKI [11,23–25,32–35]. Recent studies have suggested several important factors that influence post-LTx AKI, including hepatic ischemia-reperfusion injury (HIRI) [36–38], increased use of high-risk or marginal grafts, and transplantation of liver grafts to sicker patients with higher Model For End-Stage Liver Disease (MELD) score or with more comorbidities [23,39–51]. In our literature review, the reported incidences are a farrago, having a range between 5% to 94% [10,11,14–25,28–35,39–49,52–80]. These wide variabilities are possibly due to non-uniform definitions of AKI [10,11,14–25,28–35,39–49,52–80]. In addition, despite progress in transplant medicine, the incidence, risk factors, and mortality associated with AKI in post-LTx patients and their trends remain unclear [10,11,14–25,28–35,39–49,52–83].

Thus, we performed a systematic review to summarize the incidence (using standard AKI definitions of Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) classifications), risk factors, and mortality and their trends for AKI in patients undergoing LTx.

2. Methods

2.1. Search Strategy and Literature Review

The protocol for this systematic review was registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018100664). A systematic literature search of MEDLINE (1946 to December 2018), EMBASE (1988 to December 2018) and the Cochrane Database of Systematic Reviews (database inception to December 2018) was performed to evaluate the incidence of AKI in adult patients undergoing LTx. The systematic literature review was conducted independently by two investigators (C.T. and W.C.) using the search strategy that consolidated the terms "acute kidney injury" OR "renal failure" AND "liver transplantation," which is provided in online supplementary data 1. No language limitation was implemented. A manual search for conceivably related studies using references of the included articles was also performed. This study was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [84] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [85].

2.2. Selection Criteria

Eligible studies must be clinical trials or observational studies (cohort, case-control, or cross-sectional studies) that reported the incidence of post-LTx AKI in adult patients (age >/= 18 years old). Included studies must provide data to estimate the incidence of post-LTx AKI with 95% confidence intervals (CI). Retrieved articles were individually reviewed for eligibility by the two investigators (C.T. and W.C.). Discrepancies were addressed and solved by mutual consensus. Inclusion was not limited by the size of study.

2.3. Data Abstraction

A structured data collecting form was used to obtain the following information from each study, including title, name of the first author, year of the study, publication year, country where the study was conducted, post-LTx AKI definition, incidence of AKI post-LTx, risk factors for post-LTx AKI, and impact of post-LTx AKI on patient outcomes.

2.4. Statistical Analysis

Analyses were performed utilizing the Comprehensive Meta-Analysis 3.3 software (Biostat Inc, Englewood, NJ, USA). Adjusted point estimates from each study were consolidated by the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance [86]. Given the possibility of between-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were applied to determine the between-study heterogeneity. A value of I^2 of 0%–25% represents insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and 76–100% high heterogeneity [87]. The presence of publication bias was assessed by the Egger test [88].

3. Results

A total of 2525 potentially eligible articles were identified using our search strategy. After the exclusion of 1994 articles based on title and abstract for clearly not fulfilling inclusion criteria on the basis of type of article, patient population, study design, or outcome of interest, and 417 due to being duplicates, 114 articles were left for full-length review. Thirty-six of them were excluded from the full-length review as they did not report the outcome of interest, while 17 were excluded because they were not observational studies or clinical trials. Twenty-three studies were subsequently excluded because they did not use a standard AKI definition. Thus, we included 38 cohort studies [14,18,19,21,28–32,39,41–44,48,49,55–60,62–66,69,70,72–80] in the meta-analysis of post-LTx AKI incidence with 13,422 patients enrolled. The literature retrieval, review, and selection process are demonstrated in Figure 1. The characteristics of the included studies are presented in Table 1.

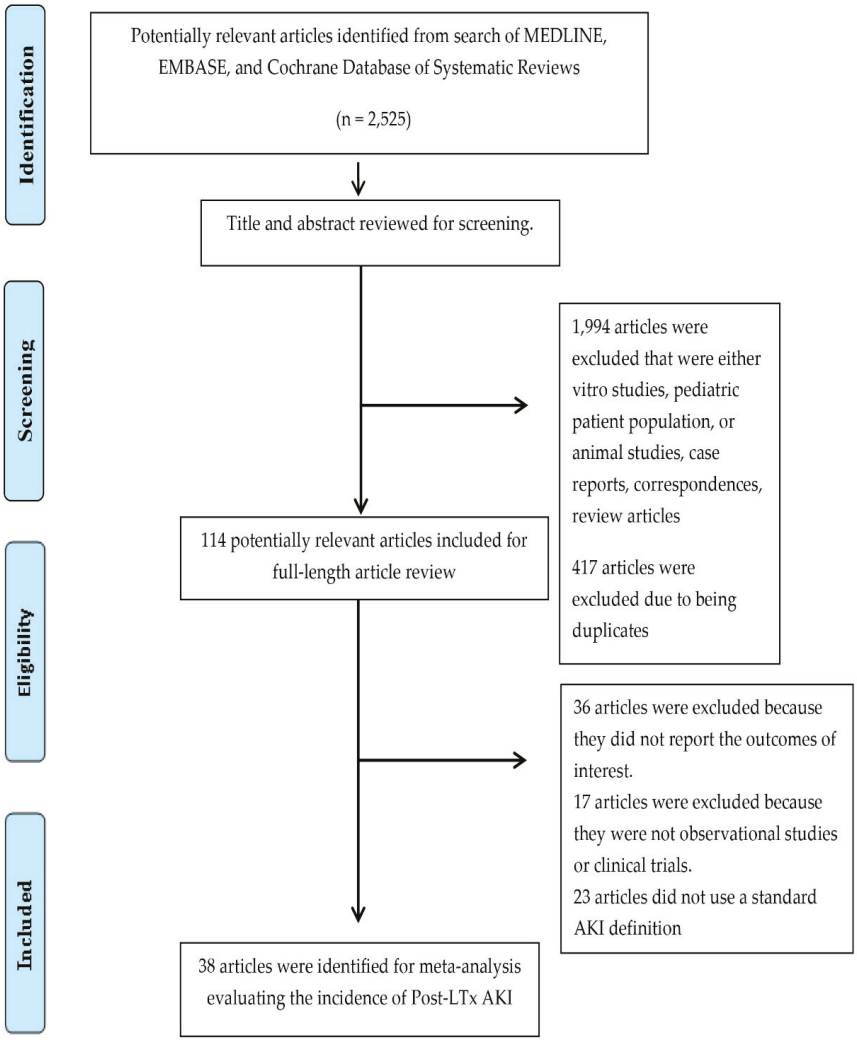

Figure 1. Outline of our search methodology.

Table 1. Main characteristics of studies included in meta-analysis of AKI in patients undergoing LTx [14,18,19,21,28–32,39,41–44,48,49,55–60,62–66,69,70,72–80].

Study	Year	Country	Procedure/Patients	Number	Deceased Donor	AKI Definition	Incidence	Mortality in AKI
O'riordan et al. [32]	2007	Ireland	Deceased donor orthotopic liver transplant	350	350 (100%)	ARI/ARF; RIFLE Injury and Failure stage within 2 weeks after transplant	ARI/ARF 129/350 (36.9%) Dialysis 68/350 (19.4%)	1-year mortality 56/129 (43%)
Kundakci et al. [41]	2010	Turkey	Orthotopic liver transplant	112	75 (67%)	AKI; RIFLE criteria	AKI 64/112 (57.1%)	1-year mortality 23/64 (36%)
Portal et al. [55]	2010	UK	Liver transplant	80	N/A	AKI; AKIN criteria within 48 hours after transplants	AKI 30/80 (37.5%)	N/A
Zhu et al. [42]	2010	China	Deceased donor orthotopic liver transplant	193	193 (100%)	AKI; AKIN criteria within 28 days after transplants	AKI 116/193 (60.1%) Dialysis 10/193 (5.2%)	1-year mortality 30/116 (26%)
Lee et al. [56]	2010	Korea	Liver transplant	431	99 (23%)	AKI; RIFLE criteria	AKI 118/431 (27.4%) Dialysis 14/431 (3.2%)	N/A
Ferreira et al. [57]	2010	Portugal	Orthotopic liver transplant	708	N/A	AKI; RIFLE criteria within 21 days after transplant	AKI 235/708 (33.2%) Dialysis 73/708 (10.3%)	Mortality 43/235 (18%)
Tinti et al. [58]	2010	Italy	Deceased donor orthotopic liver transplant	24	24 (100%)	AKI; RIFLE criteria within 15 days after transplant	AKI 9/24 (37.5%)	N/A
Chen et al. (1) [18]	2011	USA	Liver transplant	334	N/A	ARI/ARF; RIFLE Injury and Failure stage within 2 weeks after transplant within 7 days after transplant	ARI/ARF 118/334 (38.3%)	Mortality 13/118 (11%)
Umbro et al. [59]	2011	Italy	Deceased donor liver transplant	46	46 (100%)	AKI; RIFLE criteria within 7 days after transplant	AKI 26/46 (56.5%)	N/A
Karapanagiotou et al. (1) [43]	2012	Greece	Orthotopic liver transplant	75	N/A	AKI; an increase in SCr 1.5 times above baseline or value > 2.0 mg/dL within 7 days after transplant	AKI 22/75 (29.3%) Dialysis 7/75 (9.3%)	1-year mortality 11/22 (50%)
Utsumi et al. [44]	2013	Japan	Living donor liver transplant	200	0 (0%)	AKI; RIFLE criteria within 28 days after transplants	AKI 121/200 (60.5%) ARI/ARF 74/200 (37%)	Hospital mortality AKI 14/121 (12%) ARI/ARF 12/74(16%) 1-year mortality AKI 24/121 (20%) ARI/ARF 22/74 (30%)

Table 1. *Cont.*

Study	Year	Country	Procedure/Patients	Number	Deceased Donor	AKI Definition	Incidence	Mortality in AKI
Narciso et al. [60]	2013	Brazil	Liver transplant	315	181 (57%)	AKI; AKIN criteria within 48 hours after transplants	AKI 48 hours: 101/315 (32.1%) 1 week: 255/315 (81%) Hospitalization: 293/315 (93%) Dialysis Any: 48/315 (15.2%) 1 week: 31/315 (9.8%)	Dialysis 28/48 (58%)
Leithead et al. [39]	2014	UK	Liver transplant	1152	1152 (100%) DCD 112 (10%)	AKI; KDIGO criteria within 7 days after transplants	AKI 381/1152 (33.1%) Dialysis 238/1152 (20.7%)	AKI 152/381 (40%)
Karapanagiotou et al. (2) [48]	2014	Greece	Liver transplant	71	N/A	AKI; RIFLE within 7 days or AKIN criteria within 48 hours	RIFLE AKI 28/71 (39.4%) AKIN AKI 37/71 (52.1%)	6-month mortality RIFLE AKI 15/28 (54%) AKIN AKI 17/37 (46%)
Nadeem et al. [49]	2014	Saudi Arabia	Liver transplant	158	N/A	AKI; RIFLE criteria within 72 hours after transplants	AKI 57/158 (36.1%)	N/A
Lewandowska et al. [62]	2014	Poland	Orthotopic liver transplant	63	N/A	AKI; RIFLE criteria within 72 hours after transplant	AKI 35/63 (55.6%)	N/A
Barreto et al. [63]	2015	Brazil	Orthotopic liver transplant	134	N/A	AKI; AKIN criteria 2 or 3 within 72 hours after transplants	AKIN stage 2 or 3 64/134 (47.8%) Dialysis 33/134 (24.6%)	N/A
Hilmi et al. [19]	2015	USA	Deceased donor liver transplant	424	424 (100%) EDC 257 (61%)	AKI; KDIGO criteria within 72 hours after transplant	AKI 221/424 (52.1%)	30-day mortality 3/221 (1%)
Park et al. [64]	2015	Korea	Living donor liver transplant	538	0 (0%)	AKI; RIFLE criteria within 30 days after transplant	AKI 147/538 (27.3%) Dialysis 34/538 (6.3%)	Hospital mortality 26/147 (18%) 1-year mortality 29/147 (20%)
Mukhtar et al. [65]	2015	Egypt	Living donor liver transplant	303	0 (0%)	AKI; AKIN criteria within 96 hours after transplant	AKI 115/303 (38%) Dialysis 28/303 (9.2%)	N/A

Table 1. *Cont.*

Study	Year	Country	Procedure/Patients	Number	Deceased Donor	AKI Definition	Incidence	Mortality in AKI
Sang et al. [66]	2015	Korea	Living donor liver transplant	998	0 (0%)	AKI; RIFLE or AKIN criteria within 7 days after transplant	RIFLE AKI 709/998 (71.0%) AKIN AKI 593/998 (59.4%)	RIFLE AKI 79/709 (11%) AKIN AKI 66/593 (11%)
Biancofiore et al. [69]	2015	Italy	Deceased donor liver transplant	295	295 (100%)	AKI; AKIN criteria within 7 days after transplant	AKIN stage 2 AKI 51/295 (17.3%)	N/A
Jun et al. [70]	2016	Korea	Living donor liver transplant	1617	0 (0%)	AKI; KDIGO criteria within 7 days after transplant	AKI 999/1617 (61.8%) Dialysis 9/448 (2%)	N/A
Erdost et al. [72]	2016	Turkey	Liver transplant	440	194 (44%)	AKI; RIFLE, AKIN, KDIGO criteria within 7 days after transplant	RIFLE AKI 35/440 (8.0%) AKIN AKI 63/440 (14.3%) KDIGO AKI 64/440 (14.5%)	30-day mortality RIFLE AKI 8/35 (23%) AKIN AKI 34/63 (54%) KDIGO AKI 35/64 (55%)
Kamei et al. [73]	2016	Japan	Liver transplant	62	DBD 4 (6%)	AKI; RIFLE injury or failure stage within 4 weeks after transplant	AKI 13/62 (21%) Dialysis 4/62 (6.5%)	N/A
Mizota et al. (1) [74]	2016	Japan	Living donor liver transplant	320	0 (0%)	AKI; KDIGO criteria within 7 days after transplant	AKI 199/320 (62.2%)	Hospital mortality 39/199 (20%)
Sun et al. [21]	2017	USA	Liver transplant	1037	N/A	AKI; AKIN criteria within 48 hours after transplant	AKI 549/1037 (54.9%)	N/A
Chae et al. [75]	2017	Korea	Living donor liver transplant	334	0 (0%)	AKI; AKIN criteria within 48 hours after transplant	AKI 76/334 (22.7%)	Hospital mortality 10/76 (13.2%)
Mizota et al. (2) [76]	2017	Japan	Living donor liver transplant	231	0 (0%)	Severe AKI; KDIGO stage 2 or 3 criteria within 7 days after transplant	Severe AKI 71/231 (30.7%)	Hospital mortality 23/71 (32.4%)
Trinh et al. [77]	2017	Canada	Deceased donor liver transplant	491	491 (100%)	AKI; KDIGO criteria within 7 days after transplant	AKI 278/491 (56.6%)	N/A
Kalisvaart et al. [78]	2017	Netherlands	Donation after brain death liver transplant	155	155 (100%) DBD 155 (100%)	AKI; AKIN criteria within 7 days after transplant	AKI 61/155 (39.4%) Dialysis 5/155 (3.2%)	Hospital mortality 9/61 (15%)
Chen et al. (2) [79]	2017	China	Liver transplant in hepatocellular carcinoma	566	N/A	AKI; AKIN criteria within 48 hours after transplant	AKI 109/566 (19.3%) Dialysis 13/566 (2.3%)	30-day mortality 9/109 (8%)

Table 1. *Cont.*

Study	Year	Country	Procedure/Patients	Number	Deceased Donor	AKI Definition	Incidence	Mortality in AKI
Baron-Stefaniak et al. [80]	2017	Austria	Orthotopic liver transplant	45	N/A	AKI; KDIGO criteria within 48 hours after transplant	AKI 34/45 (75.6)	N/A
Zhou et al. [30]	2017	China	Donation after circulatory death orthotopic liver transplant	103	103 (100%) DCD 103 (100%)	AKI; KDIGO criteria within 7 days after transplant	AKI 42/103 (40.8%) CRRT 7/103 (6.8%)	N/A
Yoo et al. [31]	2017	Korea	Liver transplant	304	84 (28%)	AKI; RIFLE criteria within 7 days after transplant	AKI 132/304 (43.4%)	N/A
Jochmans [29]	2017	Belgium	Orthotopic liver transplant	80	80 (100%) DCD 13 (16%) DBD 67 (84%)	AKI; RIFLE criteria within 5 days after reperfusion	AKI 21/80 (26.3%) Dialysis 4/80 (5%)	1-year mortality 2/21 (10%)
Kandil et al. [28]	2017	Egypt	Living donor liver transplant	50	0 (0%)	AKI; AKIN criteria within 48 hours	AKI 23/50 (46%)	N/A
Kim et al. [14]	2018	Korea	Living donor liver transplant	583	0 (0%)	AKI; KDIGO criteria within 7 days after transplant	AKI 205/583 (35.2%)	N/A

Abbreviations: AKIN, Acute Kidney Injury Network; DCD, donation after circulatory death; EDC, extended donor criteria liver allografts; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; UK, United Kingdom; USA, United States of America.

3.1. Incidence of Post-LTx AKI

Overall, the pooled estimated incidence rates of post-LTx AKI and severe AKI requiring RRT following LTx were 40.7% (95% CI: 35.4%–46.2%, I^2 = 97%, Figure 2) and 7.7% (95% CI: 5.1%–11.4%, I^2 = 95%, Figure 3), respectively.

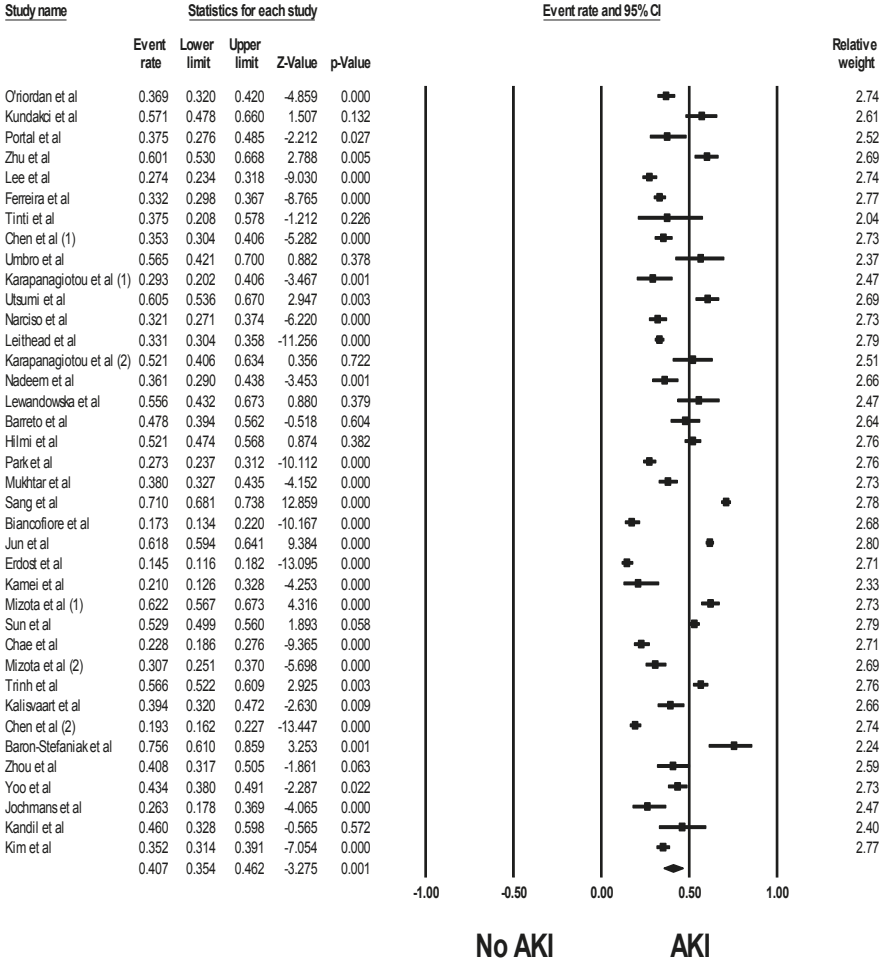

Figure 2. Forest plots of the included studies assessing incidence rates of post-LTx AKI. A diamond data marker represents the overall rate from each included study (square data marker) and 95% confidence interval.

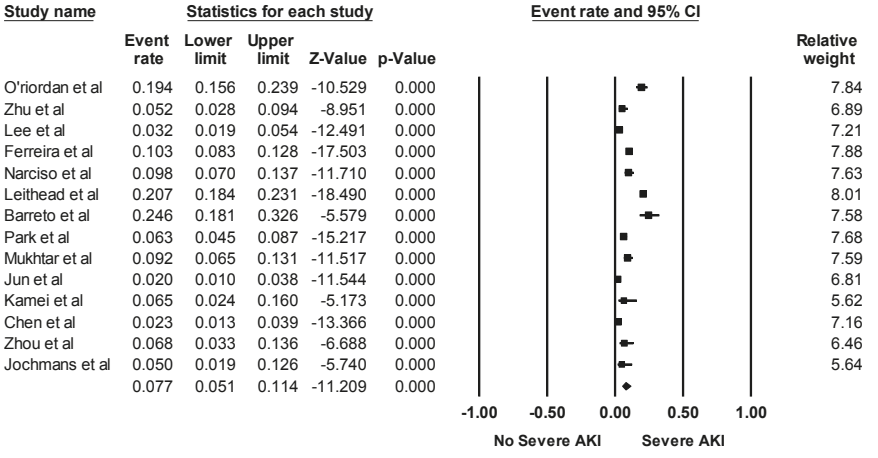

Figure 3. Forest plots of the included studies assessing incidence rates of severe AKI requiring RRT following LTx. A diamond data marker represents the overall rate from each included study (square data marker) and 95% confidence interval.

Meta-regression showed no significant impact of type of donor (deceased vs living donors) ($p = 0.33$) on the incidence of post-LTx AKI. In addition, the year of study ($p = 0.81$) did not significantly affect the incidence of post-LTx AKI (Figure 4).

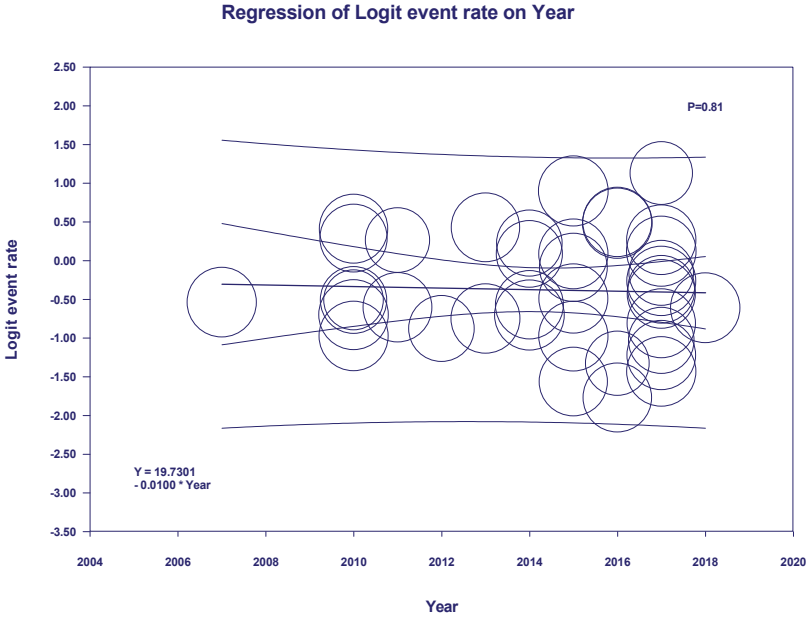

Figure 4. Meta-regression analyses showed no significant impact of year of study on the incidence of post-LTx AKI ($p = 0.81$). The solid black line represents the weighted regression line based on variance-weighted least squares. The inner and outer lines show the 95% confidence interval and prediction interval around the regression line. The circles indicate log event rates in each study.

3.2. Risk Factors for Post-LTx AKI

Reported risk factors for post-LTx AKI are demonstrated in Table 2. Higher pretransplant SCr [11,23–25,32–35], high body mass index (BMI) [39,64,66,67], high MELD/MELD-Na score [23,39–49], intraoperative blood loss and perioperative blood transfusion [18,25,39,48,54,65], high APACHE II score [25,43,48,55], hypotension and vasopressor requirement [18,24,48,54], cold and warm ischemia time [14,35,78], graft dysfunction [11,40,53], post-reperfusion syndrome [20,64,66,75,78], infection prior to transplant [25,45,48], and hypoalbuminemia [18,64,66] were consistently identified as important risk factors for Post-LTx AKI.

3.3. Impacts of Post-LTx AKI on Patient Outcomes

The impacts of post-LTx AKI on patient outcomes are demonstrated in Table 3. Overall, the pooled estimated in-hospital or 30-day mortality, and 1-year mortality rates of patients with post-LTx AKI were 16.5% (95% CI: 10.8%–24.3%, I^2 = 94%) and 31.1% (95% CI: 22.4%–41.5%, I^2 = 78%), respectively. Post-LTx AKI was associated with significantly higher mortality with a pooled OR of 2.96 (95% CI: 2.32–3.77, I^2 = 59%). In addition, severe post-LTx AKI requiring RRT was associated with significantly higher mortality with a pooled OR of 8.15 (95% CI: 4.52–14.69, I^2 = 90%). Compared to those without post-LTx AKI, recipients with post-LTx AKI had significantly increased risks of liver graft failure and CKD with pooled ORs of 3.76 (95% CI: 1.56–9.03, I^2 = 91%, Figure 5) and 2.35 (95% CI: 1.53–3.61, I^2 = 75%, Figure 6), respectively. AKI was associated with prolonged intensive care (ICU) and hospital stay [17,18,23,24,29,32,35,40,42,44,48,49,53,61,64,75,78] (Table 3).

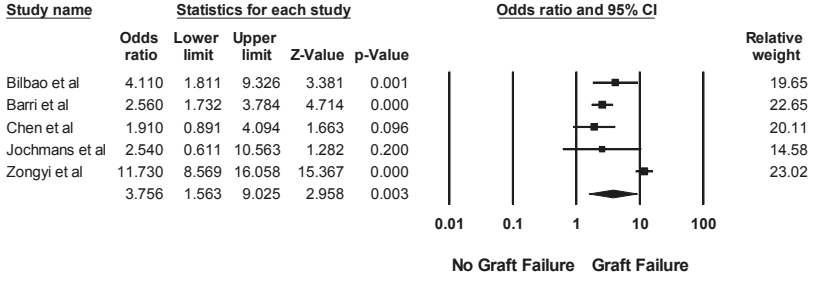

Figure 5. Forest plots of the included studies assessing liver graft failure among patients with post-LTx AKI. A diamond data marker represents the overall rate from each included study (square data marker) and 95% confidence interval.

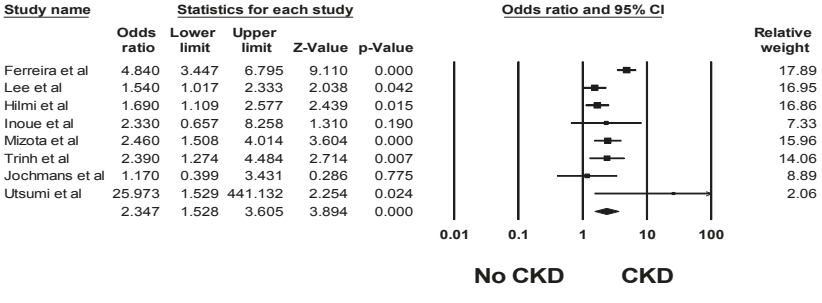

Figure 6. Forest plots of the included studies assessing CKD risk among patients with post-LTx AKI. A diamond data marker represents the overall rate from each included study (square data marker) and 95% confidence interval.

Table 2. Reported Potential Predictors/Associated-Risk Factors of Post-LTx AKI.

Donor and Graft Factors	Recipient Factors	Surgical and Postoperative Factors
Cold ischemia time [14,35,78], warm ischemic time [35,39,63,64,66] Small-for-size graft/Graft-recipient body weight ratio [40,44,65,66] Deceased donor [20,47] Graft dysfunction [11,53] DCD [39] ABO incompatibility [70] Lower donor BMI [39] Older donor age [39]	Higher MELD score/MELD-Na [23,39–49,64,67,89] APACHE II25 [43,48,55], Preoperative SCr11 [23–25,32–35] Preoperative BUN [23,24] Preoperative renal dysfunction/ARF [40,43,53] Child-Pugh score [19] SOFA [48] Male sex [42], female sex [19,31] Preoperative hepatic encephalopathy [47] Infection [25,48,71] Hypoalbuminemia [18,53,64,66] Preoperative low hemoglobin [14,72] High body weight, BMI [14,19,39,44,64,66,67,75] Pretransplant hypertension [32,54] Preoperative DM [19,44] Alcoholic liver disease [32] Pretransplant hepatitis B and/or C [54,63] Tumor as indication for transplant [47] Elevated lactate [54,63] Elevated plasma NGAL [55] Hyponatremia [39] Pulmonary hypertension [31]	Intra-operative hypotension, low MAP [24,33,34,54,66,79] Inotrope/vasopressor requirement [18,30,32,48,65], dopamine [35], intra-operative need of noradrenaline [33,67] Duration of treatment with dopamine [53] Blood loss [35,44,47,64,70,71], RBC transfusion [14,18,25,33,39,48,54,65,66,72,89] Need of cryoprecipitate [64] Anesthetic/Operation time [30,64,66,70] Post-reperfusion syndrome [20,64,66,78] SvO2 reduction with oliguria [14], Oxygen content 5 min after graft reperfusion [75] Terlipressin (protective) [65] Venovenous bypass (protective) [21] Postoperative ICU days [23,48] Duration of ventilator support [48] Aminoglycoside use [32] Duration of anhepatic phase [41,79] Intra-operative acidosis [41] Intra-operative urine output [14,24,30,33] Overexposure to calcineurin inhibitor [35,44,64] Need of diuretics [46,75] Chloride-liberal fluid received within the 24 h posttransplant [49] Crystalloid administration [14] Use of 6% HES [89] Mean blood glucose during the day of surgery [64], glucose variability [31] Peak AST occurring at 6 h [29]

Abbreviations:: ABO incompatibility, incompatibility of the ABO blood group; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ALP, alkaline phosphatase; APACHE, Acute Physiology and Chronic Health Evaluation; ARI, acute renal injury; ARF, acute renal failure; AST, aspartate aminotransferase; ATG, Anti-thymocyte globulin; BMI, body mass index; BUN, blood urea nitrogen; CMV, cytomegalovirus; DBD, graft donated after brain death; DCD, donation after circulatory death; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; HCV, hepatitis C virus; HES, hydroxyethyl starch; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine; MAP, mean arterial pressure; MELD, Model For End-Stage Liver Disease; MMF, mycophenolate mofetil; N/A, not available; NGAL, neutrophil gelatinase-associated lipocalin; PBC, primary biliary cirrhosis; RBC, red blood cell; RRT, renal replacement therapy; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SOFA, Sequential Organ Failure Assessment; SvO2, mixed venous oxygen saturation.

Table 3. Reported Outcomes of Post-LTx AKI.

Study	Outcomes	Confounder Adjustment
Bilbao et al. [11]	Mortality Dialysis: 6.47 (2.73–15.35) Graft failure Dialysis: 4.11 (1.81–9.32)	None
Contreras et al. [24]	Hospital mortality Dialysis: 9.91 (3.45–28.51) ICU LOS Dialysis: 15 ± 13 vs. 7 ± 11 days Hospital LOS Dialysis: 34 ± 27 vs. 19 ± 20 days	None
Lebrón Gallardo et al. [25]	Mortality Early renal dysfunction: 2.47 (1.29–4.72) Dialysis: 8.80 (3.65–21.23)	None
Sanchez et al. [23]	1-year mortality Dialysis: 9.07 (5.49–14.97) ICU LOS 2.1 ± 3.0 in no dialysis vs. 8.6 ± 11.6 in hemodialysis vs. 10.5 ± 12.8 days in CRRT	None
Wyatt et al. [22]	Mortality ARF without RRT: 8.69 (3.25–23.19) ARF with RRT: 12.07 (3.90–37.32)	Age, sex, race, DM, transplant centers
Cabezuelo et al. [53]	ICU LOS ARF: 12.9 ± 7.4 vs. 7.2 ± 4.0 days	N/A
O'Riordan et al. [32]	1-year mortality ARF: 2.6 (1.5–4.5) Hospital LOS 39.3 ± 79.5 in no ARI/ARF vs. 53.3 ± 72.8 in ARI vs. 73.0 ± 129.8 days in ARF	DM, pretransplant, SCr, PBC, inotrope use, CMV infection/disease, rejection
Lee et al. [40]	Hospital LOS Renal dysfunction: 75 ± 144 vs. 45.2 ± 34.5 days	N/A
Rueggeberg et al. [54]	1-year mortality AKI: 10.93 (3.64–32.83)	None
Barri et al. [17]	2-year mortality AKI: 2.33 (1.53–3.53) 2-year graft failure AKI: 2.56 (1.73–3.78) ICU LOS AKI: 8 ± 19 vs. 3 ± 5 days Hospital LOS AKI: 20 ± 24 vs. 11 ± 10 days	None
Kundakci et al. [41]	1-year mortality AKI: 6.73 (2.15–21.06)	None

Table 3. *Cont.*

Study	Outcomes	Confounder Adjustment
Zhu et al. [42]	1-year mortality AKI: 12.1 (1.57–93.54) ICU LOS AKI: 6 (4–9) vs. 4 (3–5) days Hospital LOS AKI: 29 (16–47) vs. 29 (20–48) days	Hypertension, infection and APACHE II
Ferreira et al. [57]	Mortality AKI: 0.73 (0.59–1.08) CKD AKI: 4.84 (3.45–6.80)	None
Lee et al. [56]	CKD AKI: 1.54 (1.02–2.34)	Age, sex, period of transplant, BMI, pretransplant DM, pretransplant hypertension, history of cardiovascular disease, donor type, underlying liver disease, HBV-related liver disease, hepatocellular carcinoma, use of adefovir, calcineurin inhibitors, purine metabolism inhibitors, acute rejection, pretransplant hemoglobin, pretransplant GFR, pretransplant proteinuria, hepatorenal syndrome, Child-Pugh score, MELD score
Chen et al. [18]	1-year mortality ARI/ARF: 2.79 (0.96–8.12) 1-year graft failure ARI/ARF: 1.91 (0.89–4.09) Hospital LOS 21.8 ± 22.1 in no ARI/ARF vs. 24 ± 25 in ARI and 37 ± 49 days in ARF	None
Karapanagiotou et al. [43]	1-year mortality 9.61 (1.48–62.55)	Infection, hemorrhage, MELD, APACHE score
Utsumi et al. [44]	Hospital mortality AKI: 5.04 (1.11–22.81) ARI/ARF: 5.90 (1.83–19.06) 1-year mortality AKI: 9.53 (2.18–41.56) ARI/ARF: 12.90 (4.24–39.30) CKD AKI: 15/107 (14%) vs. 0/77 (0%) ARI/ARF: 35.29 (4.51–275.82) Hospital LOS ARI/ARF: 101.5 ± 68.8 vs. 69.7 ± 48.5 days	None
Narciso et al. [60]	Mortality Dialysis: 6.7 (3.49–12.96)	None
Romano et al. [45]	Hospital mortality AKI: 1.88 (0.76–4.65)	None

Table 3. *Cont.*

Study	Outcomes	Confounder Adjustment
Leithead et al. [39]	Mortality 1.71 (1.35–2.17)	Age, sex, MELD score, eGFR, DM
Klaus et al. [46]	Mortality AKI: 5.11 (1.39–18.71) Dialysis:14.4 (4.60–45.09)	None
Kim et al. [47]	1-year mortality Dialysis: 56.5 (12.32–259.20)	None
Karapanagiotou et al. [48]	6-month mortality RIFLE: 3.08 (1.09–1.95) AKIN: 9.34 (1.20–15.69) ICU LOS RIFLE: 15.44 ± 15.41 vs. 8.65 ± 12.59 days AKIN: 13.75 ± 14.53 vs. 9.1 ± 13.08 days	Vasopressor use, RBC transfusion
Nadeem et al. [49]	ICU LOS AKI: 13.4 ± 19 vs. 5.5 ± 4.7 days	N/A
Kirnap et al. [61]	Mortality AKI: 1.85 (0.65–5.23) ICU LOS AKI: 10 ± 8 vs. 3 ± 2 days Hospital LOS AKI: 26 ± 70 vs. 16 ± 7 days	None
Barreto et al. [63]	Hospital mortality AKIN stage 2 or 3: 4.3 (1.3–14.6)	None
Hilmi et al. [19]	30-day mortality AKI: 3/221(1.4%) vs. 0/203 (0%) CKD AKI: 1.69 (1.11–2.58)	None
Park et al. [64]	Hospital mortality 3.44 (1.89–6.25) 1-year mortality AKI: 1.57 (0.95–2.58) ICU LOS 6 (6–7) in no AKI vs. 6 (6–9) in Risk vs. 7 (6–18) in Injury vs. 11 (10–85) in Failure group Hospital LOS 29 (23–42) in no AKI vs. 31 (21–43) in Risk vs. 33 (26–47) in Injury vs. 46 (16–108) in Failure group	None
Mukhtar et al. [65]	Mortality AKI: 2.1 (1.18–4.0)	Graft weight to recipient body weight ratio, baseline creatinine, MELD score, DM, Terlipressin use, massive transfusion, vasopressor use

Table 3. *Cont.*

Study	Outcomes	Confounder Adjustment
Sang et al. [66]	Mortality RIFLE AKI: 2.29 (1.29–4.05) AKIN AKI: 1.69 (1.06–2.67)	None
Wyssusek et al. [67]	Mortality AKI: 3.23 (0.43–24.27)	None
Jun et al. [70]	Mortality AKI: 0.36 (0.09–1.43)	ABO incompatibility, MELD score, hypertension, coronary artery disease, age, post-reperfusion syndrome, vasopressor, crystalloid, RBC transfusion, FFP transfusion, operation time, cold ischemic time
Inoue et al. [71]	1-year mortality AKI: 4.54 (1.27–16.32) CKD AKI: 2.33 (0.66–8.29)	None
Mizota et al. [74]	Hospital mortality AKI: 2.53 (1.23–5.22) CKD AKI: 2.46 (1.51–4.02)	Age, MELD score, blood type incompatibility, re-transplantation
Erdost et al. [72]	30-day mortality RIFLE AKI: 4.15 (1.72–10.00) AKIN AKI: 440.83 (58.24–3336.87) KDIGO AKI: 35/64 (55%) vs. 0/376	None
Chae et al. [75]	Hospital mortality AKI: 1.63 (0.73–3.60) ICU LOS AKI: 7 (6–8) vs. 7 (5–7) days Hospital LOS AKI: 28 (22–39) vs. 23 (21–31) days	None
Mizota et al. [76]	Hospital mortality Severe AKI: 3.56 (1.78–7.09)	None
Trinh et al. [77]	Mortality AKI: 1.41 (1.03–1.92) CKD stage 4–5 AKI: 2.39 (1.27–4.47)	Age, sex, MELD score, baseline eGFR, ATG induction, pretransplant hypertension and DM
Kalisvaart et al. [78]	Hospital mortality AKI: 7.96 (1.66–38.25) ICU LOS AKI: 3 (2–5) vs. 2 (2–3) days Hospital LOS AKI: 24 (19–35) vs. 17 (14–27) days	None

Table 3. *Cont.*

Study	Outcomes	Confounder Adjustment
Nadkarni et al. [16]	Hospital mortality Dialysis: 2.00 (1.55–2.59)	Not specified
Chen et al. [79]	30-day mortality AKI: 4.05 (1.02–16.18)	ALP, MELD score, operation time, blood transfusion
Zongyi et al. [35]	1-year mortality RIFLE failure stage AKI: 12.25 (8.99–16.70) 1-year graft failure RIFLE failure stage AKI: 11.73 (8.57–16.06) Hospital LOS RIFLE failure stage AKI: 16 (6–34.5) vs. 25 (18–35) days	None
Zhou et al. [30]	14-day mortality AKI: 3.35 (0.94–11.98) Hospital LOS AKI: 28.13 ± 20.04 vs. 26.16 ± 11.91 days	None
Jochmans et al. [29]	1-year mortality AKI: 6.11 (0.52–71.16) 1-year graft failure AKI: 2.54 (0.61–10.55) CKD AKI:1.17 (0.40–3.44) ICU LOS AKI: 4 (3–9) vs. 2 (2–4) Hospital LOS AKI: 23 (17–46) vs. 16 (13–26)	None

Abbreviations:: ABO incompatibility, incompatibility of the ABO blood group; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; ALP, alkaline phosphatase; APACHE, Acute Physiology and Chronic Health Evaluation; ARI, acute renal injury; ARF, acute renal failure; AST, aspartate aminotransferase; ATG, Anti-thymocyte globulin; BMI, body mass index; BUN, blood urea nitrogen; CMV, cytomegalovirus; DCD, donation after circulatory death; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; HCV, hepatitis C virus; HES, hydroxyethyl starch; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine; MAP, mean arterial pressure; MELD, Model For End-Stage Liver Disease; MMF, mycophenolate mofetil; N/A, not available; NGAL, neutrophil gelatinase-associated lipocalin; PBC, primary biliary cirrhosis; RBC, red blood cell; RRT, renal replacement therapy; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SOFA, Sequential Organ Failure Assessment; SvO2, mixed venous oxygen saturation.

3.4. Evaluation for Publication Bias

Funnel plot (Supplementary Figure S1) and Egger's regression asymmetry test were performed to evaluate for publication bias in the analysis evaluating incidence of post-LTx AKI and mortality risk of post-LTx AKI. There was no significant publication bias in meta-analysis assessing the incidence of post-LTx AKI, p-value = 0.12.

4. Discussion

In this meta-analysis, we found that AKI and severe AKI requiring RRT after LTx are common, with an incidence of 40.8% and 7.0%, respectively. In addition, our findings showed no significant correlation between the incidence of post-LTx AKI and study year for the ten years of the study. Furthermore, compared to patients without post-LTx AKI, those with post-LTx AKI carry a 2.96-fold increased risk of mortality and a 3.76-fold higher risk of liver graft failure.

The development of post-LTx AKI appears to be multifactorial with a number of preoperative, intraoperative and postoperative factors involved [90]. Pre-LTx factors include high MELD/MELD-Na score, high APACHE II score, hypoalbuminemia, and reduced eGFR [11,23–25,32–35]. Preexisting renal impairment is common among patients with end-stage liver disease [91]. Although cirrhotic patients with significant CKD are eligible to receive a combined liver-kidney transplantation [92], a lower baseline GFR among those who received LTx alone remained an important risk factor for post-operative AKI [11,23–25,32–35]. Studies have demonstrated that hepatorenal syndrome before LTx can also lead to renal insufficiency and render LTx recipients more susceptible to post-LTx AKI [22,90,93]. In addition, sepsis, graft dysfunction, thrombotic microangiopathy, and calcineurin inhibitor nephrotoxicity may all contribute to AKI [22,37,94–96].

Studies have shown that higher MELD scores were associated with post-LTx AKI [23,39–49]. In patients with high MELD scores >30, the majority required RRT post LTx [44,97]. Although SCr is an important determinant of the MELD score, other components of MELD such as pre-LTx INR has also been demonstrated to be strongly associated with post-LT AKI, suggesting that the severity of the liver disease itself, as reflected by the MELD score, is associated with post-LT AKI [45]. Identified perioperative factors for post-LTx AKI include cardiopulmonary failure, vasopressor requirement, hemodynamic effects of prolonged surgery, and blood loss/RBC transfusion [18,24,25,39,48,54,65]. Moreover, it has been hypothesized that HIRI is an important cause of post-LTx AKI [37,38]. Aspartate aminotransferase (AST), as a surrogate marker for HIRI, has been shown to be correlated with post-LTx AKI. [38,78] HIRI has a close relationship with the systemic inflammatory response, which in turn is related to AKI and multiorgan dysfunction in similar settings such as sepsis [37]. Early hepatic graft dysfunction has also been shown to be associated to post-LTx AKI [98]. In addition, recipients of donation after circulatory death (DCD) grafts are reported to have a higher incidence of post-LTx AKI compared to donation after brain death (DBD grafts). After DCD LTx, peak AST levels were an independent predictor of post-LTx AKI [99]. Other known factors that influence HIRI such as donor age, cold and warm ischemia times and graft steatosis have also been associated with post-LTx AKI [37].

As demonstrated in our study, post-LTx AKI is associated with an increased risk of death and liver graft failure. Several pharmacological and non-pharmacological interventions have been studied, but so far these have failed to demonstrate any significant benefit in the prevention of post-LTx AKI [37,100,101]. To continue efforts to mitigate post-LTx AKI, it is important to identify those who are at high-risk for post-LTx AKI in order to develop earlier protective strategies [37]. There have been many attempts to develop predictive models for post-LTx AKI [37]. Seven published predictive models addressing a diverse range of AKI definitions for post-LT AKI have been developed [19,23,24,33,47,54,55]. However, the numbers of patients in these studies were limited [19,23,24,33,47,54,55], and future prospective external validation, ideally with multi-center studies with large number of patients, is required.

Several limitations in our meta-analysis are worth mentioning. First, there were statistical heterogeneities present in our study. Possible sources for heterogeneities were the differences in the patient characteristics in the individual studies. However, we performed a meta-regression analysis which demonstrated that the type of donor (deceased vs. living donors); the year of study did not significantly affect the incidence of post-LTx AKI. Second, there is a lack of data from included studies on novel AKI biomarkers. Novel biomarkers for AKI are emerging and could be useful for the early identification and characterization of AKI. Thus, future studies evaluating predictive models with novel biomarkers are needed. Lastly, this is a systematic review and meta-analysis of cohort studies. Thus, it can demonstrate associations of post-LTx AKI with increased risk of mortality and liver graft failure, but not a causal relationship.

5. Conclusions

In conclusion, there are overall high incidence rates of post-LTx AKI and severe AKI requiring RRT of 40.8% and 7.0%. Post-LTx AKI is significantly associated with increased mortality and liver graft failure. In addition, the incidence of post-LTx AKI has remained stable over time. This study provides an epidemiological perspective to support the need for future large-scale multi-center studies to identify preventive strategies for post-LTx AKI.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/3/372/s1, Figure S1: Funnel plot evaluating for publication bias evaluating incidence of post-LTx AKI.

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References

1. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef] [PubMed]
2. Hoste, E.A.J.; Kellum, J.A.; Selby, N.M.; Zarbock, A.; Palevsky, P.M.; Bagshaw, S.M.; Goldstein, S.L.; Cerdá, J.; Chawla, L.S. Global epidemiology and outcomes of acute kidney injury. *Nat. Rev. Nephrol.* **2018**, *14*, 607–625. [CrossRef] [PubMed]
3. Mehta, R.L.; Burdmann, E.A.; Cerdá, J.; Feehally, J.; Finkelstein, F.; García-García, G.; Godin, M.; Jha, V.; Lameire, N.H.; Levin, N.W.; et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: A multinational cross-sectional study. *Lancet* **2016**, *387*, 2017–2025. [CrossRef]
4. Mehta, R.L.; Burdmann, E.A.; Cerdá, J.; Feehally, J.; Finkelstein, F.; García-García, G.; Godin, M.; Jha, V.; Lameire, N.H.; Levin, N.W.; et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): A human rights case for nephrology. *Lancet* **2015**, *385*, 2616–2643. [CrossRef]
5. Sawhney, S.; Marks, A.; Fluck, N.; Levin, A.; McLernon, D.; Prescott, G.; Black, C. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. *Kidney Int.* **2017**, *92*, 440–452. [CrossRef]
6. Ponce, D.; Balbi, A. Acute kidney injury: Risk factors and management challenges in developing countries. *Int. J. Nephrol. Renov. Dis.* **2016**, *9*, 193–200. [CrossRef]
7. Pavkov, M.E.; Harding, J.L.; Burrows, N.R. Trends in Hospitalizations for Acute Kidney Injury—United States, 2000–2014. *Morb. Mortal. Wkly. Rep.* **2018**, *67*, 289. [CrossRef]

8. United States Renal Data System. 2017. Available online: https://www.usrds.org/2017/download/v1_c05_AKI_17.pdf (accessed on 15 February 2019).
9. Mokdad, A.A.; Lopez, A.D.; Shahraz, S.; Lozano, R.; Mokdad, A.H.; Stanaway, J.; Murray, C.J.; Naghavi, M. Liver cirrhosis mortality in 187 countries between 1980 and 2010: A systematic analysis. *BMC Med.* **2014**, *12*, 145. [CrossRef] [PubMed]
10. McCauley, J.; Van Thiel, D.H.; Starzl, T.E.; Puschett, J.B. Acute and chronic renal failure in liver transplantation. *Nephron* **1990**, *55*, 121–128. [CrossRef] [PubMed]
11. Bilbao, I.; Charco, R.; Balsells, J.; Lazaro, J.L.; Hidalgo, E.; Llopart, L.; Murio, E.; Margarit, C. Risk factors for acute renal failure requiring dialysis after liver transplantation. *Clin. Transplant.* **1998**, *12*, 123–129.
12. Carmona, M.; Álvarez, M.; Marco, J.; Mahíllo, B.; Domínguez-Gil, B.; Núñez, J.R.; Matesanz, R. Global Organ Transplant Activities in 2015. Data from the Global Observatory on Donation and Transplantation (GODT). *Transplantation* **2017**, *101*, S29. [CrossRef]
13. White, S.L.; Hirth, R.; Mahillo, B.; Dominguez-Gil, B.; Delmonico, F.L.; Noel, L.; Chapman, J.; Matesanz, R.; Carmona, M.; Alvarez, M.; et al. The global diffusion of organ transplantation: Trends, drivers and policy implications. *Bull. World Health Organ.* **2014**, *92*, 826–835. [CrossRef]
14. Kim, W.H.; Lee, H.C.; Lim, L.; Ryu, H.G.; Jung, C.W. Intraoperative Oliguria with Decreased SvO Predicts Acute Kidney Injury after Living Donor Liver Transplantation. *J. Clin. Med.* **2018**, *8*, 29. [CrossRef] [PubMed]
15. Hamada, M.; Matsukawa, S.; Shimizu, S.; Kai, S.; Mizota, T. Acute kidney injury after pediatric liver transplantation: Incidence, risk factors, and association with outcome. *J. Anesth.* **2017**, *31*, 758–763. [CrossRef] [PubMed]
16. Nadkarni, G.N.; Chauhan, K.; Patel, A.; Saha, A.; Poojary, P.; Kamat, S.; Patel, S.; Ferrandino, R.; Konstantinidis, I.; Garimella, P.S.; et al. Temporal trends of dialysis requiring acute kidney injury after orthotopic cardiac and liver transplant hospitalizations. *BMC Nephrol.* **2017**, *18*, 244. [CrossRef] [PubMed]
17. Barri, Y.M.; Sanchez, E.Q.; Jennings, L.W.; Melton, L.B.; Hays, S.; Levy, M.F.; Klintmalm, G.B. Acute kidney injury following liver transplantation: Definition and outcome. *Liver Transplant.* **2009**, *15*, 475–483. [CrossRef] [PubMed]
18. Chen, J.; Singhapricha, T.; Hu, K.Q.; Hong, J.C.; Steadman, R.H.; Busuttil, R.W.; Xia, V.W. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: A matched study. *Transplantation* **2011**, *91*, 348–353. [CrossRef] [PubMed]
19. Hilmi, I.A.; Damian, D.; Al-Khafaji, A.; Planinsic, R.; Boucek, C.; Sakai, T.; Chang, C.C.; Kellum, J.A. Acute kidney injury following orthotopic liver transplantation: Incidence, risk factors, and effects on patient and graft outcomes. *Br. J. Anaesth.* **2015**, *114*, 919–926. [CrossRef]
20. Hilmi, I.A.; Damian, D.; Al-Khafaji, A.; Sakai, T.; Donaldson, J.; Winger, D.G.; Kellum, J.A. Acute kidney injury after orthotopic liver transplantation using living donor versus deceased donor grafts: A propensity score-matched analysis. *Liver Transplant.* **2015**, *21*, 1179–1185. [CrossRef]
21. Sun, K.; Hong, F.; Wang, Y.; Agopian, V.G.; Yan, M.; Busuttil, R.W.; Steadman, R.H.; Xia, V.W. Venovenous Bypass Is Associated With a Lower Incidence of Acute Kidney Injury After Liver Transplantation in Patients with Compromised Pretransplant Renal Function. *Anesth. Analg.* **2017**, *125*, 1463–1470. [CrossRef]
22. Wyatt, C.M.; Arons, R.R. The burden of acute renal failure in nonrenal solid organ transplantation. *Transplantation* **2004**, *78*, 1351–1355. [CrossRef] [PubMed]
23. Sanchez, E.Q.; Gonwa, T.A.; Levy, M.F.; Goldstein, R.M.; Mai, M.L.; Hays, S.R.; Melton, L.B.; Saracino, G.; Klintmalm, G.B. Preoperative and perioperative predictors of the need for renal replacement therapy after orthotopic liver transplantation. *Transplantation* **2004**, *78*, 1048–1054. [CrossRef] [PubMed]
24. Contreras, G.; Garces, G.; Quartin, A.A.; Cely, C.; LaGatta, M.A.; Barreto, G.A.; Roth, D.; Gomez, E. An epidemiologic study of early renal replacement therapy after orthotopic liver transplantation. *J. Am. Soc. Nephrol.* **2002**, *13*, 228–233.
25. Lebron Gallardo, M.; Herrera Gutierrez, M.E.; Seller Perez, G.; Curiel Balsera, E.; Fernandez Ortega, J.F.; Quesada Garcia, G. Risk factors for renal dysfunction in the postoperative course of liver transplant. *Liver Transplant.* **2004**, *10*, 1379–1385. [CrossRef]
26. Alvares-da-Silva, M.R.; Waechter, F.L.; Francisconi, C.F.; Barros, E.; Thome, F.; Traiber, C.; Fonseca, D.L.; Zingani, J.M.; Sampaio, J.A.; Pinto, R.D.; et al. Risk factors for postoperative acute renal failure at a new orthotopic liver transplantation program. *Transplant. Proc.* **1999**, *31*, 3050–3052. [CrossRef]

27. Rossi, A.P.; Vella, J.P. Acute Kidney Disease After Liver and Heart Transplantation. *Transplantation* **2016**, *100*, 506–514. [CrossRef] [PubMed]
28. Kandil, M.A.; Abouelenain, K.M.; Alsebaey, A.; Rashed, H.S.; Afifi, M.H.; Mahmoud, M.A.; Yassen, K.A. Impact of terlipressin infusion during and after live donor liver transplantation on incidence of acute kidney injury and neutrophil gelatinase-associated lipocalin serum levels: A randomized controlled trial. *Clin. Transplant.* **2017**, *31*, e13019. [CrossRef] [PubMed]
29. Jochmans, I.; Meurisse, N.; Neyrinck, A.; Verhaegen, M.; Monbaliu, D.; Pirenne, J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: Prospective cohort study. *Liver Transplant.* **2017**, *23*, 634–644. [CrossRef]
30. Zhou, Z.Q.; Fan, L.C.; Zhao, X.; Xia, W.; Luo, A.L.; Tian, Y.K.; Wang, X.R. Risk factors for acute kidney injury after orthotopic liver transplantation: A single-center data analysis. *J. Huazhong Univ. Sci. Technol. Med. Sci.* **2017**, *37*, 861–863. [CrossRef]
31. Yoo, S.; Lee, H.J.; Lee, H.; Ryu, H.G. Association Between Perioperative Hyperglycemia or Glucose Variability and Postoperative Acute Kidney Injury After Liver Transplantation: A Retrospective Observational Study. *Anesth. Analg.* **2017**, *124*, 35–41. [CrossRef]
32. O'Riordan, A.; Wong, V.; McQuillan, R.; McCormick, P.A.; Hegarty, J.E.; Watson, A.J. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. *Am. J. Transplant.* **2007**, *7*, 168–176. [CrossRef]
33. Xu, X.; Ling, Q.; Wei, Q.; Wu, J.; Gao, F.; He, Z.L.; Zhou, L.; Zheng, S.S. An effective model for predicting acute kidney injury after liver transplantation. *Hepatobiliary Pancreat. Dis. Int.* **2010**, *9*, 259–263.
34. De Ataide, E.C.; Perales, S.R.; Bortoto, J.B.; Peres, M.A.O.; Filho, F.C.; Stucchi, R.S.B.; Udo, E.; Boin, I. Immunomodulation, Acute Renal Failure, and Complications of Basiliximab Use After Liver Transplantation: Analysis of 114 Patients and Literature Review. *Transplant. Proc.* **2017**, *49*, 852–857. [CrossRef] [PubMed]
35. Zongyi, Y.; Baifeng, L.; Funian, Z.; Hao, L.; Xin, W. Risk factors of acute kidney injury after orthotopic liver transplantation in China. *Sci. Rep.* **2017**, *7*, 41555. [CrossRef]
36. Croome, K.P.; Lee, D.D.; Croome, S.; Chadha, R.; Livingston, D.; Abader, P.; Keaveny, A.P.; Taner, C.B. The impact of post-reperfusion syndrome during liver transplantation using livers with significant macrosteatosis. *Am. J. Transplant.* **2019**. [CrossRef] [PubMed]
37. De Haan, J.E.; Hoorn, E.J.; de Geus, H.R.H. Acute kidney injury after liver transplantation: Recent insights and future perspectives. *Best Pract. Res. Clin. Gastroenterol.* **2017**, *31*, 161–169. [CrossRef] [PubMed]
38. Leithead, J.A.; Armstrong, M.J.; Corbett, C.; Andrew, M.; Kothari, C.; Gunson, B.K.; Muiesan, P.; Ferguson, J.W. Hepatic ischemia reperfusion injury is associated with acute kidney injury following donation after brain death liver transplantation. *Transpl. Int.* **2013**, *26*, 1116–1125. [CrossRef] [PubMed]
39. Leithead, J.A.; Rajoriya, N.; Gunson, B.K.; Muiesan, P.; Ferguson, J.W. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. *J. Hepatol.* **2014**, *60*, 1180–1186. [CrossRef] [PubMed]
40. Lee, S.K.; Park, J.B.; Kim, S.J.; Choi, G.S.; Kim, D.J.; Kwon, C.H.; Joh, J.W. Early postoperative renal dysfunction in the adult living donor liver transplantation. *Transplant. Proc.* **2007**, *39*, 1517–1519. [CrossRef]
41. Kundakci, A.; Pirat, A.; Komurcu, O.; Torgay, A.; Karakayali, H.; Arslan, G.; Haberal, M. Rifle criteria for acute kidney dysfunction following liver transplantation: Incidence and risk factors. *Transplant. Proc.* **2010**, *42*, 4171–4174. [CrossRef]
42. Zhu, M.; Li, Y.; Xia, Q.; Wang, S.; Qiu, Y.; Che, M.; Dai, H.; Qian, J.; Ni, Z.; Axelsson, J.; et al. Strong impact of acute kidney injury on survival after liver transplantation. *Transplant. Proc.* **2010**, *42*, 3634–3638. [CrossRef] [PubMed]
43. Karapanagiotou, A.; Kydona, C.; Dimitriadis, C.; Sgourou, K.; Giasnetsova, T.; Fouzas, I.; Imvrios, G.; Gritsi-Gerogianni, N. Acute kidney injury after orthotopic liver transplantation. *Transplant. Proc.* **2012**, *44*, 2727–2729. [CrossRef]
44. Utsumi, M.; Umeda, Y.; Sadamori, H.; Nagasaka, T.; Takaki, A.; Matsuda, H.; Shinoura, S.; Yoshida, R.; Nobuoka, D.; Satoh, D.; et al. Risk factors for acute renal injury in living donor liver transplantation: Evaluation of the RIFLE criteria. *Transpl. Int.* **2013**, *26*, 842–852. [CrossRef] [PubMed]
45. Romano, T.G.; Schmidtbauer, I.; Silva, F.M.; Pompilio, C.E.; D'Albuquerque, L.A.; Macedo, E. Role of MELD score and serum creatinine as prognostic tools for the development of acute kidney injury after liver transplantation. *PLoS ONE* **2013**, *8*, e64089. [CrossRef]

46. Klaus, F.; Keitel da Silva, C.; Meinerz, G.; Carvalho, L.M.; Goldani, J.C.; Cantisani, G.; Zanotelli, M.L.; Duro Garcia, V.; Keitel, E. Acute kidney injury after liver transplantation: Incidence and mortality. *Transplant. Proc.* **2014**, *46*, 1819–1821. [CrossRef] [PubMed]
47. Kim, J.M.; Jo, Y.Y.; Na, S.W.; Kim, S.I.; Choi, Y.S.; Kim, N.O.; Park, J.E.; Koh, S.O. The predictors for continuous renal replacement therapy in liver transplant recipients. *Transplant. Proc.* **2014**, *46*, 184–191. [CrossRef]
48. Karapanagiotou, A.; Dimitriadis, C.; Papadopoulos, S.; Kydona, C.; Kefsenidis, S.; Papanikolaou, V.; Gritsi-Gerogianni, N. Comparison of RIFLE and AKIN criteria in the evaluation of the frequency of acute kidney injury in post-liver transplantation patients. *Transplant. Proc.* **2014**, *46*, 3222–3227. [CrossRef] [PubMed]
49. Nadeem, A.; Salahuddin, N.; El Hazmi, A.; Joseph, M.; Bohlega, B.; Sallam, H.; Sheikh, Y.; Broering, D. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. *Crit. Care.* **2014**, *18*, 625. [CrossRef]
50. Yi, Z.; Mayorga, M.E.; Orman, E.S.; Wheeler, S.B.; Hayashi, P.H.; Barritt, A.S.T. Trends in Characteristics of Patients Listed for Liver Transplantation Will Lead to Higher Rates of Waitlist Removal Due to Clinical Deterioration. *Transplantation* **2017**, *101*, 2368–2374. [CrossRef]
51. Orman, E.S.; Barritt, A.S.T.; Wheeler, S.B.; Hayashi, P.H. Declining liver utilization for transplantation in the United States and the impact of donation after cardiac death. *Liver Transplant.* **2013**, *19*, 59–68. [CrossRef]
52. Chuang, F.R.; Lin, C.C.; Wang, P.H.; Cheng, Y.F.; Hsu, K.T.; Chen, Y.S.; Lee, C.H.; Chen, C.L. Acute renal failure after cadaveric related liver transplantation. *Transplant. Proc.* **2004**, *36*, 2328–2330. [CrossRef]
53. Cabezuelo, J.B.; Ramirez, P.; Rios, A.; Acosta, F.; Torres, D.; Sansano, T.; Pons, J.A.; Bru, M.; Montoya, M.; Bueno, F.S.; et al. Risk factors of acute renal failure after liver transplantation. *Kidney Int.* **2006**, *69*, 1073–1080. [CrossRef]
54. Rueggeberg, A.; Boehm, S.; Napieralski, F.; Mueller, A.R.; Neuhaus, P.; Falke, K.J.; Gerlach, H. Development of a risk stratification model for predicting acute renal failure in orthotopic liver transplantation recipients. *Anaesthesia* **2008**, *63*, 1174–1180. [CrossRef]
55. Portal, A.J.; McPhail, M.J.; Bruce, M.; Coltart, I.; Slack, A.; Sherwood, R.; Heaton, N.D.; Shawcross, D.; Wendon, J.A.; Heneghan, M.A. Neutrophil gelatinase–associated lipocalin predicts acute kidney injury in patients undergoing liver transplantation. *Liver Transplant.* **2010**, *16*, 1257–1266. [CrossRef]
56. Lee, J.P.; Heo, N.J.; Joo, K.W.; Yi, N.J.; Suh, K.S.; Moon, K.C.; Kim, S.G.; Kim, Y.S. Risk factors for consequent kidney impairment and differential impact of liver transplantation on renal function. *Nephrol. Dial. Transplant.* **2010**, *25*, 2772–2785. [CrossRef] [PubMed]
57. Ferreira, A.C.; Nolasco, F.; Carvalho, D.; Sampaio, S.; Baptista, A.; Pessegueiro, P.; Monteiro, E.; Mourao, L.; Barroso, E. Impact of RIFLE classification in liver transplantation. *Clin. Transplant.* **2010**, *24*, 394–400. [CrossRef] [PubMed]
58. Tinti, F.; Umbro, I.; Mecule, A.; Rossi, M.; Merli, M.; Nofroni, I.; Corradini, S.G.; Poli, L.; Pugliese, F.; Ruberto, F.; et al. RIFLE criteria and hepatic function in the assessment of acute renal failure in liver transplantation. *Transplant. Proc.* **2010**, *42*, 1233–1236. [CrossRef] [PubMed]
59. Umbro, I.; Tinti, F.; Mordenti, M.; Rossi, M.; Ianni, S.; Pugliese, F.; Ruberto, F.; Ginanni Corradini, S.; Nofroni, I.; Poli, L.; et al. Model for end-stage liver disease score versus simplified acute physiology score criteria in acute renal failure after liver transplantation. *Transplant. Proc.* **2011**, *43*, 1139–1141. [CrossRef] [PubMed]
60. Narciso, R.C.; Ferraz, L.R.; Mies, S.; Monte, J.C.; dos Santos, O.F.; Neto, M.C.; Rodrigues, C.J.; Batista, M.C.; Durao, M.S., Jr. Impact of acute kidney injury exposure period among liver transplantation patients. *BMC Nephrol.* **2013**, *14*, 43. [CrossRef]
61. Kirnap, M.; Colak, T.; Baskin, E.; Akdur, A.; Moray, G.; Arslan, G.; Haberal, M. Acute renal injury in liver transplant patients and its effect on patient survival. *Exp. Clin. Transplant.* **2014**, *12* (Suppl. 1), 156–158.
62. Lewandowska, L.; Matuszkiewicz-Rowinska, J.; Jayakumar, C.; Oldakowska-Jedynak, U.; Looney, S.; Galas, M.; Dutkiewicz, M.; Krawczyk, M.; Ramesh, G. Netrin-1 and semaphorin 3A predict the development of acute kidney injury in liver transplant patients. *PLoS ONE* **2014**, *9*, e107898. [CrossRef]

63. Barreto, A.G.; Daher, E.F.; Silva Junior, G.B.; Garcia, J.H.; Magalhaes, C.B.; Lima, J.M.; Viana, C.F.; Pereira, E.D. Risk factors for acute kidney injury and 30-day mortality after liver transplantation. *Ann. Hepatol.* **2015**, *14*, 688–694. [PubMed]
64. Park, M.H.; Shim, H.S.; Kim, W.H.; Kim, H.J.; Kim, D.J.; Lee, S.H.; Kim, C.S.; Gwak, M.S.; Kim, G.S. Clinical Risk Scoring Models for Prediction of Acute Kidney Injury after Living Donor Liver Transplantation: A Retrospective Observational Study. *PLoS ONE* **2015**, *10*, e0136230. [CrossRef] [PubMed]
65. Mukhtar, A.; Mahmoud, I.; Obayah, G.; Hasanin, A.; Aboul-Fetouh, F.; Dabous, H.; Bahaa, M.; Abdelaal, A.; Fathy, M.; El Meteini, M. Intraoperative terlipressin therapy reduces the incidence of postoperative acute kidney injury after living donor liver transplantation. *J. Cardiothorac. Vasc. Anesth.* **2015**, *29*, 678–683. [CrossRef] [PubMed]
66. Sang, B.H.; Bang, J.Y.; Song, J.G.; Hwang, G.S. Hypoalbuminemia within Two Postoperative Days Is an Independent Risk Factor for Acute Kidney Injury Following Living Donor Liver Transplantation: A Propensity Score Analysis of 998 Consecutive Patients. *Crit. Care Med.* **2015**, *43*, 2552–2561. [CrossRef] [PubMed]
67. Wyssusek, K.H.; Keys, A.L.; Yung, J.; Moloney, E.T.; Sivalingam, P.; Paul, S.K. Evaluation of perioperative predictors of acute kidney injury post orthotopic liver transplantation. *Anaesth. Intensive Care* **2015**, *43*, 757–763. [CrossRef] [PubMed]
68. Aksu Erdost, H.; Ozkardesler, S.; Ocmen, E.; Avkan-Oguz, V.; Akan, M.; Iyilikci, L.; Unek, T.; Ozbilgin, M.; Meseri Dalak, R.; Astarcioglu, I. Acute Renal Injury Evaluation After Liver Transplantation: With RIFLE Criteria. *Transplant. Proc.* **2015**, *47*, 1482–1487. [CrossRef]
69. Biancofiore, G.; Bindi, M.L.; Miccoli, M.; Cerutti, E.; Lavezzo, B.; Pucci, L.; Bisa, M.; Esposito, M.; Meacci, L.; Mozzo, R.; et al. Intravenous fenoldopam for early acute kidney injury after liver transplantation. *J. Anesth.* **2015**, *29*, 426–432. [CrossRef]
70. Jun, I.G.; Lee, B.; Kim, S.O.; Shin, W.J.; Bang, J.Y.; Song, J.G.; Song, G.W.; Lee, S.G.; Hwang, G.S. Comparison of acute kidney injury between ABO-compatible and ABO-incompatible living donor liver transplantation: A propensity matching analysis. *Liver Transplant.* **2016**, *22*, 1656–1665. [CrossRef]
71. Inoue, Y.; Soyama, A.; Takatsuki, M.; Hidaka, M.; Kinoshita, A.; Natsuda, K.; Baimakhanov, Z.; Kugiyama, T.; Adachi, T.; Kitasato, A.; et al. Does the development of chronic kidney disease and acute kidney injury affect the prognosis after living donor liver transplantation? *Clin. Transplant.* **2016**, *30*, 518–527. [CrossRef]
72. Erdost, H.A.; Ozkardesler, S.; Akan, M.; Iyilikci, L.; Unek, T.; Ocmen, E.; Dalak, R.M.; Astarcioglu, I. Comparison of the RIFLE, AKIN, and KDIGO Diagnostic Classifications for Acute Renal Injury in Patients Undergoing Liver Transplantation. *Transplant. Proc.* **2016**, *48*, 2112–2118. [CrossRef] [PubMed]
73. Kamei, H.; Onishi, Y.; Nakamura, T.; Ishigami, M.; Hamajima, N. Role of cytokine gene polymorphisms in acute and chronic kidney disease following liver transplantation. *Hepatol. Int.* **2016**, *10*, 665–672. [CrossRef] [PubMed]
74. Mizota, T.; Minamisawa, S.; Imanaka, Y.; Fukuda, K. Oliguria without serum creatinine increase after living donor liver transplantation is associated with adverse post-operative outcomes. *Acta Anaesthesiol. Scand.* **2016**, *60*, 874–881. [CrossRef] [PubMed]
75. Chae, M.S.; Lee, N.; Park, D.H.; Lee, J.; Jung, H.S.; Park, C.S.; Choi, J.H.; Hong, S.H. Influence of oxygen content immediately after graft reperfusion on occurrence of postoperative acute kidney injury in living donor liver transplantation. *Medicine* **2017**, *96*, e7626. [CrossRef] [PubMed]
76. Mizota, T.; Hamada, M.; Matsukawa, S.; Seo, H.; Tanaka, T.; Segawa, H. Relationship Between Intraoperative Hypotension and Acute Kidney Injury After Living Donor Liver Transplantation: A Retrospective Analysis. *J. Cardiothorac. Vasc. Anesth.* **2017**, *31*, 582–589. [CrossRef]
77. Trinh, E.; Alam, A.; Tchervenkov, J.; Cantarovich, M. Impact of acute kidney injury following liver transplantation on long-term outcomes. *Clin. Transplant.* **2017**, *31*, e12863. [CrossRef] [PubMed]
78. Kalisvaart, M.; de Haan, J.E.; Hesselink, D.A.; Polak, W.G.; Hansen, B.E.; JNM, I.J.; Gommers, D.; Metselaar, H.J.; de Jonge, J. The postreperfusion syndrome is associated with acute kidney injury following donation after brain death liver transplantation. *Transpl. Int.* **2017**, *30*, 660–669. [CrossRef] [PubMed]
79. Chen, X.; Ding, X.; Shen, B.; Teng, J.; Zou, J.; Wang, T.; Zhou, J.; Chen, N.; Zhang, B. Incidence and outcomes of acute kidney injury in patients with hepatocellular carcinoma after liver transplantation. *J. Cancer Res. Clin. Oncol.* **2017**, *143*, 1337–1346. [CrossRef]

80. Baron-Stefaniak, J.; Schiefer, J.; Miller, E.J.; Berlakovich, G.A.; Baron, D.M.; Faybik, P. Comparison of macrophage migration inhibitory factor and neutrophil gelatinase-associated lipocalin-2 to predict acute kidney injury after liver transplantation: An observational pilot study. *PLoS ONE* **2017**, *12*, e0183162. [CrossRef]
81. Paramesh, A.S.; Roayaie, S.; Doan, Y.; Schwartz, M.E.; Emre, S.; Fishbein, T.; Florman, S.; Gondolesi, G.E.; Krieger, N.; Ames, S.; et al. Post-liver transplant acute renal failure: Factors predicting development of end-stage renal disease. *Clin. Transplant.* **2004**, *18*, 94–99. [CrossRef]
82. Lima, E.Q.; Zanetta, D.M.; Castro, I.; Massarollo, P.C.; Mies, S.; Machado, M.M.; Yu, L. Risk factors for development of acute renal failure after liver transplantation. *Ren. Fail.* **2003**, *25*, 553–560. [CrossRef]
83. Leithead, J.A.; Armstrong, M.J.; Corbett, C.; Andrew, M.; Kothari, C.; Gunson, B.K.; Mirza, D.; Muiesan, P.; Ferguson, J.W. Split liver transplant recipients do not have an increased frequency of acute kidney injury. *Transpl. Int.* **2014**, *27*, 1125–1134. [CrossRef]
84. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
85. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gotzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med.* **2007**, *4*, e296. [CrossRef] [PubMed]
86. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
87. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef] [PubMed]
88. Easterbrook, P.J.; Berlin, J.A.; Gopalan, R.; Matthews, D.R. Publication bias in clinical research. *Lancet* **1991**, *337*, 867–872. [CrossRef]
89. Hand, W.R.; Whiteley, J.R.; Epperson, T.I.; Tam, L.; Crego, H.; Wolf, B.; Chavin, K.D.; Taber, D.J. Hydroxyethyl starch and acute kidney injury in orthotopic liver transplantation: A single-center retrospective review. *Anesth. Analg.* **2015**, *120*, 619–626. [CrossRef]
90. Caragata, R.; Wyssusek, K.H.; Kruger, P. Acute kidney injury following liver transplantation: A systematic review of published predictive models. *Anaesth. Intensive Care* **2016**, *44*, 251–261. [CrossRef] [PubMed]
91. Agarwal, B.; Shaw, S.; Shankar Hari, M.; Burroughs, A.K.; Davenport, A. Continuous renal replacement therapy (CRRT) in patients with liver disease: Is circuit life different? *J. Hepatol.* **2009**, *51*, 504–509. [CrossRef]
92. Asch, W.S.; Bia, M.J. New Organ Allocation System for Combined Liver-Kidney Transplants and the Availability of Kidneys for Transplant to Patients with Stage 4-5 CKD. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 848–852. [CrossRef]
93. Ojo, A.O. Renal disease in recipients of nonrenal solid organ transplantation. *Semin. Nephrol.* **2007**, *27*, 498–507. [CrossRef] [PubMed]
94. Biancofiore, G.; Pucci, L.; Cerutti, E.; Penno, G.; Pardini, E.; Esposito, M.; Bindi, L.; Pelati, E.; Romanelli, A.; Triscornia, S.; et al. Cystatin C as a marker of renal function immediately after liver transplantation. *Liver Transplant.* **2006**, *12*, 285–291. [CrossRef]
95. Huen, S.C.; Parikh, C.R. Predicting acute kidney injury after cardiac surgery: A systematic review. *Ann. Thorac. Surg.* **2012**, *93*, 337–347. [CrossRef] [PubMed]
96. Clajus, C.; Hanke, N.; Gottlieb, J.; Stadler, M.; Weismuller, T.J.; Strassburg, C.P.; Brocker, V.; Bara, C.; Lehner, F.; Drube, J.; et al. Renal comorbidity after solid organ and stem cell transplantation. *Am. J. Transplant.* **2012**, *12*, 1691–1699. [CrossRef]
97. Schlegel, A.; Linecker, M.; Kron, P.; Gyori, G.; De Oliveira, M.L.; Mullhaupt, B.; Clavien, P.A.; Dutkowski, P. Risk Assessment in High- and Low-MELD Liver Transplantation. *Am. J. Transplant.* **2017**, *17*, 1050–1063. [CrossRef] [PubMed]
98. Wadei, H.M.; Lee, D.D.; Croome, K.P.; Mai, M.L.; Golan, E.; Brotman, R.; Keaveny, A.P.; Taner, C.B. Early Allograft Dysfunction After Liver Transplantation Is Associated With Short- and Long-Term Kidney Function Impairment. *Am. J. Transplant.* **2016**, *16*, 850–859. [CrossRef]
99. Leithead, J.A.; Tariciotti, L.; Gunson, B.; Holt, A.; Isaac, J.; Mirza, D.F.; Bramhall, S.; Ferguson, J.W.; Muiesan, P. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am. J. Transplant.* **2012**, *12*, 965–975. [CrossRef] [PubMed]

100. Jo, S.K.; Rosner, M.H.; Okusa, M.D. Pharmacologic treatment of acute kidney injury: Why drugs haven't worked and what is on the horizon. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 356–365. [CrossRef]
101. Valentino, K.L.; Gutierrez, M.; Sanchez, R.; Winship, M.J.; Shapiro, D.A. First clinical trial of a novel caspase inhibitor: Anti-apoptotic caspase inhibitor, IDN-6556, improves liver enzymes. *Int. J. Clin. Pharmacol. Ther.* **2003**, *41*, 441–449. [CrossRef]

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Acute Kidney Injury in Patients Undergoing Total Hip Arthroplasty: A Systematic Review and Meta-Analysis

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Abstract: Background: The number of total hip arthroplasties (THA) performed across the world is growing rapidly. We performed this meta-analysis to evaluate the incidence of acute kidney injury (AKI) in patients undergoing THA. Methods: A literature search was performed using MEDLINE, EMBASE and Cochrane Database from inception until July 2018 to identify studies assessing the incidence of AKI (using standard AKI definitions of RIFLE, AKIN, and KDIGO classifications) in patients undergoing THA. We applied a random-effects model to estimate the incidence of AKI. The protocol for this meta-analysis is registered with PROSPERO (no. CRD42018101928). Results: Seventeen cohort studies with a total of 24,158 patients undergoing THA were enrolled. Overall, the pooled estimated incidence rates of AKI and severe AKI requiring dialysis following THA were 6.3% (95% CI: 3.8%–10.2%) and 0.5% (95% CI: 0.1%–2.3%). Subgroup analysis based on the countries by continent was performed and demonstrated the pooled estimated incidence of AKI following THA of 9.2% (95% CI: 5.6%–14.8%) in Asia, 8.1% (95% CI: 4.9%–13.2%) in Australia, 7.4% (95% CI: 3.2%–16.3%) in Europe, and 2.8% (95% CI: 1.2%–17.0%) in North America. Meta-regression of all included studies showed significant negative correlation between incidence of AKI following THA and study year (slope = −0.37, p <0.001). There was no publication bias as assessed by the funnel plot and Egger's regression asymmetry test with p = 0.13 for the incidence of AKI in patients undergoing THA. Conclusion: The overall estimated incidence rates of AKI and severe AKI requiring dialysis in patients undergoing THA are 6.3% and 0.5%, respectively. There has been potential improvement in AKI incidence for patients undergoing THA over time.

Keywords: acute kidney injury; acute renal failure; hip arthroplasty; hip Surgery; postoperative acute kidney injury; incidence; epidemiology; systematic reviews; meta-analysis

1. Introduction

Acute kidney injury (AKI) is a complex clinical syndrome, characterized by an abrupt decrease in glomerular filtration, associated with various etiologies and pathophysiological pathways [1–6]. Globally, AKI is a common condition, affecting 13.3 million patients a year [3,4]. This complex syndrome is associated with significant morbidity, considerable mortality resulting in 1.7 million deaths a year, and increased hospital costs and subsequent burden on national health care budgets across the world [7,8].

Total hip arthroplasty (THA) is one of the most consistently successful and cost-effective orthopedic procedures performed today. It is indicated in patients with severe hip pain from a variety of conditions and ultimately provides significant improved pain relief, functionality and quality of life [9–15]. The total number of THA performed across the world is growing rapidly with close to 522,800 surgeries in the United States alone in 2014, making it the fourth most common operative procedure [16,17].

Previous studies have demonstrated different incidence of AKI following total joint arthroplasties using standard AKI criteria ranging from 0.5% to 22% based on types of joint arthroplasties [5,18–40]. The clinical and economic landscape of joint replacement surgeries including both general orthopedic and more specifically THA is rapidly changing, thus making it imperative for clinicians and administrators to understand the various risk factors and post-operative complications in order to better provide excellence in clinical and financial outcomes. However, despite progress in perioperative medicine, the incidence, incidence trend, and risk factors for AKI in patients following THA remain unclear [18–40]. In addition, complication rates such as reoperation and readmission among patients undergoing THA remain high [18–33]. Thus, we performed this systematic review to summarize the incidence and associated risk factors for AKI in patients undergoing THA.

2. Methods

2.1. Search Strategy and Literature Review

The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018101928). A systematic literature search of EMBASE (1988 to July 2018), MEDLINE (1946 to July 2018), and the Cochrane Database of Systematic Reviews (database inception to July 2018) was performed to evaluate the incidence of AKI in patients undergoing THA. The systematic literature review was undertaken independently by two investigators (C.T. and W.C) using the search strategy that combined the terms of "acute kidney injury" or "renal failure" and "hip arthroplasty" or "hip surgery" which is provided in Online Supplementary Data 1. No language limitation was applied. A manual search for conceivably relevant studies using references of the included articles was also performed. This study was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [41] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [42].

2.2. Selection Criteria

Eligible studies must be clinical trials or observational studies (cohort, case-control, or cross-sectional studies) that reported incidence of AKI in patients undergoing THA. Included studies must provide the data to estimate incidence of AKI with 95% confidence intervals (CI). Retrieved articles were individually reviewed for eligibility by the two investigators (C.T. and W.C.). Discrepancies were addressed and solved by mutual consensus. Inclusion was not limited by the size of the study.

2.3. Data Abstraction

A structured data collecting form was used to obtain the following information from each study: title, name of the first author, year of the study, publication year, country where the study was conducted, definition of THA, AKI definition, incidence of AKI, and risk factors for AKI.

2.4. Statistical Analysis

Analyses were performed utilizing the Comprehensive Meta-Analysis 3.3 software (Biostat Inc, Englewood, NJ, USA). Adjusted point estimates from each study were consolidated by the generic inverse variance approach of DerSimonian and Laird, which designated the weight of each study based on its variance [43]. Given the possibility of between-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were applied to determine the between-study heterogeneity. A value of I^2 of 0% to 25% represents insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity and 76%–100% high heterogeneity [44]. The presence of publication bias was assessed by the Egger test [45].

3. Results

A total of 410 potentially eligible articles were identified using our search strategy. After the exclusion of 162 articles based on title and abstract for clearly not fulfilling inclusion criteria on the basis of type of article, study design, population or outcome of interest, and 209 due to being duplicates, 39 articles were left for full-length review. 11 of them were excluded from the full-length review as they did not report the outcome of interest while 5 articles were excluded because they were not observational studies. Six studies [9–14] were subsequently excluded because they did not use standard AKI definitions of Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. Thus, 17 cohort studies [18–33,37] comprising 24,158 patients undergoing THA were included into the meta-analysis of associated AKI incidence. The literature retrieval, review, and selection process are demonstrated in Figure 1. The characteristics of the included studies are presented in Table 1.

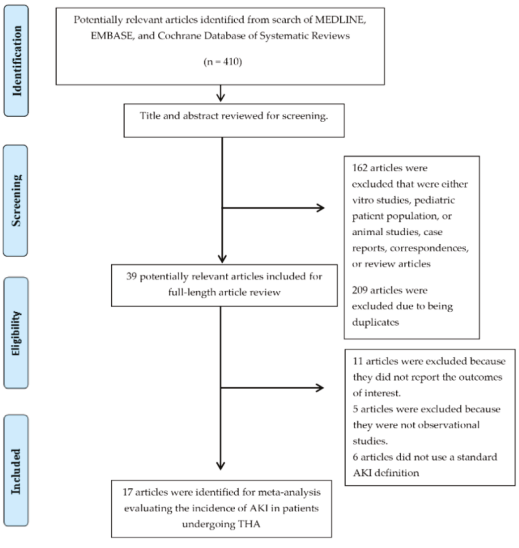

Figure 1. Outline of our search methodology.

Table 1. Main characteristic of studies included in meta-analysis of AKI incidence in patients undergoing THA [18–33].

Study	Year	Country	Study Design	Procedures/Patients	Number of Patients	AKI Definition	Incidence
Ulucay et al. [18]	2012	Turkey	Cohort	Cemented bipolar hip arthroplasty for femur neck fracture; aged ≥65 years	163	Acute kidney injury; AKIN criteria	25/163 (15.3%) Dialysis 3/163 (1.8%)
Choi et al. [1,19]	2013	South Korea	Cohort	Total hip replacement for avascular necrosis	489	Acute kidney injury; AKIN criteria	47/489 (9.6%)
Challagunda et al. [20]	2013	UK	Cohort	Elective hip surgery	112	Acute kidney injury; RIFLE criteria	33/112 (29.5%)
Craxford et al. [21]	2014	UK	Cohort	Total hip replacement	200	Acute kidney injury; RIFLE criteria	7/200 (3.5%)
Li et al. [22]	2014	China	Cohort	Total hip replacement	900	Acute kidney injury; AKIN criteria	93/900 (10.3%)
Kimmel et al. [23]	2014	Australia	Cohort	Primary elective total hip arthroplasty	173	Acute kidney injury; RIFLE criteria	14/173 (8.1%)
Hassan et al. [37]	2015	Denmark	Cohort	Primary hip replacement	586	Acute kidney injury; RIFLE criteria	81/586 (13.8%)
Warth et al. [24]	2016	USA	Cohort	Total hip arthroplasty	488	Acute kidney injury; AKIN criteria	22/488 (4.5%) Dialysis 0/488 (0%)
Nowicka et al. [25]	2016	UK	Cohort	Elective hip arthroplasty	156	Acute kidney injury; AKIN criteria	11/156 (7.1%) Dialysis 0/156 (0%)
Choi et al. [2,26]	2016	South Korea	Cohort	Total hip replacement	2467	Acute kidney injury; AKIN criteria	119/2467 (4.8%)
Johansson et al. [27]	2016	Denmark	Cohort	Elective total hip replacement	136	Acute kidney injury; KDIGO criteria	27/136 (19.9%)
Perregaard et al. [28]	2016	Denmark	Cohort	Primary elective total hip replacement	3416	Acute kidney injury; KDIGO criteria	75/3416 (2.2%)
Ferguson et al. [29]	2017	UK	Cohort	Primary hip arthroplasty	187	Acute kidney injury; KDIGO criteria	20/187 (10.7%) Dialysis 0/187 (0%)
Jiang et al. [30]	2017	USA	Cohort	Total hip arthroplasty	411	Acute kidney injury; RIFLE criteria	30/411 (7.3%)
Gharaibeh et al. [31]	2017	USA	Cohort	Total hip arthroplasty	10323	Acute kidney injury; KDIGO criteria	114/10323 (1.1%)
Weinstein et al. [32]	2018	USA	Cohort	Unilateral total hip arthroplasty with intraoperative controlled hypotension under neuraxial anesthesia	2431	Acute kidney injury; RIFLE or AKIN criteria	45/2431 (1.9%)
Tucker et al. [33]	2018	UK	Cohort	Primary hip arthroplasty	1420	Acute kidney injury; AKIN criteria	19/1420 (1.3%)

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network;KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; THA, total hip arthroplasties; UK, United Kingdom; USA, United States of America.

3.1. Incidence of AKI in Patients Undergoing THA

Overall, the pooled estimated incidence rates of AKI and severe AKI requiring dialysis following THA were 6.3% (95% CI: 3.8%–10.2%, I^2 = 97%, Figure 2A) and 0.5% (95% CI: 0.1%–2.3%, I^2 = 42%, Figure 2B), respectively. Subgroup analysis based on AKI definitions was performed and showed the pooled estimated incidence rates of AKI of 5.5% (95% CI: 1.3%–21.0%, I^2 = 98%) by RIFLE criteria, 8.4% (95% CI: 5.2%–13.3%, I^2 = 95%) by AKIN criteria, and 4.2% (95% CI: 1.9%–9.0%, I^2 = 96%) by KDIGO criteria, respectively. We conducted a sensitivity analysis by excluding with patients undergoing THA for hip fractures. The pooled estimated incidence rates of AKI following THA for non-fracture indications was 5.6% (95% CI: 3.3%–9.3%, I^2 = 97%). The pooled estimated incidence rates of AKI following THA among patients with fractures was 14.2% (95% CI: 11.8%–16.9%, I^2 = 0%).

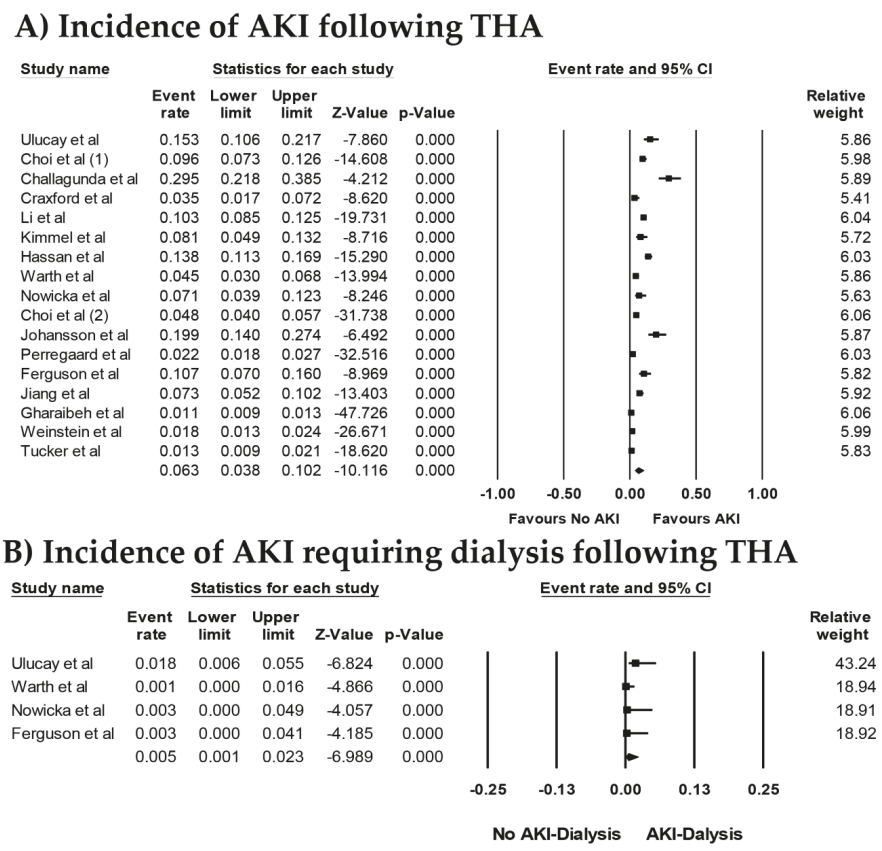

Figure 2. Forest plots of the included studies [18–33] assessing (**A**) incidence rates of AKI and (**B**) incidence rates of AKI requiring dialysis following THA. A diamond data marker represents the overall rate from each included study (square data marker) and 95% confidence interval (CI).

Subgroup analysis based on the countries by continent was performed and demonstrated pooled estimated incidence of AKI following THA of 9.2% (95% CI: 5.6%–14.8%) in Asia, 8.1% (95% CI: 4.9%–13.2%) in Australia, 7.4% (95% CI: 3.2%–16.3%) in Europe, and 2.8% (95% CI: 1.2%–17.0%) in North America.

Meta-regression of all included studies showed significant negative correlation between incidence of AKI following THA and the study year (slope = −0.37, p <0.001), as shown in Figure 3.

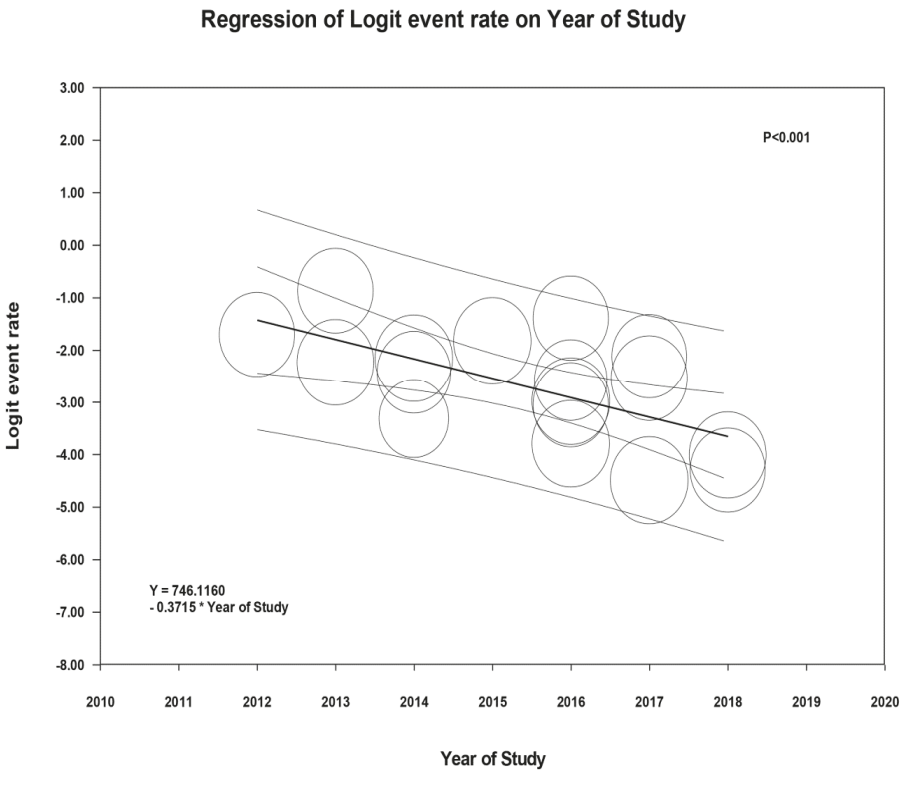

Figure 3. Meta-regression analyses showed significant negative correlation between incidence of AKI following THA and the study year (slope = −0.37, p <0.001). The solid black line represents the weighted regression line based on variance-weighted least squares. The inner and outer lines show the 95% confidence interval and prediction interval around the regression line. The circles indicate log event rates in each study.

3.2. Risk Factors for AKI in Patients Undergoing THA

Reported risk factors for AKI in patients undergoing THA are demonstrated in Table 2 [18–20,22–24,26,27,29–33,46–62]. Older age [23,24,26,29,31,55,60], higher body mass index (BMI) [19,22–24,26,30,31,46–49,56,57,59], reduced baseline estimated glomerular filtration rate (eGFR)/chronic kidney disease (CKD) [31,54,55,57,60], diabetes mellitus (DM) [24,26,31,34,47,55,57], nonsteroidal anti-inflammatory drug (NSAID) [23,32,53] use, and perioperative blood transfusion [23,47,53,55] were consistently identified as important risk factors for AKI in patients undergoing THA.

Table 2. Reported Risk Factors for AKI in patients undergoing THA [18–20,22–24,26,27,29–33,46–62].

Study	Risk Factors for AKI
Jafari et al. [46]	Elevated BMI, elevated baseline creatinine, history of COPD, liver disease, CHF, hypertension, underlying heart disease
Weingarten et al. [47]	Elevated BMI, DM, the number of baseline antihypertensive medications, cerebral or peripheral vascular disease, the use of general anesthesia, perioperative blood transfusion
Ulucay et al. [18]	Lower baseline eGFR
Choi et al. [1,19]	Transplantation, increased weight
Li et al. [22]	Transplantation, increased weight
Challagundla et al. [20]	Male, ACEI/ARB
Nielson et al. [48]	Preoperative ACEI/ARB, BMI, CAD, intra-operative hypotension
Kimmel et al. [23]	Older age, increased BMI, lower baseline eGFR, NSAID use, ACEI/ARB use, blood transfusion
Ward et al. [49]	Increased BMI
Marty et al. [50]	Postoperative resistive index
Courtney et al. [51]	Dual antibiotics prophylaxis (cefazolin + vancomycin vs. cefazolin), ASA classification, preoperative kidney disease
Opperer et al. [52]	Perioperative fluid resuscitation with 6% HES or 5% albumin
Aeng et al. [53]	Gentamicin in premanufactured bone cement, intraoperative blood transfusion, postoperative NSAID use
Warth et al. [24]	Older age, elevated BMI, DM, smoking
Tan et al. [54]	CKD
Nadkarni et al. [55]	Older age, male sex, black race, CKD, CHF, chronic liver disease, hypertension, DM, atrial fibrillation, HCV infection, postoperative sepsis, acute MI, blood transfusion, urban hospital, small hospital size
Meller et al. [56]	Morbid obesity
Choi et al. [2,26]	Postoperative anemia, older age, male sex, BMI <22 or ≥25, DM, beta-blocker, ARB use
Ferguson et al. [29]	Older age, the use of ≥1 L of postoperative fluid
Johansson et al. [27]	Gentamicin, female sex
Geller et al. [57]	Higher BMI, lower baseline hemoglobin, history of comorbid condition (DM, CKD, CVD, hypertension)
Jiang et al. [30]	Perioperative ACEI/ARB use, vancomycin use, increased BMI
Zainudheen et al. [58]	Use of renin-angiotensin antagonists
Jamsa et al. [59]	Lower preoperative eGFR, ASA classification, BMI, duration of operation
Ghareibeh et al. [31]	Entire cohort: older age, male, CKD, heart failure, diabetes, hypertension Nested case control: elevated BMI, heart failure, DM, hypertension, lower GFR, transfusion
Yadav et al. [60]	Older age, surgery for periprosthetic joint infection, CKD, total number of surgeries
Weinstein et al. [32]	Lower baseline GFR, lower baseline hemoglobin, previous NSAID use
Tucker et al. [33]	Gentamicin use
Klement et al. [61]	Co-occurrence of a mental illness and a substance abuse disorder
Abar et al. [62]	Elevated preoperative creatinine, larger postoperative drop in hemoglobin, and higher ASA classification
Hassan et al. [37]	Older age, hypertension, general anesthesia, high ASA score, low baseline systolic and diastolic blood pressure, hip fracture
Dubrovskaya et al. [34]	Hospital stay >1 day prior to surgery, knee or hip surgery, DM
Bailey et al. [38]	Prophylactic use of flucloxacillin and gentamicin versus cefuroxime alone

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; AKI, acute kidney injury; ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; NSAID, nonsteroidal anti-inflammatory drug; THA, total hip arthroplasties.

3.3. Evaluation for Publication Bias

Funnel plot (Supplementary Figure S1) and Egger's regression asymmetry test were performed to evaluate for publication bias in analysis evaluating incidence of AKI in patients undergoing THA. There was no significant publication bias in meta-analysis assessing incidence of AKI in patients undergoing THA, $p = 0.20$.

4. Discussion

In this systematic review and meta-analysis, we found that patients who underwent THA had incidences of AKI (using a standard AKI definition) and AKI requiring dialysis of 6.3% and 0.5%,

respectively. In addition, our findings showed a statistically significant negative correlation between incidence of AKI following THA and the study year, representing potential improvement in the AKI incidence for patients undergoing THA over time.

Similar to other types of perioperative AKI, the pathogenesis of THA-related AKI is multifactorial including intraoperative hypotension, perioperative anemia and blood transfusion, antibiotic-related AKI, and nephrotoxic agents such as NSAID use [18–20,22–24,26,27,29–33,46–62]. Our study demonstrated an overall low incidence of AKI following THA of 6.3%, and comparatively much lower than AKI incidence following other types of major surgeries such as coronary artery bypass grafting (AKI incidence approximately 20%) [63,64], vascular surgery (AKI incidence approximately 25%) [35,65], or heart valve replacement surgery (AKI incidence approximately 35% to 47%) [66]. In addition, the majority of AKI following THA is mild in severity [18–33] and only 0.5% of patients undergoing THA developed severe AKI requiring dialysis, as demonstrated by our meta-analysis. Despite the low incidence of AKI among patients undergoing THA, those who develop AKI following THA still carry significant increased mortality and worse outcomes including prolonged hospital stay [39,46,67,68] and hospital readmissions after THA [69,70]. In addition, it is now evident that even mild AKI is still associated with poor long-term outcomes including development of cardiovascular diseases and CKD [71,72]. Thus, perioperative medicine remains critically important in patients undergoing THA in order to prevent perioperative AKI [73].

Our study also showed a potential improvement in the AKI incidence following THA over time. This is likely explained by advances in perioperative medicine care [73]. As described earlier in this systematic review, the pathogenesis of AKI in patients undergoing THA is multifactorial. Risk factors for AKI following THA are summarized in Table 2. Since older age, higher BMI, CKD, DM were consistently identified as important risk factors for AKI in patients undergoing THA [18–20,22–24,26,27,29–33,46–62], clinicians and nephrologists should pay close attention to particular populations of patients. Limitation of nephrotoxic agents such as NSAIDs and a judicious use of perioperative blood transfusion should be considered [23,47,53,55] for preventive measures to reduce AKI following THA. In patients undergoing THA, recent studies have demonstrated significant avoidance of NSAID use in those possessing higher AKI risk, such as patients with CKD and congestive heart failure (CHF) [29,31]. In addition, in recent years, the use of hydroxyethyl starch (HES) solutions, unnecessary blood transfusions, chloride-rich intravenous fluids, and aminoglycosides have been discouraged [29,52,73]. Furthermore, although the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) and perioperative AKI risk remains controversial [2,74,75], ACEIs/ARBs have been commonly discontinued before THA to prevent intraoperative hypotension [29]. Future studies are required to assess if discontinuation of ACEIs/ARBs before THA may affect the incidence of THA-associated AKI, and whether it should be included in AKI preventative strategies and care optimization among patients undergoing THA [37,40].

Several limitations in our meta-analysis are worth mentioning. First, there are statistical heterogeneities in our study. Possible sources for heterogeneities were the differences in patient characteristics between the individual studies. Studies involving large sample size observed lower AKI incidence compared to those with small sample size. Studies outside USA observed higher AKI incidence following THA, suggesting potential differences in operative surgery, antibiotic and blood transfusion, and perioperative care. Subgroup analysis based on the countries by continent demonstrated significantly different AKI incidences in each continent. Furthermore, the meta-regression analysis that demonstrated a significant negative correlation of post-THA AKI incidence with time adds the contribution of study year as a source of heterogeneity in our study. Second, there was limited data on the AKI incidence following THA from countries in South America and Africa. Third, there is a lack of data from the included studies on novel AKI biomarkers and AKI diagnosis based on urine output criteria. Lastly, this is a systematic review and meta-analysis of cohort studies and the data from population based studies were limited. Thus, future population based studies evaluating the incidence of AKI following THA are required.

In summary, there is an overall low incidence of AKI of 6.3% among patients undergoing THA. There has also been potential improvement in AKI incidence for patients undergoing THA over time.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/1/66/s1, Online Supplementary Data 1. Search terms for systematic review, Supplementary Figure S1. Funnel plot evaluating for publication bias evaluating incidence of AKI in patients undergoing THA.

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References

1. Thongprayoon, C.; Cheungpasitporn, W.; Harrison, A.M.; Kittanamongkolchai, W.; Ungprasert, P.; Srivali, N.; Akhoundi, A.; Kashani, K.B. The comparison of the commonly used surrogates for baseline renal function in acute kidney injury diagnosis and staging. *BMC Nephrol.* **2016**, *17*, 6. [CrossRef] [PubMed]
2. Cheungpasitporn, W.; Thongprayoon, C.; Srivali, N.; O'corragain, O.A.; Edmonds, P.J.; Ungprasert, P.; Kittanamongkolchai, W.; Erickson, S.B. Preoperative renin-angiotensin system inhibitors use linked to reduced acute kidney injury: A systematic review and meta-analysis. *Nephrol. Dial. Transplant.* **2015**, *30*, 978–988. [CrossRef] [PubMed]
3. Hoste, E.A.; Kellum, J.A.; Selby, N.M.; Zarbock, A.; Palevsky, P.M.; Bagshaw, S.M.; Goldstein, S.L.; Cerdá, J.; Chawla, L.S. Global epidemiology and outcomes of acute kidney injury. *Nat. Rev. Nephrol.* **2018**, *14*, 607–625. [CrossRef] [PubMed]
4. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J. Clin. Med.* **2018**, *7*, 307. [CrossRef]
5. Sehgal, V.; Bajwa, S.J.; Sehgal, R.; Eagan, J.; Reddy, P.; Lesko, S.M. Predictors of acute kidney injury in geriatric patients undergoing total knee replacement surgery. *Int. J. Endocrinol. Metab.* **2014**, *12*, e16713. [CrossRef] [PubMed]
6. Kim, H.J.; Koh, W.U.; Kim, S.G.; Park, H.S.; Song, J.G.; Ro, Y.J.; Yang, H.S. Early postoperative albumin level following total knee arthroplasty is associated with acute kidney injury: A retrospective analysis of 1309 consecutive patients based on kidney disease improving global outcomes criteria. *Medicine* **2016**, *95*, e4489. [CrossRef] [PubMed]
7. Mehta, R.L.; Burdmann, E.A.; Cerdá, J.; Feehally, J.; Finkelstein, F.; García-García, G.; Godin, M.; Jha, V.; Lameire, N.H.; Levin, N.W.; et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: A multinational cross-sectional study. *Lancet* **2016**, *387*, 2017–2025. [CrossRef]
8. Mehta, R.L.; Cerdá, J.; Burdmann, E.A.; Tonelli, M.; García-García, G.; Jha, V.; Susantitaphong, P.; Rocco, M.; Vanholder, R.; Sever, M.S.; et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): A human rights case for nephrology. *Lancet* **2015**, *385*, 2616–2643. [CrossRef]
9. Coventry, M.B.; Beckenbaugh, R.D.; Nolan, D.R.; Ilstrup, D.M. 2012 total hip arthroplasties. A study of postoperative course and early complications. *J. Bone Joint Surg. Am.* **1974**, *56*, 273–284. [CrossRef]
10. Sharrock, N.E.; Beksac, B.; Flynn, E.; Go, G.; Della Valle, A.G. Hypotensive epidural anaesthesia in patients with preoperative renal dysfunction undergoing total hip replacement. *Br. J. Anaesth.* **2006**, *96*, 207–212. [CrossRef]
11. Jameson, S.S.; Khan, S.K.; Baker, P.; James, P.; Gray, A.; Reed, M.R.; Deehan, D.J. A national analysis of complications following hemiarthroplasty for hip fracture in older patients. *QJM* **2012**, *105*, 455–460. [CrossRef] [PubMed]

12. Horstmann, W.G.; Swierstra, M.J.; Ohanis, D.; Castelein, R.M.; Kollen, B.J.; Verheyen, C.C. Reduction of blood loss with the use of a new combined intra-operative and post-operative autologous blood transfusion system compared with no drainage in primary total hip replacement. *Bone Joint J.* **2013**, *95-B*, 616–622. [CrossRef] [PubMed]
13. Regenbogen, S.E.; Cain-Nielsen, A.H.; Norton, E.C.; Chen, L.M.; Birkmeyer, J.D.; Skinner, J.S. Costs and Consequences of Early Hospital Discharge After Major Inpatient Surgery in Older Adults. *JAMA Surg.* **2017**, *152*, e170123. [CrossRef] [PubMed]
14. Frenkel Rutenberg, T.; Daglan, E.; Heller, S.; Velkes, S. A comparison of treatment setting for elderly patients with hip fracture, is the geriatric ward superior to conventional orthopedic hospitalization? *Injury* **2017**, *48*, 1584–1588. [CrossRef] [PubMed]
15. Pulido, L.; Parvizi, J.; Macgibeny, M.; Sharkey, P.F.; Purtill, J.J.; Rothman, R.H.; Hozack, W.J. In hospital complications after total joint arthroplasty. *J. Arthroplast.* **2008**, *23* (Suppl. 1), 139–145. [CrossRef] [PubMed]
16. McDermott, K.W.; Freeman, W.J.; Elixhauser, A. Overview of Operating Room Procedures During Inpatient Stays in U.S. Hospitals, 2014: Statistical Brief #233. 2006. Available online: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb233-Operating-Room-Procedures-United-States-2014.pdf (accessed on 9 January 2019).
17. Abdel, M.P.; Watts, C.D.; Houdek, M.T.; Lewallen, D.G.; Berry, D.J. Epidemiology of periprosthetic fracture of the femur in 32 644 primary total hip arthroplasties: A 40-year experience. *Bone Joint J.* **2016**, *98-B*, 461–467. [CrossRef] [PubMed]
18. Ulucay, C.; Eren, Z.; Kaspar, E.C.; Ozler, T.; Yuksel, K.; Kantarci, G.; Altintas, F. Risk factors for acute kidney injury after hip fracture surgery in the elderly individuals. *Geriatr. Orthop. Surg. Rehabil.* **2012**, *3*, 150–156. [CrossRef] [PubMed]
19. Choi, Y.J.; Lee, E.H.; Hahm, K.D.; Kwon, K.; Ro, Y.J. Transplantation is a risk factor for acute kidney injury in patients undergoing total hip replacement arthroplasty for avascular necrosis: An observational study. *Transplant. Proc.* **2013**, *45*, 2220–2225. [CrossRef]
20. Challagundla, S.R.; Knox, D.; Hawkins, A.; Hamilton, D.; WVFlynn, R.; Robertson, S.; Isles, C. Renal impairment after high-dose flucloxacillin and single-dose gentamicin prophylaxis in patients undergoing elective hip and knee replacement. *Nephrol. Dial. Transplant.* **2013**, *28*, 612–619. [CrossRef]
21. Craxford, S.; Bayley, E.; Needoff, M. Antibiotic-associated complications following lower limb arthroplasty: A comparison of two prophylactic regimes. *Eur. J. Orthop. Surg. Traumatol.* **2014**, *24*, 539–543. [CrossRef]
22. Li, X.; Guo, D.; Shi, G.; Li, R.; Li, X.; Shen, R.; Wang, H.; Li, Y.; Yuan, F.; Han, G. Role of total hip replacement arthroplasty between transplantation and acute kidney injury. *Ren. Fail.* **2014**, *36*, 899–903. [CrossRef]
23. Kimmel, L.A.; Wilson, S.; Janardan, J.D.; Liew, S.M.; Walker, R.G. Incidence of acute kidney injury following total joint arthroplasty: A retrospective review by RIFLE criteria. *Clin. Kidney J.* **2014**, *7*, 546–551. [CrossRef]
24. Warth, L.C.; Noiseux, N.O.; Hogue, M.H.; Klaassen, A.L.; Liu, S.S.; Callaghan, J.J. Risk of Acute Kidney Injury After Primary and Revision Total Hip Arthroplasty and Total Knee Arthroplasty Using a Multimodal Approach to Perioperative Pain Control Including Ketorolac and Celecoxib. *J. Arthroplast.* **2016**, *31*, 253–255. [CrossRef] [PubMed]
25. Nowicka, A.; Selvaraj, T. Incidence of acute kidney injury after elective lower limb arthroplasty. *J. Clin. Anesth.* **2016**, *34*, 520–523. [CrossRef] [PubMed]
26. Choi, Y.J.; Kim, S.O.; Sim, J.H.; Hahm, K.D. Postoperative Anemia Is Associated with Acute Kidney Injury in Patients Undergoing Total Hip Replacement Arthroplasty: A Retrospective Study. *Anesth. Analg.* **2016**, *122*, 1923–1928. [CrossRef] [PubMed]
27. Johansson, S.; Christensen, O.M.; Thorsmark, A.H. A retrospective study of acute kidney injury in hip arthroplasty patients receiving gentamicin and dicloxacillin. *Acta Orthop.* **2016**, *87*, 589–591. [CrossRef] [PubMed]
28. Perregaard, H.; Damholt, M.B.; Solgaard, S.; Petersen, M.B. Renal function after elective total hip replacement. *Acta Orthop.* **2016**, *87*, 235–238. [CrossRef]
29. Ferguson, K.B.; Winter, A.; Russo, L.; Khan, A.; Hair, M.; MacGregor, M.S.; Holt, G. Acute kidney injury following primary hip and knee arthroplasty surgery. *Ann. R. Coll. Surg. Engl.* **2017**, *99*, 307–312. [CrossRef] [PubMed]
30. Jiang, E.X.; Gogineni, H.C.; Mayerson, J.L.; Glassman, A.H.; Magnussen, R.A.; Scharschmidt, T.J. Acute Kidney Disease After Total Hip and Knee Arthroplasty: Incidence and Associated Factors. *J. Arthroplast.* **2017**, *32*, 2381–2385. [CrossRef]

31. Gharaibeh, K.A.; Hamadah, A.M.; Sierra, R.J.; Leung, N.; Kremers, W.K.; El-Zoghby, Z.M. The Rate of Acute Kidney Injury After Total Hip Arthroplasty Is Low but Increases Significantly in Patients with Specific Comorbidities. *J. Bone Joint Surg. Am.* **2017**, *99*, 1819–1826.
32. Weinstein, S.M.; YaDeau, J.T.; Memtsoudis, S.G. Lack of Association Between Levels and Length of Intraoperative Controlled Hypotension and Acute Kidney Injury in Total Hip Arthroplasty Patients Receiving Neuraxial Anesthesia. *Reg. Anesth. Pain Med.* **2018**, *43*, 725–731. [CrossRef] [PubMed]
33. Tucker, A.; Hegarty, P.; Magill, P.J.; Blaney, J.; Armstrong, L.V.; McCaffrey, J.E.; Beverland, D.E. Acute Kidney Injury After Prophylactic Cefuroxime and Gentamicin in Patients Undergoing Primary Hip and Knee Arthroplasty-A Propensity Score-Matched Study. *J. Arthroplast.* **2018**, *33*, 3009–3015. [CrossRef] [PubMed]
34. Dubrovskaya, Y.; Tejada, R.; Bosco, I.I.I.J.; Stachel, A.; Chen, D.; Feng, M.; Rosenberg, A.; Phillips, M. Single high dose gentamicin for perioperative prophylaxis in orthopedic surgery: Evaluation of nephrotoxicity. *SAGE Open Med.* **2015**, *3*. [CrossRef] [PubMed]
35. Bell, S.; Davey, P.; Nathwani, D.; Marwick, C.; Vadiveloo, T.; Sneddon, J.; Patton, A.; Bennie, M.; Fleming, S.; Donnan, P.T. Risk of AKI with gentamicin as surgical prophylaxis. *J. Am. Soc. Nephrol.* **2014**, *25*, 2625–2632. [CrossRef] [PubMed]
36. Ross, A.D.; Boscainos, P.J.; Malhas, A.; Wigderowitz, C. Peri-operative renal morbidity secondary to gentamicin and flucloxacillin chemoprophylaxis for hip and knee arthroplasty. *Scott. Med. J.* **2013**, *58*, 209–212. [CrossRef] [PubMed]
37. Hassan, B.K.; Sahlstrom, A.; Dessau, R.B. Risk factors for renal dysfunction after total hip joint replacement; a retrospective cohort study. *J. Orthop. Surg. Res.* **2015**, *10*, 158. [CrossRef] [PubMed]
38. Bailey, O.; Torkington, M.S.; Anthony, I.; Wells, J.; Blyth, M.; Jones, B. Antibiotic-related acute kidney injury in patients undergoing elective joint replacement. *Bone Joint J.* **2014**, *96-B*, 395–398. [CrossRef]
39. Bennet, S.J.; Berry, O.M.; Goddard, J.; Keating, J.F. Acute renal dysfunction following hip fracture. *Injury* **2010**, *41*, 335–338. [CrossRef]
40. Bjerregaard, L.S.; Jorgensen, C.C.; Kehlet, H. Serious renal and urological complications in fast-track primary total hip and knee arthroplasty; a detailed observational cohort study. *Minerva Anestesiol.* **2016**, *82*, 757–776.
41. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]
42. Von Elm, E.; Altman, D.G.; Egger, M.; Pocock, S.J.; Gotzsche, P.C.; Vandenbroucke, J.P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med.* **2007**, *4*, e296. [CrossRef] [PubMed]
43. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
44. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef] [PubMed]
45. Easterbrook, P.J.; Berlin, J.A.; Gopalan, R.; Matthews, D.R. Publication bias in clinical research. *Lancet* **1991**, *337*, 867–872. [CrossRef]
46. Jafari, S.M.; Huang, R.; Joshi, A.; Parvizi, J.; Hozack, W.J. Renal impairment following total joint arthroplasty: Who is at risk? *J. Arthroplast.* **2010**, *25*, 49–53. [CrossRef] [PubMed]
47. Weingarten, T.N.; Gurrieri, C.; Jarett, P.D.; Brown, D.R.; Berntson, N.J.; Calaro, R.D., Jr.; Kor, D.J.; Berry, D.J.; Garovic, V.D.; Nicholson, W.T.; et al. Acute kidney injury following total joint arthroplasty: Retrospective analysis. *Can. J. Anaesth.* **2012**, *59*, 1111–1118. [CrossRef] [PubMed]
48. Nielson, E.; Hennrikus, E.; Lehman, E.; Mets, B. Angiotensin axis blockade, hypotension, and acute kidney injury in elective major orthopedic surgery. *J. Hosp. Med.* **2014**, *9*, 283–288. [CrossRef]
49. Ward, D.T.; Metz, L.N.; Horst, P.K.; Kim, H.T.; Kuo, A.C. Complications of Morbid Obesity in Total Joint Arthroplasty: Risk Stratification Based on BMI. *J. Arthroplast.* **2015**, *30*, 42–46. [CrossRef]
50. Marty, P.; Szatjnic, S.; Ferre, F.; Conil, J.M.; Mayeur, N.; Fourcade, O.; Silva, S.; Minville, V. Doppler renal resistive index for early detection of acute kidney injury after major orthopaedic surgery: A prospective observational study. *Eur. J. Anaesthesiol.* **2015**, *32*, 37–43. [CrossRef]
51. Courtney, P.M.; Melnic, C.M.; Zimmer, Z.; Anari, J.; Lee, G.C. Addition of Vancomycin to Cefazolin Prophylaxis Is Associated With Acute Kidney Injury After Primary Joint Arthroplasty. *Clin. Orthop. Relat. Res.* **2015**, *473*, 2197–2203. [CrossRef]

52. Opperer, M.; Poeran, J.; Rasul, R.; Mazumdar, M.; Memtsoudis, S.G. Use of perioperative hydroxyethyl starch 6% and albumin 5% in elective joint arthroplasty and association with adverse outcomes: A retrospective population based analysis. *BMJ* **2015**, *350*, h1567. [CrossRef] [PubMed]
53. Aeng, E.S.; Shalansky, K.F.; Lau, T.T.; Zalunardo, N.; Li, G.; Bowie, W.R.; Duncan, C.P. Acute Kidney Injury With Tobramycin-Impregnated Bone Cement Spacers in Prosthetic Joint Infections. *Ann. Pharmacother.* **2015**, *49*, 1207–1213. [CrossRef] [PubMed]
54. Tan, T.L.; Kheir, M.M.; Tan, D.D.; Filippone, E.J.; Tischler, E.H.; Chen, A.F. Chronic Kidney Disease Linearly Predicts Outcomes After Elective Total Joint Arthroplasty. *J. Arthroplast.* **2016**, *31*, 175–179. [CrossRef]
55. Nadkarni, G.N.; Patel, A.A.; Ahuja, Y.; Annapureddy, N.; Agarwal, S.K.; Simoes, P.K.; Konstantinidis, I.; Kamat, S.; Archdeacon, M.; Thakar, C.V. Incidence, Risk Factors, and Outcome Trends of Acute Kidney Injury in Elective Total Hip and Knee Arthroplasty. *Am. J. Orthop.* **2016**, *45*, E12–E19. [PubMed]
56. Meller, M.M.; Toossi, N.; Gonzalez, M.H.; Son, M.S.; Lau, E.C.; Johanson, N. Surgical Risks and Costs of Care are Greater in Patients Who Are Super Obese and Undergoing THA. *Clin. Orthop. Relat. Res.* **2016**, *474*, 2472–2481. [CrossRef]
57. Geller, J.A.; Cunn, G.; Herschmiller, T.; Murtaugh, T.; Chen, A. Acute Kidney Injury After First-Stage Joint Revision for Infection: Risk Factors and the Impact of Antibiotic Dosing. *J. Arthroplast.* **2017**, *32*, 3120–3125. [CrossRef]
58. Zainudheen, A.; Scott, I.A.; Caney, X. Association of renin angiotensin antagonists with adverse perioperative events in patients undergoing elective orthopaedic surgery: A case-control study. *Intern. Med. J.* **2017**, *47*, 999–1005. [CrossRef]
59. Jamsa, P.; Jamsen, E.; Lyytikainen, L.P.; Kalliovalkama, J.; Eskelinen, A.; Oksala, N. Risk factors associated with acute kidney injury in a cohort of 20,575 arthroplasty patients. *Acta Orthop.* **2017**, *88*, 370–376. [CrossRef]
60. Yadav, A.; Alijanipour, P.; Ackerman, C.T.; Karanth, S.; Hozack, W.J.; Filippone, E.J. Acute Kidney Injury Following Failed Total Hip and Knee Arthroplasty. *J. Arthroplast.* **2018**, *33*, 3297–3303. [CrossRef]
61. Klement, M.R.; Nickel, B.T.; Bala, A.; Penrose, C.T.; Green, C.L.; Wellman, S.S.; Bolognesi, M.P.; Seyler, T.M. Dual Diagnosis and Total Hip Arthroplasty. *Orthopedics* **2018**, *41*, e321–e327. [CrossRef]
62. Abar, O.; Toossi, N.; Johanson, N. Cost and determinants of acute kidney injury after elective primary total joint arthroplasty. *Arthroplast. Today.* **2018**, *4*, 335–339. [CrossRef] [PubMed]
63. Cheungpasitporn, W.; Thongprayoon, C.; Kittanamongkolchai, W.; Srivali, N.; O'Corragain, O.A.; Edmonds, P.J.; Ratanapo, S.; Spanuchart, I.; Erickson, S.B. Comparison of renal outcomes in off-pump versus on-pump coronary artery bypass grafting: A systematic review and meta-analysis of randomized controlled trials. *Nephrology* **2015**, *20*, 727–735. [CrossRef] [PubMed]
64. Sakhuja, A.; Kashani, K.; Schold, J.; Cheungpasitporn, W.; Soltesz, E.; Demirjian, S. Hospital procedure volume does not predict acute kidney injury after coronary artery bypass grafting-a nationwide study. *Clin. Kidney J.* **2017**, *10*, 769–775. [CrossRef] [PubMed]
65. Cheungpasitporn, W.; Thongprayoon, C.; Kashani, K. Transcatheter Aortic Valve Replacement: A Kidney's Perspective. *J. Ren. Inj. Prev.* **2016**, *5*, 1–7. [CrossRef] [PubMed]
66. Thongprayoon, C.; Cheungpasitporn, W.; Lin, J.; Mao, M.A.; Qian, Q. Acute kidney injury in octogenarians after heart valve replacement surgery: A study of two periods over the last decade. *Clin. Kidney J.* **2017**, *10*, 648–654. [CrossRef] [PubMed]
67. Napier, R.J.; Spence, D.; Diamond, O.; O'Brien, S.; Walsh, T.; Beverland, D.E. Modifiable factors delaying early discharge following primary joint arthroplasty. *Eur. J. Orthop. Surg. Traumatol.* **2013**, *23*, 665–669. [CrossRef] [PubMed]
68. Panteli, M.; Habeeb, S.; McRoberts, J.; Porteous, M.J. Enhanced care for primary hip arthroplasty: Factors affecting length of hospital stay. *Eur. J. Orthop. Surg. Traumatol.* **2014**, *24*, 353–358. [CrossRef] [PubMed]
69. Schairer, W.W.; Vail, T.P.; Bozic, K.J. What are the rates and causes of hospital readmission after total knee arthroplasty? *Clin. Orthop. Relat. Res.* **2014**, *472*, 181–187. [CrossRef] [PubMed]
70. Pugely, A.J.; Callaghan, J.J.; Martin, C.T.; Cram, P.; Gao, Y. Incidence of and risk factors for 30-day readmission following elective primary total joint arthroplasty: Analysis from the ACS-NSQIP. *J. Arthroplast.* **2013**, *28*, 1499–1504. [CrossRef]

71. Coca, S.G.; Yusuf, B.; Shlipak, M.G.; Garg, A.X.; Parikh, C.R. Long-term risk of mortality and other adverse outcomes after acute kidney injury: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **2009**, *53*, 961–973. [CrossRef]
72. Murugan, R.; Kellum, J.A. Acute kidney injury: what's the prognosis? *Nat. Rev. Nephrol.* **2011**, *7*, 209–217. [CrossRef] [PubMed]
73. Goren, O.; Matot, I. Perioperative acute kidney injury. *Br. J. Anaesth.* **2015**, *115* (Suppl. 2), ii3–ii14. [CrossRef] [PubMed]
74. Xu, N.; Long, Q.; He, T.; Liu, X.; Dai, H.; Lu, Y.; Wen, J.; Wu, Q.; Yuan, H. Association between preoperative renin-angiotensin system inhibitor use and postoperative acute kidney injury risk in patients with hypertension. *Clin. Nephrol.* **2018**, *89*, 403–414. [CrossRef] [PubMed]
75. Tagawa, M.; Ogata, A.; Hamano, T. Pre- and/or Intra-Operative Prescription of Diuretics, but Not Renin-Angiotensin-System Inhibitors, Is Significantly Associated with Acute Kidney Injury after Non-Cardiac Surgery: A Retrospective Cohort Study. *PLoS ONE* **2015**, *10*, e0132507. [CrossRef] [PubMed]

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Common Inflammation-Related Candidate Gene Variants and Acute Kidney Injury in 2647 Critically Ill Finnish Patients

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Abstract: Acute kidney injury (AKI) is a syndrome with high incidence among the critically ill. Because the clinical variables and currently used biomarkers have failed to predict the individual susceptibility to AKI, candidate gene variants for the trait have been studied. Studies about genetic predisposition to AKI have been mainly underpowered and of moderate quality. We report the association study of 27 genetic variants in a cohort of Finnish critically ill patients, focusing on the replication of associations detected with variants in genes related to inflammation, cell survival, or circulation. In this prospective, observational Finnish Acute Kidney Injury (FINNAKI) study, 2647 patients without chronic kidney disease were genotyped. We defined AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We compared severe AKI (Stages 2 and 3, $n = 625$) to controls (Stage 0, $n = 1582$). For genotyping we used iPLEX^{TM} Assay (Agena Bioscience). We performed the association analyses with PLINK software, using an additive genetic model in logistic regression. Despite the numerous, although contradictory, studies about association between polymorphisms rs1800629 in *TNFA* and rs1800896 in *IL10* and AKI, we found no association (odds ratios 1.06 (95% CI 0.89–1.28, $p = 0.51$) and 0.92 (95% CI 0.80–1.05, $p = 0.20$), respectively). Adjusting for confounders did not change the results. To conclude, we could not confirm the associations reported in previous studies in a cohort of critically ill patients.

Keywords: acute kidney injury; genetic variation; human genetics

1. Introduction

Acute kidney injury (AKI) is a syndrome that often complicates critical illness and is associated with significant mortality and morbidity [1,2]. Thus, efforts to distinguish patients at risk for AKI are justifiable, but despite the advances in the understanding of the pathophysiology of AKI, reliable prediction of developing AKI in different clinical scenarios remains a challenge.

In our systematic review in 2014 we found that evidence about genetic predisposition to AKI was heterogeneous, the studies were of inadequate size and the findings were generally not replicated [3]. Based on these findings, we analyzed 27 common genetic variants that situate in genes previously associated with AKI in a Finnish sample of critically ill patients.

2. Materials and Methods

2.1. Patients

We prospectively recruited patients from 17 Finnish intensive care units (ICUs) in the Finnish acute Kidney Injury (FINNAKI) study. The FINNAKI study took place in the years 2011 and 2012, and the study design has been described previously [1]. We included all patients with an emergency ICU admission of any length and elective surgical patients with an expected duration of ICU stay longer than 24 h. We excluded patients that received maintenance dialysis. The complete exclusion criteria are reported in electronic Supplementary Materials (ESM).

Consent for the study was achieved from the patients or next of kin, at the initiation of the study or deferred. A separate consent for genetic analyses was obtained from all patients or their legal representatives. The Ethics Committee of the Department of Surgery in Helsinki University Hospital gave approval for the study (18/13/03/02/2010).

2.2. Definitions

We defined AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [4]. We performed analyses using both the severe AKI phenotype (KDIGO Stages 2–3 compared to KDIGO 0) and the all-stage (1–3) AKI phenotype. We classified patients into AKI stages according to daily measurements of plasma creatinine and hourly measurements of urine output. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition [5].

2.3. Data Collection

We collected routine data into Finnish Intensive Care Consortium prospective database (Tieto Ltd., Helsinki, Finland). In addition, we completed a standardized case reporting form (CRF) on admission, as well as daily for 5 days and at discharge from ICU. These study-specific data comprised health status previously and present, medications in use, information about some known AKI risk factors, evaluation of organ dysfunctions such as sepsis, and information about treatments administered.

2.4. DNA Samples and Genotyping

Deoxyribonucleic acid (DNA) was extracted from frozen blood samples collected at enrollment. DNA isolation was performed with Chemagic 360 intrument using Chemagic DNA Blood10k Kit, as instructed by the manufacturer (Perkin Elmer, Baesweiler, Germany). For genotyping, we diluted the sample concentration into 10 ng/μL.

We performed the genotyping in two subsequent assays, in the years 2015 and 2017, at the Genotyping Unit of Institute for Molecular Medicine Finland (FIMM), University of Helsinki. The Agena MassARRAY® system, along with the iPLEXTM Gold Assay (Agena BioscienceTM, San Diego, CA, USA) were used for the genotyping. Here, 20 ng of dried genomic DNA were used for genotyping reactions in 384-well plates using manufacturer's reagents, and according to their recommendations [6]. For designing primer sequences, MassARRAY Assay Design software (Agena BioscienceTM) was used (see ESM). The MassARRAY Compact System (Agena BioscienceTM) was used for data collection and TyperAnalyzer software (Agena BioscienceTM) for genotype calling. The quality control procedure consisted of checking the success rate, duplicate samples, control wells with water and testing for Hardy–Weinberg Equilibrium (HWE). In addition, all of the genotype calls were manually checked. The genotyping personnel were unaware of the clinical status of the patients.

In the year 2015 assay 49 samples (1.7% of 2968 samples) were rejected because of low success rate in the tested polymorphisms, and in the year 2017 assay the corresponding number was five samples (0.2% of 2968 samples).

For rs699 the success rate reached only 48% due to assay failure in half of the runs; however, the remainder of allele calling was possible with new extension primer and the results are thus reported.

2.5. Variant Selection

Variations in or nearby genes related to inflammation, circulation, and cell survival have been suggested in candidate polymorphism studies regarding AKI [7–27]. Additionally, the first hypothesis-free studies in AKI genetic predisposition have been published [28–30], with some replicated associations [31]. We chose to test polymorphisms in *TNFA* (rs1800629 [8,19,21–27]), *IL6* (rs1800796 [24,26] and rs1800795 [19,24,26], rs10499563, rs1474347, rs13306435, rs2069842 and rs2069830), *CXCL8* (rs4073 [27]), *IL10* (rs1800896 [19,21,23,25,26]), *NOS3* (rs2070744 [13,24]), *NFKB1A* (rs1050851 [32]), *AGT* (rs699 and rs2493133 [24]), *VEGFA* (rs2010963 and rs3025039 [27]), *EPO* (rs1617640 [14]), *SUFU* (rs10748825 [9]), *HIF1A* (rs11549465 [15]), *PNMT* (rs876493 [17]), *MPO* (rs7208693 [16]), *COMT* (rs4680 [10–12]), *HSPB1* (rs2868371 [33]), *SFTPD* (rs2243639 and rs721917 [34]), *HAMP* (rs10421768 [35]) and *BBS9* (rs10262995 [30]) genes (see definitions for abbreviations in ESM).

2.6. Statistical Analyses

We used SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) for analyzing the clinical and demographic variables. The analyses used were the Fisher's exact test in cross tabulation for categorical variables and the Mann–Whitney U for continuous variables. The data are presented as medians (with interquartile range), or absolute count (with percentage).

We performed the association test for genetic variants and AKI phenotype with logistic regression in the PLINK software [36]. We used the additive genetic model. For haplotype analysis, we checked for haploblocks with Haploview [37]. In addition, for polymorphisms in TNFA and IL10 we performed an epistasis test. The haplotype analysis and epistasis test were performed with the PLINK software [36]. In the primary analysis we compared patients with KDIGO stage 2 or 3 AKI to patients without AKI, as the primary outcome of the study. In the secondary analysis we compared all stage AKI (KDIGO 1, 2 or 3) to no AKI. In the tertiary analysis we included patients with chronic kidney disease and compared patients with KDIGO stage 2 or 3 AKI to patients without AKI in an adjusted analysis. We used similar covariates to our previously published article [31] (liver failure, body mass index (BMI), use of nonsteroidal anti-inflammatory drugs (NSAID) or warfarin as permanent medication, use of contrast dye prior to ICU admission, use of colloids prior to ICU admission, use of albumin prior to ICU admission, minimum platelet count, and simplified acute physiology score (SAPS) II without renal and age points), omitting the infection focus for irrelevant information, and maximum leucocyte count and operative admission to avoid multicollinearity, while including cardiac surgery status as well as sepsis status. The missing data within covariates (altogether 2.4%) were addressed by imputing (see ESM for details).

For all analyses, we considered a p-value of 0.002 significant after Bonferroni correction for multiple testing ($0.05/25 = 0.002$).

2.7. Power Calculations

We performed prospective power calculations to determine an appropriate sample size [38]. Assuming an effect size of 1.2 per risk allele (1.4 per homozygote genotype) and a minor allele frequency of 0.2, setting the level of significance to 0.005, there will be 96% (93% for homozygote genotype) power to detect an association in a sample of 1200 cases and 1800 controls.

3. Results

We recruited 2968 patients in the FINNAKI genetic study (Figure 1). We excluded 199 patients (6.7% of 2968 patients) with chronic kidney disease from the primary (green dashed line) and secondary (orange dashed line) analysis. In addition, 122 DNA samples failed at isolation. Of the remaining 2647 patients, 221 (8.3% of 2647) patients had stage 2 AKI, 404 (15.3% of 2647) had stage 3 AKI, and 1582 (59.8% of 2647) patients served as controls without AKI. Overall, 228 (10.9% of 2647) patients received renal replacement therapy (RRT). Moreover, 440 (16.6% of 2647) patients had an ambiguous phenotype

(KDIGO stage 1); we excluded them from the primary and the tertiary (blue dashed line) analysis. Table 1 presents patient demographics.

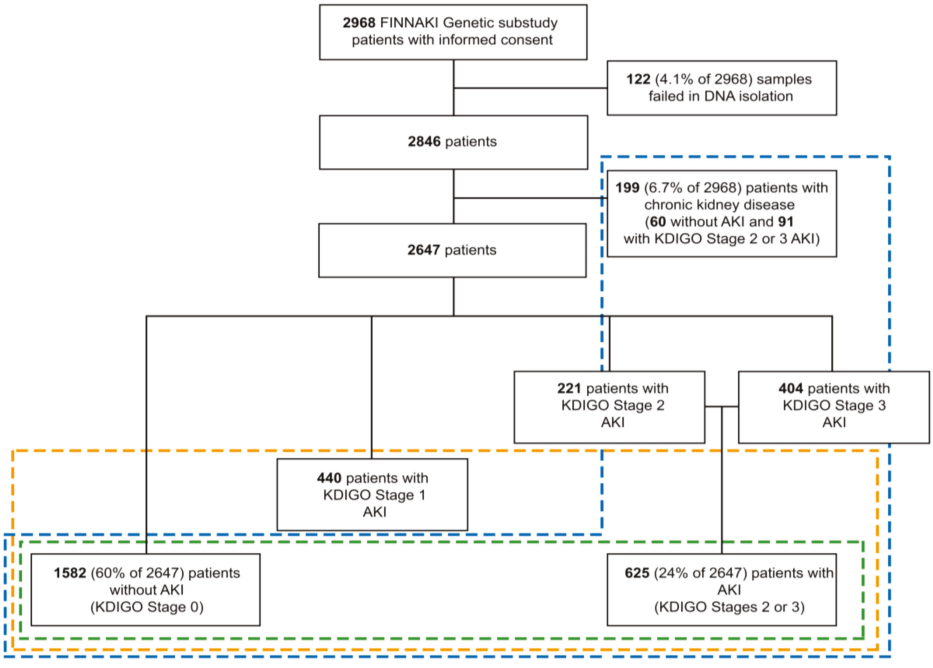

Figure 1. Study flowchart. Abbreviations: FINNAKI; Finnish Acute Kidney Injury; DNA, deoxyribonucleic acid; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

Table 1. Demographics of altogether 2647 patients in the FINNAKI genetic substudy after excluding patients with maintenance dialysis. Data are presented according to presence of severe AKI (KDIGO stage 2 or 3, n = 625), presence of all stage AKI (KDIGO stage 1, 2, 3, n = 1065), or absence of AKI (KDIGO stage 0, n = 1582).

Characteristics	Data Available	AKI		No AKI	p *
		KDIGO stage 2 or 3	KDIGO stage 1, 2, 3		
Age (years)	2647	65 (54–74)	65 (54–75)	62 (48–72)	<0.001
Gender (male)	2647	409 (65.4)	700 (65.7)	980 (61.9)	0.130
BMI (kg/m^2)	2627	27.5 (24.5–31.3)	27.5 (24.2–31.2)	25.7 (23.1–28.7)	<0.001
Co-morbidities					
Arterial hypertension	2633	333 (53.3)	561 (52.9)	641 (40.8)	<0.001
Diabetes	2643	169 (27.0)	263 (24.7)	280 (17.7)	<0.001
Arteriosclerosis	2623	94 (15.1)	159 (15.0)	160 (10.2)	0.002
Chronic obstructive pulmonary disease	2630	43 (6.9)	81 (7.7)	136 (8.6)	0.195
Chronic liver disease	2617	46 (7.4)	59 (5.6)	51 (3.3)	<0.001
Systolic heart failure	2628	79 (12.7)	129 (12.2)	139 (8.8)	0.009
Baseline plasma creatinine (μmol/L)	2643	81.0 (68.9–94.0)	81.0 (69.0–94.0)	79.0 (68.0–94.0)	0.210
Pre ICU daily medication					
ACE inhibitor or ARB	2585	263 (42.8)	428 (41.1)	475 (30.8)	<0.001
NSAID	2538	73 (12.1)	112 (10.9)	118 (7.8)	0.002
Diuretic	2596	185 (29.8)	324 (30.8)	323 (20.9)	<0.001

Table 1. *Cont.*

Characteristics	Data Available	AKI		No AKI	p *
Metformin	2606	109 (17.6)	163 (15.5)	164 (10.6)	<0.001
Statin	2603	196 (31.6)	320 (30.5)	397 (25.6)	0.005
Corticosteroids	2614	56 (9.0)	94 (8.9)	105 (6.7)	0.070
Warfarin	2608	107 (17.2)	166 (15.8)	179 (11.5)	0.001
		KDIGO stage 2 or 3	**KDIGO stage 1, 2, 3**		
Treatments administered 48 h before admission					
Contrast medium	2632	120 (19.3)	223 (21.1)	417 (26.5)	<0.001
ACE inhibitor or ARB	2601	167 (27.3)	287 (27.5)	329 (21.1)	0.002
Diuretics	2570	217 (35.8)	353 (34.3)	360 (23.4)	<0.001
Colloids (gelatin or starch)	2479	229 (38.3)	395 (39.0)	394 (26.9)	<0.001
Albumin	2584	14 (2.3)	18 (1.7)	14 (0.9)	0.018
Type of admission					
Operative	2646	180 (28.8)	343 (32.2)	557 (35.2)	0.004
Cardiac surgery	2647	35 (5.6)	80 (7.5)	147 (9.3)	0.004
Emergency	2621	575 (92.6)	962 (91.1)	1386 (88.6)	0.005
SAPS II score 24 h without renal or age components	2614	24.0 (16.0–34.0)	24.0 (16.0–32.0)	20.0 (13.0–29.3)	<0.001
Mechanical ventilation	2647	432 (69.1)	776 (72.9)	1031 (65.2)	0.080
Sepsis	2647	309 (49.4)	500 (46.9)	362 (22.9)	<0.001
White blood cell count at admission, max (10^9/L)	2186	12.0 (8.3–17.4)	11.7 (8.2–16.8)	10.9 (7.8–15.3)	<0.001
Platelet count at admission, min (10^9/L)	2419	190.0 (116.5–263.5)	194.0 (127.0–265.0)	205.0 (153.0–268.0)	<0.001

* Comparison of No AKI to KDIGO stages 2 or 3 AKI. The p-values are calculated with Fisher's exact test for categorical variables and with Mann–Whitney U test for continuous variables. Data presented as medians and interquartile ranges for continuous variables, and absolute counts and percentages for categorical variables. Abbreviations: FINNAKI; Finnish Acute Kidney Injury; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; BMI, body mass index; ICU, intensive care unit; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; SAPS II, simplified acute physiology score II.

In the primary analysis, none of the previously reported associations replicated in our sample (Figure 2). Of note, the A-allele of rs1800629 in TNFA was not associated with AKI (odds ratio, OR 1.06, 95% confidence interval, CI 0.89–1.28, $p = 0.51$). In addition, the G-allele of rs1800896 in IL10 was not associated with AKI (OR 0.92, 95% CI 0.80–1.05, $p = 0.20$) (Table 2). In the epistasis test between A-allele of rs1800629 and G-allele of rs1800896 we detected no evidence of interaction (OR 1.10, $p = 0.40$). Frequencies of genotype combinations of these two variants are presented in Table 3, grouped according to their reported effect on protein production [25].

We tested IL6 for altogether seven variants and found no association with either endpoint. We found no variation in single nucleotide polymorphisms (SNPs) rs2069842 and rs2069830 in IL6; rs10499563 in IL6 was not in HWE ($p = 0.034$). The haplotypes of the two tested haploblocks were not associated with AKI (data shown in ESM).

The T-allele of rs3025039 in VEGFA had an odds ratio (OR) of 1.20 (95% CI 1.01–1.44, $p = 0.044$) for development of stage 2 or 3 AKI. This finding prevailed in the tertiary analysis (adjusted model, OR 1.21, 95% CI 1.00–1.45, $p = 0.047$; ESM, Table S1).

In the tertiary analysis the G-allele of rs10421768 in HAMP had an OR of 0.81 (95% CI 0.69–0.95, $p = 0.0090$) for development of stage 2 or 3 AKI; however, none of the variants had a statistically significant association in this adjusted model with CKD patients included (Table S1, ESM).

In the secondary analysis with all stage AKI as the endpoint the results did not change (ESM, Table S2).

The variants we investigated had minor allele frequencies ranging from 0.03 to 0.47 and the retrospectively calculated variant-specific power varied accordingly from 13.0% to 91.2% (ESM, Table S3).

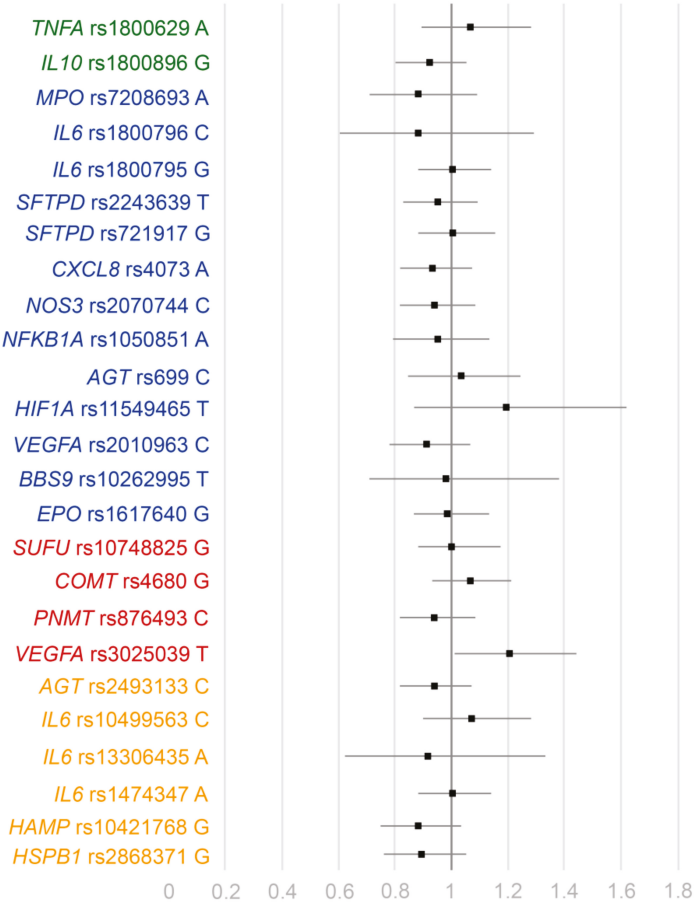

Figure 2. Odds ratios (OR) and confidence intervals (95% CI) for the minor allele for all the studied polymorphisms. For variants in green, there are several previous studies and both alleles have been reported to associate with AKI, variants in blue have been reported with same risk allele, variants in red have been reported with opposite risk allele, and variants in orange have not been previously reported in association to AKI.

Table 2. Association of genetic variants with acute kidney injury (AKI) KDIGO stages 2 and 3 compared to stage 0. Odds ratios (OR) and confidence intervals (95% CI) are reported for each copy of minor allele.

Gene	SNP	Patients	Minor Allele	MAF (Cases/Controls)	Additive Logistic OR	95% CI	*p*
TNFA	rs1800629	2174	A	0.15/0.14	1.06	0.89–1.28	0.51
IL10	rs1800896	2173	G	0.44/0.46	0.92	0.80–1.05	0.20
IL6	rs10499563	2192	C	0.15/0.14	1.07	0.90–1.28	0.45
	rs1800796	2197	C	0.03/0.03	0.88	0.60–1.29	0.51
	rs1800795	2189	G	0.47/0.47	1.00	0.88–1.14	0.97
	rs1474347	2187	A	0.47/0.47	1.00	0.88–1.14	1.00
	rs13306435	2199	A	0.03/0.03	0.91	0.62–1.33	0.62
CXCL8	rs4073	2193	A	0.42/0.42	0.93	0.82–1.07	0.31
NOS3	rs2070744	2174	C	0.34/0.36	0.94	0.82–1.08	0.37
NFKB1A	rs1050851	2196	A	0.16/0.17	0.95	0.79–1.13	0.54
AGT	rs699	1047	C	0.43/0.42	1.03	0.85–1.24	0.78
	rs2493133	2196	C	0.41/0.42	0.94	0.82–1.07	0.36
VEGFA	rs2010963	2170	C	0.22/0.24	0.91	0.78–1.06	0.22
	rs3025039	2195	T	0.16/0.14	1.20	1.01–1.44	0.044
EPO	rs1617640	2173	G	0.44/0.45	0.99	0.87–1.13	0.91
SUFU	rs10748825	2174	G	0.37/0.37	1.02	0.88–1.17	0.83
HIF1A	rs11549465	2173	T	0.05/0.04	1.19	0.87–1.62	0.28
PNMT	rs876493	2173	C	0.36/0.38	0.94	0.82–1.08	0.37
MPO	rs7208693	2174	A	0.10/0.12	0.88	0.71–1.09	0.23
COMT	rs4680	2173	G	0.47/0.45	1.06	0.93–1.21	0.39
HSPB1	rs2868371	2194	G	0.19/0.21	0.89	0.76–1.05	0.18
SFTPD	rs2243639	2199	T	0.39/0.40	0.95	0.83–1.09	0.47
	rs721917	2193	G	0.39/0.39	1.00	0.88–1.15	0.97
HAMP	rs10421768	2199	G	0.23/0.25	0.88	0.75–1.03	0.11
BBS9	rs10262995	2200	T	0.04/0.04	0.98	0.71–1.38	0.93

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; SNP, single nucleotide polymorphism; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval; *TNFA*, tumor necrosis factor alpha; *IL10*, interleukin 10; *IL6*, interleukin 6; *CXCL8*, interleukin 8; *NOS3*, nitric oxide synthase 3; *NFKB1A*, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; *AGT*, angiotensinogen; *VEGFA*, vascular endothelial growth factor; *EPO*, erythropoietin; *SUFU*, suppressor of fused homolog; *HIF1A*, hypoxia-inducible factor 1-alpha; *PNMT*, phenylethanolamine N-methyltransferase; *MPO*, myeloperoxidase; *COMT*, catechol-O-methyltransferase; *HSPB1*, heat shock protein family B (small) member 1; *SFTPD*, surfactant protein D; *HAMP*, hepcidin antimicrobial peptide; *BBS9*, Bardet–Biedl syndrome 9.

Table 3. Number of patients (percentage) with *TNFA* rs1800629 and *IL10* rs1800896 genotype combinations. Genotypes are grouped according to the reported effect in protein production. Acute kidney injury (AKI) KDIGO stages 2 and 3 (cases) compared to stage 0 (controls).

Genotype Combination	AKI (*n* = 615)	No AKI (*n* = 1558)
TNFA GG + *IL10* AA	138 (22%)	340 (22%)
TNFA GG + *IL10* GA + GG	311 (51%)	814 (52%)
TNFA GA + AA + *IL10* AA	52 (8%)	116 (8%)
TNFA GA + AA + *IL10* GA + GG	114 (19%)	288 (18%)

Abbreviations: TNFA, tumor necrosis factor alpha; IL10, interleukin 10; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; OR, odds ratio. TNFA GG: TNF-α low producer; IL10 AA: IL-10 low producer; IL10 GA + GG: IL-10 intermediate + high producer; TNFA GA + AA: TNF-α high producer.

4. Discussion

In this study involving nearly 3000 critically ill adult patients, we were unable to replicate the previously reported associations between selected inflammation-related gene variants and AKI. The 27 tested polymorphisms are within 18 candidate genes, the majority of which relate to inflammation, cell survival, or circulation. Despite the suggestive findings in VEGFA and HAMP, we did not achieve the pre-set statistical significance after correcting for multiple comparisons.

The original studies reporting genetic associations have been generally underpowered, and of moderate quality only [3]. Majority of these studies investigated candidate polymorphisms with unknown biological function. Heterogeneity in reporting has hampered conduction of meta-analyses of reported associations [3,39]. In addition, the few replication attempts have given contradicting

results. Moreover, most reports are from cardiac surgery patients, whereas septic and mixed ICU patients have been studied less [3]. In our prospective power calculation we determined that a sample of 1200 cases and 1800 controls would suffice to give a 96% power to detect an association, with realistic assumptions of minor allele frequency and effect size considering complex disease origin. However, the true effects of associations are known to be smaller than the ones reported by first authors [40,41]. In addition, false positive associations are numerous in genetic association studies to identify common variants [41]. This, along with population diversity is a possible explanation as to the failure in replication attempt [42]. Because of multiple variants tested, we used a more stringent level of significance. By using Bonferroni method we determined the acceptable level of type 1 error rate to 0.002.

The first results of hypothesis-free study designs in genetic predisposition to AKI have been published in septic [28] and cardiac surgery-associated AKI [29,30]. In their genome wide association study (GWAS), Stafford-Smith and coworkers [30] reported an association of polymorphism rs10262995 in BBS9 with cardiac surgery-associated AKI. However, in our cohort this association was not found.

One of the most studied polymorphisms is the rs1800629 in TNFA: the low producing genotype (GG) has been associated with more frequent and more severe AKI [7,8]. In addition, low producing genotype AA of variant rs1800896 in IL10 has been associated with AKI [7], along with combined genotype of rs1800629 GG + rs1800896 AA [19]. However, contradicting findings have been presented [22–26]. Additionally, TNFA and IL10 variations have been associated with sepsis development [43–45]. Of note, we were unable to detect any significant association between these polymorphisms or their combination in the epistasis test.

Vascular endothelial growth factor (VEGF) is a protein with shown effects in angiogenesis, cell survival and differentiation, as well as vascular permeability [46,47]. In our study, the T-allele in rs3025039 in VEGFA resulted in an OR of 1.20 for AKI (95% CI 1.01–1.44, $p = 0.044$); however, previously the C-allele has been reported to increase AKI risk [27]. In carriers of T-allele, the plasma VEGF levels are lower [48]. The T-allele has been suggested to relate to susceptibility to ARDS and mortality in ARDS [49,50]. Additionally, variation in VEGFA has been associated with diabetic nephropathy [51].

As the IL-6 cytokine has been associated with AKI development [52,53], we aimed to investigate the IL6 gene variation more broadly. We genotyped seven SNPs, five in addition to the two replication variants. However, two of these SNPs did not have any variation in our sample. The remaining five did not associate with AKI, even when studied as a haplotype. In sepsis, the SNP rs1800795 is not associated with susceptibility or mortality [54]. Consistently, rs1800795 does not correlate with the risk of end-stage renal disease [55]. Nevertheless, in patients with CKD, the SNP rs1800796 is suggested to predispose to sepsis and mortality [56]. However, due to multiple differing etiologies the predisposing genetic variants are generally unique to CKD [57–59].

The rs4680 in catechol-O-methyltransferase gene (COMT) causes an amino acid transition (Val158Met), which leads to lower (L) in comparison to higher (H) enzyme activity [60]. The COMT enzyme degrades catecholamines [61], and thus has been thought to contribute in vasodilatory shock and AKI [11]. The LL genotype is associated in cardiac surgery associated AKI (CSA-AKI) in two studies of modest size [11,12], yet in a larger study this association was ruled out [10]. Furthermore, endothelial NO synthase gene (NOS3) variant rs2070744 was studied in association to CSA-AKI with conflicting results [13,24]. The rs2070744 has been investigated in association with diabetic nephropathy, however, results have contradicted [62]. We did not find any association between these variants and AKI.

To our knowledge, this is the first replication of polymorphisms in *CXCL8* [27], *NFKB1A* [32], *AGT* [24], *EPO* [14], *SUFU* [9], *HIF1A* [15], *PNMT* [17], *MPO* [16], and *SFTPD* [34] in association to AKI phenotype. None of the investigated variants rendered verification for the initial hypotheses.

In addition to the candidate polymorphism replication, we tested two SNPs due to interesting biological hypotheses. Li and colleagues [33] presented in their in vitro septic AKI model that heat shock protein 27 (Hsp27) overexpression caused the renal epithelial cells to outlive. The C-allele of a

functional SNP rs2868371 in the HSPB1 gene associates with decreased expression of Hsp27 [63,64]. However, in our sample this SNP was not associated with AKI in any of the analyses. Another intriguing suggestion regarding the pathophysiology of septic AKI was presented by Schaalan and colleagues [35]: the hepcidin levels were elevated in patients with septic AKI. Hepcidin is encoded by HAMP gene, and the promoter SNP rs10421768 is suggested to affect the gene expression [65,66]. We found G-allele to be protective (OR 0.81, 95% CI 0.69–0.95, $p = 0.0090$) in the adjusted model; however, this was not a replication of an association to a human AKI model, but a pilot study on this association.

We acknowledge that our study has some limitations. First, we were unable to extract the DNA of 122 (4.1%) patients. However, this random selection is unlikely to cause bias in our remaining data.

Second, our cohort of critically ill patients consists of patients with multiple possible etiologies for AKI, rather than tightly defined phenotypes, such as cardiac surgery or sepsis. However, we did adjust for these confounders in our tertiary analysis.

Third, the actual sample size was somewhat smaller than the estimated sample size we prospectively estimated to be needed for an adequate power. However, even with samples of 2207 patients in primary analysis, 2647 patients in the secondary analysis, and 2358 patients in the tertiary analysis, the retrospectively calculated power of the study, holding to the presumptions about allele frequency and effect size, remained adequate (80.6%, 93.6% and 85.5%, respectively). The minor allele frequency was, however, lower for some of the studied SNPs, affecting the power of these specific analyses. Most SNPs had frequencies exceeding the 0.2 we anticipated. A larger sample of patients with a sub-phenotype such as septic AKI is an interesting challenge for the future.

5. Conclusions

In conclusion, we were unable to replicate previous associations between genetic variants and AKI in critically ill patients. Even if short of significance, an interesting previously unpublished variant in the HAMP gene offers possible insight into mechanism of AKI, although future studies are needed to confirm this finding. In the future, the efforts to decipher "the AKI gene" should be targeted on more carefully assigned AKI sub-phenotypes.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/3/342/s1, (1) Exclusion criteria for the study, (2) Primer sequences, (3) Abbreviations for genes, (4) Percentages of imputed values in covariates, (5) Results for analyses 2 and 3, (6) Haplotype analyses results, (7) Retrospective power calculation for each variant, (8) Summary-level data.

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References

1. Nisula, S.; Kaukonen, K.-M.M.; Vaara, S.T.; Korhonen, A.-M.M.; Poukkanen, M.; Karlsson, S.; Haapio, M.; Inkinen, O.; Parviainen, I.; Suojaranta-Ylinen, R.; et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: The FINNAKI study. *Intensive Care Med.* **2013**, *39*, 420–428. [CrossRef] [PubMed]
2. Hoste, E.A.J.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef] [PubMed]
3. Vilander, L.M.; Kaunisto, M.A.; Pettilä, V. Genetic predisposition to acute kidney injury—A systematic review. *BMC Nephrol.* **2015**, *16*, 197. [CrossRef] [PubMed]
4. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
5. Bone, R.C.; Balk, R.A.; Cerra, F.B.; Dellinger, R.P.; Fein, A.M.; Knaus, W.A.; Schein, R.M.; Sibbald, W.J. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference. *Chest J.* **1992**, *101*, 1644–1655. [CrossRef]
6. Jurinke, C.; van den Boom, D.; Cantor, C.R.; Koster, H. Automated genotyping using the DNA MassArray technology. *Methods Mol. Biol.* **2002**, *187*, 179–192. [PubMed]
7. Hashad, D.I.; Elsayed, E.T.; Helmy, T.A.; Elawady, S.M. Study of the role of tumor necrosis factor-α (–308 G/A) and interleukin-10 (–1082 G/A) polymorphisms as potential risk factors to acute kidney injury in patients with severe sepsis using high-resolution melting curve analysis. *Ren. Fail.* **2017**, *39*, 77–82. [CrossRef] [PubMed]
8. Susantitaphong, P.; Perianayagam, M.C.; Tighiouart, H.; Liangos, O.; Bonventre, J.V.; Jaber, B.L. Tumor necrosis factor alpha promoter polymorphism and severity of acute kidney injury. *Nephron* **2013**, *123*, 67–73. [CrossRef] [PubMed]
9. Henao-Martinez, A.; Agler, A.H.; LaFlamme, D.; Schwartz, D.A.; Yang, I. V Polymorphisms in the SUFU gene are associated with organ injury protection and sepsis severity in patients with Enterobacteriacea bacteremia. *Infect. Genet. Evol.* **2013**, *16*, 386–391. [CrossRef] [PubMed]
10. Kornek, M.; Deutsch, M.A.; Eichhorn, S.; Lahm, H.; Wagenpfeil, S.; Krane, M. COMT-Val158Met-polymorphism is not a risk factor for acute kidney injury after cardiac surgery. *Dis. Mark.* **2013**, *35*, 129–134. [CrossRef] [PubMed]
11. Haase-Fielitz, A.; Haase, M.; Bellomo, R.; Lambert, G.; Matalanis, G.; Story, D.; Doolan, L.; Buxton, B.; Gutteridge, G.; Luft, F.C.; et al. Decreased catecholamine degradation associates with shock and kidney injury after cardiac surgery. *J. Am. Soc. Nephrol.* **2009**, *20*, 1393–1403. [CrossRef] [PubMed]
12. Albert, C.; Kube, J.; Haase-Fielitz, A.; Dittrich, A.; Schanze, D.; Zenker, M.; Kuppe, H.; Hetzer, R.; Bellomo, R.; Mertens, P.R.; et al. Pilot study of association of catechol-O-methyl transferase rs4680 genotypes with acute kidney injury and tubular stress after open heart surgery. *Biomark. Med.* **2014**, *8*, 1227–1238. [CrossRef] [PubMed]
13. Popov, A.F.; Hinz, J.; Schulz, E.G.; Schmitto, J.D.; Wiese, C.H.; Quintel, M.; Seipelt, R.; Schoendube, F.A. The eNOS 786C/T polymorphism in cardiac surgical patients with cardiopulmonary bypass is associated with renal dysfunction. *Eur. J. Cardio-Thoracic Surg.* **2009**, *36*, 651–656. [CrossRef] [PubMed]

14. Popov, A.F.; Schulz, E.G.; Schmitto, J.D.; Coskun, K.O.; Tzvetkov, M.V.; Kazmaier, S.; Zimmermann, J.; Schondube, F.A.; Quintel, M.; Hinz, J. Relation between renal dysfunction requiring renal replacement therapy and promoter polymorphism of the erythropoietin gene in cardiac surgery. *Artif. Organs* **2010**, *34*, 961–968. [CrossRef] [PubMed]
15. Kolyada, A.Y.; Tighiouart, H.; Perianayagam, M.C.; Liangos, O.; Madias, N.E.; Jaber, B.L. A genetic variant of hypoxia-inducible factor-1alpha is associated with adverse outcomes in acute kidney injury. *Kidney Int.* **2009**, *75*, 1322–1329. [CrossRef] [PubMed]
16. Perianayagam, M.; Tighiouart, H.; Liangos, O.; Kouznetsov, D.; Wald, R.; Rao, F.; O'Connor, D.; Jaber, B. Polymorphisms in the myeloperoxidase gene locus are associated with acute kidney injuryrelated outcomes. *Kidney Int.* **2012**, *82*, 909–919. [CrossRef] [PubMed]
17. Alam, A.; O'Connor, D.T.; Perianayagam, M.C.; Kolyada, A.Y.; Chen, Y.; Rao, F.; Mahata, M.; Mahata, S.; Liangos, O.; Jaber, B.L. Phenylethanolamine N-methyltransferase gene polymorphisms and adverse outcomes in acute kidney injury. *Nephron* **2010**, *114*, 253–259. [CrossRef] [PubMed]
18. Gaudino, M.; Di Castelnuovo, A.; Zamparelli, R.; Andreotti, F.; Burzotta, F.; Iacoviello, L.; Glieca, F.; Alessandrini, F.; Nasso, G.; Donati, M.B.; et al. Genetic control of postoperative systemic inflammatory reaction and pulmonary and renal complications after coronary artery surgery. *J. Thorac. Cardiovasc. Surg.* **2003**, *126*, 1107–1112. [CrossRef]
19. Dalboni, M.A.; Quinto, B.M.; Grabulosa, C.C.; Narciso, R.; Monte, J.C.; Durao, M. Tumour necrosis factor-alpha plus interleukin-10 low producer phenotype predicts acute kidney injury and death in intensive care unit patients. *Clin. Exp. Immunol.* **2013**, *173*, 242–249. [CrossRef] [PubMed]
20. Wattanathum, A.; Manocha, S.; Groshaus, H.; Russell, J.A.; Walley, K.R. Interleukin-10 Haplotype Associated with Increased Mortality in Critically Ill Patients with Sepsis From Pneumonia But Not in Patients With Extrapulmonary Sepsis. *Chest* **2005**, *128*, 1690–1698. [CrossRef] [PubMed]
21. Chang, C.F.; Lu, T.M.; Yang, W.C.; Lin, S.J.; Lin, C.C.; Chung, M.Y. Gene polymorphisms of interleukin-10 and tumor necrosis factor-alpha are associated with contrast-induced nephropathy. *Am. J. Nephrol.* **2013**, *37*, 110–117. [CrossRef] [PubMed]
22. Boehm, J.; Eichhorn, S.; Kornek, M.; Hauner, K.; Prinzing, A.; Grammer, J. Apolipoprotein E genotype, TNF-alpha 308G/A and risk for cardiac surgery associated-acute kidney injury in Caucasians. *Ren. Fail.* **2014**, *36*, 237–243. [CrossRef] [PubMed]
23. McBride, W.T.; Prasad, P.S.; Armstrong, M.; Patterson, C.; Gilliland, H.; Drain, A. Cytokine phenotype, genotype, and renal outcomes at cardiac surgery. *Cytokine* **2013**, *61*, 275–284. [CrossRef] [PubMed]
24. Stafford-Smith, M.; Podgoreanu, M.; Swaminathan, M.; Phillips-Bute, B.; Mathew, J.P.; Hauser, E.H. Association of genetic polymorphisms with risk of renal injury after coronary bypass graft surgery. *Am. J. Kidney Dis.* **2005**, *45*, 519–530. [CrossRef] [PubMed]
25. Jaber, B.L.; Rao, M.; Guo, D.; Balakrishnan, V.S.; Perianayagam, M.C.; Freeman, R.B.; Pereira, B.J. Cytokine gene promoter polymorphisms and mortality in acute renal failure. *Cytokine* **2004**, *25*, 212–219. [CrossRef] [PubMed]
26. Jouan, J.; Golmard, L.; Benhamouda, N.; Durrleman, N.; Golmard, J.L.; Ceccaldi, R.; Trinquart, L.; Fabiani, J.N.; Tartour, E.; Jeunemaitre, X.; et al. Gene polymorphisms and cytokine plasma levels as predictive factors of complications after cardiopulmonary bypass. *J. Thorac. Cardiovasc. Surg.* **2012**, *144*, 467–473.e2. [CrossRef] [PubMed]
27. Cardinal-Fernandez, P.; Ferruelo, A.; El-Assar, M.; Santiago, C.; Gomez-Gallego, F.; Martin-Pellicer, A. Genetic predisposition to acute kidney injury induced by severe sepsis. *J. Crit. Care* **2013**, *28*, 365–370. [CrossRef] [PubMed]
28. Frank, A.J.; Sheu, C.C.; Zhao, Y.; Chen, F.; Su, L.; Gong, M.N.; Bajwa, E.; Thompson, B.T.; Christiani, D.C. BCL2 genetic variants are associated with acute kidney injury in septic shock. *Crit. Care Med.* **2012**, *40*, 2116–2123. [CrossRef] [PubMed]
29. Zhao, B.; Lu, Q.; Cheng, Y.; Belcher, J.M.; Siew, E.D.; Leaf, D.E.; Body, S.C.; Fox, A.A.; Waikar, S.S.; Collard, C.D.; et al. A Genome-Wide Association Study to Identify Single-Nucleotide Polymorphisms for Acute Kidney Injury. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 482–490. [CrossRef] [PubMed]
30. Stafford-Smith, M.; Li, Y.-J.; Mathew, J.P.; Li, Y.-W.; Ji, Y.; Phillips-Bute, B.G.; Milano, C.A.; Newman, M.F.; Kraus, W.E.; Kertai, M.D.; et al. Genome-wide association study of acute kidney injury after coronary bypass graft surgery identifies susceptibility loci. *Kidney Int.* **2015**, *88*, 823–832. [CrossRef] [PubMed]

31. Vilander, L.M.; Kaunisto, M.A.; Vaara, S.T.; Pettilä, V.; FINNAKI Study Group. Genetic variants in SERPINA4 and SERPINA5, but not BCL2 and SIK3 are associated with acute kidney injury in critically ill patients with septic shock. *Crit. Care* **2017**, *21*, 47. [CrossRef] [PubMed]
32. Bhatraju, P.; Hsu, C.; Mukherjee, P.; Glavan, B.J.; Burt, A.; Mikacenic, C.; Himmelfarb, J.; Wurfel, M. Associations between single nucleotide polymorphisms in the FAS pathway and acute kidney injury. *Crit. Care* **2015**, *19*, 368. [CrossRef] [PubMed]
33. Li, C.; Wu, J.; Li, Y.; Xing, G. Cytoprotective Effect of Heat Shock Protein 27 Against Lipopolysaccharide-Induced Apoptosis of Renal Epithelial HK-2 Cells. *Cell. Physiol. Biochem.* **2017**, *41*, 2211–2220. [CrossRef] [PubMed]
34. Liu, J.; Li, G.; Li, L.; Liu, Z.; Zhou, Q.; Wang, G.; Chen, D. Surfactant protein-D (SP-D) gene polymorphisms and serum level as predictors of susceptibility and prognosis of acute kidney injury in the Chinese population. *BMC Nephrol.* **2017**, *18*, 67. [CrossRef]
35. Schaalan, M.F.; Mohamed, W.A. Determinants of hepcidin levels in sepsis-associated acute kidney injury: Impact on pAKT/PTEN pathways? *J. Immunotoxicol.* **2016**, *13*, 751–757. [CrossRef] [PubMed]
36. Purcell, S.; Neale, B.; Todd-Brown, K.; Thomas, L.; Ferreira, M.A.; Bender, D.; Maller, J.; Sklar, P.; de Bakker, P.I.; Daly, M.J.; et al. PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **2007**, *81*, 559–575. [CrossRef] [PubMed]
37. Barrett, J.C.; Fry, B.; Maller, J.; Daly, M.J. Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics* **2005**, *21*, 263–265. [CrossRef] [PubMed]
38. Purcell, S.; Cherny, S.S.; Sham, P.C. Genetic Power Calculator: Design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* **2003**, *19*, 149–150. [CrossRef] [PubMed]
39. Larach, D.B.; Engoren, M.C.; Schmidt, E.M.; Heung, M. Genetic variants and acute kidney injury: A review of the literature. *J. Crit. Care* **2018**, *44*, 203–211. [CrossRef] [PubMed]
40. Ioannidis, J.P. Why most discovered true associations are inflated. *Epidemiology* **2008**, *19*, 640–648. [CrossRef] [PubMed]
41. Lohmueller, K.E.; Pearce, C.L.; Pike, M.; Lander, E.S.; Hirschhorn, J.N. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat. Genet.* **2003**, *33*, 177–182. [CrossRef] [PubMed]
42. Kraft, P.; Zeggini, E.; Ioannidis, J.P.A. Replication in genome-wide association studies. *Stat. Sci.* **2009**, *24*, 561–573. [CrossRef] [PubMed]
43. Teuffel, O.; Ethier, M.C.; Beyene, J.; Sung, L. Association between tumor necrosis factor-α promoter −308 A/g polymorphism and susceptibility to sepsis and sepsis mortality: A systematic review and meta-analysis. *Crit. Care Med.* **2010**, *38*, 276–282. [CrossRef] [PubMed]
44. Christaki, E.; Giamarellos-Bourboulis, E.J. The beginning of personalized medicine in sepsis: Small steps to a bright future. *Clin. Genet.* **2014**, *86*, 56–61. [CrossRef] [PubMed]
45. Pan, W.; Zhang, A.Q.; Yue, C.L.; Gao, J.W.; Zeng, L.; Gu, W.; Jiang, J.X. Association between interleukin-10 polymorphisms and sepsis: A meta-analysis. *Epidemiol. Infect.* **2015**, *143*, 366–375. [CrossRef] [PubMed]
46. Ferrara, N.; Gerber, H.-P.; LeCouter, J. The biology of VEGF and its receptors. *Nat. Med.* **2003**, *9*, 669–676. [CrossRef] [PubMed]
47. Bates, D.O. Vascular endothelial growth factors and vascular permeability. *Cardiovasc. Res.* **2010**, *87*, 262–271. [CrossRef] [PubMed]
48. Renner, W.; Kotschan, S.; Hoffmann, C.; Obermayer-Pietsch, B.; Pilger, E. A common 936 C/T mutation in the gene for vascular endothelial growth factor is associated with vascular endothelial growth factor plasma levels. *J. Vasc. Res.* **2000**, *37*, 443–448. [CrossRef] [PubMed]
49. Medford, A.R.L.; Keen, L.J.; Bidwell, J.L.; Millar, A.B. Vascular endothelial growth factor gene polymorphism and acute respiratory distress syndrome. *Thorax* **2005**, *60*, 244–248. [CrossRef] [PubMed]
50. Zhai, R.; Gong, M.N.; Zhou, W.; Thompson, T.B.; Kraft, P.; Su, L.; Christiani, D.C. Genotypes and haplotypes of the VEGF gene are associated with higher mortality and lower VEGF plasma levels in patients with ARDS. *Thorax* **2007**, *62*, 718–722. [CrossRef] [PubMed]
51. Nazir, N.; Siddiqui, K.; Al-Qasim, S.; Al-Naqeb, D. Meta-analysis of diabetic nephropathy associated genetic variants in inflammation and angiogenesis involved in different biochemical pathways. *BMC Med. Genet.* **2014**, *15*, 103. [CrossRef] [PubMed]

52. Nechemia-Arbely, Y.; Barkan, D.; Pizov, G.; Shriki, A.; Rose-John, S.; Galun, E.; Axelrod, J.H. IL-6/IL-6R axis plays a critical role in acute kidney injury. *J. Am. Soc. Nephrol.* **2008**, *19*, 1106–1115. [CrossRef] [PubMed]
53. Simmons, E.M.; Himmelfarb, J.; Sezer, M.T.; Chertow, G.M.; Mehta, R.L.; Paganini, E.P.; Soroko, S.; Freedman, S.; Becker, K.; Spratt, D.; et al. Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int.* **2004**, *65*, 1357–1365. [CrossRef] [PubMed]
54. Gao, J.; Zhang, A.; Pan, W.; Yue, C.; Zeng, L.; Gu, W.; Jiang, J. Association between IL-6-174G/C polymorphism and the risk of sepsis and mortality: A systematic review and meta-analysis. *PLoS ONE* **2015**, *10*, e0118843. [CrossRef] [PubMed]
55. Feng, Y.; Tang, Y.; Zhou, H.; Xie, K. A meta-analysis on correlation between interleukin-6 -174G/C polymorphism and end-stage renal disease. *Ren. Fail.* **2017**, *39*, 350–356. [CrossRef] [PubMed]
56. Panayides, A.; Ioakeimidou, A.; Karamouzos, V.; Antonakos, N.; Koutelidakis, I.; Giannikopoulos, G.; Makaritsis, K.; Voloudakis, N.; Toutouzas, K.; Rovina, N.; et al. -572 G/C single nucleotide polymorphism of interleukin-6 and sepsis predisposition in chronic renal disease. *Eur. J. Clin. Microbiol. Infect. Dis.* **2015**, *34*, 2439–2446. [CrossRef] [PubMed]
57. Agrawal, S.; Agarwal, S.; Naik, S. Genetic contribution and associated pathophysiology in end-stage renal disease. *Appl. Clin. Genet.* **2010**, *3*, 65–84. [CrossRef] [PubMed]
58. Wuttke, M.; Köttgen, A. Insights into kidney diseases from genome-wide association studies. *Nat. Rev. Nephrol.* **2016**, *12*, 549–562. [CrossRef] [PubMed]
59. O'Seaghdha, C.M.; Fox, C.S. Genome-wide association studies of chronic kidney disease: What have we learned? *Nat. Rev. Nephrol.* **2011**, *8*, 89–99. [CrossRef] [PubMed]
60. Chen, J.; Lipska, B.K.; Halim, N.; Ma, Q.D.; Matsumoto, M.; Melhem, S.; Kolachana, B.S.; Hyde, T.M.; Herman, M.M.; Apud, J.; et al. Functional Analysis of Genetic Variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, Protein, and Enzyme Activity in Postmortem Human Brain. *Am. J. Hum. Genet.* **2004**, *75*, 807–821. [CrossRef] [PubMed]
61. Axelrod, J. O-Methylation of Epinephrine and Other Catechols in vitro and in vivo. *Science* **1957**, *126*, 400–401. [CrossRef] [PubMed]
62. Dellamea, B.; Leitão, C.; Friedman, R.; Canani, L. Nitric oxide system and diabetic nephropathy. *Diabetol. Metab. Syndr.* **2014**, *6*, 17. [CrossRef] [PubMed]
63. Guo, H.; Bai, Y.; Xu, P.; Hu, Z.; Liu, L.; Wang, F.; Jin, G.; Wang, F.; Deng, Q.; Tu, Y.; et al. Functional promoter -1271G/C variant of HSPB1 predicts lung cancer risk and survival. *J. Clin. Oncol.* **2010**, *28*, 1928–1935. [CrossRef] [PubMed]
64. Pang, Q.; Wei, Q.; Xu, T.; Yuan, X.; Lopez Guerra, J.L.; Levy, L.B.; Liu, Z.; Gomez, D.R.; Zhuang, Y.; Wang, L.-E.; et al. Functional Promoter Variant rs2868371 of HSPB1 Is Associated with Risk of Radiation Pneumonitis After Chemoradiation for Non-Small Cell Lung Cancer. *Int. J. Radiat. Oncol.* **2013**, *85*, 1332–1339. [CrossRef] [PubMed]
65. Liang, L.; Liu, H.; Yue, J.; Liu, L.; Han, M.; Luo, L.; Zhao, Y.; Xiao, H. Association of Single-Nucleotide Polymorphism in the Hepcidin Promoter Gene with Susceptibility to Extrapulmonary Tuberculosis. *Genet. Test. Mol. Biomark.* **2017**, *21*, 351–356. [CrossRef] [PubMed]
66. Parajes, S.; González-Quintela, A.; Campos, J.; Quinteiro, C.; Domínguez, F.; Loidi, L. Genetic study of the hepcidin gene (HAMP) promoter and functional analysis of the c.-582A > G variant. *BMC Genet.* **2010**, *11*, 110. [CrossRef] [PubMed]

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Does Beta-Trace Protein (BTP) Outperform Cystatin C as a Diagnostic Marker of Acute Kidney Injury Complicating the Early Phase of Acute Pancreatitis?

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Abstract: Acute pancreatitis (AP) belongs to the commonest acute gastrointestinal conditions requiring hospitalization. Acute kidney injury (AKI) often complicates moderately severe and severe AP, leading to increased mortality. Among the laboratory markers proposed for early diagnosis of AKI, few have been studied in AP, including cystatin C and neutrophil gelatinase-associated lipocalin (NGAL). Beta-trace protein (BTP), a low-molecular-weight glycoprotein proposed as an early marker of decreased glomerular filtration, has never been studied in AP. We investigated the diagnostic usefulness of serum BTP for early diagnosis of AKI complicating AP in comparison to previously studied markers. BTP was measured in serum samples collected over the first three days of hospital stay from 73 adult patients admitted within 24 h of mild to severe AP. Thirteen patients (18%) developed AKI in the early phase of AP. Serum BTP was higher in patients who developed AKI, starting from the first day of hospitalization. Strong correlations were observed between BTP and serum cystatin C but not serum or urine NGAL. On admission, BTP positively correlated with endothelial dysfunction. The diagnostic usefulness of BTP for AKI was similar to cystatin C and lower than NGAL. Increased BTP is an early predictor of AKI complicating AP. However, it does not outperform cystatin C or NGAL.

Keywords: beta-trace protein; cystatin C; acute pancreatitis; severity; acute kidney injury

1. Introduction

Beta-trace protein (BTP), also known as lipocalin-type prostaglandin D2 synthase, is a monomeric 168-aminoacid protein belonging to the lipocalin family. Its molecular weight varies according to glycosylation pattern and equals from 23 to 29 kDa [1]. BTP was initially detected in cerebrovascular fluid and was shown to be synthesized in the central nervous system. Currently, BTP serves as a laboratory marker of cerebrovascular fluid leakage, and, for that purpose, robust automated

measurement method has been developed and is available in routine laboratories [2,3]. Further studies revealed BTP is expressed in other organs, e.g., heart, lungs or kidneys, and the protein is present in biological fluids such as blood and urine [4]. The low molecular weight allows for free glomerular filtration of BTP present in blood. These characteristics enabled the use of BTP as a laboratory marker of renal filtration [5].

Increased concentrations of BTP in serum or plasma and in urine correlate well with decreased glomerular filtration in patients with chronic kidney disease and the significant increase is observed in the early stages of the disease [5–9]. Moreover, increased BTP has been proposed as a marker of cardiovascular risk in patients with coronary artery disease and those with heart failure [1]. In patients with decompensated heart failure and after acute myocardial infarction, higher serum BTP was associated with long-term mortality [10,11].

Acute pancreatitis (AP) belongs to the most common acute gastrointestinal conditions requiring hospitalization [12]. Although the initial symptoms of acute abdominal pain, nausea and vomiting are serious, in most patients, the disease resolves without complications. Moderately severe or severe AP associated with local and/or systemic complications develops in approximately 20–30% of patients. The systemic complications, i.e., organ failure, including cardiovascular system, lungs or kidneys, may develop both in the early phase of AP (first 7–10 days) or later and lead to mortality in 20–30% of patients [13,14].

Acute kidney injury (AKI) is estimated to affect 7–20% of all in-hospital patients, and it is even more common in surgery and intensive care units [15,16]. The decline of renal function develops over several hours to several days. AKI is a heterogeneous syndrome, often caused by multiple insults [17]. However, in most patients, it is associated with hypoxia affecting renal medulla, caused by constriction or insufficient perfusion of renal arteries, leading to tubular necrosis and decreased glomerular filtration [18]. In severe acute pancreatitis (SAP), AKI is a common complication and may develop either in early phase in result of hypovolemia, systemic inflammation, and endothelial dysfunction, or in the late phase of AP, in association with sepsis [19–21]. The mortality of patients with SAP complicated with AP is twice as high as among those without AKI [13,19].

It is commonly recognized that early diagnosis of AKI may allow more efficient treatment and prevent the high mortality. Therefore, significant efforts are undertaken to find a laboratory marker (or a panel of markers) that would allow early diagnosis or prediction of AKI. Although several markers have been proposed [22,23], only few of them are currently available in routine laboratories and can be measured with short (2–3-h) turn-around times required for timely diagnosis. BTP is one of the markers that can be measured by fast automated immunonephelometric method that is available in most medical laboratories and is routinely used to measure such analytes as cystatin C, C-reactive protein, prealbumin or immunoglobulin chains. Moreover, the half-life of BTP in blood has been estimated to be shorter in comparison to other low-molecular-weight proteins [24]—in humans, it is estimated to be 1.2 h [25]. Thus, one may expect that the dynamic changes in renal function may be well reflected by serum BTP. However, studies evaluating BTP as a marker of AKI are scarce, and we were not able to identify any studies on BTP in AP.

The aim of the present study was the assessment of the diagnostic utility of serum BTP concentrations measured with automated immunonephelometric method for the prognosis of AKI in the early phase of AP. The diagnostic utility of serum BTP concentrations were compared with better characterized markers, i.e., serum cystatin C and serum and urine neutrophil gelatinase-associated lipocalin (NGAL).

2. Methods

2.1. Study Design and Patients

The retrospective study included two cohorts of patients admitted to hospital surgery departments with the diagnosis of AP. The first cohort was recruited at the Surgery Department, District Hospital in Sucha Beskidzka, Poland, between January and December 2014 [26]. The second cohort was recruited

in the Department of Surgery, Complex of Health Care Centers in Wadowice, Poland, between March 2014 and December 2015 [27]. In July 2016, the available stored samples of serum collected from the patients were used to measure BTP. The Bioethical Committee of Jagiellonian University, Kraków, Poland (approval no KBET/247/B/2013) and the Bioethical Committee of the Beskidy Medical Chamber, Bielsko-Biała, Poland (2014/02/06/1) gave agreement for patients' recruitment and the use of patients' samples for the present study.

In both medical centers, patients were recruited according to following criteria:

- consecutive adult patients admitted to surgery department with symptoms of AP lasting no longer than 24 hours before admission were asked to join the study, and those who signed the informed consent were included in the study;
- the diagnosis of AP was based on revised 2012 Atlanta classification [28], i.e., AP was diagnosed when two of three diagnostic criteria were met, i.e., characteristic abdominal pain, characteristic signs in abdominal imaging (magnetic resonance imaging, contrast-enhanced computed tomography or ultrasonography); serum amylase or lipase exceeding the upper reference limit more than three times;
- patients with chronic pancreatitis, active cancer, or chronic liver diseases (viral hepatitis, liver cirrhosis) were excluded.

The collected demographic and clinical data included: age and sex; comorbidities including ischemic heart disease, diabetes, pulmonary and renal conditions, obesity defined as body mass index (BMI) >30 kg/m^2; etiology of AP, pancreatic necrosis or pleural effusions present in imaging, development of systemic inflammatory response syndrome (SIRS), transient or persistent organ failure, need for surgery or parenteral nutrition during the hospital stay, length of hospital stay, severity of AP, and outcome (discharge or death).

Based on clinical and laboratory data obtained on day 1 of the study, the bedside index of severity in AP (BISAP) was calculated [29]. The final severity of AP was defined according to the revised 2012 Atlanta classification [28], taking into account the persistent or transient cardiovascular, pulmonary, or renal failure as defined by modified Marshall scoring system (MMSS) [28], the systemic complications (exacerbation of comorbidities), and the local complications.

AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria [30] based on increase in serum creatinine of more than 50% or 26.5 μmol/L over 48 h. Renal failure was defined in agreement with MMSS [28] as serum creatinine concentration exceeding 170 μmol/L.

2.2. Laboratory Tests

In both centers, patients' blood samples were collected on admission (study day 1) and on two consecutive days (study days 2 and 3). A part of laboratory tests were performed on the day of collection in the centers recruiting the patients, these included complete blood counts with leukocyte differential counts, routine biochemistry (serum amylase, urea, creatinine, glucose, bilirubin, C-reactive protein), and coagulation tests (citrated plasma D-dimer). Moreover, urine samples were collected from patients treated in the District Hospital in Sucha Beskidzka on the three days of the study and the measurements of NGAL in urine were performed in the center's laboratory.

Excess serum samples collected on study days 1 to 3 were aliquoted and stored in −80 °C. BTP, cystatin C, soluble fms-like tyrosine kinase-1 (sFlt-1), and angiopoietin-2 were measured in samples from both study centers. Serum NGAL and uromodulin concentrations were only measured in samples collected in the District Hospital in Sucha Beskidzka.

BTP and cystatin C in sera were measured using immunonephelometric method on Nephelometer II analyzer (Siemens Healthcare, Erlangen, Germany). Serum sFlt-1 was measured by electrochemiluminescence immunoassay using the Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany). The reference intervals for BTP and cystatin C in serum were <0.70 mg/L and 0.59–1.04 mg/L, respectively. The concentrations of sFlt-1 in healthy subjects were 63–108 pg/mL [31].

The measurements were performed in the Department of Diagnostics, University Hospital in Krakow. Serum angiopoietin 2 and NGAL were measured by enzyme immunoassays using commercially available kits: Quantikine ELISA Human Angiopoietin 2 Immunoassay (R&D Systems, McKinley Place, MN, USA), Human Uromodulin ELISA and Human Lipocalin-2/NGAL ELISA (BioVendor, Brno, Czech Republic). The reference values determined by the manufacturers of the kits were 1.065–8.907 ng/mL for serum angiopoietin 2 and 37.0–501.0 ng/mL for serum uromodulin. The readings were made with an automatic microplate reader Automatic Micro ELISA Reader ELX 808 (BIO-TEK® Instruments Inc., Winooski, VT, USA). The measurements were performed in the Department of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian University Medical College, Kraków, Poland. Urine NGAL concentrations were measured with chemiluminescent microparticle immunoassay on Architect analyzer (Abbott Diagnostics, Lake Forest, IL, USA).

2.3. Statistical Analysis

Number of patients and percentage of appropriate group were reported for categories. The contingency tables were analyzed with Pearson's chi-squared test. Median (lower; upper quartiles) were reported for quantitative variables as most of the variables were non-normally distributed (the Shapiro–Wilk's test was used to assess normality). The differences between groups were assessed with Mann–Whitney's test or Kruskal–Wallis's analysis of variance. Spearman's rank coefficient was computed for simple correlations. Logistic regression analysis was used to check whether the differences between AKI and non-AKI subjects remain significant after adjustment for the confounders, i.e., age and prediagnosed renal comorbidity. Odds ratios (OR) for unit change were reported with 95% confidence intervals (95% CI). Receiver operating characteristic (ROC) curves were analyzed to compare the diagnostic accuracy of studied markers. The values of area under the ROC curve (AUC) were reported with 95% CI. The AUCs were compared using a method of Hanley et al. [32]. All statistical tests were two-tailed and the p-values of <0.05 indicated significant results. Statistica 12 (StatSoft, Tulsa, OK, USA) with Medical Bundle 3.0 (StatSoft, Kraków, Poland) was used for computation.

3. Results

Serum samples of 73 patients were available for the measurements of BTP, including 46 patients recruited in the Surgery Department, District Hospital in Sucha Beskidzka, Poland and 27 patients recruited in the Department of Surgery, Complex of Health Care Centers in Wadowice, Poland. In every case (73 patients), at least one sample was available of those collected within the first two days of the study (i.e., first 48 h of hospital stay). Therefore, we decided to report the maximum result of BTP obtained during the 48 h of hospital stay (or the only result, if only one sample from that time period was available) as our baseline measure.

Further, we also analyzed the BTP results obtained on separate study days. There were 65 samples available from day 1, 63 samples from day 2, and 45 samples from day 3. The whole set of samples (collected on days 1 to 3) allowing for the assessment of BTP changes over the study period was available in 33 patients.

Among 73 patients included in the study, 13 (18%) were diagnosed with AKI (Table 1). Patients with AKI were older and suffered from more severe AP, reflected by higher BISAP scores already on the day of admission, more common organ failure throughout the course of AP, a longer hospital stay and higher mortality (Table 1). A history of renal disease was significantly associated with AKI, although the number of patients with preexisting renal conditions was low (Table 1). The patients who developed AKI were characterized by more pronounced laboratory abnormalities during the first two days of hospital stay: lower hematocrit, higher CRP, higher D-dimer, angiopoietin-2 and sFlt-1 as well as higher results of laboratory tests associated with renal function (serum urea, creatinine, cystatin C and BTP, serum and urine NGAL) (Table 1). No difference was observed between AKI and non-AKI patients regarding minimum serum uromodulin (Table 1).

Table 1. Clinical characteristics of patients with acute pancreatitis (AP) and the maximum laboratory results obtained on first two days (48 h) of hospital stay (or minimum result in case of uromodulin). The quantitative data were presented as median (lower; upper quartile).

Characteristic	AKI (n = 13)	No AKI (n = 60)	p
Age, years	75 (67; 81)	56 (40; 72)	0.003
Male sex, n (%)	7 (54)	29 (48)	0.7
Preexisting comorbidities, n (%)	11 (85)	38 (63)	0.1
Ischemic heart disease, n (%)	6 (46)	16 (27)	0.2
Diabetes, n (%)	3 (23)	6 (10)	0.2
Pulmonary diseases, n (%)	1 (8)	5 (8)	0.9
Renal diseases, n (%)	3 (23)	1 (2)	0.002
BMI >30 kg/m^2, n (%)	0	9 (15)	0.2
AP etiology			
Billiary, n (%)	9 (69)	28 (47)	0.3
Alcohol, n (%)	1 (8)	14 (23)	
Hyperlipemia, n (%)	0	6 (10)	
Other or idiopathic, n (%)	3 (23)	12 (20)	
Pancreatic necrosis, n (%)	1 (8)	6 (10)	0.8
Pleural effusion, n (%)	8 (62)	27 (45)	0.3
SIRS, n (%)	8 (62)	23 (38)	0.1
BISAP score at 24 h, points	3 (2; 3)	1 (0; 2)	0.002
BISAP ≥3 points, n (%)	8 (62)	7 (12)	<0.001
Organ failure according to MMSS			
Transient, n (%)	8 (62)	15 (25)	0.010
Persistent, n (%)	4 (31)	3 (5)	0.004
AP severity			
MAP, n (%)	1 (8)	37 (62)	<0.001
MSAP, n (%)	8 (62)	20 (33)	
SAP, n (%)	4 (31)	3 (5)	
Surgery, n (%)	0	5 (8)	0.3
Parenteral nutrition, n (%)	2 (15)	3 (5)	0.2
Length of hospital stay, days	11 (8; 25)	7 (5; 11)	0.012
Mortality, n (%)	3 (23)	1 (2)	0.002
Amylase, U/L	829 (619; 1526)	1027 (537; 1897)	0.5
Hematocrit, %	37.4 (33.5; 45.2)	43.4 (41.0; 46.9)	0.011
Leukocyte count, ×10^3/µL	14.8 (12.3; 22.9)	12.1 (9.9; 16.2)	0.1
Neutrophil count, ×10^3/µL	11.4 (8.6; 19.6)	9.4 (7.5; 12.9)	0.2
CRP, mg/L	258 (182; 313)	104 (49; 229)	0.018
Glucose, mmol/L	8.93 (8.33; 12.25)	7.78 (6.56; 10.11)	0.06
Bilirubin, µmol/L	48.7 (36.4; 81.0)	35.5 (17.8; 65.1)	0.07
Urea, mmol/L	11.68 (6.72; 15.80)	5.83 (4.21; 6.57)	<0.001
Creatinine, µmol/L	120 (95; 207)	71 (61; 85)	<0.001
Cystatin C, mg/L	2.05 (0.84; 2.70)	0.86 (0.69; 1.13)	0.002
BTP, mg/L	0.897 (0.291; 1.470)	0.459 (0.254; 0.631)	0.019
Serum NGAL, ng/mL	313 (275; 489)	142 (101; 232)	<0.001
Urine NGAL, ng/mL	837 (551; 1252)	38 (20; 68)	0.002
Uromodulin, ng/mL	105 (90; 152)	146 (95; 205)	0.2
D-dimer, µg/mL	6.32 (3.82; 15.69)	2.90 (1.33; 4.20)	0.003
Angiopoietin 2, ng/mL	14.48 (5.77; 23.69)	3.25 (2.37; 5.33)	<0.001
sFlt-1, pg/mL	215 (192; 250)	140 (114; 173)	<0.001

AKI, acute kidney injury; AP, acute pancreatitis; BISAP, bedside index of severity in acute pancreatitis; BMI, body mass index; BTP, beta-trace protein; CRP, C-reactive protein; MAP, mild acute pancreatitis; MMSS, modified Marshall scoring system; MSAP, moderately severe acute pancreatitis; n, number of patients; NGAL, neutrophil gelatinase-associated lipocalin; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; sFlt-1, soluble fms-like tyrosine kinase-1.

As shown in Figure 1A–C, serum BTP concentrations on day 1 and day 3 of the study were also significantly higher in patients who developed AKI (n = 12 on day 1, n = 13 on day 2, and n = 8 on day 3) as compared to those who did not. Moreover, BTP concentrations on days 1 to 3 differed significantly between subjects who developed renal failure (diagnosed according to MMSS; n = 6 on day 1, n = 6 on day 2, and n = 5 on day 3) and those who did not (Figure 1D–F). In contrast, serum BTP did not differ significantly between patients with mild, moderately severe and severe AP (Figure 2). Only day 3

BTP concentrations significantly correlated with BISAP score (R = 0.60; $p < 0.001$) and the duration of hospital stay (R = 0.34; $p = 0.030$). No statistically significant changes in BTP concentrations over the three days of the study were observed.

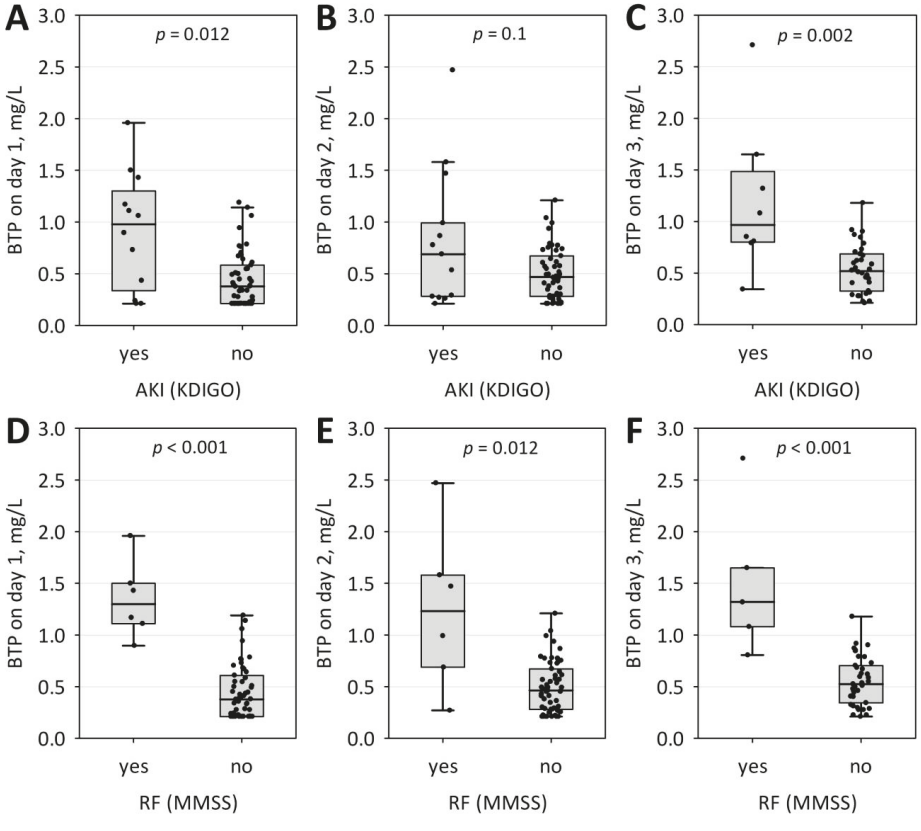

Figure 1. Serum beta-trace protein (BTP) concentrations on day 1 (**A**,**D**), 2 (**B**,**E**) and 3 (**C**,**F**) of hospital stay among patients with AP complicated with acute kidney injury (AKI) diagnosed according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines (**A**–**C**) or renal failure (RF) diagnosed according to modified Marshall scoring system (MMSS) (**D**–**F**) versus patients without these complications. Data are shown as raw data (points), median (central line), interquartile range (box), and non-outlier range (whiskers).

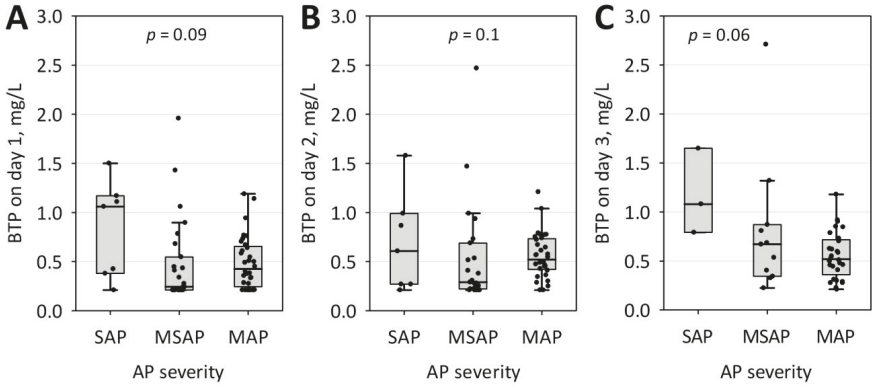

Figure 2. Serum BTP concentrations on day 1 (**A**), 2 (**B**) and 3 (**C**) of hospital stay among patients with acute pancreatitis (AP) of various severity (SAP, severe; MSAP, moderately severe; and MAP, mild) diagnosed according to the modified 2012 Atlanta classification. Data are shown as raw data (points), median (central line), interquartile range (box), and non-outlier range (whiskers).

Strong positive correlations were observed over the studied period between serum BTP and other studied laboratory markers increasing in result of impaired renal filtration, i.e., serum creatinine, cystatin C and urea (Table 2). Consequently, negative correlations were observed between serum BTP and serum uromodulin. In contrast, there was no significant correlation between BTP and the marker of tubular injury, i.e., urine NGAL, and the positive correlations between BTP and serum NGAL were not consistent throughout the study (Table 2). BTP measured on day 1 following admission as well as the maximum concentrations recorded on the first two days of hospital stay were also positively correlated with the studied markers of endothelial dysfunction: angiopoietin 2 and sFlt-1 (Table 2). No correlations were observed between BTP and the markers of inflammation: C-reactive protein, white blood cell and neutrophil counts (Table 2).

Table 2. Simple correlations between serum BTP concentrations in the whole studied group of AP patients and other markers of kidney dysfunction, epithelial dysfunction and inflammation measured at the specified time-points.

Variable	Serum BTP Concentrations			
	Maximum of Day 1 and 2* (n = 73)	**Day 1 (n = 65)**	**Day 2 (n = 63)**	**Day 3 (n = 45)**
Urea	R = 0.52; $p < 0.001$	R = 0.50; $p < 0.001$	R = 0.41; $p < 0.001$	R = 0.73; $p < 0.001$
Creatinine	R = 0.56; $p < 0.001$	R = 0.63; $p < 0.001$	R = 0.52; $p < 0.001$	R = 0.71; $p < 0.001$
Cystatin C	R = 0.60; $p < 0.001$	R = 0.68; $p < 0.001$	R = 0.63; $p < 0.001$	R = 0.91; $p < 0.001$
Serum NGAL	R = 0.17; $p = 0.3$	R = 0.43; $p = 0.007$	R = 0.22; $p = 0.2$	R = 0.35; $p = 0.023$
Urine NGAL	R = 0.23; $p = 0.3$	R = 0.17; $p = 0.38$	R = 0.30; $p = 0.1$	R = 0.37; $p = 0.07$
Uromodulin	R = −0.42; $p = 0.004$	R = −0.43; $p = 0.007$	R = −0.44; $p = 0.003$	R = −0.33; $p = 0.037$
D-dimer	R = 0.05; $p = 0.7$	R = 0.31; $p = 0.012$	R = −0.07; $p = 0.6$	R = −0.04; $p = 0.8$
Angiopoietin-2	R = 0.26; $p = 0.045$	R = 0.37; $p = 0.007$	R = 0.11; $p = 0.4$	R = 0.22; $p = 0.2$
sFlt-1	R = 0.25; $p = 0.044$	R = 0.34; $p = 0.011$	R = −0.03; $p = 0.8$	no data
Leukocytes	R = 0.11; $p = 0.4$	R = 0.07; $p = 0.6$	R = −0.02; $p = 0.9$	R = 0.05; $p = 0.8$
Neutrophils	R = 0.10; $p = 0.4$	R = −0.01; $p = 0.9$	R = −0.03; $p = 0.8$	R = 0.09; $p = 0.6$
CRP	R = −0.10; $p = 0.4$	R = 0.15; $p = 0.2$	R = −0.19; $p = 0.1$	R = −0.08; $p = 0.6$

* Minimum of day 1 and day 2 concentrations in case of uromodulin.

Serum BTP was highly correlated with patients' age (R = 0.65 for maximum BTP recorded during first two days of hospital stay; R from 0.65 on day 1 to 0.77 on day 3; $p < 0.001$ for all correlations). In logistic regression, the association between BTP and AKI became statistically insignificant after

adjustment for age and preexisting renal pathology ($p > 0.05$ throughout the study), and only BTP concentrations on day 3 of hospital stay were significantly associated with AKI after adjustment for preexisting renal disease only (Table 3). This contrasts with cystatin C that proved a significant predictor of AKI after adjustment for renal comorbidity (Table 3).

Table 3. Odds ratios for the diagnosis of AKI according to KDIGO obtained in logistic regression adjusted for prediagnosed kidney comorbidity.

	BTP, per 1 mg/L		Cystatin C, per 1 mg/L	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Maximum of day 1 and 2	1.29 (0.72–2.33)	0.4	2.10 (30.1–698)	0.002
Day 1	1.31 (0.72–2.37)	0.4	14.0 (2.34–83.6)	0.003
Day 2	1.15 (0.53–2.50)	0.7	5.12 (1.24–21.2)	0.021
Day 3	125 (2.7–5796)	0.001	33.2 (2.45–451)	0.006

OR, odds ratio; CI, confidence interval.

In ROC curve analysis, maximum BTP concentrations observed during the first two days of the study as well as BTP concentrations on day 1 and day 3 showed moderate diagnostic accuracy for AKI (AUC from 0.621 to 0.803; Figure 3A). For comparison, we presented the ROC curves for serum cystatin C, serum NGAL and urine NGAL in the diagnosis of AKI (Figure 3B–D). The values of AUC for these markers did not differ significantly from the AUCs of BTP at all the studied time-points ($p > 0.05$ for all comparisons). However, it should be noted that the diagnostic accuracy of serum BTP and cystatin C was very similar while the estimations of AUC for both serum and urine NGAL were consistently higher throughout the study.

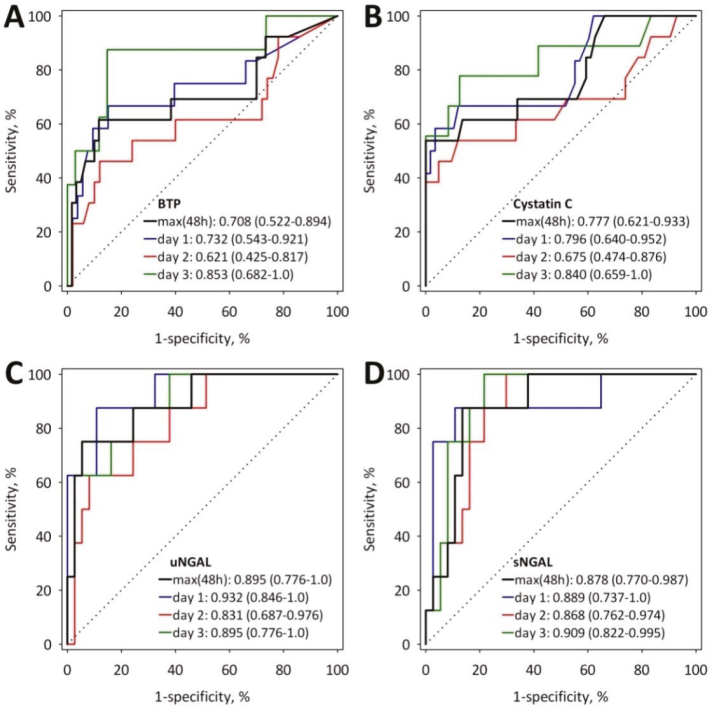

Figure 3. ROC curves showing the diagnostic accuracy of serum BTP (**A**), cystatin C (**B**), urine NGAL

(**C**) and serum NGAL (**D**) measured at the specified time-points for the diagnosis of AKI. The values of AUC with 95% CI are shown on the graphs; max(48h), maximum value observed during the first two days (or 48 h) of hospital stay.

4. Discussion

Most laboratory markers proposed for the fast prognosis or diagnosis of AKI have not been studied in AP [19]. Previously, serum cystatin C has been shown to predict AKI in AP with high diagnostic accuracy [33]. Our study shows for the first time that serum BTP, a marker of glomerular filtration, is increased early in patients with AP who develop AKI, in parallel to serum cystatin C. BTP concentrations were highly correlated with serum creatinine and cystatin C. The diagnostic accuracy of BTP for early diagnosis of AKI in the early phase of AP was comparable to that of serum cystatin C. However, it seemed lower than the diagnostic accuracy of serum and urine NGAL. Moreover, in logistic regression analysis, the association between increased BTP and AKI was dependent on previous renal disease, in contrast to what was found for serum cystatin C.

Although creatinine currently remains the main clinically used marker of glomerular filtration, and the only one acknowledged in clinical guidelines for the diagnosis of AKI [30], it is also commonly regarded the late marker of AKI. Significant increase in serum creatinine is not observed in mild renal impairment, in contrast to serum BTP and cystatin C [1,34]. Moreover, there are many non-renal factors associated with altered production of creatinine that affect serum creatinine concentrations, such as muscle mass, age, sex, race, or liver dysfunction [35,36]. Serum cystatin C and BTP seem less affected by non-renal determinants. However, the evidence is mostly based on the studies including patients with chronic kidney disease [35,36]. Of note, serum creatinine production is diminished in liver dysfunction, while BTP concentrations are not affected [37]. This is of importance, as hepatic dysfunction often accompanies SAP. As a marker of glomerular filtration, serum BTP may have an advantage over serum cystatin C in patients treated with glucocorticoids, including those after renal transplantation [1]. On the other hand, recent study that compared serum BTP with serum cystatin C in elderly patients showed better correlation of cystatin C based estimated glomerular filtration rate with measured filtration rate [38].

In AKI, there are very limited data on diagnostic accuracy of BTP. Recently, Saydam et al. [39] evaluated serum BTP, cystatin C and NGAL in comparison with serum creatinine in 57 patients after cardiopulmonary bypass of whom 24 developed AKI. Higher preoperative cystatin C and BTP were associated with AKI, reflecting higher risk for AKI in patients with chronic kidney impairment. Postoperative increase in cystatin C was better predictive marker of AKI than BTP. In our study, serum BTP and cystatin C measured on first three days of AP had similar diagnostic accuracy for AKI (similar areas under the ROC curves). However, the association between BTP and the development of AKI was more affected by kidney disease preceding AP and became insignificant after adjustment for age. Older age is associated with a decrease in glomerular filtration rate, and this decrease results in chronically increased serum concentrations of BTP [38]. Kidney disease preceding the development of AP in our patients could also be a cause of chronically decreased glomerular filtration and increased BTP. We may hypothesize that the increase in BTP associated with the development of AKI is less dynamic in such patients as compared with the increase in cystatin C. However, this interpretation needs to be tested in larger study as the numbers of patients with AKI in our study is low, adversely affecting the power of multiple statistical models, and the number of patients with prediagnosed renal disease in our study is very low.

Serum cystatin C has been evaluated as a marker of AKI in various settings, including sepsis [40,41] and AP [33]. Recent study in over 200 patients with AP reported excellent diagnostic accuracy for AKI (area under ROC curve of 0.948) [33]. In our study, the diagnostic accuracy of cystatin C was lower. However, both SAP and AKI were more prevalent in our study group (9.6% and 18% versus 5% and 7.6%, respectively). Our study included patients admitted within 24 h from the onset of AP symptoms; this time-period was not defined in the study of Chai et al. [33] and might be longer. Moreover, Chai et al. [33]

excluded patients with prediagnosed renal disease, whereas in our group four patients had kidney disease diagnosed before the onset of AP.

Serum and urine NGAL are known markers of AKI [23]. In AP, good diagnostic accuracy for AKI of both serum and urine NGAL was previously reported by Siddappa et al. [42] (AUCs of 0.8 to 0.9), comparable with our present results. To our knowledge, there is no published evidence comparing the accuracy of NGAL and BTP in the diagnosis of AKI. Our findings suggest that in AP, the decrease in glomerular filtration reflected by increased BTP is not strictly accompanied by simultaneous increase in NGAL (we did not observe consistent correlations between the markers over the study period). Moreover, the diagnostic accuracy of both serum and urine NGAL for AKI was better than observed for BTP, although it must be remembered that NGAL measurements were available only in patients from one study center.

Cystatin C and BTP are both the low-molecular-weight proteins, easily filtered in renal glomeruli. Increased serum concentrations of both proteins reflect decreased renal function (decreased glomerular filtration rate). Both proteins may be easily measured in serum with automated laboratory methods. However, an international standard is only available for cystatin C, allowing the standardization of the assays [43]. In contrast, the measurements of serum NGAL have not been automated. Moreover, neutrophils are important source of NGAL in serum of patients with acute inflammation, which may decrease the diagnostic accuracy of this marker for AKI as has been shown in septic patients [44]. Urinary NGAL may be measured with an automated laboratory method. However, the sample—urine—may not be available in some patients with AKI. Increased NGAL reflects the injury to proximal and distal renal tubules, irrespective of glomerular function. A combination of a functional marker, i.e., serum BTP or cystatin C with the marker of tubular injury, i.e., serum or preferably urine NGAL might be proposed for the diagnosis of AKI in AP, to be verified in a larger, prospective study.

AP is associated an acute inflammation, which influences the concentrations of many serum proteins. We have not found significant correlations between serum BTP and the inflammatory markers (C-reactive protein, white blood cell and neutrophil count), even though higher CRP was observed in patients with AKI. BTP concentrations did not differ significantly between patients with severe, moderately severe and mild AP. The finding is in line with the evidence regarding patients with chronic kidney disease [25]. However, BTP has been assigned proinflammatory role in allergies and ulcerative colitis and immunomodulatory role has been suggested in bacterial infections [4]. Thus, larger studies are needed to exclude the weak association between serum BTP and acute systemic inflammation.

On day 1 following patients' admission, we have found significant positive correlations between serum BTP and the markers of endothelial dysfunction or injury, i.e., serum angiopoietin-2 and sFlt-1. Both these endothelial markers have been shown to predict the severity of AP [26,31,45,46] and have increased in patients with kidney injury complicating AP [26] or have correlated with impaired renal function [46]. Angiopoietin-2 has also been shown to predict AKI in other patient populations, e.g., after myocardial infarction [47], after cardiopulmonary bypass [48], with acute respiratory distress syndrome [49], or among patients of intensive care unit [50]. Endothelial injury and vascular leak syndrome are important pathophysiological factors of organ (including kidney) injury and failure in SAP [51]. BTP synthesis is induced in endothelial cells under shear stress. Through prostaglandin D2 synthesis, BTP exerts vasodilating effects [52]. However, the role of BTP in endothelial dysfunction associated with systemic inflammation or sepsis remains to be elucidated.

Our study has several limitations. It was a post-hoc analysis of a small number of patients recruited in two centers. Although the percentage of patients with AKI was within the range previously reported in AP [19], the number of patients with AKI was low, which must be acknowledged as the main limitation of the study. Larger prospective studies are needed to confirm our preliminary results. We measured BTP in available samples stored frozen in −80 °C for a period of one–two years. However, BTP concentrations have been shown to remain stable over long periods in frozen serum samples [53].

In conclusion, our study showed for the first time that serum BTP increases in the early phase of AP in patients who develop AKI in parallel with serum cystatin C and creatinine. Increased BTP is

an early predictor of AKI complicating AP.However, its diagnostic accuracy does not seem better as compared to serum cystatin C or serum and urine NGAL. Serum BTP concentrations in the early phase of AP are not affected by the severity of inflammation but correlates with endothelial dysfunction.

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References

1. Orenes-Piñero, E.; Manzano-Fernández, S.; López-Cuenca, Á.; Marín, F.; Valdés, M.; Januzzi, J.L. β-Trace protein: From GFR marker to cardiovascular risk predictor. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 873–881. [CrossRef]
2. Meco, C.; Oberascher, G.; Arrer, E.; Moser, G.; Albegger, K. β-trace protein test: New guidelines for the reliable diagnosis of cerebrospinal fluid fistula. *Otolaryngol.-Head Neck. Surg.* **2003**, *129*, 508–517. [CrossRef]
3. Bachmann, G.; Petereit, H.; Djenabi, U.; Michel, O. Predictive Values of β-Trace Protein (Prostaglandin D Synthase) by Use of Laser-Nephelometry Assay for the Identification of Cerebrospinal Fluid. *Neurosurgery* **2002**, *50*, 571–577.
4. Joo, M.; Sadikot, R.T. PGD Synthase and PGD 2 in Immune Response. *Mediators Inflamm.* **2012**, *2012*, 1–6. [CrossRef]
5. Donadio, C.; Lucchesi, A.; Ardini, M.; Donadio, E.; Giordani, R. Serum levels of beta-trace protein and glomerular filtration rate–preliminary results. *J. Pharm. Biomed. Anal.* **2003**, *32*, 1099–1104. [CrossRef]
6. Donadio, C. Serum and urinary markers of early impairment of GFR in chronic kidney disease patients: Diagnostic accuracy of urinary β-trace protein. *Am. J. Physiol. Renal Physiol.* **2010**, *299*, F1407–F1423. [CrossRef] [PubMed]
7. Spanaus, K.S.; Kollerits, B.; Ritz, E.; Hersberger, M.; Kronenberg, F.; Von Eckardstein, A. Serum creatinine, cystatin C, and β-trace protein in diagnostic staging and predicting progression of primary nondiabetic chronic kidney disease. *Clin. Chem.* **2010**, *56*, 740–749. [CrossRef] [PubMed]
8. Donadio, C.; Bozzoli, L. Urinary β-trace protein. A unique biomarker to screen early glomerular filtration rate impairment. *Medicine* **2016**, *95*, e5553. [CrossRef] [PubMed]
9. Bacci, M.R.; Cavallari, M.R.; de Rozier-Alves, R.M.; Alves, B.D.C.A.; Fonseca, F.L.A. The impact of lipocalin-type-prostaglandin-D-synthase as a predictor of kidney disease in patients with type 2 diabetes. *Drug Des. Devel. Ther.* **2015**, *9*, 3179–3182. [PubMed]
10. Manzano-Fernández, S.; López-Cuenca, Á.; Januzzi, J.L.; Parra-Pallares, S.; Mateo-Martínez, A.; Sánchez-Martínez, M.; Pérez-Berbel, P.; Orenes-Piñero, E.; Romero-Aniorte, A.I.; Avilés-Plaza, F.; et al. Usefulness of β-trace protein and cystatin C for the prediction of mortality in non ST segment elevation acute coronary syndromes. *Am. J. Cardiol.* **2012**, *110*, 1240–1248. [CrossRef] [PubMed]
11. Manzano-Fernández, S.; Januzzi, J.L.; Boronat-Garcia, M.; Bonaque-González, J.C.; Truong, Q.A.; Pastor-Pérez, F.J.; Muñoz-Esparza, C.; Pastor, P.; Albaladejo-Otón, M.D.; Casas, T.; et al. β-trace protein and cystatin C as predictors of long-term outcomes in patients with acute heart failure. *J. Am. Coll. Cardiol.* **2011**, *57*, 849–858. [CrossRef] [PubMed]
12. Peery, A.F.; Dellon, E.S.; Lund, J.; Crockett, S.D.; McGowan, C.E.; Bulsiewicz, W.J.; Gangarosa, L.M.; Thiny, M.T.; Stizenberg, K.; Morgan, D.R.; et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* **2012**, *143*, 1179–1187. [CrossRef] [PubMed]
13. Párniczky, A.; Kui, B.; Szentesi, A.; Balázs, A.; Szűcs, Á.; Mosztbacher, D.; Czimmer, J.; Sarlós, P.; Bajor, J.; Gódi, S.; et al. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. *PLoS ONE* **2016**, *11*, e0165309. [CrossRef] [PubMed]
14. Lankisch, P.G.; Apte, M.; Banks, P.A. Acute pancreatitis. *Lancet* **2015**, *386*, 85–96. [CrossRef]

15. Susantitaphong, P.; Cruz, D.N.; Cerda, J.; Abulfaraj, M.; Alqahtani, F.; Koulouridis, I.; Jaber, B.L. Acute Kidney Injury Advisory Group of the American Society of Nephrology World incidence of AKI: A meta-analysis. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 1482–1493. [CrossRef]
16. Hoste, E.A.J.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef]
17. Druml, W.; Lenz, K.; Laggner, A.N. Our paper 20 years later: From acute renal failure to acute kidney injury—The metamorphosis of a syndrome. *Intensive Care Med.* **2015**, *41*, 1941–1949. [CrossRef]
18. Ostermann, M.; Liu, K. Pathophysiology of AKI. *Best Pract. Res. Clin. Anaesthesiol.* **2017**, *31*, 305–314. [CrossRef]
19. Wajda, J.; Dumnicka, P.; Maraj, M.; Ceranowicz, P.; Kuźniewski, M.; Kuśnierz-Cabala, B. Potential prognostic markers of acute kidney injury in the early phase of acute pancreatitis. *Int. J. Mol. Sci.* **2019**, *20*, 3714. [CrossRef]
20. Lin, H.-Y.; Lai, J.-I.; Lai, Y.-C.; Lin, P.-C.; Chang, S.-C.; Tang, G.-J. Acute renal failure in severe pancreatitis: A population-based study. *Ups. J. Med. Sci.* **2011**, *116*, 155–159. [CrossRef]
21. Nassar, T.I.; Qunibi, W.Y. AKI Associated with Acute Pancreatitis. *Clin. J. Am. Soc. Nephrol.* **2019**, *14*, 106–1115. [CrossRef] [PubMed]
22. Beker, B.M.; Corleto, M.G.; Fieiras, C.; Musso, C.G. Novel acute kidney injury biomarkers: Their characteristics, utility and concerns. *Int. Urol. Nephrol.* **2018**, *50*, 705–713. [CrossRef] [PubMed]
23. Schrezenmeier, E.V.; Barasch, J.; Budde, K.; Westhoff, T.; Schmidt-Ott, K.M. Biomarkers in acute kidney injury—Pathophysiological basis and clinical performance. *Acta Physiol.* **2017**, *219*, 554–572. [CrossRef] [PubMed]
24. Li, W.; Mase, M.; Inui, T.; Shimoda, M.; Isomura, K.; Oda, H.; Yamada, K.; Urade, Y. Pharmacokinetics of recombinant human lipocalin-type prostaglandin D synthase/β-trace in canine. *Neurosci. Res.* **2008**, *61*, 289–293. [CrossRef]
25. Chen, H.H. β-trace protein versus cystatin C: which is a better surrogate marker of renal function versus prognostic indicator in cardiovascular diseases? *J. Am. Coll. Cardiol.* **2011**, *57*, 859–860. [CrossRef] [PubMed]
26. Sporek, M.; Dumnicka, P.; Gala-Błądzińska, A.; Ceranowicz, P.; Warzecha, Z.; Dembiński, A.; Stępień, E.; Walocha, J.; Drożdż, R.; Kuźniewski, M.; et al. Angiopoietin-2 is an early indicator of acute pancreatic-renal syndrome in patients with acute pancreatitis. *Mediators Inflamm.* **2016**, *5780903*, 1–7. [CrossRef] [PubMed]
27. Kolber, W.; Kuśnierz-Cabala, B.; Dumnicka, P.; Maraj, M.; Mazur-Laskowska, M.; Pędziwiatr, M.; Ceranowicz, P. Serum Urokinase-Type Plasminogen Activator Receptor Does Not Outperform C-Reactive Protein and Procalcitonin as an Early Marker of Severity of Acute Pancreatitis. *J. Clin. Med.* **2018**, *7*, 305. [CrossRef]
28. Banks, P.A.; Bollen, T.L.; Dervenis, C.; Gooszen, H.G.; Johnson, C.D.; Sarr, M.G.; Tsiotos, G.G.; Vege, S.S. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut* **2013**, *62*, 102–111. [CrossRef]
29. Wu, B.U.; Johannes, R.S.; Sun, X.; Tabak, Y.; Conwell, D.L.; Banks, P. The early prediction of mortality in acute pancreatitis: a large population-based study. *Gut* **2008**, *57*, 1698–1703. [CrossRef]
30. Kellum, J.A.; Lameire, N.; Aspelin, P.; Barsoum, R.S.; Burdmann, E.A.; Goldstein, S.L.; Herzog, C.A.; Joannidis, M.; Kribben, A.; Levey, A.S.; et al. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int. Suppl.* **2012**, *2*, 1–138.
31. Dumnicka, P.; Kuśnierz-Cabala, B.; Sporek, M.; Mazur-Laskowska, M.; Gil, K.; Kuźniewski, M.; Ceranowicz, P.; Warzecha, Z.; Dembiński, A.; Bonior, J.; et al. Serum concentrations of angiopoietin-2 and soluble fms-like tyrosine kinase 1 (sFlt-1) are associated with coagulopathy among patients with acute pancreatitis. *Int. J. Mol. Sci.* **2017**, *18*, 735. [CrossRef] [PubMed]
32. Hanley, J.A.; Hajian-Tilaki, K.O. Sampling variability of nonparametric estimates of the areas under receiver operating characteristic curves: An update. *Acad. Radiol.* **1997**, *4*, 49–58. [CrossRef]
33. Chai, X.; Huang, H.-B.; Feng, G.; Cao, Y.-H.; Cheng, Q.-S.; Li, S.-H.; He, C.-Y.; Lu, W.-H.; Qin, M.-M. Baseline Serum Cystatin C Is a Potential Predictor for Acute Kidney Injury in Patients with Acute Pancreatitis. *Dis. Markers* **2018**, *2018*, 1–7. [CrossRef] [PubMed]

34. Basu, R.K.; Wong, H.R.; Krawczeski, C.D.; Wheeler, D.S.; Manning, P.B.; Chawla, L.S.; Devarajan, P.; Goldstein, S.L. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J. Am. Coll. Cardiol.* **2014**, *64*, 2753–2762. [CrossRef]
35. Juraschek, S.P.; Coresh, J.; Inker, L.A.; Levey, A.S.; Köttgen, A.; Foster, M.C.; Astor, B.C.; Eckfeldt, J.H.; Selvin, E. Comparison of serum concentrations of β-trace protein, β2-microglobulin, cystatin C, and creatinine in the US population. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 584–592. [CrossRef]
36. Liu, X.; Foster, M.C.; Tighiouart, H.; Anderson, A.H.; Beck, G.J.; Contreras, G.; Coresh, J.; Eckfeldt, J.H.; Feldman, H.I.; Greene, T.; et al. Non-GFR Determinants of Low-Molecular-Weight Serum Protein Filtration Markers in CKD. *Am. J. Kidney Dis.* **2016**, *68*, 892–900. [CrossRef]
37. Chakraborty, D.; Akbari, A.; Knoll, G.A.; Flemming, J.A.; Lowe, C.; Akbari, S.; White, C.A. Serum BTP concentrations are not affected by hepatic dysfunction. *BMC Nephrol.* **2018**, *19*, 87. [CrossRef]
38. Werner, K.; Pihlsgård, M.; Elmståhl, S.; Legrand, H.; Nyman, U.; Christensson, A. Combining Cystatin C and Creatinine Yields a Reliable Glomerular Filtration Rate Estimation in Older Adults in Contrast to β-Trace Protein and β2-Microglobulin. *Nephron* **2017**, *137*, 29–37. [CrossRef]
39. Saydam, O.; Türkmen, E.; Portakal, O.; Arici, M.; Doğan, R.; Demircin, M.; Paşaoğlu, İ.; Yilmaz, M. Emerging biomarker for predicting acute kidney injury after cardiac surgery: Cystatin C. *Turkish J. Med. Sci.* **2018**, *48*, 1096–1103. [CrossRef]
40. Dai, X.; Zeng, Z.; Fu, C.; Zhang, S.; Cai, Y.; Chen, Z. Diagnostic value of neutrophil gelatinase-associated lipocalin, cystatin C, and soluble triggering receptor expressed on myeloid cells-1 in critically ill patients with sepsis-associated acute kidney injury. *Crit. Care* **2015**, *19*, 223. [CrossRef]
41. Leem, A.Y.; Park, M.S.; Park, B.H.; Jung, W.J.; Chung, K.S.; Kim, S.Y.; Kim, E.Y.; Jung, J.Y.; Kang, Y.A.; Kim, Y.S.; et al. Value of Serum Cystatin C Measurement in the Diagnosis of Sepsis-Induced Kidney Injury and Prediction of Renal Function Recovery. *Yonsei Med. J.* **2017**, *58*, 604. [CrossRef] [PubMed]
42. Siddappa, P.K.; Kochhar, R.; Sarotra, P.; Medhi, B.; Jha, V.; Gupta, V. Neutrophil gelatinase-associated lipocalin: An early biomarker for predicting acute kidney injury and severity in patients with acute pancreatitis. *JGH Open* **2018**, *3*, 105–110. [CrossRef] [PubMed]
43. Ebert, N.; Delanaye, P.; Shlipak, M.; Jakob, O.; Martus, P.; Bartel, J.; Gaedeke, J.; van der Giet, M.; Schuchardt, M.; Cavalier, E.; et al. Cystatin C standardization decreases assay variation and improves assessment of glomerular filtration rate. *Clin. Chim. Acta.* **2016**, *456*, 115–121. [CrossRef] [PubMed]
44. Aydoğdu, M.; Gürsel, G.; Sancak, B.; Yeni, S.; Sari, G.; Taşyürek, S.; Türk, M.; Yüksel, S.; Senes, M.; Özis, T.N. The use of plasma and urine neutrophil gelatinase associated lipocalin (NGAL) and Cystatin C in early diagnosis of septic acute kidney injury in critically ill patients. *Dis. Markers* **2013**, *34*, 237–246. [CrossRef]
45. Buddingh, K.T.; Koudstaal, L.G.; van Santvoort, H.C.; Besselink, M.G.; Timmer, R.; Rosman, C.; van Goor, H.; Nijmeijer, R.M.; Gooszen, H.; Leuvenink, H.G.D.; et al. Early angiopoietin-2 levels after onset predict the advent of severe pancreatitis, multiple organ failure, and infectious complications in patients with acute pancreatitis. *J. Am. Coll. Surg.* **2014**, *218*, 26–32. [CrossRef]
46. Dumnicka, P.; Sporek, M.; Mazur-Laskowska, M.; Ceranowicz, P.; Kuźniewski, M.; Drożdż, R.; Ambroży, T.; Olszanecki, R.; Kuśnierz-Cabala, B. Serum soluble fms-Like tyrosine kinase 1 (sFlt-1) predicts the severity of acute pancreatitis. *Int. J. Mol. Sci.* **2016**, *17*, 2038. [CrossRef]
47. Liu, K.L.; Lee, K.T.; Chang, C.H.; Chen, Y.C.; Lin, S.M.; Chu, P.H. Elevated plasma thrombomodulin and angiopoietin-2 predict the development of acute kidney injury in patients with acute myocardial infarction. *Crit. Care* **2014**, *18*, R100. [CrossRef]
48. Jongman, R.M.; Van Klarenbosch, J.; Molema, G.; Zijlstra, J.G.; De Vries, A.J.; Van Meurs, M.; Long, D. Angiopoietin/Tie2 dysbalance is associated with acute kidney injury after cardiac surgery assisted by cardiopulmonary bypass. *PLoS ONE* **2015**, *10*, e0136205. [CrossRef]
49. Araújo, C.B.; de Oliveira Neves, F.M.; de Freitas, D.F.; Arruda, B.F.T.; de Macêdo Filho, L.J.M.; Salles, V.B.; Meneses, G.C.; Martins, A.M.C.; Libório, A.B. Angiopoietin-2 as a predictor of acute kidney injury in critically ill patients and association with ARDS. *Respirology* **2019**, *24*, 345–351. [CrossRef]
50. Robinson-Cohen, C.; Katz, R.; Price, B.L.; Harju-Baker, S.; Mikacenic, C.; Himmelfarb, J.; Liles, W.C.; Wurfel, M.M. Association of markers of endothelial dysregulation Ang1 and Ang2 with acute kidney injury in critically ill patients. *Crit. Care* **2016**, *20*, 1–8. [CrossRef]

51. Dumnicka, P.; Maduzia, D.; Ceranowicz, P.; Olszanecki, R.; Drożdż, R.; Kuśnierz-Cabala, B. The interplay between inflammation, coagulation and endothelial injury in the early phase of acute pancreatitis: Clinical implications. *Int. J. Mol. Sci.* **2017**, *18*, 354. [CrossRef] [PubMed]
52. Song, W.L.; Ricciotti, E.; Liang, X.; Grosser, T.; Grant, G.R.; FitzGerald, G.A. Lipocalin-like prostaglandin D synthase but not hemopoietic prostaglandin D synthase deletion causes hypertension and accelerates thrombogenesis in mice. *J. Pharmacol. Exp. Ther.* **2018**, *367*, 425–432. [CrossRef] [PubMed]
53. Juraschek, S.P.; Coresh, J.; Inker, L.A.; Rynders, G.P.; Eckfeldt, J.H.; Selvin, E. The effects of freeze–thaw on β-trace protein and β2-microglobulin assays after long-term sample storage. *Clin. Biochem.* **2012**, *45*, 694–696. [CrossRef] [PubMed]

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Long-Term Outcomes in Patients with Incident Chronic Obstructive Pulmonary Disease after Acute Kidney Injury: A Competing-Risk Analysis of a Nationwide Cohort

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Abstract: Both acute kidney injury (AKI) and chronic obstructive pulmonary disease (COPD) are associated with increased morbidity and mortality. However, the incidence of de novo COPD in patients with AKI, and the impact of concurrent COPD on the outcome during post-AKI care is unclear. Patients who recovered from dialysis-requiring AKI (AKI-D) during index hospitalizations between 1998 and 2010 were identified from nationwide administrative registries. A competing risk analysis was conducted to predict the incidence of adverse cardiovascular events and mortality. Among the 14,871 patients who recovered from temporary dialysis, 1535 (10.7%) were identified as having COPD (COPD group) one year after index discharge and matched with 1473 patients without COPD (non-COPD group) using propensity scores. Patients with acute kidney disease superimposed withs COPD were associated with a higher risk of incident ischemic stroke (subdistribution hazard ratio (sHR), 1.52; 95% confidence interval (95% CI), 1.17 to 1.97; $p = 0.002$) and congestive heart failure (CHF; sHR, 1.61; (95% CI), 1.39 to 1.86; $p < 0.001$). The risks of incident hemorrhagic stroke, myocardial infarction, end-stage renal disease, and mortality were not statistically different between the COPD and non-COPD groups. This observation adds another dimension to accumulating evidence regarding pulmo-renal consequences after AKI.

Keywords: acute kidney injury; chronic obstructive pulmonary disease; congestive heart failure; stroke

1. Introduction

The incidence of acute kidney injury (AKI) in hospitalized patients is increasing [1] and has been associated with high mortality and morbidity worldwide over the past decade [2]. The incidence of AKI requiring dialysis (AKI-D) is increasing by 10% per year in the United States and is higher than that of end-stage renal disease (ESRD) [3]. Patient survival from an episode of AKI has been improved by advances in critical care medicine and dialysis technology increasing the survival rate of hospitalized patients discharged after temporary dialysis [4]. Previous studies showed that patients with a history of AKI have a higher incidence of coronary events [5], stroke [6], congestive heart failure (CHF) [7], ESRD, and mortality [8] than individuals without AKI. The American Society of Nephrology AKI Advisory Group has highlighted the transition of care as a potential opportunity to reduce the long-term impact of AKI [9]. To improve the situation of dialysis patients, novel renal replacement therapies, such as an implantable artificial renal assist device, are under development. The artificial renal assist device strategy utilizes micromachining techniques to fabricate a biohybrid system able to mimic renal morphology and function [10]. Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease characterized by airflow limitations. Comorbidities are common in COPD, including cardiovascular [11], cerebrovascular [12], and chronic kidney diseases [13]. These comorbidities are possibly attributed to a chronic inflammatory state in COPD and are increasingly recognized as important determinants of COPD prognosis [13].

Each injured organ can initiate various complex pathways affecting distant organs through hemodynamic, neurohormonal, and cell signaling feedback mechanisms [14]. The kidney plays a key role in fluid, electrolyte, acid-base and clearance homeostasis so that AKI provides a significant impulse for the initiation of organ crosstalk. At the cellular level, the renal tubular epithelium plays a fundamental role in regulating the inflammatory processes [7]. A study has shown that lung inflammation is a consistent finding after ischemic AKI [15]. Nonetheless, there is no study addressing the incidence of COPD in patients with AKI-D. In addition, metabolic and respiratory acidosis is a common and severe complication observed in patients with AKI-D and COPD. When COPD occurs in patients with renal failure, the compensatory role of the kidneys and lungs in acidosis may be less effective, resulting in a more severe acidosis status. The recent Kidney Disease Improving Global Outcomes (KDIGO) guideline introduced a new conceptual model, called acute kidney disease (AKD), to emphasize the need to follow patients who survived AKI episodes. The AKD period, linking AKI to chronic kidney disease (CKD), requires intensive care to manage possible hypertension and cardiovascular disease [16]. However, no study has ascertained the contributing role of COPD in patients with a history of AKI in aggravating subsequent morbidity and mortality. With the increasing recognition that COPD and kidney disease extend beyond the pulmo-renal syndrome, interest in lung–kidney–cardiovascular interactions has increased. Using the Taiwan National Health Insurance research dataset, we designed a nationwide, population-based cohort study to examine the long-term risk of adverse cardiovascular incidents, chronic dialysis events, and mortality in patients with COPD during the AKD period.

2. Methods

2.1. Data Sources

This population-based cohort study used medical information from Taiwan's National Health Insurance (NHI) database, a compulsory universal health insurance program that covers outpatient visits, hospital admissions, prescriptions, interventions, disease profiles, and vital status of nearly all 23.7 million Taiwan residents. The NHI database is one of the largest and most comprehensive health-care registries worldwide. Patients were anonymous in our study; thus, informed consent was not required. Additionally, since the identification numbers of all individuals in the database were encrypted to protect their privacy, this study was exempt from a full ethical review by the National Taiwan University Hospital institutional review board (201212021RINC).

2.2. Study Group

The first AKI-D after hospitalization was defined as the index hospitalization for each individual. AKI was defined using the International Classification of Diseases-9 (ICD-9) codes 584.X, 634.3, 635.3, 636.3, 637.3, 638.3, 639.3, 669.3, and 958.5 and procedure codes for acute dialysis. Dialysis certificate data in Taiwan are highly reliable because they are used for insurance payments [17]. We extracted all newly diagnosed AKI patients with de novo AKI-D (identified using the procedure codes) during their index hospitalizations who subsequently recovered from AKI-D (dialysis withdrawal) at least 30 days after discharge between 1 January 1998 and 31 December 2010. Pre-admission comorbidities were identified during at least three outpatient visits or during one inpatient claim within 1 year preceding the index admission. In Taiwan's National Health Insurance Research Database, ICD-9 codes are used to define diseases. We excluded individuals who had a previous diagnosis of AKI; received a kidney transplant; undergone creation of hemodialysis vascular accesses, peritoneal dialysis catheter implantation, or any form of dialysis preceding the index hospitalization; hospitalizations >180 days with AKI; or those who died during the index hospitalization. Our study enrolled only patients who survived the index hospitalization and had no re-dialysis 30 days after discharge. This identification procedure avoided selective bias [18,19].

The COPD group comprised patients with AKI who recovered from dialysis and incidental COPD within 1 year after the index hospitalization. To ensure accuracy, the diagnosis of COPD was validated based on one inpatient or three outpatient records with ICD-9-CM codes 490–492, 494, and 496 [20,21] and received at least one bronchodilator during the follow-up period [22]. Patients without COPD and no recorded previous asthma or COPD medication prescriptions were included in the control (non-COPD) group (Figure 1).

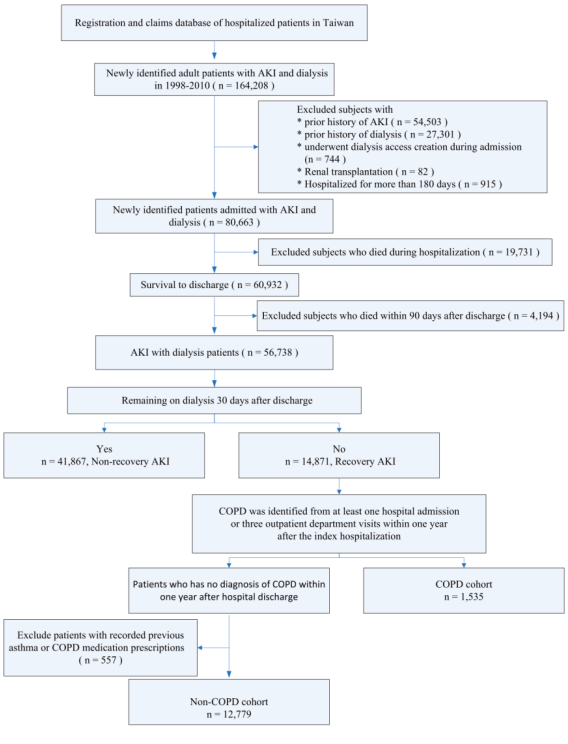

Figure 1. Flow Chart of the enrollee.

2.3. Baseline Characteristics

The baseline comorbidities were identified from at least three outpatient visits or one inpatient claim within one year preceding the index hospitalization. This identification method has been well validated with good predictive power [18,23–26]. The Charlson comorbidity index (CCI) was calculated by weighting baseline comorbidities. We collected concomitant medication data associated with the outcomes of interest. According to the Taiwan NHI reimbursement policy, erythropoiesis-stimulating agents may only be prescribed for pre-dialysis chronic kidney disease (CKD) patients with anemia, hematocrits $\leq$28%, and serum creatinine levels >6 mg/dL (equivalent to an estimated glomerular filtration rate of <15 mL/min/1.73 m^2, CKD stage 5). We defined this combination of CKD diagnosis codes and pre-dialysis patients using erythropoiesis-stimulating agents as having "advanced CKD" [27].

2.4. Outcomes

In order to avoid immortal time bias, the observation period began one year after the index hospitalization discharge and continued until the first documented outcome of interest or the end of the study (31 December 2010), whichever occurred first. The outcomes of interest included all-cause mortality, hospitalization, or death with a principal diagnosis of ischemic stroke (ICD-9-CM code 433.x, 434.x, or 436), hemorrhagic stroke (ICD-9-CM code 431 or 432) [6], CHF (ICD-9-CM code 428.x), major adverse cardiovascular events (MACE), and ESRD [28].

Stroke was defined as one of the following conditions [29]: (a) records of emergency room service or hospitalization claims for >1 day or records of emergency room service with ICD-9-CM codes followed by claims for various brain-imaging technologies (computed tomography, magnetic resonance imaging, transcranial or carotid Doppler sonography) or claims for rehabilitation and anti-coagulation prescriptions customarily used for ischemic stroke; or (b) records of three or more consecutive outpatient visits with the above codes and claims for examinations, services, or prescriptions as described in (a) [24]. A reproducibility study found that the ICD-9 stroke codes from the Taiwan National Health Research Institutes at hospital discharge were highly accurate with a substantial kappa test [26]. Furthermore, prior studies have shown that the algorithms using ICD-9 diagnostic codes have a positive predictive value (>95%) for heart failure hospitalizations [26,30].

MACE included nonfatal myocardial infarction (ICD-9-CM code 410.x) [26], coronary artery bypass grafts, and percutaneous transluminal coronary angioplasty [31]. Records of coronary artery bypass grafts and angiography were reliable because they were constructed based on NHI procedure codes that were tied to the audited NHI reimbursement system. In Taiwan, patients who continue dialysis for >90 days receive a catastrophic illness registration card, which ensures the accuracy of our dialysis continuation definition.

2.5. Statistical Analysis

Continuous variables were compared using an unpaired t-test and are expressed as a mean $\pm$ standard deviation (SD). Categorical variables were compared using the χ^2 test and expressed as a percentage.

Given the differences in baseline characteristics and the risk of cardiovascular disease between the incident COPD and non-COPD groups, we matched COPD patients to non-COPD patients using a greedy matching algorithm with a caliper width of 0.2 SDs of the log of the odds of the estimated propensity score with a 1:1 ratio (Supplementary Table S1). Crude hazard ratios (HR) with 95% confidence intervals (CIs) for the outcomes of interest were derived from Cox proportional hazards models. Matched individuals without COPD constituted the reference group. Because of the high mortality rate in patients with COPD after AKI-D, competing risk regression was also performed using the Fine and Gray model considering the subdistribution hazard [32,33]. We used R software version 2.8.1 (Free Software Foundation, Inc., Boston, MA, USA) for the time-varying Cox model and Stata/MP

version 14 (Stata Corporation, Lakeway Drive College Station, TX, USA) for the competing risk analysis. Two-sided p values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the Study Population

A total of 14,871 individuals after short-term dialysis who survived after hospital discharge were eligible. Among these patients, incident COPD was identified in 1535 (10.7%); 557 with recorded previous asthma or COPD medication prescriptions were excluded. The remaining 12,779 patients were non-COPD controls (Figure 1). The mean age of the COPD group was 73.91 ± 11.25 years, and the proportion of men was 66.94%. After propensity score matching, we identified 1473 patients with COPD and 1473 matched controls with similar baseline characteristics. Detailed demographic information of the individuals with or without COPD before and after propensity score matching is shown in Table 1 and Supplementary Figure S1.

Table 1. AKI patients after temporary dialysis with and without COPD, before and after propensity score matching.

	Before Matching			After Matching		
	Non COPD (n = 12,779)	COPD (n = 1535)	p-Value	Non COPD (n = 1473)	COPD (n = 1473)	p-Value
Age (year, SD)	63.63 ± 16.39	74.02 ± 11.31	<0.001	73.95 ± 11.28	73.91 ± 11.25	0.888
Male gender	6715 (52.55%)	1044 (68.01%)	<0.001	960 (65.17%)	986 (66.94%)	0.331
Monthly income, US dollars						
<600	7865 (61.55%)	923 (60.13%)		903 (61.30%)	890 (60.42%)	
600–1300	4484 (35.09%)	581 (37.85%)	0.004	530 (35.98%)	554 (37.61%)	0.304
≥1300	430 (3.36%)	31 (2.02%)		40 (2.72%)	29 (1.97%)	
Hospital location						
Urban	5276 (41.29%)	604 (39.35%)		559 (37.95%)	579 (39.31%)	
Suburban	2947 (23.06%)	320 (20.85%)	0.005	311 (21.11%)	312 (21.18%)	0.696
Rural	4556 (35.65%)	611 (39.80%)		603 (40.94%)	582 (39.51%)	
Baseline comorbidities						
Charlson comorbidity index	2.17 ± 2.03	2.61 ± 2.06	<0.001	2.59 ± 2.09	2.61 ± 2.08	0.736
Myocardial infarction	542 (4.24%)	75 (4.89%)	0.232	68 (4.62%)	75 (5.09%)	0.607
Congestive heart failure	1956 (15.31%)	349 (22.74%)	<0.001	326 (22.13%)	336 (22.81%)	0.691
Peripheral vascular disease	244 (1.91%)	25 (1.63%)	0.487	29 (1.97%)	25 (1.70%)	0.681
Cerebrovascular disease	1382 (10.81%)	276 (17.98%)	<0.001	246 (16.70%)	256 (17.38%)	0.659
Dementia	315 (2.46%)	98 (6.38%)	<0.001	91 (6.18%)	91 (6.18%)	0.999
Reumatologic disease	243 (1.90%)	18 (1.17%)	0.043	16 (1.09%)	18 (1.22%)	0.863
Peptic ulcer disease	1791 (14.02%)	273 (17.79%)	<0.001	265 (17.99%)	259 (17.58%)	0.81
Hemiplegia or paraplegia	117 (0.92%)	26 (1.69%)	0.006	16 (1.09%)	26 (1.77%)	0.161
Diabetes	4956 (38.78%)	582 (37.92%)	0.524	544 (36.93%)	569 (38.63%)	0.362
Moderate or severe liver disease	1036 (8.11%)	98 (6.38%)	0.019	89 (6.04%)	94 (6.38%)	0.76
Chronic kidney disease	4034 (31.57%)	445 (28.99%)	0.041	447 (30.35%)	437 (29.67%)	0.718
Hypertension	6630 (51.88%)	950 (61.89%)	<0.001	889 (60.35%)	911 (61.85%)	0.427
Dyslipidemia	1765 (13.81%)	167 (10.88%)	0.001	185 (12.56%)	164 (11.13%)	0.254
Medication for hypertension before index hospitalization						
Alpha-blocker	1326 (10.38%)	206 (13.42%)	<0.001	201 (13.65%)	201 (13.65%)	0.999
Beta-blocker	4696 (36.75%)	509 (33.16%)	0.006	507 (34.42%)	494 (33.54%)	0.641
CCB	6807 (53.27%)	946 (61.63%)	<0.001	881 (59.81%)	903 (61.30%)	0.429
Diuretic	6657 (52.09%)	926 (60.33%)	<0.001	859 (58.32%)	887 (60.22%)	0.311
ACEI or ARB	5577 (43.64%)	767 (49.97%)	<0.001	719 (48.81%)	744 (50.51%)	0.376
Other medication						
Aspirin	1107 (8.66%)	163 (10.62%)	0.013	171 (11.61%)	156 (10.59%)	0.412
Clopidogrel	640 (5.01%)	107 (6.97%)	0.002	97 (6.59%)	105 (7.13%)	0.61
Ticlopidine	471 (3.69%)	76 (4.95%)	0.017	70 (4.75%)	74 (5.02%)	0.798
Dipyridamole	2851 (22.31%)	357 (23.26%)	0.4	358 (24.30%)	348 (23.63%)	0.698
Nitrate	93 (0.73%)	22 (1.43%)	0.006	19 (1.29%)	19 (1.29%)	0.999
Statin	2009 (15.72%)	191 (12.44%)	0.001	209 (14.19%)	184 (12.49%)	0.193
NSAID	6375 (49.89%)	859 (55.96%)	<0.001	822 (55.80%)	819 (55.60%)	0.941
PPI	1214 (9.50%)	201 (13.09%)	<0.001	165 (11.20%)	191 (12.97%)	0.158

Table 1. *Cont.*

	Before Matching			After Matching		
	Non COPD (*n* = 12,779)	**COPD (*n* = 1535)**	***p*-Value**	**Non COPD (*n* = 1473)**	**COPD (*n* = 1473)**	***p*-Value**
Index hospital comorbidity						
Cardiovascular	1148 (8.98%)	150 (9.77%)	0.301	153 (10.39%)	142 (9.64%)	0.539
Respiratory	2819 (22.06%)	635 (41.37%)	<0.001	602 (40.87%)	582 (39.51%)	0.475
Hepatic	267 (2.09%)	15 (0.98%)	0.002	22 (1.49%)	14 (0.95%)	0.24
Neurologic	250 (1.96%)	37 (2.41%)	0.247	35 (2.38%)	35 (2.38%)	0.999
Hematologic	201 (1.57%)	16 (1.04%)	0.121	17 (1.15%)	15 (1.02%)	0.859
Metabolic	365 (2.86%)	35 (2.28%)	0.219	41 (2.78%)	35 (2.38%)	0.561
ICU admission	8492 (66.45%)	1189 (77.46%)	<0.001	1141 (77.46%)	1130 (76.71%)	0.661
Operation	1314 (10.28%)	151 (9.84%)	0.624	136 (9.23%)	139 (9.44%)	0.899
Renal function status at AKD periods (1 year after index hospitalization)						
CKD	4958 (38.80%)	642 (41.82%)	0.023	532 (36.12%)	622 (42.23%)	0.001
Advanced CKD	2410 (18.86%)	206 (13.42%)	<0.001	199 (13.51%)	201 (13.65%)	0.957

All data were descripted as number (%), except mean age. Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; AKD, acute kidney disease; ARB, Angiotensin II receptor blockers; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; ICU, intensive care unit; NSAIDs, Non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitor; SD, standard deviation.

3.2. Long-Term Risks of Death, Stroke, and CHF

After a mean follow-up period of 3.32 years, a total of 1050 (71.28%) and 971 (65.92%) patients in the COPD and the non-COPD groups, respectively, died (Table 2). The incidences of all-cause mortality were 226.6 per 1000 person-years in the COPD group and 188.2 per 1000 person-years in the non-COPD group (Table 3). The disparity in all-cause mortality between the two groups was not statistically significant after adjusting the propensity score and renal function status during the AKD period (adjusted HR, 1.04; 95% CI, 0.96–1.14; $p = 0.331$).

Table 2. Long-term outcomes the first year after index hospitalization discharge.

Events	**Before Matching**			**After Matching**		
	Non-COPD (*n* = 12,779)	**COPD (*n* = 1535)**	***p*-Value**	**Non-COPD (*n* = 1473)**	**COPD (*n* = 1473)**	***p*-Value**
All-cause death	6931 (54.24%)	1096 (71.40%)	<0.001	971 (65.92%)	1050 (71.28%)	0.002
Stroke	1044 (8.17%)	172 (11.21%)	<0.001	121 (8.21%)	170 (11.54%)	0.003
Ischemic stroke	774 (6.06%)	144 (9.38%)	<0.001	95 (6.45%)	143 (9.71%)	0.001
Hemorrhagic stroke	327 (2.56%)	36 (2.35%)	0.668	30 (2.04%)	35 (2.38%)	0.616
CHF	2541 (19.88%)	458 (29.84%)	<0.001	296 (20.10%)	448 (30.41%)	<0.001
MACE *	802 (6.28%)	96 (6.25%)	0.999	87 (5.91%)	95 (6.45%)	0.592
ESRD	3362 (26.31%)	311 (20.26%)	<0.001	299 (20.30%)	302 (20.50%)	0.927

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; MACE, major adverse cardiovascular events; SD, standard deviation; * MACE includes myocardial infarction, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty.

Table 3. Incidence and risk of outcomes of interest among patients after temporary dialysis with and without chronic obstructive pulmonary disease.

	COPD			Non-COPD			Crude		Adjusted †		Compete Risk ††	
	Event	Person-Year	Incidence Rate (per 1000 Person-Years)	Event	Person-Year	Incidence Rate (per 1000 Person-Years)	HR (95%CI)	*p* Value	HR (95%CI)	*p* Value	sHR (95%CI)	*p* Value
Before Propensity Score Matching												
All-cause death	1096	4848.71	226.0	6931	57,368.8	120.8	1.55 [1.45,1.65]	<0.001	0.96 [0.90,1.04]	0.323	NA	NA
Stroke	172	4368.39	39.4	1044	53,890	19.4	1.70 [1.45,2.00]	<0.001	1.27 [1.06,1.53]	0.009	1.30 [1.07,1.56]	0.007
Ischemic stroke	144	4413.14	32.6	774	54,369.5	14.2	1.88 [1.57,2.24]	<0.001	1.33 [1.09,1.63]	0.006	1.37 [1.11,1.69]	0.004
Hemorrhagic stroke	36	4783.3	7.5	327	56,658.6	5.8	1.18 [0.84,1.67]	0.349	1.08 [0.74,1.57]	0.691	1.05 [0.72,1.54]	0.8
CHF	458	3769.6	121.5	2541	50,533.8	50.3	1.89 [1.71,2.09]	<0.001	1.37 [1.22,1.53]	<0.001	1.39 [1.24,1.56]	<0.001
MACE	127	4595.71	27.6	1127	54,737.5	20.6	1.20 [1.00,1.44]	0.055	0.89 [0.73,1.09]	0.270	0.89 [0.72,1.08]	0.240
ESRD	311	4073.25	76.4	3362	45,620.2	73.7	0.81 [0.72,0.91]	<0.001	0.90 [0.80,1.02]	0.102	0.91 [0.80,1.03]	0.120
After Propensity Score Matching												
All-cause death	1050	4633.13	226.6	971	5159.11	188.2	1.08 [0.99,1.17]	0.104	1.04 [0.96,1.14]	0.331	NA	NA
Stroke	170	4156.28	40.9	121	4788.18	25.3	1.45 [1.14,1.83]	0.002	1.42 [1.12,1.79]	0.004	1.43 [1.13,1.81]	0.003
Ischemic stroke	143	4201.03	34.0	95	4831.49	19.7	1.52 [1.17,1.97]	0.002	1.48 [1.14,1.92]	0.003	1.52 [1.17,1.97]	0.002
Hemorrhagic stroke	35	4567.72	7.7	30	5107.35	5.9	1.26 [0.77,2.05]	0.362	1.26 [0.77,2.05]	0.361	1.19 [0.73,1.96]	0.480
CHF	448	3583.99	125.0	296	4547.46	65.1	1.62 [1.40,1.88]	<0.001	1.59 [1.37,1.84]	<0.001	1.61 [1.39,1.86]	<0.001
MACE *	126	4391.31	28.7	116	4871.23	23.8	1.13 [0.87,1.45]	0.357	1.12 [0.87,1.44]	0.396	1.09 [0.84,1.40]	0.520
ESRD	302	3870.54	78.0	299	4367.31	68.5	0.97 [0.83,1.14]	0.695	0.96 [0.81,1.12]	0.579	0.95 [0.81,1.12]	0.550

CHF, congestive heart failure; CI, confidence interval; ESRD, end stage renal disease; HR, hazard ratio; MACE, major adverse cardiovascular events, NA, not available; sHR, subdistribution hazard ratio; * MACE includes myocardial infarction, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty. † Adjusted for propensity score and renal function status 1 year after index hospitalization. †† Death was calculated as a competing risk, adjusted for propensity score and renal function status 1 year after index hospitalization.

In contrast to the non-COPD group, the COPD group had a higher long-term risk of incident CHF (sHR, 1.61; 95% CI, 1.39–1.86; $p < 0.001$; Figure 2a) and ischemic stroke (sHR, 1.52; 95% CI, 1.17–1.97; $p = 0.002$; Figure 2b), but had a similar risk of hemorrhagic stroke (sHR, 1.19; 95% CI, 0.73–1.96; $p = 0.480$; Figure 2c) after considering mortality as a competing risk.

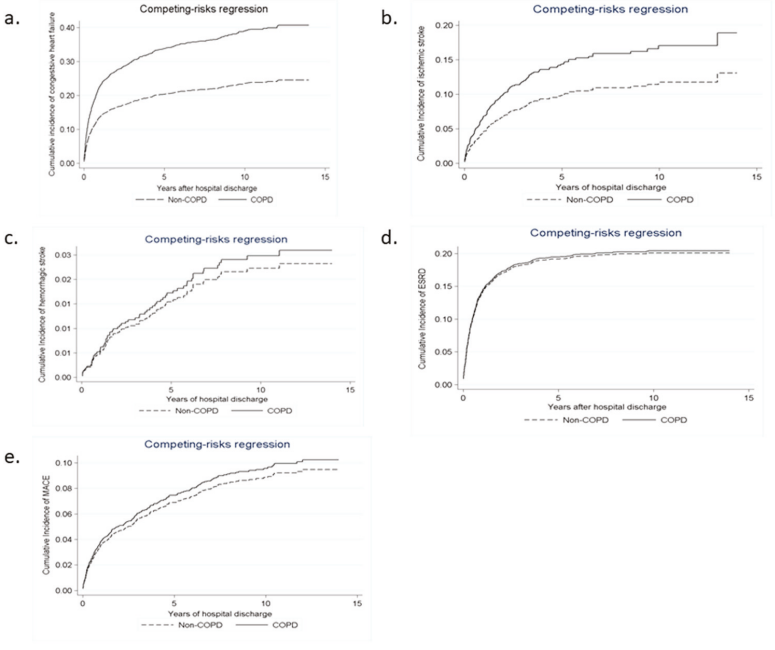

Figure 2. Cumulative probability of (**a**) congestive heart failure (HR 1.61; $p < 0.001$), (**b**) ischemic stroke (HR 1.52; $p = 0.002$), (**c**) hemorrhagic stroke (HR 1.19; $p = 0.480$), (**d**) end- stage renal disease (HR 0.95; $p = 0.550$), and (**e**) major adverse cardiovascular events (HR 1.09; $p = 0.520$) in the matched patients after acute kidney injury with or without chronic obstructive pulmonary disease, using mortality as a competing risk.

3.3. Long-Term Risks of MACE and ESRD

A total of 95 (6.45%) patients in the COPD group and 87 (5.91%) in the non-COPD group experienced MACE, but the difference was not statistically significant (Table 2; $p = 0.592$). The COPD group had similar risks of ESRD compared with the matched non-COPD group ($p = 0.927$). After adjusting for in-hospital death as a competing risk, the analysis yielded consistent results (Figure 2d,e). The subdistribution hazard ratio for MACE was 1.09 (95% CI, 0.84–1.40; $p = 0.520$) and 0.95 (95% CI, 0.81–1.12; $p = 0.550$) for ESRD (Table 3).

3.4. Subgroup Analysis with Comorbidities

A subgroup analysis of baseline characteristics and comorbidities was performed to investigate whether the COPD group consistently had a higher long-term risk of ischemic stroke and CHF compared to the non-COPD group. Using participant characteristics, we found that COPD was associated with a higher risk of ischemic stroke and CHF in most patients after AKI regardless of any prior history of COPD (Figure 3a,b).

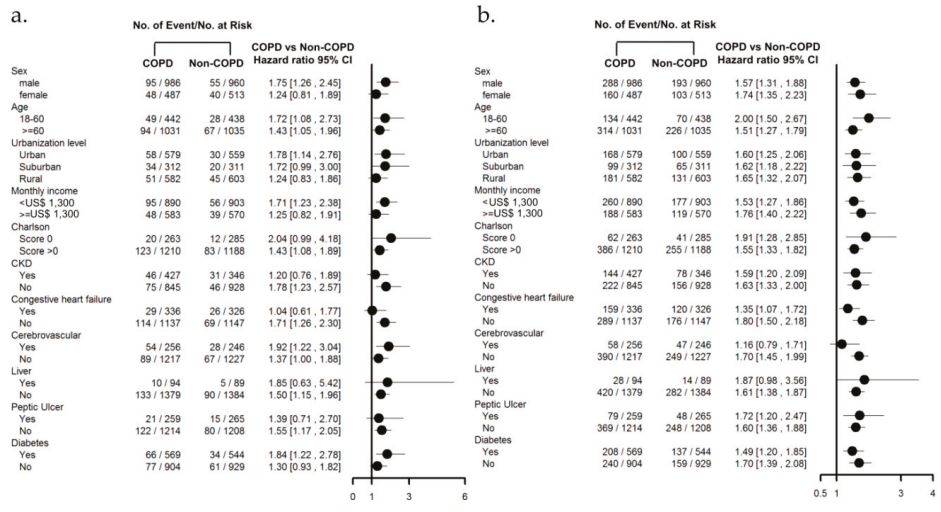

Figure 3. Risk of (**a**) ischemic stroke, and (**b**) congestive heart failure in matched patients after AKI with or without COPD using participant characteristics.

4. Discussion

In this large population-based group study, we found that more than one-tenth of patients were likely to have COPD early after temporary dialysis. In patients who recovered from AKI-D, concomitant COPD was associated with a higher risk of incident ischemic stroke and CHF; however, the risks of all-cause mortality, MACE, and ESRD were similar to those who did not have COPD. These results remained constant even after the identification of severe kidney sequelae during the AKD period and when accounting for death as a competing risk.

4.1. Risk of COPD after AKI-D

The current study revealed that 10.7% of patients who recovered from temporary dialysis were concomitantly diagnosed with COPD one year after index hospitalization. To our knowledge, this is the first study addressing the incidence of COPD after AKI-D. The age-standardized reported prevalence of COPD was 3.2% in males and 2.0% in females [34]. A population-based study demonstrated that the diagnosis of COPD was recorded in 2.6% of hospitalized patients [35]. The incidence of COPD in patients with AKI-D is much higher than in the general population. Data from animal models support the supposition that cardiogenic pulmonary edema and non-cardiogenic pulmonary edema (from endothelial injury due to inflammation and apoptosis) can occur in AKI [36]. Lung inflammation is a consistent finding after ischemic AKI, especially after prolonged AKI with more than 7 days of dialysis [15]. Accumulated evidence from animal models and patients with AKI suggests that IL-6, IL-8, TNF, and caspase-3-mediated apoptosis are mediators of lung injury after AKI [36–38]. These cytokines play an important role in many immunopathological processes of COPD [39,40] and could lead to the development of COPD [40,41].

4.2. Stroke Risk in Patients with COPD after AKI-D

Our results further showed that patients with COPD after recovery from AKI-D, compared to those without COPD, have an approximately 52% increased risk of ischemic stroke. According to the results of our specificity analysis (Figure 3a), the incidence is especially high for male patients and for those with diabetes.

In patients with COPD, systemic inflammation secondary to pulmonary inflammation can elicit unstable atherosclerotic plaques and a pro-thrombotic status, with an eventual ischemic stroke [42,43]. Our findings raise the possibility that in AKI patients, COPD may further trigger a cascade of perturbations that never completely resolve. Some nontraditional risk factors such as endothelial dysfunction, impaired endothelial progenitor cells, oxidative stress, and inflammation during AKI may be involved in the pathogenic mechanisms of lung–kidney–brain interactions [44–46]. Acid–base disturbances in patients with COPD after AKI-D may also contribute to the increased risk of ischemic stroke. Acidemia fully protonates free fatty acids forming an oil phase that may fuse with the endothelium and initiate plaque formation [47]. Respiratory acidosis could further serve as a risk factor for thrombus formation [48] and involves the accumulation of serum calcium and phosphate ions which has a major influence on the vascular endothelium [49].

Soluble Klotho could exert multiple actions, including anti-oxidation, anti-senescence, autophagy, anti-apoptosis, and anti-fibrosis [50]. AKI is a state of acute Klotho deficiency. Klotho deficiency exerts multiple negative systemic effects on numerous organs including the cardiovascular system [51]. Importantly, Klotho expression was also reduced in lung alveolar macrophages and peripheral blood mononuclear cells of COPD patients [52]. The enhanced deficiency of Klotho in AKI patients superimposed with COPD will further lead to impaired endothelium-dependent vasodilation and impaired angiogenesis and is related to ischemic stroke [53] and cardiomyopathy [54].

4.3. CHF Risk in Patients with COPD after AKI-D

Our results also showed that patients with COPD after recovery from AKI-D have an approximately 61% increased risk of CHF compared with those without COPD. AKI itself could cause a number of systemic vascular endothelial alterations that impact cardiovascular health [55]. In type 3 cardiorenal syndrome, AKI can lead to cardiac dysfunction by fluid overload, electrolytes, acid–base shift, and renin-angiotensin-aldosterone system or central nervous system activation [7]. Among COPD patients, the prevalence of ventricular dysfunction was 12–17% [56,57]. Patients with COPD were more likely to develop new-onset heart failure during their hospital stay [58]. In addition, pulmonary hypertension is common in severe COPD and can lead to heart failure. Chronic severe hypoxia, on the other hand, increases plasma norepinephrine and aldosterone, but suppresses renin activity and causes salt and water retention in humans [59]. When COPD occurs in AKI-D patients, the compensatory role of the kidney and lung in acidosis is less effective, resulting in a more severe acidosis state which is known to reduce left ventricle contractility [60]. These are possible mechanisms by which COPD confers additional risks to CHF among AKI survivors.

Human neutrophil gelatinase-associated lipocalin (NGAL), initially identified as a protein isolated from the secondary granules of human neutrophils, is actively secreted by certain cells such as respiratory epithelial cells and renal tubule cells [61]. It was reported to be an important player in vascular remodeling, atherosclerotic plaque stability, and thrombus formation [62]. NGAL from neutrophils may drive COPD epithelial mesenchymal transitions [63] and could reflect the state of systemic inflammation in COPD. In light of this, plasma NGAL which supposedly accumulates in AKI patients with COPD during the AKD period, could serve as a predictor of stroke [64] and heart failure [65].

4.4. Risk of MI and ESRD in Patients with COPD after AKI-D

AKI as well as COPD increases the risk of MI [5,66]. However, our study showed that the incidence of MI was not further increased in AKI-D patients with COPD, as compared to those without COPD. This finding implies that shared risk factors of AKI and COPD accounts for much of the elevated risk, and that COPD does not confer a large additional risk. Similarly, previous research suggested that AKI is associated with an increased risk of ESRD [3]. Since AKI already has a strong association with MACE and ESRD, the presence of COPD adds little attributable risk of MACE and ESRD in the nationwide population.

4.5. Care of Patients with COPD after AKI-D

Clinicians should be alert to the presence of COPD among patients with AKI-D. AKI and COPD are now global health problems; however, the AKD period has not been listed as a clinically important consequence in clinical guidelines of lung diseases [67]. Findings of the current study are noteworthy from the perspective of a clinician caring for a patient with COPD after recovery from AKI-D. Attention should be given to the importance of raising awareness about the co-existence of COPD with AKI and cardiovascular risks. A public health initiative is needed to monitor and control subsequent adverse cardiovascular events, including ischemic stroke and CHF, among AKI-D patients with COPD especially after discharge. Optimizing the control of respiratory and uremic conditions, early detection of cardiovascular complications, and decreasing inflammatory status may be the best strategies for improving the quality of health care. Additionally, the pathophysiologic link between kidney and lung disease deserves further investigation, particularly during AKD care.

4.6. Limitation and Strength

A few clinical and research implications emerged from our study. The NHI database has a large national sample size, a long follow-up, and we used a propensity score method to reduce imbalances in key characteristics between COPD and non-COPD groups. The ICD-9-CM codes and procedure codes for AKI and COPD were well validated. Although smaller studies would need to rely on changes in estimated glomerular filtration rates or albuminuria as kidney end points, the availability of incident ESRD, major adverse cardiac events, and mortality as primary outcomes in this study is a notable strength. However, the present study has some limitations that should also be acknowledged. First, like all claims databases, the data describing lifestyle factors such as body mass index and smoking are not available, and residual confounding may be contributing to the association of COPD with outcomes. However, these missing confounding factors were adjusted by obesity and smoking-related disorders such as hyperlipidemia, hypertension, and ischemic heart disease. Second, the NHI research database does not contain information on several potential confounders, including nutritional conditions, proteinuria data, and the adequacy of glycemic, lipid, and blood pressure control. Finally, certain medications used by COPD patients may serve as potential confounders. For example, combined inhalers, containing a long-acting β2-agonist and an anticholinergic, when compared to monotherapy, were associated with an increased risk of heart failure [68].

5. Conclusions

In a large cohort study, more than one-tenth of the patients who recovered from AKI-D were diagnosed with COPD at their one-year follow-up. Adverse cardiovascular events including CHF and ischemic stroke are more prevalent in these patients; however, the risk of ESRD, myocardial infarction, or mortality are not different in patients with or without COPD. A public health initiative is needed to monitor and control subsequent adverse cardiovascular events among COPD patients during the AKD period, even those who have recovered from temporary dialysis.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/9/237/s1, Figure S1: Standardized difference between each covariate before and after propensity score matching, Table S1: Risk factors predicting COPD in AKI patients after temporary dialysis as components in the propensity score.

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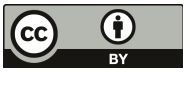
References

1. Ali, T.; Khan, I.; Simpson, W.; Prescott, G.; Townend, J.; Smith, W.; Macleod, A. Incidence and outcomes in acute kidney injury: A comprehensive population-based study. *J. Am. Soc. Nephrol.* **2007**, *18*, 1292–1298. [CrossRef] [PubMed]
2. Liangos, O.; Wald, R.; O'Bell, J.W.; Price, L.; Pereira, B.J.; Jaber, B.L. Epidemiology and outcomes of acute renal failure in hospitalized patients: A national survey. *Clin. J. Am. Soc. Nephrol.* **2006**, *1*, 43–51. [CrossRef] [PubMed]
3. Ishani, A.; Xue, J.L.; Himmelfarb, J.; Eggers, P.W.; Kimmel, P.L.; Molitoris, B.A.; Collins, A.J. Acute kidney injury increases risk of ESRD among elderly. *J. Am. Soc. Nephrol.* **2009**, *20*, 223–228. [CrossRef] [PubMed]
4. Waikar, S.S.; Winkelmayer, W.C. Chronic on acute renal failure: Long-term implications of severe acute kidney injury. *JAMA* **2009**, *302*, 1227–1229. [CrossRef] [PubMed]
5. Wu, V.C.; Wu, C.H.; Huang, T.M.; Wang, C.Y.; Lai, C.F.; Shiao, C.C.; Chang, C.H.; Lin, S.L.; Chen, Y.Y.; Chen, Y.M.; et al. Long-term risk of coronary events after AKI. *J. Am. Soc. Nephrol.* **2014**, *25*, 595–605. [CrossRef] [PubMed]
6. Wu, V.C.; Wu, P.C.; Wu, C.H.; Huang, T.M.; Chang, C.H.; Tsai, P.R.; Ko, W.J.; Chen, L.; Wang, C.Y.; Chu, T.S.; et al. The impact of acute kidney injury on the long-term risk of stroke. *J. Am. Heart Assoc.* **2014**, *3*, e000933. [CrossRef] [PubMed]
7. Husain-Syed, F.; McCullough, P.A.; Birk, H.W.; Renker, M.; Brocca, A.; Seeger, W.; Ronco, C. Cardio-pulmonary-renal interactions: A multidisciplinary approach. *J. Am. Coll. Cardiol.* **2015**, *65*, 2433–2448. [CrossRef] [PubMed]
8. Wu, V.C.; Shiao, C.C.; Chang, C.H.; Huang, T.M.; Lai, C.F.; Lin, M.C.; Chiang, W.C.; Chu, T.S.; Wu, K.D.; Ko, W.J.; et al. Long-term outcomes after dialysis-requiring acute kidney injury. *Biomed. Res. Int.* **2014**, *2014*, 365186. [CrossRef] [PubMed]
9. Goldstein, S.L.; Jaber, B.L.; Faubel, S.; Chawla, L.S.; Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: A potential opportunity to detect and prevent CKD. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 476–483. [CrossRef] [PubMed]
10. Attanasio, C.; Latancia, M.T.; Otterbein, L.E.; Netti, P.A. Update on renal replacement therapy: Implantable artificial devices and bioengineered organs. *Tissue Eng. Part B Rev.* **2016**, *22*, 330–340. [CrossRef] [PubMed]
11. Anthonisen, N.R.; Connett, J.E.; Enright, P.L.; Manfreda, J.; Lung Health Study Research Group. Hospitalizations and mortality in the lung health study. *Am. J. Respir. Crit. Care Med.* **2002**, *166*, 333–339. [CrossRef] [PubMed]
12. Hansell, A.L.; Walk, J.A.; Soriano, J.B. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur. Respir. J.* **2003**, *22*, 809–814. [CrossRef] [PubMed]
13. Chen, C.Y.; Liao, K.M. Chronic obstructive pulmonary disease is associated with risk of chronic kidney disease: A nationwide case-cohort study. *Sci. Rep.* **2016**, *6*, 25855. [CrossRef] [PubMed]
14. Virzi, G.; Day, S.; de Cal, M.; Vescovo, G.; Ronco, C. Heart-kidney crosstalk and role of humoral signaling in critical illness. *Crit. Care* **2014**, *18*, 201. [CrossRef] [PubMed]
15. Andres-Hernando, A.; Altmann, C.; Bhargava, R.; Okamura, K.; Bacalja, J.; Hunter, B.; Ahuja, N.; Soranno, D.; Faubel, S. Prolonged acute kidney injury exacerbates lung inflammation at 7 days post-acute kidney injury. *Physiol. Rep.* **2014**, *2*, e12084. [CrossRef] [PubMed]

16. Chawla, L.S.; Bellomo, R.; Bihorac, A.; Goldstein, S.L.; Siew, E.D.; Bagshaw, S.M.; Bittleman, D.; Cruz, D.; Endre, Z.; Fitzgerald, R.L.; et al. Acute kidney disease and renal recovery: Consensus report of the acute disease quality initiative (ADQI) 16 workgroup. *Nat. Rev. Nephrol.* **2017**, *13*, 241–257. [CrossRef] [PubMed]
17. Chao, C.T.; Hou, C.C.; Wu, V.C.; Lu, H.M.; Wang, C.Y.; Chen, L.; Kao, T.W. The impact of dialysis-requiring acute kidney injury on long-term prognosis of patients requiring prolonged mechanical ventilation: Nationwide population-based study. *PLoS ONE* **2012**, *7*, e50675. [CrossRef] [PubMed]
18. Wang, W.J.; Chao, C.T.; Huang, Y.C.; Wang, C.Y.; Chang, C.H.; Huang, T.M.; Lai, C.F.; Huang, H.Y.; Shiao, C.C.; Chu, T.S.; et al. The impact of acute kidney injury with temporary dialysis on the risk of fracture. *J. Bone Miner. Res.* **2013**, *29*, 676–684. [CrossRef] [PubMed]
19. Wu, P.C.; Wu, C.J.; Lin, C.J.; Wu, V.C.; National Taiwan University Study Group on Acute Renal Failure Group. Long-term risk of upper gastrointestinal hemorrhage after advanced AKI. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 353–362. [CrossRef] [PubMed]
20. Li, C.H.; Chen, W.C.; Liao, W.C.; Tu, C.Y.; Lin, C.L.; Sung, F.C.; Chen, C.H.; Hsu, W.H. The association between chronic obstructive pulmonary disease and Parkinson's disease: A nationwide population-based retrospective cohort study. *QJM* **2015**, *108*, 39–45. [CrossRef] [PubMed]
21. Huang, J.Y.; Jian, Z.H.; Nfor, O.N.; Ku, W.Y.; Ko, P.C.; Lung, C.C.; Ho, C.C.; Pan, H.H.; Huang, C.Y.; Liang, Y.C.; et al. The effects of pulmonary diseases on histologic types of lung cancer in both sexes: A population-based study in Taiwan. *BMC Cancer* **2015**, *15*, 834. [CrossRef] [PubMed]
22. Liao, K.M.; Chen, C.Y. Incidence and risk factors of atrial fibrillation in Asian COPD patients. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2017**, *12*, 2523–2530. [CrossRef] [PubMed]
23. Wu, V.C.; Hu, Y.H.; Wu, C.H.; Kao, C.C.; Wang, C.Y.; Yang, W.S.; Lee, H.H.; Chang, Y.S.; Lin, Y.H.; Wang, S.M.; et al. Administrative data on diagnosis and mineralocorticoid receptor antagonist prescription identified patients with primary aldosteronism in Taiwan. *J. Clin. Epidemiol.* **2014**, *67*, 1139–1149. [CrossRef] [PubMed]
24. Wu, C.S.; Lai, M.S.; Gau, S.S.; Wang, S.C.; Tsai, H.J. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. *PLoS ONE* **2014**, *9*, e112257. [CrossRef] [PubMed]
25. Chu, Y.T.; Wu, S.C.; Lee, Y.C.; Lai, M.S.; Tam, S.C. Assessing measures of comorbidity using national health insurance databases. *Taiwan J. Public Health* **2010**, *29*, 191–200.
26. Cheng, C.L.; Kao, Y.H.; Lin, S.J.; Lee, C.H.; Lai, M.L. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol. Drug Saf.* **2011**, *20*, 236–242. [CrossRef] [PubMed]
27. Wu, C.H.; Yang, Y.W.; Hung, S.C.; Kuo, K.L.; Wu, K.D.; Wu, V.C.; Hsieh, T.C.; National Taiwan University Study Group on Acute Renal Failure. Ketoanalogues supplementation decreases dialysis and mortality risk in patients with anemic advanced chronic kidney disease. *PLoS ONE* **2017**, *12*, e0176847.
28. Ou, S.M.; Chen, Y.T.; Chao, P.W.; Lee, Y.J.; Liu, C.J.; Yeh, C.M.; Chen, T.J.; Chen, T.W.; Yang, W.C.; Li, S.Y. Nonsteroidal anti-inflammatory drug use is associated with cancer risk reduction in chronic dialysis patients. *Kidney Int.* **2013**, *84*, 198–205. [CrossRef] [PubMed]
29. Chen, H.J.; Bai, C.H.; Yeh, W.T.; Chiu, H.C.; Pan, W.H. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke* **2006**, *37*, 1060–1064. [CrossRef] [PubMed]
30. Go, A.S.; Lee, W.Y.; Yang, J.; Lo, J.C.; Gurwitz, J.H. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* **2006**, *296*, 2105–2111. [CrossRef] [PubMed]
31. Kip, K.E.; Hollabaugh, K.; Marroquin, O.C.; Williams, D.O. The problem with composite end points in cardiovascular studies: The story of major adverse cardiac events and percutaneous coronary intervention. *J. Am. Coll. Cardiol.* **2008**, *51*, 701–707. [CrossRef] [PubMed]
32. Wu, V.C.; Chang, C.H.; Wang, C.Y.; Lin, Y.H.; Kao, T.W.; Lin, P.C.; Chu, T.S.; Chang, Y.S.; Chen, L.; Wu, K.D.; et al. Risk of fracture in primary aldosteronism: A population-based cohort study. *J. Bone Miner. Res.* **2017**, *32*, 743–752. [CrossRef] [PubMed]
33. Wu, V.C.; Chueh, S.J.; Chen, L.; Chang, C.H.; Hu, Y.H.; Lin, Y.H.; Wu, K.D.; Yang, W.S.; Taiwan Primary Aldosteronism Investigation Study Group. Risk of new-onset diabetes mellitus in primary aldosteronism: A population study over 5 years. *J. Hypertens.* **2017**, *35*, 1698–1708. [CrossRef] [PubMed]

34. Soriano, J.B.; Abajobir, A.A.; Abate, K.H.; Abera, S.F.; Agrawal, A.; Ahmed, M.B.; Aichour, A.N.; Aichour, I.; Aichour, M.T.E.; Alam, K.; et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: A systematic analysis for the global burden of disease study 2015. *Lancet Respi. Med.* **2017**, *5*, 691–706. [CrossRef]
35. Baty, F.; Putora, P.M.; Isenring, B.; Blum, T.; Brutsche, M. Comorbidities and burden of COPD: A population based case-control study. *PLoS ONE* **2013**, *8*, e63285. [CrossRef] [PubMed]
36. Faubel, S.; Edelstein, C.L. Mechanisms and mediators of lung injury after acute kidney injury. *Nat. Rev. Nephrol.* **2016**, *12*, 48–60. [CrossRef] [PubMed]
37. Lie, M.L.; White, L.E.; Santora, R.J.; Park, J.M.; Rabb, H.; Hassoun, H.T. Lung T lymphocyte trafficking and activation during ischemic acute kidney injury. *J. Immunol.* **2012**, *189*, 2843–2851. [CrossRef] [PubMed]
38. Altmann, C.; Andres-Hernando, A.; McMahan, R.H.; Ahuja, N.; He, Z.; Rivard, C.J.; Edelstein, C.L.; Barthel, L.; Janssen, W.J.; Faubel, S. Macrophages mediate lung inflammation in a mouse model of ischemic acute kidney injury. *Am. J. Physiol. Ren. Physiol.* **2012**, *302*, 421–432. [CrossRef] [PubMed]
39. Caramori, G.; Adcock, I.M.; Di Stefano, A.; Chung, K.F. Cytokine inhibition in the treatment of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2014**, *9*, 397–412. [PubMed]
40. Pandey, K.C.; De, S.; Mishra, P.K. Role of proteases in chronic obstructive pulmonary disease. *Front. Pharmacol.* **2017**, *8*, 512. [CrossRef] [PubMed]
41. Martinez-Aguilar, N.E.; Vargas-Camano, M.E.; Hernandez-Pliego, R.R.; Chaia-Semerena, G.M.; Perez-Chavira, M.R. Immunopathology of chronic obstructive pulmonary disease. *Rev. Alerg. Mex.* **2017**, *64*, 327–346. [PubMed]
42. Polosa, R.; Malerba, M.; Cacciola, R.R.; Morjaria, J.B.; Maugeri, C.; Prosperini, G.; Gullo, R.; Spicuzza, L.; Radaeli, A.; Di Maria, G.U. Effect of acute exacerbations on circulating endothelial, clotting and fibrinolytic markers in COPD patients. *Intern. Emerg. Med.* **2013**, *8*, 567–574. [CrossRef] [PubMed]
43. Muir, K.W.; Tyrrell, P.; Sattar, N.; Warburton, E. Inflammation and ischaemic stroke. *Curr. Opin. Neurol.* **2007**, *20*, 334–342. [CrossRef] [PubMed]
44. Wu, V.C.; Young, G.H.; Huang, P.H.; Lo, S.C.; Wang, K.C.; Sun, C.Y.; Liang, C.J.; Huang, T.M.; Chen, J.H.; Chang, F.C.; et al. In acute kidney injury, indoxyl sulfate impairs human endothelial progenitor cells: Modulation by statin. *Angiogenesis* **2013**, *16*, 609–624. [CrossRef] [PubMed]
45. Bonventre, J.V. Pathophysiology of AKI: Injury and normal and abnormal repair. *Contrib. Nephrol.* **2010**, *165*, 9–17. [PubMed]
46. Hosohata, K. Role of oxidative stress in drug-induced kidney injury. *Int. J. Mol. Sci.* **2016**, *17*, 1826. [CrossRef] [PubMed]
47. Reis, A.H. Acidemia and blood free fatty acids: Analysis of cardiovascular risk factors in a new context. *Discov. Med.* **2017**, *23*, 183–188. [PubMed]
48. Gorter, K.A.; Stehouwer, M.C.; Van Putte, B.P.; Vlot, E.A.; Urbanus, R.T. Acidosis induced by carbon dioxide insufflation decreases heparin potency: A risk factor for thrombus formation. *Perfusion* **2017**, *32*, 214–219. [CrossRef] [PubMed]
49. Checherita, I.A.; David, C.; Ciocalteu, A.; Lascar, I.; Budala, L. Oral treatment of metabolic acidosis in hemodialyzed patients and the implications on the hemodynamic status. *Rom. J. Morphol. Embryol.* **2013**, *54*, 539–543. [PubMed]
50. Hu, M.C.; Shiizaki, K.; Kuro-o, M.; Moe, O.W. Fibroblast growth factor 23 and Klotho: Physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu. Rev. Physiol.* **2013**, *75*, 503–533. [CrossRef] [PubMed]
51. Hu, M.C.; Shi, M.; Cho, H.J.; Adams-Huet, B.; Paek, J.; Hill, K.; Shelton, J.; Amaral, A.P.; Faul, C.; Taniguchi, M.; et al. Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. *J. Am. Soc. Nephrol.* **2015**, *26*, 1290–1302. [CrossRef] [PubMed]
52. Li, L.; Wang, Y.; Gao, W.; Yuan, C.; Zhang, S.; Zhou, H.; Huang, M.; Yao, X. Klotho reduction in alveolar macrophages contributes to cigarette smoke extract-induced inflammation in chronic obstructive pulmonary disease. *J. Biol. Chem.* **2015**, *290*, 27890–27900. [CrossRef] [PubMed]
53. Majumdar, V.; Nagaraja, D.; Christopher, R. Association of the functional kL-VS variant of Klotho gene with early-onset ischemic stroke. *Biochem. Biophys. Res. Commun.* **2010**, *403*, 412–416. [CrossRef] [PubMed]

54. Xie, J.; Yoon, J.; An, S.W.; Kuro-o, M.; Huang, C.L. Soluble Klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. *J. Am. Soc. Nephrol.* **2015**, *26*, 1150–1160. [CrossRef] [PubMed]
55. Druml, W. Acute renal failure is not a "cute" renal failure! *Intensive. Care Med.* **2004**, *30*, 1886–1890. [CrossRef] [PubMed]
56. Griffo, R.; Spanevello, A.; Temporelli, P.L.; Faggiano, P.; Carone, M.; Magni, G.; Ambrosino, N.; Tavazzi, L.; Investigators, S. Frequent coexistence of chronic heart failure and chronic obstructive pulmonary disease in respiratory and cardiac outpatients: Evidence from suspirium, a multicentre Italian survey. *Eur. J. Prev. Cardiol.* **2017**, *24*, 567–576. [CrossRef] [PubMed]
57. Macchia, A.; Rodriguez Moncalvo, J.J.; Kleinert, M.; Comignani, P.D.; Gimeno, G.; Arakaki, D.; Laffaye, N.; Fuselli, J.J.; Massolin, H.P.; Gambarte, J.; et al. Unrecognised ventricular dysfunction in COPD. *Eur. Respir. J.* **2012**, *39*, 51–58. [CrossRef] [PubMed]
58. Agarwal, M.; Agrawal, S.; Garg, L.; Garg, A.; Bhatia, N.; Kadaria, D.; Reed, G. Effect of chronic obstructive pulmonary disease on in-hospital mortality and clinical outcomes after ST-segment elevation myocardial infarction. *Am. J. Cardiol.* **2017**, *119*, 1555–1559. [CrossRef] [PubMed]
59. Anand, I.S.; Chandrashekhar, Y.; Rao, S.K.; Malhotra, R.M.; Ferrari, R.; Chandana, J.; Ramesh, B.; Shetty, K.J.; Boparai, M.S. Body fluid compartments, renal blood flow, and hormones at 6000 m in normal subjects. *J. Appl. Physiol.* **1993**, *74*, 1234–1239. [CrossRef] [PubMed]
60. Walley, K.R.; Lewis, T.H.; Wood, L.D. Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output in dogs. *Circ. Res.* **1990**, *67*, 628–635. [CrossRef] [PubMed]
61. Mishra, J.; Ma, Q.; Prada, A.; Mitsnefes, M.; Zahedi, K.; Yang, J.; Barasch, J.; Devarajan, P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J. Am. Soc. Nephrol.* **2003**, *14*, 2534–2543. [CrossRef] [PubMed]
62. Solak, Y.; Yilmaz, M.I.; Siriopol, D.; Saglam, M.; Unal, H.U.; Yaman, H.; Gok, M.; Cetinkaya, H.; Gaipov, A.; Eyileten, T.; et al. Serum neutrophil gelatinase-associated lipocalin is associated with cardiovascular events in patients with chronic kidney disease. *Int. Urol. Nephrol.* **2015**, *47*, 1993–2001. [CrossRef] [PubMed]
63. Wang, Y.; Jia, M.; Yan, X.; Cao, L.; Barnes, P.J.; Adcock, I.M.; Huang, M.; Yao, X. Increased neutrophil gelatinase-associated lipocalin (NGAL) promotes airway remodelling in chronic obstructive pulmonary disease. *Clin. Sci. (Lond).* **2017**, *131*, 1147–1159. [CrossRef] [PubMed]
64. Hasegawa, M.; Ishii, J.; Kitagawa, F.; Takahashi, H.; Sugiyama, K.; Tada, M.; Kanayama, K.; Takahashi, K.; Hayashi, H.; Koide, S.; et al. Plasma neutrophil gelatinase-associated lipocalin as a predictor of cardiovascular events in patients with chronic kidney disease. *BioMed Res. Int.* **2016**, *2016*, 8761475. [CrossRef] [PubMed]
65. Nymo, S.H.; Ueland, T.; Askevold, E.T.; Flo, T.H.; Kjekshus, J.; Hulthe, J.; Wikstrand, J.; McMurray, J.; Van Veldhuisen, D.J.; Gullestad, L.; et al. The association between neutrophil gelatinase-associated lipocalin and clinical outcome in chronic heart failure: Results from CORONA*. *J. Intern. Med.* **2012**, *271*, 436–443. [CrossRef] [PubMed]
66. Donaldson, G.C.; Hurst, J.R.; Smith, C.J.; Hubbard, R.B.; Wedzicha, J.A. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* **2010**, *137*, 1091–1097. [CrossRef] [PubMed]
67. Qaseem, A.; Wilt, T.J.; Weinberger, S.E.; Hanania, N.A.; Criner, G.; van der Molen, T.; Marciniuk, D.D.; Denberg, T.; Schunemann, H.; Wedzicha, W.; et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann. Int. Med.* **2011**, *155*, 179–191. [CrossRef] [PubMed]
68. Suissa, S.; Dell'Aniello, S.; Ernst, P. Concurrent use of long-acting bronchodilators in COPD and the risk of adverse cardiovascular events. *Eur. Respir. J.* **2017**, *49*. [CrossRef] [PubMed]



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Renal Tubular TRPA1 as a Risk Factor for Recovery of Renal Function from Acute Tubular Necrosis

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Abstract: Background: Transient receptor potential ankyrin 1 (TRPA1), a redox-sensing Ca^{2+}-influx channel, serves as a gatekeeper for inflammation. However, the role of TRPA1 in kidney injury remains elusive. Methods: The retrospective cohort study recruited 46 adult patients with acute kidney injury (AKI) and biopsy-proven acute tubular necrosis (ATN) and followed them up for more than three months. The subjects were divided into high- and low-renal-tubular-TRPA1-expression groups for the comparison of the total recovery of renal function and mortality within three months. The significance of TRPA1 in patient prognosis was evaluated using Kaplan–Meier curves and logistic regression analysis. Results: Of the 46 adult AKI patients with ATN, 12 totally recovered renal function. The expression level of tubular TRPA1 was detected by quantitative analysis of the immunohistochemistry of biopsy specimens from ATN patients. The AKI patients with high tubular TRPA1 expression showed a high incidence of nontotal renal function recovery than those with low tubular TRPA1 expression (OR = 7.14; 95%CI 1.35–37.75; $p = 0.02$). High TRPA1 expression was independently associated with nontotal recovery of renal function (adjusted OR = 6.86; 95%CI 1.26–37.27; $p = 0.03$). Conclusion: High tubular TRPA1 expression was associated with the nontotal recovery of renal function. Further mechanistic studies are warranted.

Keywords: acute kidney injury; acute tubular necrosis; TRPA1; recovery of renal function

1. Introduction

Acute kidney injury (AKI) is characterized by a sharp decline in the glomerular filtration rate and manifests as azotemia [1,2]. A large portion of patients with severe complications of AKI requires renal replacement therapy [3]. AKI also results in serious health burdens because of its association with high morbidity and mortality [4]. Patients with AKI are at risk of chronic kidney disease (CKD). Over the

years, most severe CKD eventually proceeds to end-stage renal disease (ESRD) [5–7]. If available, immediate treatment of AKI would not only reduce morbidity and mortality, but also subsequent CKD.

Acute tubular necrosis (ATN), including renal tubular cell damage and death, is the most common cause of AKI in hospitalized patients. ATN can be precipitated by acute ischemic or toxic event or sepsis [8]. Oxidative stress plays a crucial role in the pathophysiology of ATN [9]. Oxidative stress characterized by increases in reactive oxygen species (ROS) and/or reactive nitrogen species after an insult to the kidneys can initiate a complex mechanism that directly or indirectly leads to tubular injury [10,11]. However, a valid antioxidant treatment for AKI remains lacking [12].

Transient receptor potential ankyrin 1 (TRPA1) is a nonselective transmembrane cation channel involving Ca^{2+} permeability, which can be activated by toxic or inflammatory mediators, such as ROS [13]. Previous studies reported that TRPA1 in neurons acts as a gatekeeper of inflammation [14]. Recent studies have shown that TRPA1 is expressed in various types of non-neuronal cells, including renal tubular cells [15]. Activation of TRPA1 in these non-neuronal cells may aggravate the inflammatory response [16,17]. However, two experimental animal studies suggested that TRPA1 protects against sepsis or angiotensin-II induced kidney injury [18,19]. Consequently, the role of renal TRPA1 in AKI is not exactly known.

The present study identified the association between renal tubular TRPA1 expression with oxidative stress, which is an activator of TRPA1, and the severity of renal injury in patients with ATN. It also investigated the association of tubular TRPA1 expression with total recovery of renal function and mortality.

2. Materials and Methods

2.1. Study Design and Participants

We retrospectively enrolled 52 adult inpatients with AKI and biopsy-proven ATN at Changhua Christian Hospital on 1 January 2000. The biopsy-proven ATN patients who meet the criteria of Acute Kidney Injury Network (AKIN) and were aged ≥18 years were included. The AKI inpatients admitted due to obstructive etiologies (as determined by renal ultrasound), chronic dialysis patients, kidney transplant recipients, and patients with active malignancy were excluded. Each patient was followed up for three months so that renal recovery from AKI could be assessed. Six patients who underwent follow-up for less than three months were excluded; hence, 46 patients were finally selected for further investigation. In addition, six patients with normal renal function and no other remarkable comorbidities underwent nephrectomy for localized circumscribed tumors and the uninvolved poles of their removed kidneys were regarded as normal renal tissues. The study was approved by the Institutional Review Board of Changhua Christian Hospital (approval number 150912). Written informed consent was obtained from all subjects.

Renal function was measured during follow-up visits until total recovery of estimated glomerular filtration rate (eGFR), death, or the end of follow-up. The endpoint was the total (return to baseline eGFR, within a 10% margin of error) recovery of eGFR within three months following AKI and mortality. Baseline renal function was determined from the last available serum creatinine value within one year before hospitalization or the lowest inpatient serum creatinine value after AKI if outpatient serum creatinine value was unavailable.

Demographic data, including gender, age, comorbidities, and medications, as well as urine protein excretion rate measured by the urine protein-to-creatinine ratio, were recorded at the time of AKI. Heart failure included the diagnoses of congestive or systolic heart failure, diastolic heart failure, or cardiomyopathy based on the manual review of medical charts before or at the time of AKI. The diagnosis of diabetes mellitus was based on the American Diabetes Association criteria, and hypertension was dependent on medical history and/or the use of antihypertensive medication.

2.2. Laboratory Data

Serum levels of hemoglobin, creatinine, albumin, total cholesterol, triglyceride, uric acid, sodium, and potassium and urine levels of creatinine and protein were measured in accordance with standardized procedures at the Department of Laboratory Medicine, Changhua Christian Hospital. eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, was utilized to evaluate renal function.

2.3. Immunohistochemistry (IHC)

Formalin-fixed, paraffin-embedded renal tissue sections (4 μm) were placed on coated slides, dewaxed with xylene, and rehydrated in serial dilutions of alcohol, followed by washing with phosphate buffered saline solution. Activity of endogenous peroxidase was blocked by incubation in 3% H_2O_2. Antigen retrieval was performed by boiling in 10 mM citrate buffer for 20 min. The slides were washed three times with PBS after incubation with rabbit polyclonal anti-TRPA1 antibodies (Alomone Labs., Jerusalen, Israel) at 1:2000 dilution and mouse monoclonal 8-hydroxy-2′-deoxyguanosine antibodies (ab48508, Abcam, Cambridge, MA, USA) at 1:500 dilution for 30 min at room temperature, respectively. The reaction was visualized using the polymer-based MACH4 DAB Detection Kit (Biocare Medical, Concord, CA, USA) in accordance with the manufacturer's instructions, and the slides were incubated with horseradish peroxidase/Fab polymer conjugate for another 30 min. Finally, peroxidase activity was visualized by incubation with 3,3′-diaminobenzidine tetrahydrochloride (DAB) as the substrate for 5 min and hematoxylin as the counterstain.

Computer-assisted quantitative analysis was performed as previously described. In brief, we randomly selected at least five glomeruli and 10 nonoverlapping high-power fields for each renal cortical section and captured images by Olympus Microscope BX51 (Olympus, Tokyo, Japan) equipped with a digital color camera (DP21; Olympus, Tokyo, Japan). The captured images were then analyzed using Image Pro-Plus software (Version 6.0; Media Cybernetics, Silver Spring, MD, USA). Quantitative immunohistochemical staining value was calculated as the integrated optical density divided by the total area occupied by the DAB-stained and hematoxylin-stained cells of each slide [20].

2.4. Histopathology

Formalin-fixed, paraffin-embedded renal tissues including ATN and normal control were sectioned at 4 μm thickness and stained for histological examination. These sections were stained with a periodic acid-Schiff staining kit (Merck Millipore, Billerica, MA, USA) and Masson's trichrome Kit (American Master Tech Scientific, Lodi, CA, USA) to determine the severity of tubular injury and percentage of interstitial fibrosis, respectively. All sections were examined by a pathologist (T.-C.S.) unaware of the clinical and laboratory data. The characteristics of tubular injury included tubular cell swelling, loss of brush border, or nuclear condensation. The severity of tubular injury was scored from 0 to 4 according to the percentage of the injured area of the section (0—no change; 1—changes affecting 1–25%; 2—changes affecting 25–50%; 3—changes affecting 50–75%; 4—changes affecting 75–100% of the section).

2.5. Statistical Analysis

Results are expressed as a percentage, median (interquartile range, IQR), or mean ± standard deviation. Kolmogorov–Smirnov test was utilized for all variables to test normal distribution. Non-normally distributed variables were analyzed by nonparametric statistical tests. Mann–Whitney U test and Pearson's chi-squared test or Fisher's exact test were performed to compare two groups for continuous and categorical variables, respectively. We performed univariate logistic regression analysis to calculate the crude of odds ratio (OR) of nonrecovery of total renal function or death within three months after ATN for all variables. Subsequently, multivariate logistic regression analysis was performed to calculate the adjusted OR for age, sex, and each variable. We calculated the cumulative

incidences of mortality and total recovery of renal function during the follow-up period by using the Kaplan–Meier method and compared the results between the high and low TRPA1 expression groups by using the log-rank test. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was considered at $p < 0.05$ in two-tailed tests.

3. Results

3.1. Demographic and Clinical Characteristics of Patients

Fifty-two patients with biopsy-proven ATN were enrolled in the retrospective cohort study. Of the 52 patients, six were excluded because of follow-up less than three months. No patients started dialysis at the time of kidney biopsy. During the follow-up period, 12 patients (26.09%) completely recovered renal function. Among the 34 patients (73.91%) without complete recovery of renal function, 10 patients (21.74%) died, as seen in Figure 1. Table 1 shows the baseline demographic, laboratory data, and renal histopathology of the ATN patients. These patients are divided into patients with complete recovery of renal function (recovery group, $n = 12$) and those without complete recovery of renal function (nonrecovery or death group, $n = 34$). Patients of both groups were similar in age; gender distribution; presence of diabetic mellitus, hypertension, and heart failure; severity of AKI; levels of serum albumin, cholesterol, triglyceride, uric acid, sodium, and potassium; scores of tubular injury and interstitial inflammation; percentage of interstitial fibrosis; use of angiotensin-converting-enzyme inhibitors or angiotensin-II receptor blockers; and immunosuppressive treatment. Compared with the nonrecovery group, the complete recovery group had lower baseline serum creatinine level, higher baseline eGFR and hemoglobin levels, and lower percentage of tubular atrophy in the renal interstitium (all $p < 0.05$).

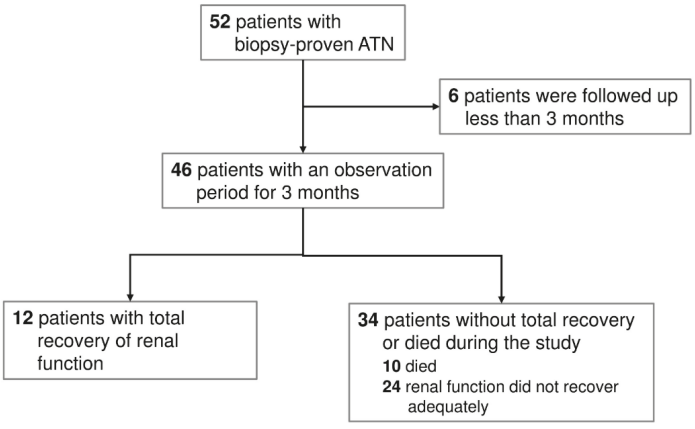

Figure 1. Flowchart presenting the selected biopsy-proven acute tubular necrosis (ATN) population.

Table 1. Baseline demographic and laboratory data and renal histopathology of acute tubular necrosis patients with and without total recovery of renal function within three months.

Characteristics	Total Recovery ($n = 12$)	Nonrecovery or Death [a] ($n = 34$)	p [b]
Demographics			
Age (years)	46.2 ± 21.7	56.8 ± 17.8	0.15 [b]
Male (n (%))	8 (66.7%)	21 (61.8%)	0.76 [c]
Diabetes mellitus (n (%))	1 (8.3%)	13 (38.2%)	0.05 [d]
Hypertension (n (%))	2 (16.7%)	10 (29.4%)	0.33 [d]
Heart failure (n (%))	0 (0%)	3 (8.8%)	0.39 [d]
Severity of AKI	3 (25%)	8 (23.5%)	0.60 [d]
AKIN stage I (n (%))	9 (75%)	26 (76.5%)	
AKIN stage II or III (n (%))	46.2 ± 21.7	56.8 ± 17.8	

Table 1. *Cont.*

Characteristics	Total Recovery (n = 12)	Nonrecovery or Death [a] (n = 34)	p [b]
Laboratory data			
Baseline serum creatinine (mg/dL)	1.0 (0.8–1.2)	1.5 (0.9–2.7)	0.03 [b]
Baseline eGFR (CKD-EPI) (mL/min/1.73m^2)	88.7 (64.7–113.5)	47.7 (20.7–87.5)	0.004 [b]
Urinary PCR (mg/g)	96.4 (30.0–976.0)	661.5 (100.0–5432.0)	0.05 [b]
Hemoglobin (g/dL)	11.7 (9.1–13.4)	9.6 (8.7–10.8)	0.03 [b]
Serum albumin (g/dL)	2.6 (1.8–3.2)	2.8 (2.2–3.3)	0.57 [b]
Serum cholesterol (mg/dL)	131 (119.0–260)	193 (157–252)	0.33 [b]
Serum triglyceride (mg/dL)	197.4 ± 132.6	165.6 ± 94.6	0.53 [b]
Serum uric acid (mg/dL)	8.6 (7.7–13.4)	8.4 (6.6–9.6)	0.44 [b]
Serum sodium (mmol/L)	137 (133.5–140.0)	133.5 (131–140)	0.51 [b]
Serum potassium (mmol/L)	4.4 (3.5–4.9)	3.9 (3.4–4.1)	0.15 [b]
Histopathology			
Tubular injury score	2 (1–3)	2 (1–4)	0.18 [b]
Tubular atrophy (%)	0 (0–1.5)	6 (3–10)	<0.001 [b]
Interstitial inflammation score	1 (0–1)	1 (1–1)	0.06 [b]
Interstitial fibrosis (%)	7.0 ± 4.9	10.4 ± 8.4	0.37 [b]
Medications			
ACEI or ARB (n (%))	2 (16.7%)	7 (20.6%)	0.57 [d]
Immunosuppressants (n (%))	2 (16.7%)	13 (38.2%)	0.16 [d]

Data are expressed as n (%) for categorical data and as mean ± standard deviation or median (interquartile range) for continuous data. AKI—acute kidney injury; AKIN—Acute Kidney Injury Network; CKD-EPI—Chronic Kidney Disease Epidemiology Collaboration; eGFR—estimated glomerular filtration rate; PCR—protein-to-creatinine ratio; ACEI—angiotensin-converting-enzyme inhibitors; ARB —angiotensin II receptor blockers. [a] Includes partial recoveries and nonrecoveries. [b] Mann–Whitney U test. [c] Pearson's chi-squared test. [d] Fisher's exact test.

3.2. Association of Tubular Expression of TRPA1 with Expression of 8-OHdG or Tubular Injury Score Among Patients with ATN and Normal Subjects

The expression of renal TRPA1 on renal biopsy specimen was significantly higher in the patients with ATN than in the normal controls, as seen in Figure 2A. These ATN patients with high expression of renal TRPA1 had higher expression of renal 8-OHdG than those with low expression of renal TRPA1, as seen in Figure 2A,B (p = 0.033). Moreover, the patients with ATN and high renal TRPA1 expression had severe tubular injury according to the tubular injury scoring scale compared with those with low renal TRPA1 expression, as seen in Figure 2A,C (p = 0.006).

3.3. Association of Tubular TRPA1 Expression with Complete Recovery of Renal Function

Our patients were divided into two groups according to renal tubular TRPA1 expression: those with high (n = 22) and low (n = 24) expression of renal tubular TRPA1. Kaplan–Meier analysis revealed a higher incidence of complete recovery of renal function during the three-month follow-up in the low TRPA1 expression group than in the high tubular TRPA1 expression group (p = 0.02), as seen in Figure 3. In univariable and age- and sex-adjusted logistical regression analysis, as seen in Table 2, high tubular TRPA1 expression remained significantly associated with noncomplete recovery of renal function during the three-month follow-up (p = 0.02, p = 0.03, respectively). Compared with the AKI patients with low tubular TRPA1 expression, the OR for noncomplete recovery of renal function during the three-month follow-up was 7.14 (95%CI 1.35–37.75) in the AKI patients with high tubular TRPA1 expression. After adjustment for age and gender, high expression of tubular TRPA1 remained a significant risk factor for noncomplete recovery of renal function during the three-month follow-up (adjusted OR 6.86; 95%CI 1.26–37.27). In addition to the high expression of TRPA1, univariable and age- and sex-adjusted logistical regression analysis found that high tubular atrophy, low baseline eGFR, and low level of hemoglobin were also significantly associated with noncomplete recovery of renal function during the three-month follow-up (all $p < 0.05$).

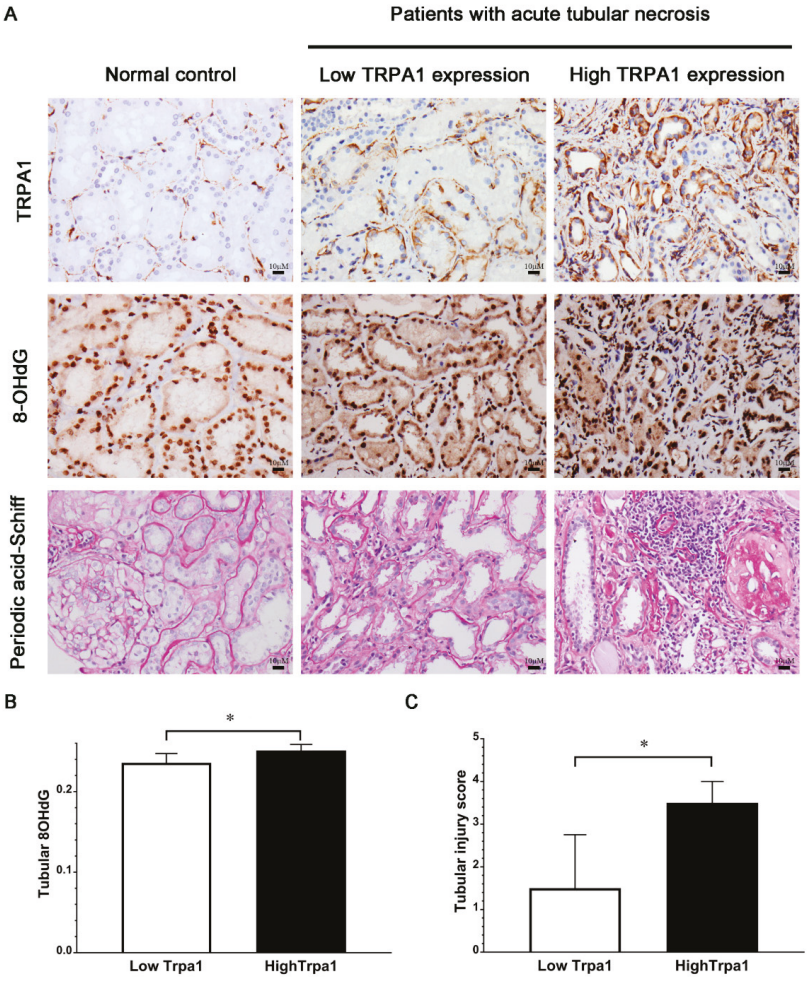

Figure 2. Different staining of kidney tissues from patients with ATN and association of TRPA1 expression with oxidative stress or tubular injury score. (**A**) Representative images of immunohistochemical staining of TRPA1, 8-OHdG, and periodic acid-Schiff staining of kidney tissues from patients with ATN and normal controls; 8-OHdG, an oxidative stress marker (**B**) QISV of tubular 8-OHdG (**C**) Tubular injury score. ATN patients were stratified into high and low expression groups by the cutoff value of 0.194 for tubular TRPA1 QISV based on the ROC curve analysis. Data are expressed as mean ± SD. * $p < 0.05$; TRPA1—Transient receptor potential ankyrin 1; 8-OHdG—8-hydroxy-2′-deoxyguanosine; QISV—quantitative immunohistochemical staining value; ROC—receiver operating characteristic; SD—standard deviation.

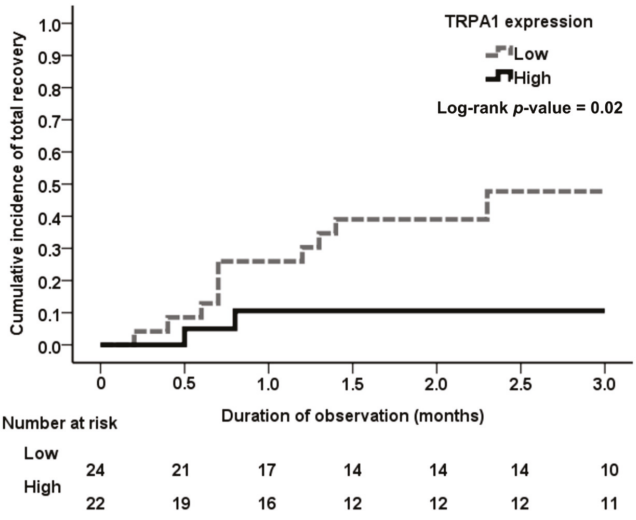

Figure 3. Cumulative incidence of total recovery of renal function among the ATN patients with different expression levels of tubular TRPA1. Incidence rate of the events of total recovery of renal function was significantly higher in the low tubular TRPA1 expression group than in the high tubular TRPA1 expression group during the follow-up period (log-rank test; $p = 0.02$).

Table 2. Logistical regression for nonrecovery of total renal function or death within three months after acute tubular necrosis.

Variables	Univariable		Model 1 (Adjusted for Age and Sex)	
	OR (95%CI)	*p* Value	OR (95%CI)	*p* Value
High tubular TRPA1 expression	7.14 (1.35–37.75)	0.02	6.86 (1.26–37.27)	0.03
Hypertension	2.08 (0.39–11.27)	0.39	1.84 (0.33–10.28)	0.49
Diabetes mellitus	6.81 (0.78–59.10)	0.08	5.34 (0.58–49.25)	0.14
Tubular atrophy (%)	1.96 (1.16–3.32)	0.01	2.01 (1.14–3.55)	0.02
Interstitial fibrosis (%)	1.08 (0.96–1.21)	0.19	1.06 (0.95–1.19)	0.29
Baseline eGFR (mL/min/1.73 m^2)	0.97 (0.94–0.99)	0.01	0.97 (0.95–0.99)	0.02
Urinary protein-to-creatinine ratio (10 mg/mg)	1.00 (1.00–1.01)	0.14	1.00 (1.00–1.01)	0.14
Hemoglobin (g/dL)	0.65 (0.45–0.93)	0.02	0.68 (0.47–0.99)	0.04
Concomitant use of ACEIs or ARBs	1.30 (0.23–7.32)	0.77	1.30 (0.22–7.80)	0.78
Concomitant use of immunosuppressants	3.10 (0.58–16.41)	0.18	4.41 (0.74–26.29)	0.10

OR—Odds ratio; CI—Confidence Interval; TRPA1—Transient receptor potential ankyrin 1; ACEI—Angiotensin-converting enzyme inhibitor; ARB—angiotensin-II receptor blocker; eGFR—estimated glomerular filtration rate.

3.4. Association of Tubular TRPA1 Expression with Mortality

Kaplan–Meier analysis revealed a higher incidence trend of mortality in ATN patients with high tubular TRPA1 expression during the three-month follow-up than in those with low tubular TRPA1 expression ($p = 0.07$), as seen in Figure 4.

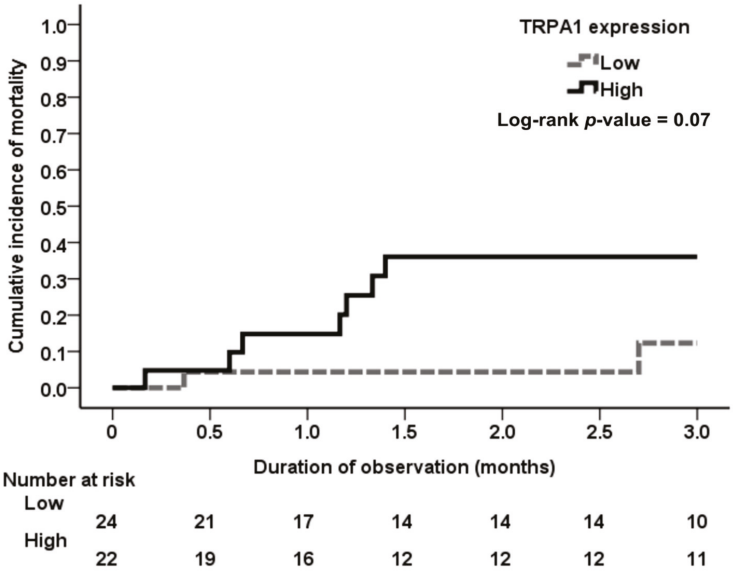

Figure 4. Cumulative incidence of mortality among the ATN patients with different expression levels of tubular TRPA1. Although ATN patients with high expression of tubular TRPA1 had a higher incidence of all-cause mortality than those with low expression of tubular TRPA1 during the follow-up period, the result was not statistically significant (log-rank test; $p = 0.07$). The severity of acute kidney injury may play a mediating role in all-cause mortality. Therefore, further research excluding the mediating factor is warranted.

4. Discussion

In this clinical observational study, TRPA1 was upregulated in the renal tubules of patients with ATN. In these patients with ATN, the tubular expression of TRPA1, a redox-sensing Ca^{2+}-influx channel [21], is positively associated with 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage and oxidative stress [22]. We also have demonstrated the positive correlation of TRPA1 expression level with the severity of tubular injury.

The generation of oxidative stress after AKI is a major determinant of AKI; however, the effects of AKI on the renal redox system remains elusive [23]. TRPA1, an oxidative stress-sensitive Ca^{2+}-permeable channel, can be activated by endogenous inflammatory agents produced on oxidative stress, such as H_2O_2, 4-hydroxynonenal, 4-oxononenal, and cyclopentenone prostaglandin 15-deoxy-delta (12,14)-prostaglandin J (2) (15d-PGJ(2)) [24,25]. Therefore, the positive correlation between TRPA1 expression and oxidative stress is expected.

TRPA1 is an oxidative sensor and gatekeeper for inflammation. However, the role of TRPA1 in tissue inflammation and injury remains controversial. Some studies demonstrated that TRPA1 promotes inflammation and tissue injury in neurons or non-neuronal cells [13,17,26–29]. By contrast, a few studies suggested that TRPA1 exerts antioxidative, anti-inflammatory, organ-protective effects [30,31]. Literature with regard to TRPA1 and AKI is limited. A recent experimental animal study has suggested that TRPA1 plays a protective role in Ang II-induced renal injury possibly by inhibiting macrophage-mediated inflammation [19]. Another experimental animal study demonstrated TRPA1 may protect against sepsis-induced kidney injury by modulating mitochondrial biogenesis and mitophagy [18]. However, our previous study showed that renal tubular epithelial TRPA1 may act as an oxidative stress sensor to mediate ischemia-reperfusion-induced kidney injury through

mitogen-activated protein kinases (MAPKs) and nuclear factor-*k*B (NF-*k*B) signaling. Thus, the role of TRPA1 in renal injury warrants further investigation.

In the present study, the AKI patients with high tubular TRPA1 expression had severe tubular injury. The result suggests that high TRPA1 expression in renal tubules may be a risk factor of tubular injury in AKI patients. However, the corresponding clinical role of renal tubular TRPA1 after AKI remains elusive. Therefore, we further investigated the association between clinical outcomes in AKI patients with ATN and TRPA1 expression in renal tubules.

The incidence of complete recovery of renal function was low in AKI patients with high expression of renal tubular TRPA1, and the patients with high expression of renal tubular TRPA1 had high odds of nonrecovery of renal function. This result suggests TRPA1 is associated with the progression of AKI to CKD. Progression of chronic kidney disease after acute kidney injury has a strong effect on long-term mortality [32]. As expected, the incidence of mortality in AKI patients with high TRPA1 expression was high because these patients had poor renal outcomes following AKI, although the result did not achieve statistical significance ($p = 0.07$) due to low case numbers.

The present study has several limitations. First, clinically, renal biopsy is not routinely performed in AKI patients, especially in AKI patients whose causes of AKI are known. Therefore, our results do not represent the association of TRPA1 with ATN in the total AKI population. Second, the relatively small sample size in the study lessens the statistical power of the results. Third, compared with prospective studies, retrospective cohort studies have lower statistical quality because of some unmeasured confounders. Fourth, although tubular 8-OHdG is an oxidative marker, it is not a direct activator of renal tubular TRPA1. Conversely, 4-hydroxy-2-nonenal (4-HNE) is an oxidative marker and a direct activator of renal tubular TRPA1 and thus requires further investigation to confirm the conclusion drawn from 8-OHdG staining. Fifth, this retrospective cohort study is correlational research, and thus cannot comprehensively elaborate on the causality of different expression levels of tubular TRPA1, tubular injury, and renal outcome. Therefore, the association of tubular TRPA1 expression with renal function or histopathology or clinical renal outcome of the different TRPA1 expression levels may be attributed to the severity of ATN. The role of tubular TRPA1 in AKI and its participatory mechanism in AKI remain to be elucidated. Further large prospective clinical studies or basic studies are warranted to investigate the biological role of TRPA1 in renal tubular injury after AKI.

In conclusion, high tubular TRPA1 expression was associated with a low probability of renal recovery in patients with ATN. High tubular TRPA1 expression was associated with the severity of tubular injury and poor renal outcomes following AKI. These findings suggest that tubular TRPA1 is a potential therapeutic target for AKI. The mechanism of TRPA1 in different AKI models warrants further investigation to confirm the roles of TRPA1 in AKI.

5. Conclusions

High renal tubular TRPA1 expression in AKI patients with biopsy-proven ATN was associated with the nontotal recovery of renal function.

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References

1. Gameiro, J.; Agapito Fonseca, J.; Jorge, S.; Lopes, J.A. Acute kidney injury definition and diagnosis: A narrative review. *J. Clin. Med.* **2018**, *7*, E307. [CrossRef] [PubMed]
2. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef] [PubMed]
3. Bagshaw, S.M.; Wald, R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Int.* **2017**, *91*, 1022–1032. [CrossRef] [PubMed]
4. Sawhney, S.; Fraser, S.D. Epidemiology of aki: Utilizing large databases to determine the burden of aki. *Adv. Chronic Kidney Dis.* **2017**, *24*, 194–204. [CrossRef] [PubMed]
5. Rangaswamy, D.; Sud, K. Acute kidney injury and disease: Long-term consequences and management. *Nephrology (Carlton)* **2018**, *23*, 969–980. [CrossRef]
6. Shiao, C.C.; Wu, P.C.; Wu, V.C.; Lin, J.H.; Pan, H.C.; Yang, Y.F.; Lai, T.S.; Huang, T.M.; Wu, C.H.; Yang, W.S.; et al. Nationwide epidemiology and prognosis of dialysis-requiring acute kidney injury (nep-aki-d) study: Design and methods. *Nephrology (Carlton)* **2016**, *21*, 758–764. [CrossRef]
7. Negi, S.; Koreeda, D.; Kobayashi, S.; Yano, T.; Tatsuta, K.; Mima, T.; Shigematsu, T.; Ohya, M. Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. *Semin. Dial.* **2018**, *31*, 519–527. [CrossRef]
8. Hanif, M.O.; Ramphul, K. Acute renal tubular necrosis. In *Statpearls*; StatePearls Publishing: Treasure Island, FL, USA, 2019.
9. Pavlakou, P.; Liakopoulos, V.; Eleftheriadis, T.; Mitsis, M.; Dounousi, E. Oxidative stress and acute kidney injury in critical illness: Pathophysiologic mechanisms-biomarkers-interventions, and future perspectives. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 6193694. [CrossRef]
10. Ratliff, B.B.; Abdulmahdi, W.; Pawar, R.; Wolin, M.S. Oxidant mechanisms in renal injury and disease. *Antioxid. Redox Signal.* **2016**, *25*, 119–146. [CrossRef]
11. Gorin, Y. The kidney: An organ in the front line of oxidative stress-associated pathologies. *Antioxid. Redox Signal.* **2016**, *25*, 639–641. [CrossRef]
12. de Caestecker, M.; Harris, R. Translating knowledge into therapy for acute kidney injury. *Semin. Nephrol.* **2018**, *38*, 88–97. [CrossRef] [PubMed]
13. Viana, F. Trpa1 channels: Molecular sentinels of cellular stress and tissue damage. *J. Physiol.* **2016**, *594*, 4151–4169. [CrossRef] [PubMed]
14. Bautista, D.M.; Pellegrino, M.; Tsunozaki, M. Trpa1: A gatekeeper for inflammation. *Ann. Rev. Physiol.* **2013**, *75*, 181–200. [CrossRef] [PubMed]
15. Dembla, S.; Hasan, N.; Becker, A.; Beck, A.; Philipp, S.E. Transient receptor potential a1 channels regulate epithelial cell barriers formed by mdck cells. *FEBS Lett.* **2016**, *590*, 1509–1520. [CrossRef] [PubMed]
16. Nassini, R.; Pedretti, P.; Moretto, N.; Fusi, C.; Carnini, C.; Facchinetti, F.; Viscomi, A.R.; Pisano, A.R.; Stokesberry, S.; Brunmark, C.; et al. Transient receptor potential ankyrin 1 channel localized to non-neuronal airway cells promotes non-neurogenic inflammation. *PLoS ONE* **2012**, *7*, e42454. [CrossRef] [PubMed]
17. Kanda, Y.; Yamasaki, Y.; Sasaki-Yamaguchi, Y.; Ida-Koga, N.; Kamisuki, S.; Sugawara, F.; Nagumo, Y.; Usui, T. Trpa1-dependent reversible opening of tight junction by natural compounds with an alpha,beta-unsaturated moiety and capsaicin. *Sci. Rep.* **2018**, *8*, 2251. [CrossRef] [PubMed]
18. Zhu, J.; Zhang, S.; Geng, Y.; Song, Y. Transient receptor potential ankyrin 1 protects against sepsis-induced kidney injury by modulating mitochondrial biogenesis and mitophagy. *Am. J. Transl. Res.* **2018**, *10*, 4163–4172.
19. Ma, S.; Zhang, Y.; He, K.; Wang, P.; Wang, D.H. Knockout of trpa1 exacerbates angiotensin ii-induced kidney injury. *Am. J. Physiol. Renal. Physiol.* **2019**, *317*, F623–F631. [CrossRef]
20. Tseng, W.C.; Yang, W.C.; Yang, A.H.; Hsieh, S.L.; Tarng, D.C. Expression of tnfrsf6b in kidneys is a novel predictor for progression of chronic kidney disease. *Mod. Pathol.* **2013**, *26*, 984–994. [CrossRef]
21. Nilius, B.; Appendino, G.; Owsianik, G. The transient receptor potential channel trpa1: From gene to pathophysiology. *Pflugers Arch.* **2012**, *464*, 425–458. [CrossRef]

22. Yokozawa, T.; Fujioka, K.; Oura, H. Increase in kidney 8-hydroxydeoxyguanosine level with the progression of renal failure. *Nephron* **1992**, *61*, 236–237. [CrossRef] [PubMed]
23. Kasuno, K.; Shirakawa, K.; Yoshida, H.; Mori, K.; Kimura, H.; Takahashi, N.; Nobukawa, Y.; Shigemi, K.; Tanabe, S.; Yamada, N.; et al. Renal redox dysregulation in aki: Application for oxidative stress marker of aki. *Am. J. Physiol. Renal. Physiol.* **2014**, *307*, F1342–F1351. [CrossRef] [PubMed]
24. Sawada, Y.; Hosokawa, H.; Matsumura, K.; Kobayashi, S. Activation of transient receptor potential ankyrin 1 by hydrogen peroxide. *Eur. J. Neurosci.* **2008**, *27*, 1131–1142. [CrossRef] [PubMed]
25. Weng, Y.; Batista-Schepman, P.A.; Barabas, M.E.; Harris, E.Q.; Dinsmore, T.B.; Kossyreva, E.A.; Foshage, A.M.; Wang, M.H.; Schwab, M.J.; Wang, V.M.; et al. Prostaglandin metabolite induces inhibition of trpa1 and channel-dependent nociception. *Mol. Pain* **2012**, *8*, 75. [CrossRef] [PubMed]
26. Fernandes, E.S.; Fernandes, M.A.; Keeble, J.E. The functions of trpa1 and trpv1: Moving away from sensory nerves. *Br. J. Pharmacol.* **2012**, *166*, 510–521. [CrossRef]
27. Bautista, D.M.; Jordt, S.E.; Nikai, T.; Tsuruda, P.R.; Read, A.J.; Poblete, J.; Yamoah, E.N.; Basbaum, A.I.; Julius, D. Trpa1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell* **2006**, *124*, 1269–1282. [CrossRef]
28. Feng, J.; Yang, P.; Mack, M.R.; Dryn, D.; Luo, J.; Gong, X.; Liu, S.; Oetjen, L.K.; Zholos, A.V.; Mei, Z.; et al. Sensory trp channels contribute differentially to skin inflammation and persistent itch. *Nat. Commun.* **2017**, *8*, 980. [CrossRef]
29. Lin, A.H.; Liu, M.H.; Ko, H.K.; Perng, D.W.; Lee, T.S.; Kou, Y.R. Lung epithelial trpa1 transduces the extracellular ros into transcriptional regulation of lung inflammation induced by cigarette smoke: The role of influxed ca(2)(+). *Mediators Inflamm.* **2015**, *2015*, 148367. [CrossRef]
30. Kun, J.; Szitter, I.; Kemeny, A.; Perkecz, A.; Kereskai, L.; Pohoczky, K.; Vincze, A.; Godi, S.; Szabo, I.; Szolcsanyi, J.; et al. Upregulation of the transient receptor potential ankyrin 1 ion channel in the inflamed human and mouse colon and its protective roles. *PLoS ONE* **2014**, *9*, e108164. [CrossRef]
31. Lowin, T.; Apitz, M.; Anders, S.; Straub, R.H. Anti-inflammatory effects of n-acylethanolamines in rheumatoid arthritis synovial cells are mediated by trpv1 and trpa1 in a cox-2 dependent manner. *Arthritis Res. Ther.* **2015**, *17*, 321. [CrossRef]
32. An, J.N.; Hwang, J.H.; Kim, D.K.; Lee, H.; Ahn, S.Y.; Kim, S.; Park, J.T.; Kang, S.W.; Oh, Y.K.; Kim, Y.S.; et al. Chronic kidney disease after acute kidney injury requiring continuous renal replacement therapy and its impact on long-term outcomes: A multicenter retrospective cohort study in korea. *Crit. Care Med.* **2017**, *45*, 47–57. [CrossRef] [PubMed]

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The Predictive Value of Hyperuricemia on Renal Outcome after Contrast-Enhanced Computerized Tomography

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Abstract: The aim of this study was to determine whether elevated serum level of uric acid (sUA) could predict renal outcome after contrast-enhanced computerized tomography (CCT). We used a historical cohort of 58,106 non-dialysis adult patients who received non-ionic iso-osmolar CCT from 1 June 2008 to 31 March 2015 to evaluate the association of sUA and renal outcome. The exclusion criteria were patients with pre-existing acute kidney injury (AKI), multiple exposure, non-standard volume of contrast, and missing data for analysis. A total of 1440 patients were enrolled. Post-contrast-AKI (PC-AKI), defined by the increase in serum creatinine ≥ 0.3 mg/dL within 48 h or ≥50% within seven days after CCT, occurred in 180 (12.5%) patients and the need of hemodialysis within 30 days developed in 90 (6.3%) patients, both incidences were increased in patients with higher sUA. sUA ≥ 8.0 mg/dL was associated with an increased risk of PC-AKI (odds ratio (OR) of 2.62; 95% confidence interval (CI), 1.27~5.38, $p = 0.009$) and the need of hemodialysis (OR, 5.40; 95% CI, 1.39~21.04, $p = 0.015$). Comparing with sUA < 8.0 mg/dL, patients with sUA ≥ 8.0 mg/dL had higher incidence of PC-AKI (16.7% vs. 11.1%, $p = 0.012$) and higher incidence of hemodialysis (12.1% vs. 4.3%, $p < 0.001$). We concluded that sUA ≥ 8.0 mg/dL is associated with worse renal outcome after CCT. We suggest that hyperuricemia may have potential as an independent risk factor for PC-AKI in patients receiving contrast-enhanced image study.

Keywords: uric acid; contrast media; acute kidney injury; hemodialysis; chronic kidney disease

1. Introduction

Post-contrast acute kidney injury (PC-AKI) is one of the most common causes of acute kidney injury (AKI), independently associated with both morbidity and mortality [1–6]. Early awareness of the risk factors to eliminate the potentially preventable AKI after contrast-enhanced image studies is a critical healthcare issue [7]. Although estimated glomerular filtration rate (eGFR) has been widely accepted to detect the high-risk patients of AKI after contrast-enhanced image studies, there are several episodes of PC-AKI that have developed in patients without advanced chronic kidney disease (CKD). Thus, further studies are needed to identify more risk factors for predicting PC-AKI.

Hyperuricemia has been linked to AKI and progression of CKD via both crystal-dependent and crystal-independent mechanisms [8]. Both urate and calcium phosphate crystals could induce

oxidative stress and the expression of chemokine, and lead to the renal tubular epithelium and acute alterations in auto-regulation of renal blood flow which contribute to the decrease of renal perfusion and the subsequent injury of renal tubule [8–11]. Elevated serum level of uric acid has been reported as a novel marker for predicting AKI and mortality in several clinical settings, such as admission, percutaneous coronary intervention, and surgery, especially cardiovascular survey [12–19].

The traditional risk factors for predicting contrast-induced nephropathy include pre-existing renal disease, elderly people, diabetes mellitus, congestive heart failure, hypovolemic status, administration of nephrotoxic agents, or a large amount of contrast medium [20,21]. Metabolic syndrome and pre-diabetes have been proposed as new risk factors for contrast–induced nephropathy [22].

However, the predictive value of serum level of uric acid on the risk of PC-AKI after contrast-enhanced computerized tomography (CCT) has not been examined. The aim of this study was to determine whether serum uric acid could predict the risk of developing AKI and the need of dialysis after CCT, as well as the impact of PC-AKI on long-term change of renal function.

2. Patients and Methods

2.1. Study Design and Clinical Data Retrieval

We used a history cohort of 58,106 non-dialysis adult patients who received non-ionic iso-osmolar contrast, iodixanol (visipaque, Chicago, IL, USA), enhanced CT from 1 June 2008 to 31 March 2015 and had available a baseline serum level of creatinine and uric acid within two weeks before CCT to evaluate the association of serum uric acid and renal outcome. The exclusion criteria were patients with pre-existing AKI, recent exposure to contrast media within 30 days, volume of contrast medium ≠ 100cc (regular contrast volume for CCT), missing baseline serum creatinine, missing baseline serum uric acid (data within two weeks before CCT), and missing post-contrast serum creatinine within one week after CCT. The informed consent was waived because the study is on the basis of data collection from routine care. The institute review board of Taichung Veterans General Hospital approved this study (IRB TCVGH No: CE16164B).

There was no formal protocol for the prevention of contrast-induced nephropathy at this hospital at the time of this study. We calculated the eGFR using the four variables chronic kidney disease epidemiology collaboration (CKD-EPI) equation [23].

To find the cutoff values of baseline serum uric acid potentially associated with renal outcome, patients were classified into five groups stratified by baseline serum uric acid level: ≤3.9, 4–5.9, 6–7.9, 8–9.9, ≥10 mg/dL.

2.2. Outcome Variables

The renal outcome was determined by the primary and secondary endpoints. The primary renal endpoint was PC-AKI, which is defined by absolute increase of serum creatinine ≥0.3 mg/dL from baseline within 48 h or ≥50% within seven days after CCT, the Kidney Disease Improving Global Outcomes (KDIGO) criteria of AKI [1]. We did not include the criteria of urine volume of KDIGO criteria of AKI, because we could not collect enough data of urine volume in our study cohort. The secondary endpoint studied was the need of emergent hemodialysis after CCT. We identified the first procedure of hemodialysis within 30 days after CCT as PC-AKI requiring emergent hemodialysis. We also examined the differences in patient's characteristics, clinical factors, and incidence of AKI after CCT between serum uric acid ≥8.0 mg/dL and <8.0 mg/dL.

2.3. Statistical Analysis

All statistical analyses were performed using the SPSS software (Statistical Package for the Social Science, version 20.0, Armonk, NY, USA). Quantitative data are expressed as mean ± standard deviation. Nominal and categorical variables were compared using the chi-squared likelihood ratio or Fisher exact test with post-hoc analyses to detect difference between each pair with bonferroni. Continuous variables were compared using the nonparametric Wilcoxon test. Stepwise multivariate logistic regression analysis was used to examine the independent association of PC-AKI with patient-related characteristics and clinical factors. Association between serum uric acid ≥8.0 mg/dL and the risk of acute kidney injury and dialysis within 30 days after contrast-enhanced computerized tomography was calculated by odds ratio (OR) and 95% confidence interval (CI). A two-sided p value of <0.05 was set to represent the statistical significance.

3. Results

3.1. Study Population

A total of 1440 eligible patients who received CCT were enrolled in the final study cohort (Figure 1). The age of study subjects ranged from 20 to 98 years (mean age 66.2 ± 15.7 years) and 66.9% patients were male. Among them, 354 (24.6%) participants had serum uric acid ≥8 mg/dL and 865 (60.1%) participants had eGFR greater than 60 mL/min/1.73 m^2. Mean serum level of uric acid was 6.3 ± 2.7 mg/dL, mean serum creatinine level was 1.7 ± 2.1 mg/dL, and mean eGFR was 75.9 ± 48.0 mL/min/1.73 m^2. The average times of measurement of baseline serum uric acid and serum creatinine were 6.4 ± 3.2 days and 5.2 ± 3.7 days before CCT. The high incidence of comorbidities was observed and listed in Table 1. Four subgroups were created after stratification by baseline serum levels of uric acid. There were 270, 430, 386, 225, and 129 patients in the groups of serum uric acid ≤3.9, 4–5.9, 6–7.9, 8–9.9, and ≥10 mg/dL, respectively. Higher baseline serum uric acid was associated with higher prevalence of old age, stage 3~5 CKD, hypertension, coronary arterial disease, heart failure, atrial fibrillation, and chronic liver disease (Table 1).

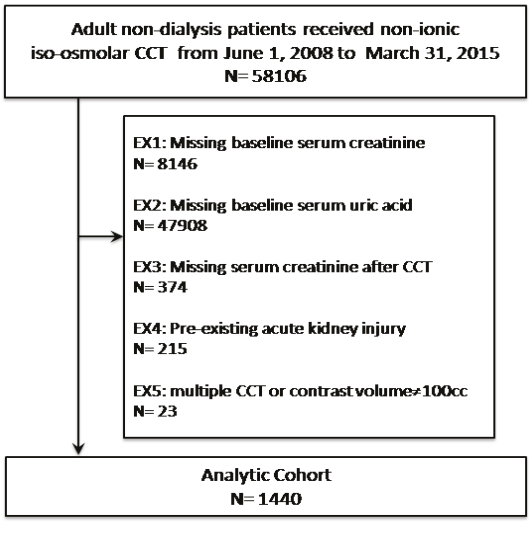

Figure 1. Study population selection flow diagram. CCT = Contrast-enhanced computerized tomography. EX = Exclusion.

Table 1. Baseline characteristics.

Serum Uric Acid (Number)	≤3.9 (N = 270)	4.0–5.9 (N = 430)	6.0–7.9 (N = 386)	8–9.9 (N = 225)	≥10 (N = 129)	Total (N = 1440)	*p* Value
Clinical characteristics							
Age (years)	63.2 ± 17.0	65.2 ± 15.5	67.5 ± 14.5	68.8 ± 14.5	67.5 ± 16.9	66.2 ± 15.7	<0.0001
Age ≥ 65 years *	131 (48.5%)	229 (53.3%)	244 (63.2%)	141 (62.7%)	76 (59%)	821 (57%)	<0.0001
Male sex *	176 (65.2%)	279 (64.9%)	254 (65.8%)	162 (72%)	93 (72.1%)	964 (66.9%)	0.233
Status of renal function							
Stage 1 CKD	175 (64.8%)	177 (41.2%)	71 (18.4%)	20 (8.9%)	8 (6.2%)	451 (31.3%)	<0.0001
Stage 2 CKD	56 (20.7%)	135 (31.4%)	133 (34.5%)	60 (26.7%)	30 (23.3%)	414 (28.8%)	
Stage 3A CKD	14 (5.2%)	57 (13.3%)	72 (18.7%)	53 (23.6%)	19 (14.7%)	215 (14.9%)	
Stage 3B CKD	10 (3.7%)	27 (6.3%)	43 (11.1%)	31 (13.8%)	33 (25.6%)	144 (10%)	
Stage 4 CKD	4 (1.5%)	14 (3.3%)	30 (7.8%)	29 (12.9%)	23 (17.8%)	100 (6.9%)	
Stage 5 CKD	11 (4.1%)	20 (4.7%)	37 (9.6%)	32 (14.2%)	16 (12.4%)	116 (8.1%)	
Comorbidity							
Cancer *	82 (30.4%)	141 (32.8%)	115 (29.8%)	77 (34.2%)	37 (28.7%)	452 (31.4%)	0.689
Diabetic mellitus *	93 (34.4%)	153 (35.6%)	132 (34.2%)	87 (38.7%)	49 (38%)	514 (35.7%)	0.786
Hypertension *	125 (46.3%)	233 (54.2%)	271 (70.2%)	154 (68.4%)	87 (67.4%)	870 (60.4%)	<0.0001
CAD *	48 (17.8%)	107 (24.9%)	127 (32.9%)	60 (26.7%)	47 (36.4%)	389 (27%)	<0.0001
Heart failure *	15 (5.6%)	30 (7%)	28 (7.3%)	14 (6.2%)	23 (17.8%)	110 (7.6%)	<0.0001
Atrial fibrillation *	27 (10%)	45 (10.5%)	59 (15.3%)	25 (11.1%)	35 (27.1%)	191 (13.3%)	<0.0001
CVA *	43 (15.9%)	100 (23.3%)	87 (22.5%)	47 (20.9%)	27 (20.9%)	304 (21.1%)	0.197
Chronic liver disease *	21 (7.8%)	34 (7.9%)	32 (8.3%)	24 (10.7%)	21 (16.3%)	132 (9.2%)	0.036
PAOD *	5 (1.9%)	19 (4.4%)	24 (6.2%)	14 (6.2%)	9 (7%)	71 (4.9%)	0.061
Shock *	30 (11.1%)	18 (4.2%)	14 (3.6%)	11 (4.9%)	14 (10.9%)	87 (6%)	<0.0001
GI bleeding *	12 (4.4%)	9 (2.1%)	15 (3.9%)	11 (4.9%)	9 (7%)	56 (3.9%)	0.098
Laboratory data							
Serum Albumin	3.0 ± 0.6	3.4 ± 0.8	3.4 ± 0.7	3.4 ± 0.7	3.3 ± 0.7	3.3 ± 0.7	<0.0001
Hemoglobin	10.3 ± 2.4	11.5 ± 2.6	11.3 ± 2.6	11.3 ± 2.6	10.8 ± 2.6	11.1 ± 2.6	<0.0001

CAD: Coronary arterial disease; CVA: Cerebral vascular attack; PAOD: Peripheral arterial occlusive disease; GI bleeding: Gastrointestinal bleeding. Data are expressed as mean ± standard deviation unless otherwise stated. * Data are n (%).

3.2. Renal Outcome Rates after CCT

In total, 180 (12.5%) patients developed PC-AKI, the primary endpoint, and 90 (6.3%) patients received emergent hemodialysis within 30 days. Not unexpectedly, the incidence of PC-AKI increased from 7.1% in stage 1 CKD to 29% in stage 4 CKD (Figure 2A, $p < 0.001$), but decreased to 17.2 in stage 5 CKD. The incidence of emergent hemodialysis within 30 days after CCT increased from 1.8% in stage 1 CKD to 38.8% in stage 5 CKD (Figure 2B, $p < 0.001$). The Chi-square tests were used to detect the significant differences of PC-AKI and emergent hemodialysis within 30 dyas after CCT among all pairs of populations with different stages of chronic kidney disease, both $p < 0.001$. Result of post-hoc analyses are shown in Figure 2.

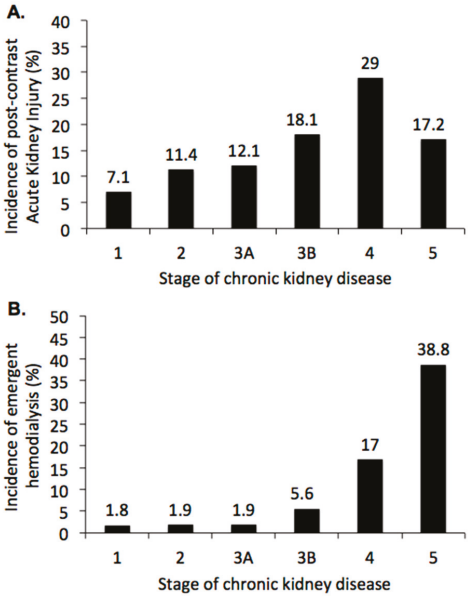

Figure 2. Renal outcome after contrast-enhanced computerized tomography (CCT) by the stage of chronic kidney disease: (**A**) Incidence of post-contrast acute kidney injury, defined by absolute increase of serum creatinine ≥0.3 mg/dL from baseline within 48 h or ≥50% within seven days after CCT. Chi-square tests were used to detect the significant differences among all pairs of populations with different stages of chronic kidney disease, $p < 0.001$. Post-hoc analysis showed $p = 0.004$ in stage 1 vs. 3B, $p = 0.026$ in stage 1 vs. 4, $p = 0.001$ in stage 1 vs. 5, $p = 0.001$ in stage 2 vs. 4, $p = 0.006$ in stage 3A vs. 4. (**B**) Incidence of emergent hemodialysis within 30 days after CCT. Chi-square tests were used to to detect the significant differences among all pairs of populations with different stages of chronic kidney disease, $p < 0.001$. Post-hoc analysis showed $p < 0.001$ in stage 1 vs. 4, $p < 0.001$ in stage 1 vs. 5, $p < 0.001$ in stage 2 vs. 4, $p < 0.001$ in stage 2 vs. 5, $p < 0.001$ in stage 3A vs. 4, $p < 0.001$ in stage 3A vs. 5, $p < 0.001$ in stage 3B vs. 5, $p < 0.007$ in stage 4 vs. 5, respectively.

Moreover, the incidence of PC-AKI decreased in lower ranges of serum uric acid, from 17.8% in patients with serum uric acid ≥10 mg/dL to 8.1% in patients with serum uric acid 4–5.9 mg/dL (Figure 3A, $p < 0.001$), but increased to 12.2% in patients with serum uric acid ≤3.9 mg/dL. There was a J-shaped relationship between serum uric acid and PC-AKI after CCT. The incidence of emergent hemodialysis within 30 days after CCT increased from 2.2% in patients with serum uric acid <4 mg/dL to 15.5% in patients with serum uric acid ≥ 10 mg/dL (Figure 3B, $p < 0.001$). The Chi-square tests were used to detect the significant differences among all pairs of populations with different ranges of serum uric acid, both $p < 0.001$. Result of post-hoc analyses are shown in Figure 3.

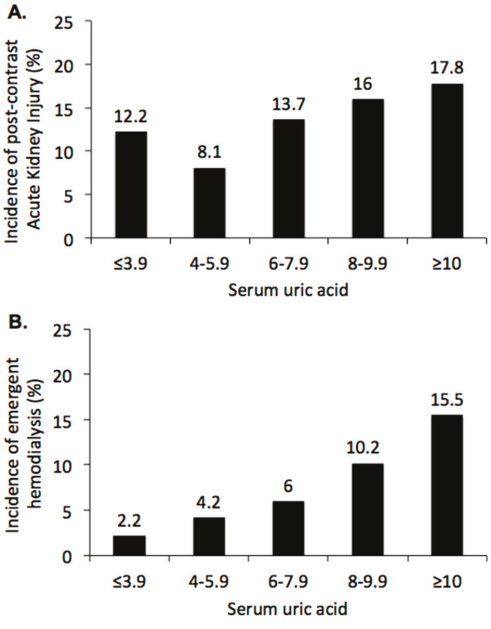

Figure 3. Renal outcome after contrast-enhanced computerized tomography stratified by baseline serum uric acid: (**A**) Incidence of post-contrast acute kidney injury, defined by absolute increase of serum creatinine ≥0.3 mg/dL from baseline within 48 h or ≥50% within seven days after CCT. Chi-square tests were used to detect the significant differences among all pairs of populations with different ranges of serum uric acid, $p < 0.001$. Post-hoc analysis showed $p = 0.033$ in sUA 4–5.9 vs. 8–9.9 mg/dL, $p = 0.028$ in sUA 4–5.9 vs. ≥10 mg/dL, respectively. (**B**) Incidence of emergent hemodialysis within 30 days after contrast enhanced computerized tomography. Chi-square tests were used to detect the significant differences among all pairs of populations with different ranges of serum uric acid, $p < 0.001$. Post-hoc analysis showed $p = 0.002$ in sUA ≤ 3.9 vs. 8–9.9 mg/dL, $p < 0.001$ in sUA ≤ 3.9 vs. ≥10 mg/dL, $p = 0.036$ in sUA ≤ 3.9 vs. 6–9.9 mg/dL, $p < 0.001$ in sUA 4–5.9 vs. ≥10 mg/dL, $p = 0.015$ in sUA 6–7.9 vs. ≥10 mg/dL, respectively.

3.3. Sensitivity Analysis: Impact of Serum Acid on Renal Outcome after CCT

Table 2 shows that the baseline serum uric acid ≥8.0 mg/dL was significantly associated with PC-AKI (OR, 1.54; 95% CI, 1.10~2.18, $p = 0.013$) and emergent hemodialysis within 30 days after CCT (OR, 2.93; 95% CI, 1.90~4.52, $p < 0.001$). Serum uric acid remained associated with PC-AKI (OR, 2.62, 95% CI, 1.27~5.38, $p = 0.009$) and emergent hemodialysis within 30 days after CCT (OR, 5.40, 95% CI, 1.39~21.04, $p = 0.015$) after adjustment for the age, gender, comorbidities (cancer, diabetic mellitus, hypertension, coronary arterial disease, heart failure, atrial fibrillation, cerebral vascular attack, chronic liver disease, peripheral arterial occlusive disease, gastrointestinal bleeding, and shock) and baseline laboratory data (serum albumin, hemoglobin) and medications (diuretics, ACEi/ARB, N-acetylcyestine, sodium bicarbonate, NSAID).

Table 2. Association between serum uric acid ≥8.0 mg/dL and the risk of acute kidney injury and dialysis within 30 days after contrast-enhanced computerized tomography.

	Odd Ratio	95% Confident Interval	*p* Value
Risk of acute kidney injury			
Unadjusted	1.54	1.10~2.18	0.013
Adjusted, model 1	2.40	1.31~4.42	0.005
Adjusted, model 2	2.62	1.27~5.38	0.009
Risk of dialysis within 30 days after CCT			
Unadjusted	2.93	1.90~4.52	<0.0001
Adjusted, model 1	6.42	1.91~21.56	0.003
Adjusted, model 2	5.40	1.39~21.04	0.015

Definition of acute kidney injury is absolute increase of serum creatinine ≥0.3 mg/dL from baseline within 48 h or ≥50% within seven days after contrast-enhanced computerized tomography. Model 1, adjusted by the comorbidities listed in Table 1. Model 2, adjusted by hemoglobin, serum albumin, bilirubin, uric acid, usage of diuretics, usage of ACE inhibitors/ARB, usage of N-acetylcysteine, usage of sodium bicarbonate, usage of non-steroidal anti-inflammatories, plus covariates listed in Model 1.

Incidence of serum uric acid ≥8.0 mg/dL significantly increased as the progression of renal function, from 6.2% in stage 1 CKD to 52% in stage 4 CKD, and decreased slightly to 41.4% in stage 5 CKD (Figure 4A, $p < 0.001$). Notably, in patients with stage 1 and 2 CKD, but not in patients with stage 3~5 CKD, serum uric acid ≥8.0 mg/dL was significantly associated with higher incidence of PC-AKI when comparing with serum uric acid < 8.0 mg/dL (Figure 4B, $p < 0.05$ in both stage 1 and stage 2 CKD). Patients with serum uric acid ≥ 8.0 mg/dL had higher incidence of emergent hemodialysis within 30 days after CCT in stage 2, 3A, and 3B CKD (Figure 4C). Overall, when comparing with serum uric acid < 8.0 mg/dL, patients with serum uric acid ≥ 8.0 mg/dL had higher incidence of PC-AKI (16.7% vs. 11.1%, $p = 0.012$, Figure 4D) and higher incidence of emergent hemodialysis within 30 days after CCT (12.1% vs. 4.3%, $p < 0.001$, Figure 4D). Compared to male patients, female patients had significantly higher risk to receive hemodialysis within 30 days after CCT (8.1% vs. 4.7%, $p = 0.012$), but not in PC-AKI (15.9% vs. 12.3%, $p = 0.075$). However, gender is not an independent risk factor when we perform regression analysis to detect the potential risk factor of post-contrast AKI.

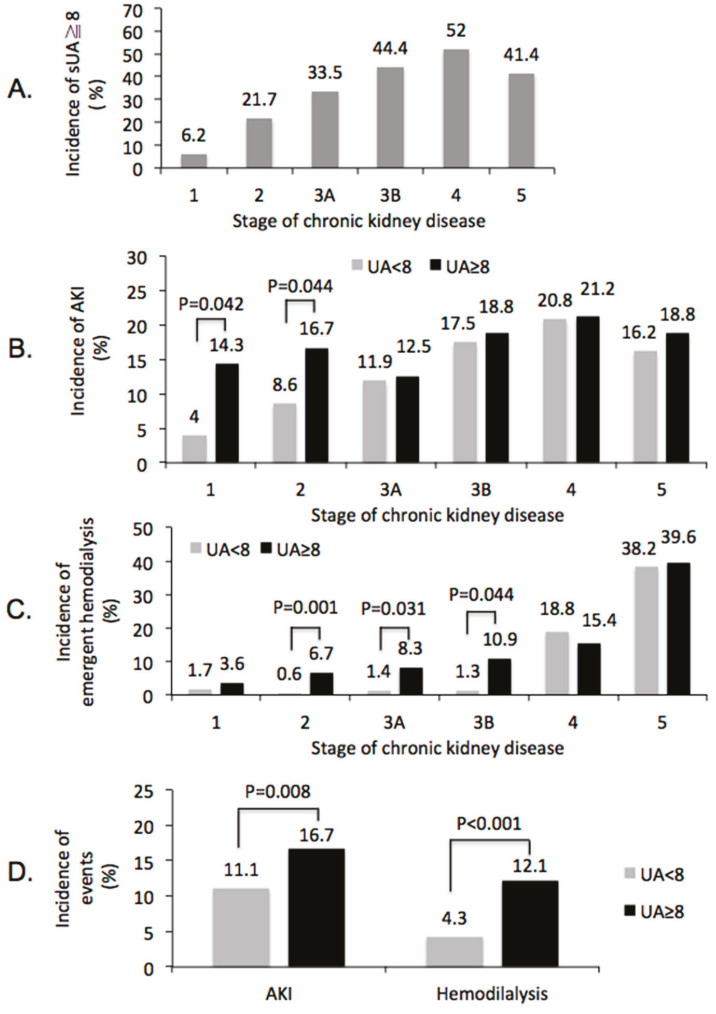

Figure 4. Impact of sUA ≥8.0 mg/dL on renal outcome after contrast-enhanced computerized tomography. (**A**) percentages of patients with sUA ≥ 8 mg/dL by stage of CKD, Chi-square tests were used to detect the significant differences among all pairs of populations with different stages of CKD, $p < 0.001$. (**B**) incidence of post-contrast AKI by stage of CKD. (**C**) Incidence of emergent hemodialysis within 30 days by stage of CKD. (**D**) difference of renal events, post-contrast AKI, and emergent hemodialysis with 30 days after contrast-enhanced computerized tomography, between patients with sUA <8 and ≥8 mg/dL. sUA = Serum uric acid. AKI = Acute kidney injury. CKD = Chronic kidney disease.

3.4. Analysis of Renal Outcome in three Months after CCT

We further collected renal function three months after CCT to compare the change of eGFR between AKI and non-AKI groups. The mean eGFR decreased 19.6 ± 37.4% in the AKI group and increased 1.3 ± 36.0% in the non-AKI group ($p < 0.001$, Figure 5A). Among them, 53.8% of patients with AKI had eGFR decreased by ≥20% compared to only 25.9% in patients without AKI ($p < 0.001$, Figure 5B).

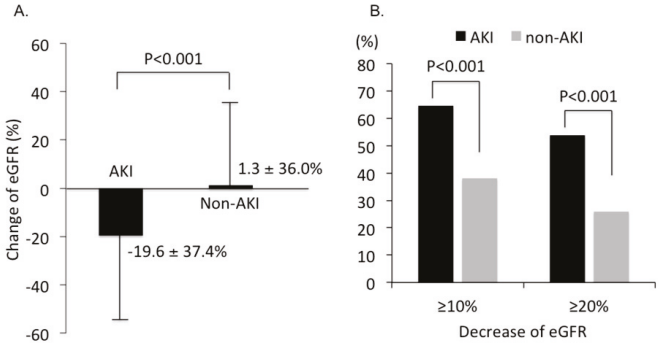

Figure 5. Impact of post-contrast acute kidney injury on renal outcome at three months after contrast-enhanced computerized tomography. (**A**) Change of eGFR at three months after contrast-enhanced computerized tomography. (**B**) Percentage of patients with eGFR decreased by ≥10% and ≥20% in patients with or without AKI, respectively. sUA = Serum uric acid. AKI = Acute kidney injury. eGFR = Estimated glomerular filtration rate.

3.5. Subgroups Analysis of Renal Outcome after CCT

In the subgroups analysis, we found the incidences of serum uric acid ≥ 8.0 mg/dL were 24.7% of 984 patients aged ≥60 years, 19.7% of 476 female patients, 26.4% of 870 hypertensive patients, and 24.3% of 452 patients with cancer. The odds ratios of serum uric acid ≥8.0 mg/dL for the predicting PC-AKI were 2.61 (95% CI = 1.02~2.24, $p = 0.040$) in patients aged ≥60 years, and 2.19 (95% CI = 1.21~3.94, $p = 0.009$) in female patients. The odds ratios of serum uric acid ≥8.0 mg/dL for the predicting emergent hemodialysis within 30 days after CCT were 2.07 (95% CI = 1.23~3.49, $p = 0.006$) in patients aged ≥60 years, 7.03 (95% CI = 3.01~16.44, $p < 0.0001$) in patients aged <60 years, 2.68 (95% CI = 1.02~5.89, $p = 0.014$) in female patients, 3.06 (95% CI = 1.81~5.17, $p < 0.0001$) in male patients, 3.00 (95% CI = 1.82~4.94, $p < 0.0001$) in hypertensive patients, 2.43 (95% CI = 1.34~4.41, $p = 0.003$) in diabetic patients, 3.49 (95% CI = 1.82~6.66, $p < 0.0001$) in non-diabetic patients, 2.73 (95% CI = 1.24~6.01, $p = 0.013$) in patients with coronary arterial disease, and 3.00 (95% CI = 1.78~5.05, $p < 0.0001$) in patients without coronary arterial disease.

4. Discussion

The primary finding of this study is the strong association between hyperuricemia and the risk of PC-AKI and the need of emergent hemodialysis within 30 days after CCT. Even after adjustment for patient characteristics, comorbidities, laboratory data, and medications, pre-contrast serum uric acid continued to be strongly associated with renal outcome after CCT. Our findings provide proof of concept that hyperuricemia, especially when serum uric acid is ≥8.0 mg/dL, was associated with higher risk of PC-AKI after CCT. The association between hyperuricemia and PC-AKI occurs more significantly in patients without advanced CKD stage 4 and 5.

The estimated GFR has been widely used to assess the risk of PC-AKI when patients need to receive contrast-enhanced image studies [2]. Regardless of the fact that hyperuricemia is more common in patients with advanced CKD, 11.6% of 865 patients with stage 1 and 2 CKD had serum uric acid ≥8.0 mg/dL in this study. These patients without advanced stage 3~5 CKD are generally considered to have relatively lower risk of PC-AKI. However, the incidence of PC-AKI and emergent hemodialysis within 30 days after CCT were 9.1% and 1.8%, respectively, in patients with eGFR ≥ 60 mL/min/1.73 m^2. In this study, we suggest that hyperuricemia could be one of the independent risk factors for the prediction of renal outcome after CCT. The impact of PC-AKI was further demonstrated by the fact that a significantly higher percentage of eGFR decreased ≥20% after three months of CCT.

The possible explanations for the increased risk of PC-AKI in patients with elevated serum uric acid include both crystal-dependent and crystal-independent mechanisms [8,24]. Elevated serum uric acid can induce renal vasoconstriction and impair auto-regulation, which leads to reduced renal blood flow and GFR [9,10]. A mild elevation of serum uric acid in rats could cause renal vasoconstriction in a crystal-independent pathway [11]. Several recent studies demonstrated that hyperuricemia could worsen the injury of the renal tubule via pro-inflammatory pathways involving activation of the renin-angiotensin system, chemokine expression, and endothelial dysfunction [8,9]. Importantly, contrast medium may increase the burden of hyperuricemia-induced kidney injury.

The association between hyperuricemia and an increased risk for developing AKI has been demonstrated in patients receiving cardiovascular surgery and percutaneous coronary interventions and acute paraquat intoxication [12–19]. Moreover, hyperuricemia has been proposed as a novel marker for early detection of AKI [25]. In this study, we demonstrate that hyperuricemia is an important predictor of developing PC-AKI and the need for emergent hemodialysis within 30 days after CCT.

Interestingly, the association between serum uric acid ≥ 8.0 mg/dL and PC-AKI was more significant in patients with stage 1 and 2 CKD, which accounts for 60.1% in this study cohort. Recently, Kuwabara and colleagues also reported that change in SUA is independently associated with change in eGFR over time in patients with eGFR ≥ 60 mL/min/1.73 m^2 [26]. These findings suggest that the impact of hyperuricemia, sUA ≥ 8.0 mg/dL, on PC-AKI is more prominent in early stage CKD patients. However, we do not have enough sUA after contrast CT to evaluate if the change of sUA will also impact on the development of PC-AKI.

On the other hand, female patients have significantly higher risk of receiving hemodialysis within 30 days after CCT, but not in PC-AKI. In general, the female population has lower average sUA than the male population. Although our results could not support the female gender as an independent risk factor to predict PC-AKI, more study is necessary to clarify the gender effect in the association of sUA and PC-AKI.

Even though increasing evidence support the idea that hyperuricemia may increase the risk of AKI development, interventions by lowering serum level of uric acid to prevent AKI remain scarce. A small-scale randomized control study showed that lowering serum uric acid by rasburicase, an urate oxidase, did not reduce the development of AKI after cardiac surgery by using traditional and non-traditional markers [27]. It is worth mentioning that hyperuricemia could be a reflection of diminished renal perfusion. Prerenal azotemia may lead to enhanced proximal tubular reabsorption of salt, water, urea, as well as uric acid [28].

In support of our findings, Lapsia and coworker demonstrated a J-shaped relationship between hyperuricemia and postoperative AKI [12]. An explanation for the higher risk of AKI in patients with lower serum levels of uric acid, <4 mg/dL for example, is due to oxidative stress, as uric acid can act as both an anti-oxidant and pro-oxidant agent [29,30]. Malnutrition and inflammation were also suggested to be important factors for lower serum levels of uric acid and a worse outcome [19]. Moreover, the systematic review and meta-analysis among the patients undergoing coronary angiography and/or percutaneous coronary intervention showed that hyperuricemia is independently associated with the occurrence of contrast–induced AKI and the risk of renal replacement therapy [31].

There are several important limitations in this study. This is a single-center historic cohort study. Out of 58,106 study subjects, only 1440 patients were included in analysis. The result is subject to selection bias and the finding might have limited generalizability. The statistical power was limited to detect the impact of hyperuricemia in AKI requiring dialysis in eGFR ≥ 60 mL/min/1.73 m^2 (n = 16, 1.8%) and serum uric acid < 4 mg/dL (n = 6, 2.2%), which is an important clinical end point. On the other hand, there is also no data available to evaluate if the intervention of lower serum uric acid will reduce the risk of PC-AKI. Since this study is an observational study in nature, it is difficult to show the causality. We do not have renal biopsy data to confirm the cause of PC-AKI. A multi-center, prospective large-scale study is eventually required to address these limitations.

5. Conclusions

Our findings provide additional evidence to demonstrate that elevated serum uric acid is an independent risk factor for AKI in patients undergoing contrast-enhanced image study PC-AKI. Moreover, we provide further evidence that PC-AKI is associated with the need of dialysis and long-term renal function progression. We suggest that serum level of uric acid, together with eGFR, is necessary for patients scheduled to receive CCT.

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Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Okusa, M.D.; Davenport, A. Reading between the (guide)lines—The KDIGO practice guideline on acute kidney injury in the individual patient. *Kidney Int.* **2014**, *85*, 39–48. [CrossRef] [PubMed]
2. Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.* **2012**, *120*, c179–c184. [CrossRef] [PubMed]
3. Hsu, R.K.; McCulloch, C.E.; Heung, M. Exploring potential reasons for the temporal trend in dialysis-requiring AKI in the United States. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 14–20. [CrossRef] [PubMed]
4. McCullough, P.A. Contrast-induced acute kidney injury. *J. Am. Coll. Cardiol.* **2008**, *51*, 1419–1428. [CrossRef]
5. Barrett, B.J. Contrast nephrotoxicity. *J. Am. Soc. Nephrol.* **1994**, *5*, 125–137. [PubMed]
6. Weisbord, S.D.; Mor, M.K.; Resnick, A.L.; Hartwig, K.C.; Palevsky, P.M.; Fine, M.J. Incidence and outcomes of contrast-induced AKI following computed tomography. *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 1274–1281. [CrossRef] [PubMed]
7. Horton, R.; Berman, P. Eliminating acute kidney injury by 2025: An achievable goal. *Lancet* **2015**, *385*, 2551–2552. [CrossRef]
8. Shimada, M.; Johnson, R.J.; May, W.S.J.; Lingegowda, V.; Sood, P.; Nakagawa, T.; Van, Q.C.; Dass, B.; Ejaz, A.A. A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome. *Nephrol. Dial. Transplant.* **2009**, *24*, 2960–2964. [CrossRef]
9. Umekawa, T.; Chegini, N.; Khan, S.R. Increased expression of monocyte chemoattractant protein-1 (MCP-1) by renal epithelial cells in culture on exposure to calcium oxalate, phosphate and uric acid crystals. *Nephrol. Dial. Transplant.* **2003**, *18*, 664–669. [CrossRef]
10. Devarajan, P. Update on mechanisms of ischemic acute kidney injury. *J. Am. Soc. Nephrol.* **2006**, *17*, 1503–1520. [CrossRef]
11. Sánchez-Lozada, L.G.; Tapia, E.; Santamaría, J.; Avila-Casado, C.; Soto, V.; Nepomuceno, T.; Rodríguez-Iturbe, B.; Johnson, R.J.; Herrera-Acosta, J. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int.* **2005**, *67*, 237–247. [CrossRef] [PubMed]
12. Lapsia, V.; Johnson, R.J.; Dass, B.; Shimada, M.; Kambhampati, G.; Ejaz, N.I.; Arif, A.A.; Ejaz, A.A. Elevated uric acid increases the risk for acute kidney injury. *Am. J. Med.* **2012**, *125*, 9–17. [CrossRef] [PubMed]
13. Lee, E.H.; Choi, J.H.; Joung, K.W.; Kim, J.Y.; Baek, S.H.; Ji, S.M.; Chin, J.H.; Choi, I.C. Relationship between serum uric acid concentration and acute kidney injury after coronary artery bypass surgery. *J. Korean Med. Sci.* **2015**, *30*, 1509–1516. [CrossRef] [PubMed]
14. Durante, P.; Romero, F.; Pérez, M.; Chávez, M.; Parra, G. Effect of uric acid on nephrotoxicity induced by mercuric chloride in rats. *Toxicol. Ind. Health* **2010**, *26*, 163–174. [CrossRef] [PubMed]

15. Hillis, G.S.; Cuthbertson, B.H.; Gibson, P.H.; McNeilly, J.D.; Maclennan, G.S.; Jeffrey, R.R.; Buchan, K.G.; El-Shafei, H.; Gibson, G.; Croal, B.L. Uric acid levels and outcome from coronary artery bypass grafting. *J. Thorac. Cardiovasc. Surg.* **2009**, *138*, 200–205. [CrossRef]
16. Joung, K.W.; Jo, J.Y.; Kim, W.J.; Choi, D.K.; Chin, J.H.; Lee, E.H.; Choi, I.C. Association of preoperative uric acid and acute kidney injury following cardiovascular surgery. *J. Cardiothorac. Vasc. Anesth.* **2014**, *28*, 1440–1447. [CrossRef] [PubMed]
17. Liu, Y.; Tan, N.; Chen, J.; Zhou, Y.L.; Chen, L.L.; Chen, S.Q.; Chen, Z.J.; Li, L.W. The relationship between hyperuricemia and the risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with relatively normal serum creatinine. *Clinics* **2013**, *68*, 19–25. [CrossRef]
18. Park, S.H.; Shin, W.Y.; Lee, E.Y.; Gil, H.W.; Lee, S.W.; Lee, S.J.; Jin, D.K.; Hong, S.Y. The impact of hyperuricemia on in-hospital mortality and incidence of acute kidney injury in patients undergoing percutaneous coronary intervention. *Circ. J.* **2011**, *75*, 692–697. [CrossRef]
19. Cheungpasitporn, W.; Thongprayoon, C.; Harrison, A.M.; Erickson, S.B. Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients. *Clin. Kidney J.* **2016**, *9*, 51–56. [CrossRef]
20. Mehran, R.; Dangas, G.D.; Weisbord, S.D. Contrast-Associated Acute Kidney Injury. *N. Engl. J. Med.* **2019**, *380*, 2146–2155. [CrossRef]
21. Silver, S.A.; Shah, P.M.; Chertow, G.M.; Harel, S.; Wald, R.; Harel, Z. Risk prediction models for contrast induced nephropathy: Systematic review. *BMJ* **2015**, *351*, h4395. [CrossRef] [PubMed]
22. Toprak, O. Conflicting and new risk factors for contrast induced nephropathy. *J. Urol.* **2007**, *178*, 2277–2283. [CrossRef] [PubMed]
23. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Coresh, J.; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular filtration rate. *Ann. Int. Med.* **2009**, *150*, 604–612. [CrossRef] [PubMed]
24. Ejaz, A.A.; Dass, B.; Kambhampati, G.; Ejaz, N.I.; Maroz, N.; Dhatt, G.S.; Arif, A.A.; Faldu, C.; Lanaspa, M.A.; Shah, G.; et al. Lowering serum uric acid to prevent acute kidney injury. *Med. Hypotheses* **2012**, *78*, 796–799. [CrossRef] [PubMed]
25. Ejaz, A.A.; Beaver, T.M.; Shimada, M.; Sood, P.; Lingegowda, V.; Schold, J.D.; Kim, T.; Johnson, R.J. Uric acid: A novel risk factor for acute kidney injury in high-risk cardiac surgery patients? *Am. J. Nephrol.* **2009**, *30*, 425–429. [CrossRef] [PubMed]
26. Kuwabara, M.; Bjounstad, P.; Hisatome, I.; Niwa, K.; Roncal-Jimenez, C.A.; Andres-Hernando, A.; Jensen, T.; Milagres, T.; Sato, Y.; Garcia, G.; et al. Elevated Serum Uric Acid Level Predicts Rapid Decline in Kidney Function. *Am. J. Nephrol.* **2017**, *45*, 330–337. [CrossRef] [PubMed]
27. Ejaz, A.A.; Dass, B.; Lingegowda, V.; Shimada, M.; Beaver, T.M.; Ejaz, N.I.; Abouhamze, A.S.; Johnson, R.J. Effect of uric acid lowering therapy on the prevention of acute kidney injury in cardiovascular surgery. *Int. Urol. Nephrol.* **2013**, *45*, 449–458. [CrossRef]
28. Steinhäuslin, F.; Burnier, M.; Magnin, J.L.; Munafo, A.; Buclin, T.; Diezi, J.; Biollaz, J. Fractional excretion of trace lithium and uric acid in acute renal failure. *J. Am. Soc. Nephrol.* **1994**, *4*, 1429–1437.
29. Kaneko, K.; Taniguchi, N.; Tanabe, Y.; Nakano, T.; Hasui, M.; Nozu, K. Oxidative imbalance in idiopathic renal hypouricemia. *Pediatr. Nephrol.* **2009**, *24*, 869–871. [CrossRef]
30. Sánchez-Lozada, L.G.; Soto, V.; Tapia, E.; Avila-Casado, C.; Sautin, Y.Y.; Nakagawa, T.; Franco, M.; Rodríguez-Iturbe, B.; Johnson, R.J. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. *Am. J. Physiol. Renal Physiol.* **2008**, *295*, F1134–F1141. [CrossRef]
31. Zuo, T.; Jiang, L.; Mao, S.; Liu, X.; Guo, L. Hyperuricemia and contrast-induced acute kidney injury: A systematic review and meta-analysis. *Int. J. Cardiol.* **2016**, *224*, 286–294. [CrossRef] [PubMed]

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Acute Kidney Injury and Septic Shock—Defined by Updated Sepsis-3 Criteria in Critically Ill Patients

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Abstract: Sepsis is commonly associated with acute kidney injury (AKI), particularly in those requiring dialysis (AKI-D). To date, Sepsis-3 criteria have not been applied to AKI-D patients. We investigated sepsis prevalence defined by Sepsis-3 criteria and evaluated the outcomes of septic-associated AKI-D among critically ill patients. Using the data collected from a prospective multi-center observational study, we applied the Sepsis-3 criteria to critically ill AKI-D patients treated in intensive care units (ICUs) in 30 hospitals between September 2014 and December 2015. We described the prevalence, outcomes, and characteristics of sepsis as defined by the screening Sepsis-3 criteria among AKI-D patients, and compared the outcomes of AKI-D patients with or without sepsis using the Sepsis-3 criteria. A total of 1078 patients (median 70 years; 673 (62.4%) men) with AKI-D were analyzed. The main etiology of AKI was sepsis (71.43%) and the most frequent indication for acute dialysis was oliguria (64.4%). A total of 577 (53.3% of 1078 patients) met the Sepsis-3 criteria, and 206 among the 577 patients (19.1%) had septic shock. Having sepsis and septic shock were independently associated with 90-day mortality among these ICU AKI-D patients (hazard ratio (HR) 1.23 ($p = 0.027$) and 1.39 ($p = 0.004$), respectively). Taking mortality as a competing risk factor, AKI-D patients with septic shock had a significantly reduced chance of weaning from dialysis at 90 days than those without sepsis (HR 0.65, $p = 0.026$). The combination of the Sepsis-3 criteria with the AKI risk score led to better performance in forecasting 90-day mortality. Sepsis affects more than 50% of ICU AKI patients requiring dialysis, and one-fifth of these patients had septic shock. In AKI-D patients, coexistent with or induced by sepsis (as screened by the Sepsis-3 criteria), there is a significantly higher mortality and reduced chance of recovering sufficient renal function, when compared to those without sepsis.

Keywords: Sepsis-3; acute dialysis; qSOFA; acute kidney injury

1. Introduction

Sepsis is considered the most frequent cause of acute kidney injury (AKI) in critically ill patients in the intensive care unit (ICU) [1]. It is a heterogeneous syndrome caused by an unbalanced host response to an infection, often resulting in variable clinical signs and symptoms. Until the early 1990s, sepsis was not formally defined, and numerous different criteria were used in research and clinical practice. In 2016, the 'Sepsis-3' consensus definition was published. Accordingly, sepsis constitutes life-threatening organ dysfunction that is caused by a dysregulated host response to infection and defined by an acute change in total Sequential Organ Failure Assessment (SOFA) score by ≥2 points (delta SOFA). In addition, the concept of the quick SOFA (qSOFA) was introduced as a possible tool to identify patients with sepsis outside the ICU [2]. The qSOFA describes the presence of any two of the following three factors: Respiratory rate ≥ 22/min, altered mentation or systolic blood pressure ≤ 100 mmHg. Septic shock is recognized as a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities as evidenced by a serum lactate concentration >2 mmol/L and vasopressor requirement to maintain a mean arterial pressure (MAP) of at least 65 mmHg in the absence of hypovolemia. Of note, the terms systemic inflammatory response syndrome (SIRS) and severe sepsis were removed.

An analysis of data from a large cohort of patients admitted to 409 hospitals in the USA in 2004–2009 revealed that more than 40% of patients with sepsis, as defined by the Sepsis-3 criteria, also had AKI [3]. In patients with AKI, mortality and long-term outcomes are worst in those treated with renal replacement (RRT), also known as 'AKI with dialysis' (AKI-D) [2,4]. To date, the prevalence and outcomes of sepsis defined by the Sepsis-3 criteria among AKI-D patients has not been well reported. It is unclear whether the two criteria of the Sepsis-3 definition are equally predictive when used in association with AKI-D patients.

The aims of our project were: (i) To describe the incidence, outcomes, and characteristics of sepsis, as defined by the screening Sepsis-3 criteria, among AKI-D patients; and (ii) to show the outcomes of AKI-D patients without or with sepsis.

2. Methods

2.1. Study Population

We analyzed data of the Taiwan Consortium for Acute Kidney Injury and Renal Diseases (CAKs) study. The CAKS study was approved by the institutional review boards of the participating institutions. The need for informed consent was waived because all personal data was fully de-identified and only data that were routinely collected for clinical purposes were analyzed (approval number NRPB2014050014). The CAKs study has been extensively described previously [5,6]. In brief, it is a prospective observational study of ICU patients with AKI-D admitted to one of 30 hospitals in Taiwan. The hospitals are distributed widely through the various geographical regions of Taiwan (north, middle, south, and east) and there is a 1:1 ratio of tertiary medical centers to regional hospitals in each region. We analyzed patients who had been enrolled in four distinct months (October 2014, January 2015, April 2015 and July 2015) and were followed-up for at least three months after hospital discharge. Patients receiving chronic dialysis before the index hospitalization were excluded.

2.2. Dialysis Initiation

The pre-determined indications for RRT protocol or algorithm or simply clinician judgement were: (1) Presence of azotemia (blood urea nitrogen (BUN) > 80 mg/dL and serum creatinine (sCr) > 2 mg/dL) and uremic symptoms (encephalopathy, pericarditis or pleurisy); (2) oliguria (urine output < 400 mL/24 h) or anuria refractory to fluid challenges and diuretics; (3) fluid overload refractory to diuretics with a central venous pressure (CVP) > 12 mmHg or pulmonary edema with a PaO2/FiO2 < 300 mmHg; (4) hyperkalemia (serum potassium > 5.5 mmol/L) refractory to medical treatment, and/or (5) metabolic acidosis (arterial pH < 7.2) [7–9].

2.3. Infection and Sepsis

The medical records of all patients were independently reviewed by two investigators to identify AKI-D patients who met the Sepsis-3 criteria at initiation of RRT. In case of any discordance, a third investigator (VCW) acted as an adjudicator.

To be classified as having sepsis, patients with a suspected or confirmed infection had to have at least two qSOFA criteria [10] or an acute increase in total SOFA score by ≥2 within the 24 h period before acute RRT was started (distribution as Figure S1). Infection was defined as body fluids with positive culture or antibiotics started as a criterion of suspected infection. In patients with a nosocomial infection in whom a pre-admission SOFA score was not available, the first SOFA value at hospital admission qualified as baseline score (1). Patients with hepatic dysfunction who received acute RRT within 24 h of ICU admission, were assigned a baseline SOFA score of four, and in case of chronic respiratory impairment, a baseline score of two was assigned [11]. In all other cases, the baseline SOFA score was considered to be zero [2]. Consistent with previous studies, missing values were considered to be normal [10].

2.4. Outcomes

The primary study outcome was 90-day mortality after hospital discharge. Secondary outcomes were inability to wean from acute RRT and/or a composite outcome of mortality or RRT dependence at 90 days after hospital discharge [12].

2.5. Clinical Data Collection

In patients with AKI-D at initiation of RRT, we extracted the following data: Baseline characteristics and demographics, severity of illness scores including SOFA score, acute physiology and chronic health evaluation II (APACHE II) score and multiple organ dysfunction syndrome (MODS) score, comorbidities and the presumed etiology of AKI. AKI was defined by the serum creatinine criteria of the Kidney Disease Improving Global Outcome classification [13]. We also calculated the AKI risk prediction score as proposed by Demirjian et al. [14] (Table S1). The worst physiological and biochemical values during the initial 24-h period before RRT were recorded, together with the severity of illness scores and vasopressor administration at initiation of RRT [15].

The pre-determined indications for RRT were mentioned above and as in supplemental methods.

2.6. Statistical Analyses

Continuous data were expressed as mean ± standard deviation (SD) and group comparisons were conducted using χ 2 tests for equal proportions, t tests for normally distributed data, and Wilcoxon rank sum tests otherwise.

We performed multivariable analyses of all factors that were significant in univariate analyses, including age, sex, baseline comorbidities, indication for RRT, etiology of AKI, renal parameters and SOFA score at initiation of RRT and modality of RRT. The significance levels for entry (SLE) and for stay (SLS) were set at a conservative level of 0.15. The best candidate final logistic regression model was identified manually by dropping the covariates with a p value > 0.05 one at a time until all regression coefficients were significantly different from zero.

Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analysis were used to examine the role of the Sepsis-3 criteria to stratify individuals into higher or lower risk categories (reclassification) [16,17]. Focusing on 90-day mortality, an increase in NRI was calculated in a model containing the Sepsis-3 criteria in combination with the AKI risk prediction or SOFA score. The results were compared with the individual criteria of the Sepsis-3 definition. We distinguished between three risk categories (0%–40%, 40%–80%, and >80%) and reclassified the patients who died from all-causes or were still dialysis dependent at 90 days after hospital discharge (according to decision curve analysis, Figure S2).

All analyses were performed with R software, version 3.2.2 (Free Software Foundation, Inc., Boston, MA, USA), MedCalc Statistical Software, version 15.11.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015) and Stata version 12 (StataCorp LP, College Station, TX, USA) for competing-risk analysis. A p-value < 0.05 was considered significant.

3. Results

3.1. Patient Cohort

We enrolled a total of 1078 critically ill patients with AKI-D (median age 70 years; 673 (62.4%) male). At initiation of RRT, their median SOFA score was 12, APACHE II score 24 and MODS score was 11. A total of 577 (53.5%) patients had sepsis, of whom 206 (19.1%) met the criteria for septic shock (Figure 1). Supplementary Figure S1 shows the distribution of the qSOFA and SOFA scores. The main source of infection was the respiratory tract (53.6%), followed by the genitourinary tract (31.4%). The missing data were mainly come from bilirubin (n = 4, 3.7%) and coagulation INR (5, 4.6%).

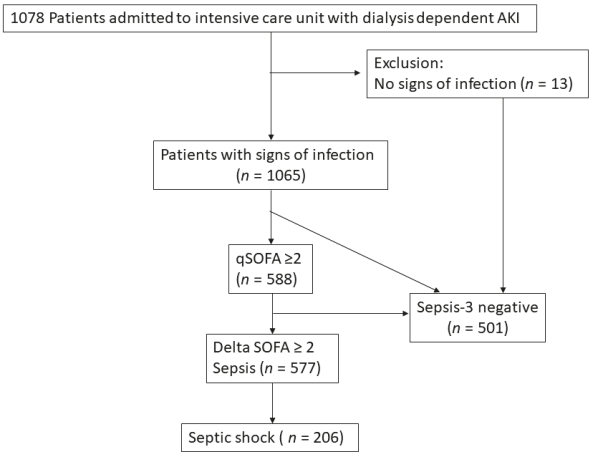

Figure 1. Algorithm of enrollee.

Based on judgment by the clinicians treating the patients, the main etiologies of AKI were sepsis (71.4%), shock (57.1%) and rhabdomyolysis (14.4%). The most frequent indication for acute RRT was oliguria (64.4%), followed by fluid overload (56.0%), azotemia (54.4%) and metabolic acidosis (49.6%).

3.2. Impact of Sepsis

Patients with AKI-D who had sepsis (53.5%) or septic shock (19.1%) at initiation of RRT were significantly older, had better baseline renal function and a higher serum lactate result on admission to ICU compared to AKI-D patients without sepsis (Table 1).

3.3. Comparison between 90-Day Survivors and Non-Survivors

Mortality and composite outcome (mortality or RRT dependence) at 90 days were 62.3%, and 76.4% in the 1078 AKI-D patients, respectively (Table 2). Sepsis and septic shock were more common among non-survivors compared to survivors (63.2% and 25.6% versus 37.4% and 8.4%, respectively). Other significant differences between 90-day survivors and non-survivors were older age, a higher comorbidity score, lower baseline serum creatinine and a higher prevalence of liver cirrhosis and cancer in non-survivors.

Table 1. Clinical characteristics of patients with and without sepsis.

	Non-Sepsis (n = 501)	Sepsis (n = 371)	Septic Shock (n = 206)	p Value
Patient characteristics				
Age, median (range)	71.8 (60.6–80.3)	69.3 (57.6–79.7)	65.8 (54.3–76.3)	0.011
Male gender, n (%)	299 (59.68%)	228 (61.46%)	146 (70.87%)	0.018
BMI, median (range)	23.9 (21.4–27.2)	24 (21–27.2)	23.9 (21–26.9)	0.579
Charlson comorbidity index	7 (5–9)	7 (5–9)	6 (5–8)	0.020
Baseline sCr (mg/dL), median (range)	1.7 (1–3.3)	1.4 (0.9–2.4)	1 (0.8–1.7)	<0.001
eGFR (ml/min/1.73 m^2), median (range)	32.5 (15.5–63.3)	44 (21.9–73.8)	63.9 (35.2–88)	<0.001
Comorbidities, n (%)				
Diabetes mellitus, n (%)	276 (55.09%)	189 (50.94%)	97 (47.09%)	0.131
Liver cirrhosis, n (%)	56 (11.18%)	58 (15.63%)	40 (19.42%)	0.011
COPD, n (%)	43 (8.58%)	29 (7.82%)	12 (5.83%)	0.462
CAD, n (%)	156 (31.14%)	102 (27.49%)	52 (25.24%)	0.233
CVA, n (%)	78 (15.57%)	59 (15.90%)	22 (10.68%)	0.185
Hemiplegia, n (%)	22 (4.39%)	20 (5.39%)	6 (2.91%)	0.383
GI bleeding, n (%)	129 (25.75%)	109 (29.38%)	58 (28.16%)	0.479
Dementia, n (%)	11 (2.20%)	12 (3.23%)	9 (4.37%)	0.282
Cancer, n (%)	86 (17.17%)	79 (21.29%)	63 (30.58%)	<0.001
Congestive heart failure, n (%)	194 (48.7%)	159 (58.49%)	68 (44.66%)	<0.001
Laboratory data at ICU admission				
BUN (mg/dL), median (range)	61 (34.5–95.9)	57.7 (27–92)	42 (23.2–68.8)	<0.001
sCr (mg/dL), median (range)	3.7 (2–6.4)	2.7 (1.4–5)	2.3 (1.3–3.8)	<0.001
Lactate (mmol/L), median (range)	2.5 (1.4–5.6)	2.4 (1.3–4.8)	6.3 (2.9–10)	<0.001
Etiology of AKI (except sepsis), n (%)				
Shock	225 (44.91%)	203 (54.72%)	188 (91.26%)	<0.001
Cardiorenal syndrome	206 (41.12%)	134 (36.12%)	53 (25.73%)	<0.001
Drug nephrotoxicity	26 (5.19%)	18 (4.85%)	10 (4.85%)	0.969
Rhabdomyolysis	34 (6.79%)	24 (6.47%)	23 (11.17%)	0.086
Intravascular hemolysis	16 (3.19%)	10 (2.70%)	8 (3.88%)	0.735
Hepatorenal	26 (5.19%)	22 (5.93%)	21 (10.19%)	0.043
ATIN	4 (0.80%)	5 (1.35%)	0 (0%)	0.276
Contrast	38 (7.58%)	24 (6.47%)	13 (6.31%)	0.750
Obstructive	8 (1.60%)	3 (0.81%)	1 (0.49%)	0.472
Others	117 (23.35%)	56 (15.09%)	24 (11.65%)	<0.001

Table 1. *Cont.*

	Non-Sepsis	Sepsis	Septic Shock	*p* Value
At initiation of RRT				
Urine output (mL/24 h), median (range)	450 (150–1095)	250 (70–620)	130 (50–418)	<0.001
AKI risk prediction score, median (range)	22 (17–28)	27 (21–33)	33.5 (26–40)	<0.001
Lactate (mmol/L), median (range)	2.2 (1.3–5.2)	1.6 (1–3.1)	6.6 (3.4–10.7)	<0.001
SOFA score, median (range)	10 (7–13)	12 (10–15)	15 (13–17)	<0.001
qSOFA, median (range)	1 (1–1)	2 (2-3)	2 (2–3)	<0.001
APACHE II score, median (range)	20 (16–25)	25 (21–30)	27 (22.8–33)	<0.001
MODS score, median (range)	9 (7–11)	12 (10–14)	12 (10–15)	<0.001
Site of infection, *n* (%)				
Respiratory	227 (45.31%)	237 (63.88%)	114 (55.34%)	<0.001
GU	156 (31.14%)	129 (34.77%)	53 (25.73%)	0.080
Bacteremia	96 (19.16%)	84 (22.64%)	57 (27.67%)	0.043
Abdomen	41 (8.18%)	40 (10.78%)	33 (16.02%)	0.009
Others	56 (11.18%)	38 (10.24%)	21 (10.19%)	0.880
Indication for dialysis, *n* (%)				
Azotemia	291 (58.08%)	225 (60.65%)	70 (33.98%)	<0.001
Fluid overload	245 (48.90%)	225 (60.65%)	134 (65.05%)	<0.001
Electrolyte imbalance	190 (37.92%)	148 (39.89%)	79 (38.35%)	0.835
Metabolic acidosis	210 (41.92%)	192 (51.75%)	133 (64.56%)	<0.001
Oliguria	275 (54.89%)	255 (68.73%)	164 (79.61%)	<0.001
Uremic encephalopathy	46 (9.18%)	26 (7.01%)	6 (2.91%)	0.014
Dialysis modality, *n* (%)				<0.001
CVVH	128 (25.55%)	110 (29.65%)	133 (64.56%)	
IHD	334 (66.67%)	252 (67.92%)	58 (28.16%)	
SLEDD	39 (7.78%)	9 (2.43%)	15 (7.28%)	
Outcomes of interest				
Dialysis days in hospital, median (range)	12 (4–26)	10 (4–27)	6 (3–15)	0.012
Hospital mortality, *n* (%)	221 (44.11%)	228 (61.46%)	167 (81.07%)	<0.001
90-day ICU free days	63 (0–85)	1 (0–78)	0 (0–0)	<0.001
90-day hospital free days	30 (0–70)	0 (0–53)	0 (0–0)	<0.001
90-day mortality, *n* (%)	246 (49.10%)	253 (68.19%)	172 (83.49%)	<0.001
90-day composite outcome, *n* (%)	352 (70.26%)	296 (79.78%)	175 (84.95%)	<0.001

Paired comparison between the groups. Abbreviations: AKI, acute kidney injury; APACHE; acute physiology and chronic health evaluation; ATIN, acute tubule-interstitial nephritis; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; CVVH, continuous veno-venous hemofiltration; CPR, cardio-pulmonary resuscitation; eGFR, estimated glomerular filtration rate; GSC, Glasgow Coma Scale; GI, gastrointestinal; GU, genitourinary; IABP, intra-aortic balloon pump; ICU, intensive care unit; IHD, intermittent hemodialysis; IQR, interquartile range; MODS, multiple organ dysfunction; RRT, renal replacement therapy; sCr, serum creatinine; SLEDD, sustained low efficiency daily dialysis; SOFA, Sequential Organ Failure Assessment.

Table 2. Clinical characteristics of survivors and non-survivors.

	All	90 Day Survivors	90 Day Mortality	*p* Value	No Dialysis Dependence or Mortality at 90 Days	Dialysis Dependence or Mortality at 90 Days	*p* Value
	(*n* = 1078)	(*n* = 406)	(*n* = 672)		(*n* = 254)	(*n* = 824)	
Baseline characteristics							
Age, median (range)	70 (57.8–79.5)	69 (56.7–77.4)	71 (58.9–81)	0.014	67.7 (53.9–76.8)	70.9 (59.8–80.4)	<0.001
Male gender, *n* (%)	673 (62.43%)	247 (60.84%)	426 (63.39%)	0.401	158 (62.20%)	515 (62.50%)	0.932
BMI, median (range)	23.95 (21.2–27.1)	24.2 (21.5–27.6)	23.7 (21–26.8)	0.870	24.6 (22–27.9)	23.7 (21–26.8)	0.598
Charlson comorbidity index, median (range)	7 (5–9)	7 (5–8.3)	7 (5–9)	0.001	6 (4–8)	7 (5–9)	<0.001
Baseline sCr (mg/dL), median (range)	1.4 (0.9–2.7)	1.8 (1–3.6)	1.3 (0.9–2.3)	<0.001	1.2 (0.9–2.1)	1.5 (0.9–2.8)	<0.001
eGFR (mL/min/1.73 m^2), median (range)	41.79 (20.4–73.6)	31.9 (14.6-64.3)	48.2 (24.4-77.1)	<0.001	49.9 (25.3-78)	40.5 (18.2-71.7)	0.040
Comorbidities							
Diabetes mellitus, *n* (%)	562 (52.13%)	228 (56.16%)	334 (49.70%)	0.040	139 (54.72%)	423 (51.33%)	0.344
Liver cirrhosis, *n* (%)	154 (14.29%)	26 (6.40%)	128 (19.05%)	<0.001	19 (7.48%)	135 (16.38%)	<0.001
COPD, *n* (%)	84 (7.79%)	31 (7.64%)	53 (7.89%)	0.881	19 (7.48%)	65 (7.89%)	0.832
CAD, *n* (%)	310 (28.76%)	130 (32.02%)	180 (26.79%)	0.066	77 (30.31%)	233 (28.28%)	0.530
CVA, *n* (%)	159 (14.75%)	61 (15.02%)	98 (14.58%)	0.843	30 (11.81%)	129 (15.66%)	0.131
Hemiplegia, *n* (%)	48 (4.45%)	19 (4.68%)	29 (4.32%)	0.779	11 (4.33%)	37 (4.49%)	0.914
GI bleeding, *n* (%)	296 (27.46%)	89 (21.92%)	207 (30.80%)	0.002	53 (20.87%)	243 (29.49%)	0.007
Dementia, *n* (%)	32 (2.97%)	7 (1.72%)	25 (3.72%)	0.061	6 (2.36%)	26 (3.16%)	0.515
Cancer, *n* (%)	228 (21.15%)	60 (14.78%)	168 (25.00%)	<0.001	40 (15.75%)	188 (22.82%)	0.016
Congestive heart failure, *n* (%)	553 (51.30%)	205 (50.49%)	348 (50.79%)	0.787	122 (48.41%)	431 (52.31%)	0.019
Parameters at ICU admission							
BUN (mg/dL), median (range)	56 (29.2–89)	63 (35–91)	50.5 (26.4–88)	0.001	51 (26–80.5)	57.7 (30–91.6)	0.192
sCr (mg/dL), median (range)	3 (1.7–5.5)	4.1 (2.2–6.9)	2.6 (1.4–4.5)	<0.001	3 (1.9–5.3)	3 (1.6–5.6)	0.984
Lactate (mmol/L), median (range)	3.1 (1.7–7)	2.6 (1.3–5.2)	3.7 (2–8.6)	<0.001	3 (1.6–6.1)	3.2 (1.7–7.3)	0.030
Etiology of AKI, *n* (%)							
Shock, *n* (%)	616 (57.14%)	165 (40.64%)	451 (67.11%)	<0.001	132 (51.97%)	484 (58.74%)	0.057
Sepsis, *n* (%)	770 (71.43%)	242 (59.61%)	528 (78.57%)	<0.001	153 (60.24%)	617 (74.88%)	<0.001
Cardiorenal syndrome, *n* (%)	393 (36.46%)	170 (41.87%)	223 (33.18%)	0.010	93 (36.61%)	300 (36.41%)	0.952
Nephrotoxic drugs, *n* (%)	54 (5.01%)	27 (6.65%)	27 (4.02%)	0.055	22 (8.66%)	32 (3.88%)	0.002
Rhabdomyolysis, *n* (%)	81 (7.51%)	33 (8.13%)	48 (7.14%)	0.552	28 (11.02%)	53 (6.43%)	0.015
Intravascular hemolysis, *n* (%)	34 (3.15%)	14 (3.45%)	20 (2.98%)	0.667	11 (4.33%)	23 (2.79%)	0.220
Hepatorenal syndrome, *n* (%)	69 (6.40%)	4 (0.99%)	65 (9.67%)	<0.001	4 (1.57%)	65 (7.89%)	<0.001
ATIN, *n* (%)	9 (0.83%)	5 (1.23%)	4 (0.60%)	0.309	2 (0.79%)	7 (0.85%)	0.999
Contrast exposure, *n* (%)	75 (6.96%)	33 (8.13%)	42 (6.25%)	0.240	22 (8.66%)	53 (6.43%)	0.222
Obstruction, *n* (%)	12 (1.11%)	6 (1.48%)	6 (0.89%)	0.375	3 (1.18%)	9 (1.09%)	1.000
Others, *n* (%)	197 (18.27%)	103 (25.37%)	94 (13.99%)	<0.001	61 (24.02%)	136 (16.50%)	0.007

Table 2. *Cont.*

	All	90 Day Survivors	90 Day Mortality	*p* Value	No Dialysis Dependence or Mortality at 90 Days	Dialysis Dependence or Mortality at 90 Days	*p* Value
	(*n* = 1078)	(*n* = 406)	(*n* = 672)		(*n* = 254)	(*n* = 824)	
Parameters at RRT initiation							
Urine output (mL/24 h), median (range)	300 (90–822.5)	490 (160–1223)	204 (70–595)	<0.001	520 (180–1305)	250 (75–670)	<0.001
AKI risk prediction score	25 (19–33)	21 (16–28.3)	27.5 (22–35)	<0.001	22 (17–29.3)	26 (21–34)	<0.001
Lactate (mmol/L), median (range)	3.2 (1.6–7.6)	2.3 (1.2–5.4)	3.9 (1.9–9.1)	<0.001	2.8 (1.4–6.5)	3.3 (1.6–8.2)	0.090
SOFA score, median (range)	12 (8–15)	9 (7–12)	13 (10–16)	<0.001	10 (7–13)	12 (9–15)	<0.001
qSOFA, median (range)	2 (1–2)	1 (1–2)	2 (1–2)	<0.001	1 (1–2)	2 (1–2)	<0.001
qSOFA ≥ 2, *n* (%)	582 (53.99%)	153 (37.66%)	429 (63.84%)	<0.001	107 (42.13%)	475 (57.65%)	<0.001
APACHE II score, median (range)	24 (19–28)	20 (16–25)	25 (21–30)	<0.001	21 (16–26)	24 (20–29)	<0.001
MODS score, median (range)	11 (9–13)	10 (7–12)	11 (9–14)	<0.001	10 (7.5–13)	11 (9–13)	0.008
Sepsis 3 criteria							
Sepsis, *n* (%)	577 (53.53%)	152 (37.44%)	425 (63.24%)	<0.001	106 (41.73%)	471 (57.16%)	<0.001
Septic shock, *n* (%)	206 (19.11%)	34 (8.37%)	172 (25.60%)	<0.001	31 (12.20%)	175 (21.24%)	0.001
Site of infection, *n* (%)							
Respiratory	578 (53.62%)	188 (46.31%)	390 (58.04%)	<0.001	1113 (44.49%)	465 (56.43%)	0.001
GU	338 (31.35%)	134 (33.00%)	204 (30.36%)	0.364	83 (32.68%)	255 (30.95%)	0.603
Bacteremia	237 (21.99%)	60 (14.78%)	177 (26.34%)	<0.001	43 (16.93%)	194 (23.54%)	0.026
Abdomen	114 (10.58%)	39 (9.61%)	75 (11.16%)	0.421	32 (12.60%)	82 (9.95%)	0.230
Others	115 (10.67%)	37 (9.11%)	78 (11.61%)	0.199	25 (9.84%)	90 (10.92%)	0.626
Indication for RRT							
Azotemia, *n* (%)	586 (54.36%)	220 (54.19%)	366 (54.46%)	0.929	113 (44.49%)	473 (57.40%)	<0.001
Fluid overload, *n* (%)	604 (56.03%)	200 (49.26%)	404 (60.12%)	0.001	132 (51.97%)	472 (57.28%)	0.136
Electrolyte imbalance, *n* (%)	417 (38.68%)	160 (39.41%)	257 (38.24%)	0.704	108 (42.52%)	309 (37.50%)	0.151
Metabolic acidosis, *n* (%)	535 (49.63%)	180 (44.33%)	355 (52.83%)	0.007	114 (44.88%)	421 (51.09%)	0.084
Oliguria, *n* (%)	694 (64.38%)	205 (50.49%)	489 (72.77%)	<0.001	122 (48.03%)	572 (69.42%)	<0.001
Uremic encephalopathy, *n* (%)	78 (7.24%)	38 (9.36%)	40 (5.95%)	0.036	16 (6.30%)	62 (7.52%)	0.510
First Dialysis modality, *n* (%)				<0.001			0.239
CVVH	371 (34.42%)	97 (23.89%)	274 (40.77%)		79 (31.10%)	292 (35.44%)	
IHD	644 (59.74%)	289 (71.18%)	355 (52.83%)		163 (64.17%)	481 (58.37%)	
SLEDD	63 (5.84%)	20 (4.93%)	43 (6.40%)		12 (4.72%)	51 (6.19%)	
Outcomes of interest							
90-day ICU free days	7 (0–81)	81 (69–86)	0(0–1)	<0.001	80 (68–86)	0 (0–54.5)	<0.001
90-day hospital free days	0 (0–59.25)	63 (44.5–76)	0(0–0)	<0.001	63 (42–76)	0 (0–2.5)	<0.001
Days of RRT in hospital, median (range)	10 (4–24)	11 (3–26)	9.5 (4–22.8)	0.461	5.5 (2–13.3)	12 (4–27.8)	<0.001

Abbreviations: AKI, acute kidney injury; APACHE; acute physiology and chronic health evaluation; ATIN, acute tubule-interstitial nephritis; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; CVVH, continuous veno-venous hemofiltration; CPR, cardio-pulmonary resuscitation; eGFR, estimated glomerular filtration rate; GSC, Glasgow Coma Scale; GI, gastrointestinal; GU, genitourinary; IABP, intra-aortic balloon pump; ICU, intensive care unit; IHD, intermittent hemodialysis; IQR, interquartile range; MODS, multiple organ dysfunction; RRT, renal replacement therapy; sCr, serum creatinine; SLEDD, sustained low efficiency daily dialysis; SOFA, Sequential Organ Failure Assessment.

3.4. Sepsis-3 Criteria versus 90-Day Outcomes

Multivariable analysis showed that AKI-D patients with sepsis or septic shock at initiation of RRT had a significantly higher risk of mortality at 90 days compared to AKI-D patients without sepsis (Table 3 and Figure 2a). There was a positive correlation between the Sepsis-3 criteria and APACHE II score ($r = 0.385$, $p < 0.001$), SOFA score ($r = 0.391$, $p < 0.001$) and AKI risk prediction score ($r = 0.359$, $p < 0.001$). AKI-D patients with septic shock had a greater incremental increase in 90-day mortality across all deciles of APACHE II at initiation of RRT compared to AKI-D patients with qSOFA ≥ 2 (Figure S4, Table S2).

Table 3. Multivariable risk model for hospital mortality or composite outcome at discharge.

Sepsis	Non-Shock Sepsis vs Non-Sepsis			Septic Shock vs. Non-Sepsis		
Outcome of interests	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Hospital mortality	1.12	0.91–1.37	0.276	1.48	1.17–1.88	0.001
Hospital composite outcomes	0.97	0.80–1.17	0.732	1.24	1.08–1.47	0.047
For 90-day mortality	1.23	1.02–1.47	0.027	1.39	1.11–1.75	0.004
For 90-day composite outcome	1.26	1.03–1.53	0.022	1.45	1.15–1.83	0.002
For 90-day weaning from dialysis	0.96	0.76–1.22	0.760	0.65	0.45–0.95	0.026

p; paired comparison between the groups. All relevant covariates included in the multi-variable analysis, including age, sex, baseline comorbidities, indication for dialysis, etiology of AKI, kidney profile and SOFA score at dialysis initiation, dialysis modality, and some of their interactions. Abbreviations: AKI, acute kidney injury; CI, confidence interval.

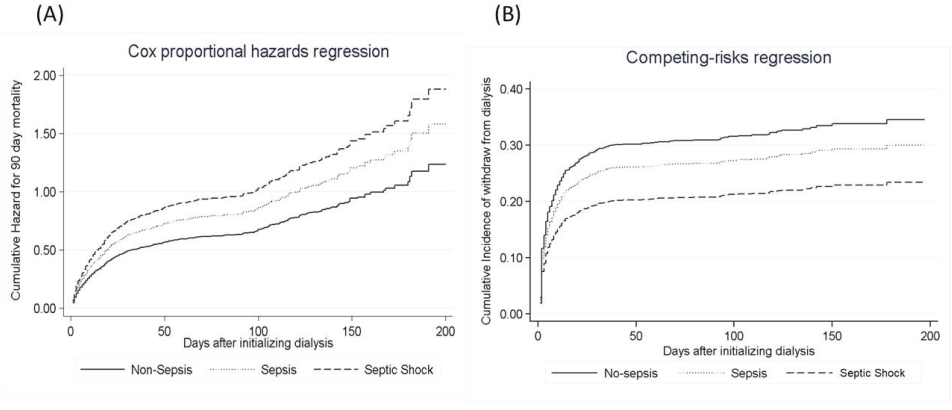

Figure 2. Cox proportional hazards models. (**A**) Cox proportional hazards models are plotted to model the probability of free from 90 days mortality, stratified by Sepsis-3 status. (**B**) Model the risk of chronic dialysis, taking mortality as a competing risk.

3.5. Sepsis per Sepsis-3 Criteria versus the Risk of Dialysis Dependence

Multivariable analysis showed that after controlling for mortality, AKI-D patients with septic shock who survived had a significantly lower likelihood of weaning from dialysis, when compared to AKI-D patients without sepsis (hazard ratio (HR), 0.65, $p = 0.026$) (Table 3). There was no significant difference in likelihood of weaning from dialysis at 90 days between AKI-D patients without sepsis and AKI-D patients with sepsis but without septic shock (HR 0.96, $p = 0.760$) (Table 3, Figure 2b).

3.6. Evaluation of Sepsis-3 Criteria in Combination with AKI Risk Prediction Score and SOFA Score versus the 90 Days Mortality

Combining the Sepsis-3 criteria with the AKI risk prediction score at initiation of RRT led to a significant increase in risk stratification (total NRI = 0.07; 95% CI, 0.02–0.11; $p < 0.01$). The majority of

this effect came from those without death (NRI event = 0.04; 95% CI, 0.01–0.07; $p = 0.039$). Likewise, the total IDI was significant (0.02, 95% CI, 0.01–0.02; $p < 0.001$).

In case of sequential diagnosis of sepsis according to the Sepsis-3 criteria, we added Sepsis-3 to the qSOFA criteria in estimating the risk of 90-day mortality after initiation of dialysis. This led to a significant increase in risk stratification (total NRI = 0.11; 95% CI, 0.04–0.19; $p = 0.004$). The majority of this effect came from those without death (NRI event = 0.07; $p = 0.03$), whereas the NRI with death was 0.05 (NRI non-event = 0.04, $p = 0.049$) (Figure S3). Similarly, the total integrated discrimination improvement (IDI) was significant at 0.06 (95% CI, 0.03 to 0.05; $p < 0.001$).

4. Discussion

To our best knowledge, this is the first study that applied the most recent Sepsis-3 screening criteria to the patients with AKI-D. The key findings of this large multi-center prospective study are that sepsis affects 53.5% of patients with AKI-D, and that at time of RRT 19.1% of patients had septic shock. The chances of renal recovery at 90 days were significantly lower in AKI-D patients with septic shock compared to those without sepsis. Presence of sepsis per Sepsis-3 criteria in AKI-D patients is associated with higher mortality rate and composite outcome at 90 days. Combining the Sepsis-3 criteria with the AKI risk score or SOFA criteria led to a further improvement in risk identification.

A 53.5% prevalence of sepsis among AKI-D patients is slightly higher than previously reported [18]. This may be a reflection of our specific patient cohort of critically ill ICU patients or a result of using the Sepsis-3 criteria. Similarly, in-hospital mortality rate of this cohort was high, including its non-septic controls (44.1%), which again may be explained by the characteristics of our patient population (older age, high comorbidity and acute severity of illness scores) and the criteria used to identify patients.

4.1. Association of Mortality and Non-Recovery from Dialysis

Patients with AKI requiring RRT constitute a high-risk group. An accurate prognostic assessment is crucial for clinical management and planning of future care. The Sepsis-3 criteria identified AKI-D patients with a suspected or confirmed infection who were at increased risk of mortality, and a combo endpoint of mortality or dialysis dependence at 90 days. Our data also showed that the criteria to define septic shock (i.e., a raised serum lactate level and the need for inotropic support) indeed identified the subgroup of patients with the highest mortality (>80%).

The Sepsis-3 criteria correlated with SOFA and APACHE II scores at initiation of dialysis which underpins the potential use of Sepsis-3 in a critical care setting. It can be hypothesized that a higher Sepsis-3 score also reflects a higher degree of systemic inflammation.

Data on the risk of long-term dialysis dependence in AKI-D patients with sepsis are conflicting [18, 19], similar to a French multicentric study [19]. We found a statistically significant trend towards reduced likelihood of recovery from dialysis in AKI-D patients with septic shock compared to those without sepsis. In contrast, Bagshaw and colleagues analyzed data from 2000/2001 and reported improved renal recovery in patients with septic AKI compared to patients without sepsis [18]. It is important to note that there were differences in patient characteristics, criteria to define sepsis and clinical care. Moreover, our analysis has extra strength by including mortality as a competing outcome for analysis of dialysis dependence.

4.2. Sepsis-3 Criteria and Outcome

It is important to emphasize that most AKI patients already had a SOFA score of two or more at the time when RRT was initiated simply as a result of AKI and oliguria. It is possible that different delta SOFA cut-off points are necessary for this patient cohort to differentiate sepsis from non-sepsis (Figure S6). As such, our results provide confirmation that AKI-D patients with sepsis, as defined by Sepsis-3 criteria, had higher mortality and less withdraw from dialysis in AKI-D patients with septic shock.

Combining the Sepsis-3 criteria with a clinical AKI risk prediction score resulted in greater IDI and NRI, and improved the ability associating subsequent death. Given the lack of appropriate risk

stratification tools for septic AKI patients requiring RRT, the new Sepsis-3 criteria may associate patients outcome (Figures S3 and S5).

4.3. Strengths and Limitations

This is the first study that applied the new consensus criteria for sepsis to AKI-D patients, a cohort of patients that is known to have a high risk of sepsis and also a high risk of poor outcomes. Using a large multi-center national database with prospectively collected representative data from 30 ICUs, we showed for the first time that the Sepsis-3 criteria identified a group of patients that were at higher risk of dying or remaining dialysis dependent after discharge. With complete follow-up for 90 days after discharge from hospital, we focused on patient-centered outcomes (mortality and long-term dialysis dependence) and provide important data for a group of patients that is commonly seen in ICUs worldwide. Further in-depth studies are mandatory before we can make any positive comment on this issue.

The limitations of our study are related to any observational cohort study and include the possibility of both unmeasured and residual confounding factors. We could not identify how many patients received early goal-directed therapy in our cohort, however the nationwide education program instituted in Taiwan is able to positively change critical-care physician behavior in sepsis care following the Surviving Sepsis Campaign guidelines. We also acknowledge that we recorded the worst value of SOFA criteria within 24 h before initiation of dialysis. Although this approach is consistent with clinical practice, the daily SOFA score or qSOFA value may not reflect the value immediately before initiation of RRT.

5. Conclusions

More than half of the critically ill AKI patients treated with dialysis had sepsis, as defined by the Sepsis-3 criteria, at dialysis initiation, and one-fifth of AKI-D patients had septic shock screened by Sepsis-3 criteria. Having sepsis and septic shock were independently associated with 90-day mortality among these ICU AKI-D patients. Among survivors, AKI-D patients with septic shock had a significantly reduced chance of recovering sufficient renal function to wean-off dialysis, when compared to those without sepsis. These findings provide support for the use of Sepsis-3 criteria in the AKI-D patients.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/10/1731/s1, Figure S1: Distribution of Patients by SOFA Score, and qSOFA Score at initiation of acute dialysis (n = 1,078), X axis is %, Figure S2: Prognostic Accuracy of Sepsis-3 components among AKI-D patients with suspected or confirmed infection at dialysis initiation. a) 90 day mortality Receiver-operator characteristic curves discriminate (denoted area under the receiver operating characteristic curve): Sepsis-3, (0.650), qSOFA score ≥ 2 (0.631), AKI risk prediction score (0.688) and increased SOFA ≥ 2 (0.520). b) 90 day composite outcome. Receiver-operator characteristic curves discriminate (denoted area under the receiver operating characteristic curve): Sepsis-3, (0.587), qSOFA score ≥ 2 (0.578), AKI risk prediction score (0.596) and increased SOFA ≥ 2 (0.501), Figure S3: Decision curve analysis (DCA) plot to assess the clinical consequences of screening AKI-D patients for risk of 90 day mortality using sepsis-3 score in addition to AKI risk prediction score. Y-axis is the net benefit of the decision strategy. Net benefit is the net proportion of patients with 90 day mortality in whom a prediction model would provide benefit without applying a prediction model to patients with good outcomes. For AKI patients initiated on dialysis, forecasting with the AKI predicting model and Sepsis-3 criteria in combination would yield no net benefit. For risk thresholds between 30 and 80% the superior strategy, forecasting with the AKI risk prediction score and Sepsis-3 is beneficial. For moderate to high-risk thresholds (80 to 100%), there is no net benefit from using the AKI risk prediction score together with the Sepsis-3 model, Figure S4. Hazard Ratios for 90-day Mortality comparing different criteria of Sepsis-3 definition, Figure S5: Scatter plot of AKI risk prediction forecasted probabilities without and with the Sepsis-3 score. Note that some AKI-D patients have higher predicted risks in the model with Sepsis-3 values than in the model without Sepsis-3 (dots in right lower corner of the graph), Figure S6. Generalized additive model (GAM) plot for the probability of 90-day mortality against delta SOFA, in term of the difference of SOFA at initializing dialysis and ICU admission, initiating the subject-specific (longitudinal) random effects expressed as the logarithm of the odds (logit). The relationship of delta SOFA with these variables was further illustrated by GAM analysis, adjusted for Acute Physiology and Chronic Health Evaluation (APACHEII) at ICU admission, sex and age, showing that qSOFA levels at dialysis initializing could predict risk of mortality. GAM results showed the best cut-off points predicting 90 day mortality were a change of SOFA score by more than 10, Table S1: Integer risk score for prediction of 60-day mortality in critically ill patients with AKI requiring dialysis, Table S2. Diagnostic performance of Sepsis-3 criteria in prediction of 90-day hospital mortality.

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Abbreviations

APACHEII	Acute Physiology and Chronic Health Evaluation II
AKI	acute kidney injury
AKI-D	acute kidney injury with dialysis
MODS	multiple organ dysfunction syndrome
qSOFA	quick Sequential Organ Failure Assessment
RRT	renal replacement therapy
SOFA	Sequential Organ Failure Assessment
ICU	intensive care units

References

1. Hoste, E.A.; Bagshaw, S.M.; Bellomo, R.; Cely, C.M.; Colman, R.; Cruz, D.N.; Edipidis, K.; Forni, L.G.; Gomersall, C.D.; Govil, D.; et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med.* **2015**, *41*, 1411–1423. [CrossRef] [PubMed]
2. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 801–810. [CrossRef] [PubMed]
3. Rhee, C.; Dantes, R.; Epstein, L.; Murphy, D.J.; Seymour, C.W.; Iwashyna, T.J.; Kadri, S.S.; Angus, D.C.; Danner, R.L.; Fiore, A.E.; et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009–2014. *JAMA* **2017**, *318*, 1241–1249. [CrossRef] [PubMed]

4. Hsu, C.Y.; McCulloch, C.E.; Fan, D.; Ordonez, J.D.; Chertow, G.M.; Go, A.S. Community-based incidence of acute renal failure. *Kidney Int.* **2007**, *72*, 208–212. [CrossRef] [PubMed]
5. Shiao, C.C.; Wu, P.C.; Wu, V.C.; Lin, J.H.; Pan, H.C.; Yang, Y.F.; Lai, T.S.; Huang, T.M.; Wu, C.H.; Yang, W.S.; et al. Nationwide epidemiology and prognosis of dialysis-requiring acute kidney injury (NEP-AKI-D) study: Design and methods. *Nephrology (Carlton)* **2016**, *21*, 758–764. [CrossRef] [PubMed]
6. Chen, Y.Y.; Wu, V.C.; Huang, W.C.; Yeh, Y.C.; Wu, M.S.; Huang, C.C.; Wu, K.D.; Fang, J.T.; Wu, C.J.; CAKS Group. Norepinephrine Administration Is Associated with Higher Mortality in Dialysis Requiring Acute Kidney Injury Patients with Septic Shock. *J. Clin. Med.* **2018**, *7*, 274. [CrossRef] [PubMed]
7. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.S.; Chen, Y.W.; Chen, Y.M.; Hu, F.C.; Lin, Y.H.; Tsai, P.R.; Wu, K.D. Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: Effect on postoperative outcomes. *J. Am. Coll. Surg.* **2007**, *205*, 266–276. [CrossRef] [PubMed]
8. Lin, Y.F.; Ko, W.J.; Wu, V.C.; Chen, Y.S.; Chen, Y.M.; Hu, F.C.; Shiao, C.C.; Wu, M.S.; Chen, Y.W.; Li, W.Y.; et al. A modified sequential organ failure assessment score to predict hospital mortality of postoperative acute renal failure patients requiring renal replacement therapy. *Blood Purif.* **2008**, *26*, 547–554. [CrossRef] [PubMed]
9. Shiao, C.C.; Ko, W.J.; Wu, V.C.; Huang, T.M.; Lai, C.F.; Lin, Y.F.; Chao, C.T.; Chu, T.S.; Tsai, H.B.; Wu, P.C.; et al. U-curve association between timing of renal replacement therapy initiation and in-hospital mortality in postoperative acute kidney injury. *PLoS ONE* **2012**, *7*, e42952. [CrossRef] [PubMed]
10. Seymour, C.W.; Liu, V.X.; Iwashyna, T.J.; Brunkhorst, F.M.; Rea, T.D.; Scherag, A.; Rubenfeld, G.; Kahn, J.M.; Shankar-Hari, M.; Singer, M.; et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 762–774. [CrossRef] [PubMed]
11. Raith, E.P.; Udy, A.A.; Bailey, M.; McGloughlin, S.; MacIsaac, C.; Bellomo, R.; Pilcher, D.V. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA* **2017**, *317*, 290–300. [CrossRef] [PubMed]
12. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.W.; Lin, Y.F.; Shiao, C.C.; Chen, Y.M.; Chen, Y.S.; Tsai, P.R.; Hu, F.C.; et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive Care Med.* **2008**, *34*, 101–108. [CrossRef] [PubMed]
13. Bellomo, R.; Kellum, J.A.; Ronco, C.; Wald, R.; Martensson, J.; Maiden, M.; Bagshaw, S.M.; Glassford, N.J.; Lankadeva, Y.; Vaara, S.T.; et al. Acute kidney injury in sepsis. *Intensive Care Med.* **2017**, *43*, 816–828. [CrossRef] [PubMed]
14. Demirjian, S.; Chertow, G.M.; Zhang, J.H.; O'Connor, T.Z.; Vitale, J.; Paganini, E.P.; Palevsky, P.M.; VA/NIH Acute Renal Failure Trial Network. Model to predict mortality in critically ill adults with acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 2114–2120. [CrossRef] [PubMed]
15. Chen, Y.S.; Ko, W.J.; Lin, F.Y.; Huang, S.C.; Chou, T.F.; Chou, N.K.; Hsu, R.B.; Wang, S.S.; Chu, S.H. Preliminary result of an algorithm to select proper ventricular assist devices for high-risk patients with extracorporeal membrane oxygenation support. *J. Heart Lung Transplant.* **2001**, *20*, 850–857. [CrossRef]
16. Shu, K.H.; Wang, C.H.; Wu, C.H.; Huang, T.M.; Wu, P.C.; Lai, C.H.; Tseng, L.J.; Tsai, P.R.; Connolly, R.; Wu, V.C. Urinary pi-glutathione S-transferase Predicts Advanced Acute Kidney Injury Following Cardiovascular Surgery. *Sci. Rep.* **2016**, *6*, 26335. [CrossRef] [PubMed]
17. Wang, J.J.; Chi, N.H.; Huang, T.M.; Connolly, R.; Chen, L.W.; Chueh, S.J.; Kan, W.C.; Lai, C.C.; Wu, V.C.; Fang, J.T.; et al. Urinary biomarkers predict advanced acute kidney injury after cardiovascular surgery. *Crit. Care* **2018**, *22*, 108. [CrossRef] [PubMed]
18. Bagshaw, S.M.; Uchino, S.; Bellomo, R.; Morimatsu, H.; Morgera, S.; Schetz, M.; Tan, I.; Bouman, C.; Macedo, E.; Gibney, N.; et al. Septic acute kidney injury in critically ill patients: Clinical characteristics and outcomes. *Clin. J. Am. Soc. Nephrol.* **2007**, *2*, 431–439. [CrossRef] [PubMed]
19. Venot, M.; Weis, L.; Clec'h, C.; Darmon, M.; Allaouchiche, B.; Goldgran-Toledano, D.; Garrouste-Orgeas, M.; Adrie, C.; Timsit, J.F.; Azoulay, E. Acute Kidney Injury in Severe Sepsis and Septic Shock in Patients with and without Diabetes Mellitus: A Multicenter Study. *PLoS ONE* **2015**, *10*, e0127411. [CrossRef] [PubMed]

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Outcome Prediction of Acute Kidney Injury Biomarkers at Initiation of Dialysis in Critical Units

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Abstract: The ideal circumstances for whether and when to start RRT remain unclear. The outcome predictive ability of acute kidney injury (AKI) biomarkers measuring at dialysis initializing need more validation. This prospective, multi-center observational cohort study enrolled 257 patients with AKI undergoing renal replacement therapy (RRT) shortly after admission. At the start of RRT, blood and urine samples were collected for relevant biomarker measurement. RRT dependence and all-cause mortality were recorded up to 90 days after discharge. Areas under the receiver operator characteristic (AUROC) curves and a multivariate generalized additive model were applied to predict outcomes. One hundred and thirty-five (52.5%) patients died within 90 days of hospital discharge. Plasma c-terminal FGF-23 (cFGF-23) had the best discriminative ability (AUROC, 0.687) as compared with intact FGF-23 (iFGF-23) (AUROC, 0.504), creatinine-adjusted urine neutrophil gelatinase-associated lipocalin (AUROC, 0.599), and adjusted urine cFGF-23 (AUROC, 0.653) regardless whether patients were alive or not on day 90. Plasma cFGF-23 levels above 2050 RU/mL were independently associated with higher 90-day mortality (HR 1.76, $p = 0.020$). Higher cFGF-23 levels predicted less weaning from dialysis in survivors (HR, 0.62, $p = 0.032$), taking mortality as a competing risk. Adding cFGF-23 measurement to the AKI risk predicting score significantly improved risk stratification and 90-day mortality prediction (total net reclassification improvement = 0.148; $p = 0.002$). In patients with AKI who required RRT, increased plasma cFGF-23 levels correlated with higher 90-day overall mortality after discharge and predicted worse kidney recovery in survivors. When coupled to the AKI risk predicting score, cFGF-23 significantly improved mortality risk prediction. This observation adds evidence that cFGF-23 could be used as an optimal timing biomarker to initiate RRT.

Keywords: acute kidney injury; biomarker; fibroblast growth factor-23; kidney injury molecule-1; mortality; neutrophil gelatinase-associated lipocalin; renal replacement therapy

1. Background

Renal replacement therapy (RRT) is life-saving in patients with acute kidney injury (AKI) but is not devoid of serious complications and severe adverse events [1]. Patients who, even temporarily, require RRT also may develop more frequently long-term or end-stage renal disease (ESRD) and have a higher mortality risk [2]. The need for and the optimal timing to initiate RRT are crucial yet unresolved issues [1,3].

Nephrologists continuously look out for kidney specific biomarkers that assist in fine-tuning of diagnosis, treatment, and prognosis of AKI [4]. Few biomarkers were validated as outcome-specific biomarkers in critically ill patients at initiation of RRT. Urine neutrophil gelatinase-associated lipocalin (NGAL) was one of the first biomarkers to be validated for predicting short-term mortality in patients with advanced AKI [5] and recently became part of the indicators to decide early start of dialysis [6]. Interleukin-18 (IL-18) at the commencement of dialysis could also predict hospital mortality in critically ill patients [7]. Adding plasma interleukin-8 to a parsimonious clinical model (i.e., age, mean arterial pressure, mechanical ventilation, and bilirubin) augmented prediction of renal recovery and AKI mortality compared with using only the clinical variables [8].

Fibroblast growth factor 23 (FGF-23), a peptide initially recognized for its phosphaturic role in rare genetic or acquired hypophosphatemia disorders [9], is one of the most recently proposed kidney biomarkers. FGF-23 acts as a hormone that significantly influences phosphate, vitamin D, and bone mineral homeostasis [10]. Several research groups have proposed cFGF-23 as a biomarker for predicting early occurrence of AKI, evaluating prognosis of chronic kidney disease (CKD), and estimating cardiovascular morbidity and mortality [11–15].

An important area of AKI research particularly focuses on reinforcing current dialysis requiring AKI by adding measurement of (a) sensitive biomarker (s) to assess the impact of RRT on relevant patient outcome variables. Within this perspective, we designed a study to evaluate the predictive capacity of various structural and functional kidney biomarkers (including the novel markers cFGF-23 and iFGF-23) and disease severity scores, measured at initiation of RRT, on survival and renal function recovery in a cohort of AKI patients.

2. Methods

2.1. Registration of Clinical Trials

This study was approved by the University's Institutional Review Board (201409024RINB in National Taiwan University Hospital, 01-X16-059 in Buddhist Tzu Chi General Hospital, and TYGH104007 in Taoyuan General Hospital) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT01503710, Principal investigator: V.-C.W, Date of registration: 28 February 2012).

2.2. Study Population

The study was conducted by the National Taiwan University Study Group on Acute Renal Failure (NSARF) and based on a prospectively created AKI database [16–20]. From August 2011 until January 2015, 257 AKI patients who required RRT after intensive care unit (ICU) admission were prospectively enrolled. Exclusion criteria included: age <18 years, previous nephrectomy, renal transplantation or RRT treatment, ICU or hospital length of stay of respectively <2 days and >180 days during the index hospitalization, and AKI caused by urologic surgery induced injury, vasculitis, obstruction, glomerulonephritis, interstitial nephritis, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.

2.3. Data Collection

Baseline characteristics, including demographic data, co-morbidities, the cause of AKI. For the risk prediction before initializing dialysis, the individual AKI risk predicting score was calculated [21]. The worst physiological values and biochemical data on the index day were recorded.

Baseline serum creatinine (sCr) was the nadir value obtained after the previous admission in those who had more than one admission within 1 year before the index admission, or estimated with the Modification of Diet in Renal Disease equation (assuming an average eGFR of 75 mL/min/1.73 m^2) [22]. Peak sCr was defined as the highest sCr before RRT initiation in the ICU. Indication for dialysis and organ failure were defined as previously reported [16,23,24] (Supplemental Data file).

RRT modalities in each patient were initially chosen by the attending physician and adapted according to hemodynamic evaluation and evolution by the critical care nephrologist (Supplemental Data file).

2.4. Measurements of Kidney Biomarkers

The urine samples, collected in separate polypropylene tubes containing sodium azide at dialysis initiation, were stored at −80 °C until required. Each specimen was centrifuged (800× *g* at 4 °C for 5 min) and the supernatant was collected for ELISA analysis.

Kidney biomarker levels were assessed with a human FGF-23 C-terminal/intact-terminal ELISA kit (Immutopics; San Clemente, CA, USA), a human KIM-1, and a lipocalin-2/NGAL ELISA kit (R&D Systems, Inc., Minneapolis, MN, USA).

The cFGF-23 and iFGF-23 values were expressed in relative units (RU)/mL and pg/mL, respectively. The coefficient of variation was 4.4% for iFGF-23 and 4.0% for cFGF-23. The lower limits for detection of cFGF-23, iFGF-23, KIM-1 and NGAL were 0.156 RU/mL, 0.2 pg/mL, 0.046 ng/mL, and 0.04 ng/mL, respectively were completed as described by the manufacturer's protocol and performed in duplicate. 1,25 di hydroxyvitamin D was measured using DiaSorin radioimmunoassay assays kit (Stillwater, MN, USA) and total 25-hydroxyvitamin D was measured using an electro-chemiluminescence (Elecsys® Vitamin D total, Cobas, Roche©). Urine creatinine levels were measured with the Jaffe assay, with standardization of the isotope dilution mass spectrometry traceable reference.

2.5. Outcome Definitions

Primary clinical endpoints were 90-day mortality after hospital discharge and dialysis dependency at 90 days in survivors. Secondary end-points included a 90-day composite outcome (ongoing dialysis or 90-day mortality after discharge), in-hospital mortality, and a composite outcome at discharge (ongoing dialysis or mortality at discharge). All patients were followed until death or for a time span exceeding 90 days after discharge, whichever occurred first. Successful withdrawal from dialysis was defined as surviving without dialysis at the end of study.

2.6. Statistical Analysis

All the univariate significant and non-significant relevant covariates, including age, sex, baseline comorbidities, indication for dialysis, etiology of AKI, kidney function profile (e.g., baseline eGFR and candidate biomarkers, candidate biomarkers and SOFA score at dialysis initiation, dialysis modality, and some of their interactions were put on the variable lists to be selected (Table 1). Two-sample student's *t*-test was used to analyze continuous data and χ^2 test or Fisher's exact test was used to analyze categorical data. The accumulated hazard ratio was modeled by Cox regression models and adjusted for the covariates for the outcomes of interest (Supplemental Data file). The significance levels for entry (SLE) and for stay (SLS) were set to 0.15 for being conservative. Then, with the aid of substantive knowledge, the best candidate final logistic regression model was identified manually by dropping the covariates with $p > 0.05$ one at a time until all regression coefficients were significantly different from 0.

Table 1. Clinical characteristics of patient grouped by 90 days outcome.

	All	90-Day Survival	90-Day Mortality	*p*	90-Day Composite Outcome (−)	90-Day Composite Outcome (+)	*p*
	(*n* = 257)	(*n* = 122)	(*n* = 135)		(*n* = 76)	(*n* = 181)	
Patient characteristics							
Age	65.7 ± 16.6	63.4 ± 16.0	67.8 ± 16.9	0.035	61.3 ± 17.5	67.6 ± 15.9	0.005
Gender (male (%))	167 (65.0%)	82 (67.2%)	85 (63.0%)	0.514	54 (71.1%)	113 (62.4%)	0.200
Baseline creatinine (mg/dL)	2.0 ± 1.6	2.5 ± 1.9	1.5 ± 1.1	<0.001	1.8 ± 1.3	2.1 ± 1.7	0.220
eGFR (MDRD) (mL/min/1.73 m^2)	55.6 ± 41.0	48.3 ± 44.2	62.2 ± 36.9	0.006	63.3 ± 47.6	52.3 ± 37.6	0.428
Co-morbidities							
Diabetes mellitus	115 (44.7%)	61 (50.0%)	54 (40.0%)	0.132	33 (43.4%)	82 (45.3%)	0.891
Cirrhosis	9 (3.5%)	3 (2.5%)	6 (4.4%)	0.505	2 (2.6%)	7 (3.9%)	0.999
COPD	15 (5.8%)	5 (4.1%)	10 (7.4%)	0.297	5 (6.6%)	10 (5.5%)	0.777
CAD	54 (21.0%)	24 (19.7%)	30 (22.2%)	0.648	18 (23.7%)	36 (19.9%)	0.505
CVA	24 (9.3%)	9 (7.4%)	15 (11.1%)	0.392	4 (5.3%)	20 (11.0%)	0.166
Congestive heart failure				0.683			0.780
0	67 (26.1%)	33 (27.0%)	34 (25.2%)		19 (25.0%)	48 (26.5%)	
I	100 (38.9%)	43 (35.2%)	57 (42.2%)		28 (36.8%)	72 (39.8%)	
II	51 (19.8%)	24 (19.7%)	27 (20.0%)		14 (18.4%)	37 (20.4%)	
III	31 (12.1%)	17 (13.9%)	14 (10.4%)		12 (15.8%)	19 (10.5%)	
Laboratory data at ICU admission							
BUN (mg/dL)	48.0 ± 33.5	58.1 ± 34.5	38.9 ± 29.9	<0.001	48.9 ± 36.6	47.7 ± 32.2	0.783
pH	7.4 ± 0.1	7.4 ± 0.8	7.4 ± 0.1	0.659	7.4 ± 0.1	7.4 ± 0.1	0.612
FiO_2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.916	5 ± 0.2	0.5 ± 0.2	0.218
SBP (mmHg)	121.0 ± 28.4	129.8 ± 28.8	113.0 ± 25.6	<0.001	126.0 ± 25.6	118.8 ± 29.3	0.063
GCS	11.9 ± 4.2	12.3 ± 4.0	11.6 ± 4.4	0.164	11.9 ± 4.1	11.9 ± 4.3	0.948
SOFA	8.9 ± 3.5	8.3 ± 3.1	9.5 ± 3.7	0.008	8.7 ± 3.4	9.1 ± 3.6	0.410
APACHE II	16.3 ± 6.2	15.6 ± 6.0	9.5 ± 3.8	0.094	15.0 ± 6.4	16.9 ± 6.0	0.025
MODS	5.9 ± 3.7	5.5 ± 3.4	6.4 ± 3.8	0.040	5.7 ± 3.3	6.0 ± 3.8	0.507

Table 1. *Cont.*

	All	90-Day Survival	90-Day Mortality	*p*	90-Day Composite Outcome (−)	90-Day Composite Outcome (+)	*p*
	(*n* = 257)	(*n* = 122)	(*n* = 135)		(*n* = 76)	(*n* = 181)	
Etiology of AKI							
Shock	150 (58.4%)	56 (5.9%)	94 (69.6)	<0.001	40 (52.6%)	110 (60.8%)	0.268
Sepsis	98 (38.1%)	26 (23.8%)	69 (51.1%)	<0.001	22 (28.9%)	76 (42.0%)	0.067
Drug-induced	3 (1.2%)	0 (0%)	3 (2.2%)	0.249	0 (0%)	3 (1.7%)	0.557
Rhabdomyolysis	9 (3.5%)	5 (4.1%)	4 (3.0%)	0.740	4 (5.3%)	5 (2.8%)	0.457
Pigmentation	6 (2.3%)	4 (3.3%)	2 (1.5%)	0.427	4 (5.3%)	2 (1.1%)	0.065
Contrast	37 (14.4%)	22 (18.0%)	15 (11.1%)	0.154	13 (17.1%)	24 (13.3%)	0.440
Other	26 (10.1%)	16 (13.1%)	10 (7.4%)	0.150	7 (9.2%)	19 (10.5%)	0.825
At initiating dialysis							
Admission to dialysis (days)	40.3 ± 27.1	42.0 ± 31.8	37.1 ± 47.5	0.335	45.8 ± 33.9	36.8 ± 43.1	0.106
Mechanical Ventilation	185 (72.0%)	74 (60.7%)	111 (82.2%)	<0.001	49 (64.5%)	136 (75.1%)	0.095
Emergency Surgery	100 (38.9%)	49 (40.2%)	51 (37.8%)	0.703	33 (43.4%)	67 (37.0%)	0.400
IABP	27 (10.5%)	10 (8.2%)	17 (12.6%)	0.310	7 (9.2%)	20 (11.0%)	0.824
Urine output (mL/24 h)	591.7 ± 790.3	750.3 ± 1013.0	448.3 ± 472.1	0.002	869.7 ± 1188.7	474.9 ± 503.1	<0.001
AKI risk prediction score	22.6 ± 6.9	20.2 ± 6.5	24.9 ± 6.5	<0.001	20.8 ± 6.4	23.4 ± 7.0	0.004
Body weight (kg)	66.8 ± 14.3	68.6 ± 15.9	67.8 ± 16.9	0.055	70.0 ± 15.9	65.5 ± 13.4	0.021
IE	8.2 ± 15.0	4.7 ± 8.3	11.3 ± 18.7	<0.001	5.24 ± 9.32	9.43 ± 16.75	0.041
SOFA	10.9 ± 3.9	9.1 ± 3.2	12.6 ± 3.8	<0.001	9.4 ± 3.3	11.6 ± 4.0	<0.001
APACHE II	17.8 ± 6.4	15.6 ± 5.4	19.8 ± 6.7	<0.001	15.5 ± 5.7	18.7 ± 6.5	<0.001
MODS	8.1 ± 4.1	6.5 ± 3.7	9.5 ± 3.9	<0.001	7.0 ± 3.6	8.6 ± 4.2	0.005
Phosphate (mg/dL)	4.5 ± 1.7	4.8 ± 1.6	4.3 ± 1.8	0.085	4.8 ± 1.5	4.4 ± 1.8	0.333
25 OH Vit D, ng/mL	11.7 ± 5.6	10.8 ± 5.5	12.9 ± 5.9	0.471	11.2 ± 7.1	12.0 ± 5.2	0.812
1,25 diOH Vit D, pg/mL	27.3 ± 6.5	25.5 ± 6.4	29.7 ± 6.4	0.545	28.9 ± 6.8	26.6 ± 6.6	0.545

Table 1. *Cont.*

	All	90-Day Survival	90-Day Mortality	*p*	90-Day Composite Outcome (−)	90-Day Composite Outcome (+)	*p*
	(*n* = 257)	(*n* = 122)	(*n* = 135)		(*n* = 76)	(*n* = 181)	
Kidney function marker							
BUN (mg/dL)	82.4 ± 47.2	82.7 ± 51.5	82.5 ± 45.4	0.922	82.3 ± 51.5	82.5 ± 45.4	0.978
Creatinine (mg/dL)	2.0 ± 1.6	4.1 ± 2.2	4.2 ± 2.4	0.745	4.1 ± 2.2	4.2 ± 2.4	0.745
Urine NGAL (ng/mL)	197.5 ± 85.3	191.0 ± 93.3	203.5 ± 77.1	0.254	189.2 ± 97.6	201.0 ± 79.7	0.330
Urine NGAL/Cre	6.9 ± 11.1	6.8 ± 12.5	6.9 ± 9.7	0.912	5.0 ± 6.9	7.7 ± 12.4	0.085
Urine KIM1 (ng/mL)	6.0 ± 5.8	5.8 ± 5.8	6.2 ± 5.8	0.529	5.9 ± 6.5	5.7 ± 5.4	0.139
Urine KIM1/Cre	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.1	0.993	0.1 ± 0.1	0.1 ± 0.2	0.699
Urine cFGF-23/Cre	877.4 ± 994.3	671.4 ± 924.9	1063.5 ± 1021.2	<0.001	699.1 ± 1015.0	952.2 ± 978.6	0.062
Plasma iFGF-23 (pg/mL)	304.2 ± 468.0	395.1 ± 635.6	269.0 ± 385.2	0.265	320.4 ± 551.8	300.2 ± 449.5	0.875
Plasma cFGF-23 (RU/mL)	2630.1 ± 2259.5	1926.7 ± 1745.4	3265.9 ± 2479.0	<0.001	1925.3 ± 1917.3	2926.1 ± 2330.0	0.001
Indication for dialysis							
Azotemia	123 (47.9%)	58 (47.5%)	65 (48.1%)	0.999	32 (42.1%)	91 (50.3%)	0.274
Fluid overload	111 (43.2%)	51 (41.8%)	60 (44.4%)	0.706	30 (39.5%)	81 (44.8%)	0.491
Electrolyte disorders	18 (7.0%)	10 (8.2%)	18 (5.9%)	0.626	7 (9.2%)	11 (6.1%)	0.423
Metabolic acidosis	46 (17.9%)	17 (13.9%)	29 (21.5%)	0.143	11 (14.5%)	35 (19.3%)	0.380
Oliguria	166 (64.6%)	69 (56.6%)	97 (71.9%)	0.013	46 (56.6%)	123 (68.0%)	0.088
Uremic encephalopathy	12 (4.7%)	9 (7.4%)	3 (2.2%)	0.074	6 (7.9%)	6 (3.3%)	0.191
Dialysis modality							
CVVH	62 (21.1%)	16 (13.1)	46 (34.1%)	<0.001	15 (19.7%)	47 (26.0%)	0.296
IHD	62 (29.2%)	47 (38.5%)	28 (20.7%)		27 (35.5%)	48 (26.5%)	
SLED	120 (46.7%)	59 (48.5%)	61 (45.2%)		34 (44.7%)	86 (47.5%)	
Relevant outcome parameters							
Hospital length of stay (days)	54.7 ± 50.4	52.3 ± 41.1	56.9 ± 57.6	0.459	59.0 ± 46.3	52.9 ± 52.0	0.383
Duration of hospital dialysis (days)	82.4 ± 60.7	42.0 ± 31.8	37.1 ± 47.5	0.335	45.8 ± 33.9	36.8 ± 43.1	0.745

Abbreviations: AKI, acute kidney injury; APACHE; Acute Physiology and Chronic Health Evaluation, BMI, body mass index; CABG, coronary artery bypass graft; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; Cre, creatinine; CVA, cerebrovascular accident; CVVH, continuous venovenous hemofiltration; eGFR, estimated glomerular filtration rate; FGF-23, Fibroblast growth factor-23; GCS, Glasgow Coma Scale; IABP: intra-aortic balloon pump; IE, inotropic equivalent; ICU, intensive care unit; IHD, intermittent hemodialysis; KIM-1, Kidney Injury Molecule-1; LVEF, Left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MODS, Multiple Organ Dysfunction Syndrome; NGAL, neutrophil gelatinase-associated lipocalin; SLED, sustained low efficiency dialysis; SOFA, Sequential Organ Failure Assessment; Vit D, vitamin D.

Area under the receiver operating characteristic (AUROC) curves were generated to evaluate biomarker performance. We use the methods of Hanley & McNeil (PMID, 6878708) for the calculation of the Standard Error of the Area Under the Curve (AUC) and of the difference between two AUCs. A generalized additive model (GAM) (with spline), incorporating the subject-specific (longitudinal) random effects, was plotted with adjustment for other clinical parameters to assess outcome-predictive effects of candidate biomarkers in individual patients [25,26].

Nonlinear effects of continuous covariates were explored with simple and multiple GAMs, which determine appropriate cut-off point(s) for discriminating candidate biomarkers, if necessary, during the stepwise variable selection procedure. The optimal cut-off value was defined as the log odd equaling zero [27].

Because of the high mortality rate among dialysis patients, competing-risk regression using the Fine and Gray model by considering the subdistribution hazard was also performed [28].

Net re-classification improvement (NRI) and integrated discrimination improvement (IDI) were used to evaluate the ability of candidate biomarkers for more accurate stratification of individuals into higher or lower risk categories (re-classification). Regarding 90-day mortality, an increase in NRI was calculated in a model containing both the AKI risk predicting score [21] and the cFGF-23 measurements, and the result was compared with the AKI risk predicting score alone. We defined 0–20%, 20–80%, and >80% as risk categories and re-classified patients with mortality by decision curve analysis and scatter plot (Supplemental Data file). A $p < 0.05$ was considered significant.

3. Results

3.1. Clinical Characteristics

Two hundred and fifty-seven patients (mean age 65.7 years; 167 (65%) male) with AKI who required RRT were studied. Average SOFA, APACHE II, and MODS scores were respectively 8.9, 16.3, and 5.9.

The main causes of AKI were shock (58.4%), sepsis (38.1%) and contrast nephrotoxicity (14.4%). Nine patients (3.5%) had stage 1 AKI, 58 (22.6%) patients had stage 2 AKI, and 190 (73.9%) patients had stage 3 AKI at RRT initiation. The most frequent indication for RRT was oliguria (64.6%), followed by azotemia (47.9%) and fluid overload (43.2%) (Table 1).

3.2. Hospital and 90-Day Outcomes

The in-hospital mortality rate, composite outcome at discharge, 90-day mortality rate and 90-day composite outcome rate were respectively 48.2%, 67.3%, 52.5%, and 70.4%. Table 1 shows baseline characteristics, pre-RRT and outcome parameters of patients categorized by 90-day mortality and 90-day composite outcome, respectively. Patients who did not survive at 90 days or with a 90–day composite outcome were older, had lower urine output, higher disease severity, risk predicting scores and received higher doses of inotropic equivalents than survivals (Table 1).

Importantly, only higher plasma cFGF-23 levels enabled to differentiate patients with both 90-day mortality/composite outcomes from those without events ($p = 0.001$).

3.3. Discriminative Power of Biomarkers for 90-Day Relevant Outcomes

Levels of SOFA (AUROC, 0.706), AKI risk predicting score (0.677), sCr (0.619), cFGF-23 (0.687), plasma iFGF-23 (0.504), creatinine-adjusted urine NGAL (0.599), adjusted urine cFGF-23 (0.653) and adjusted urine KIM-1 (0.547) at initiation of dialysis could predict 90-day mortality. Plasma cFGF-23 demonstrated better discriminative ability than NGAL for mortality at 90 days ($p = 0.001$ by AUROC comparison) (Figure 1, p at Table S1).

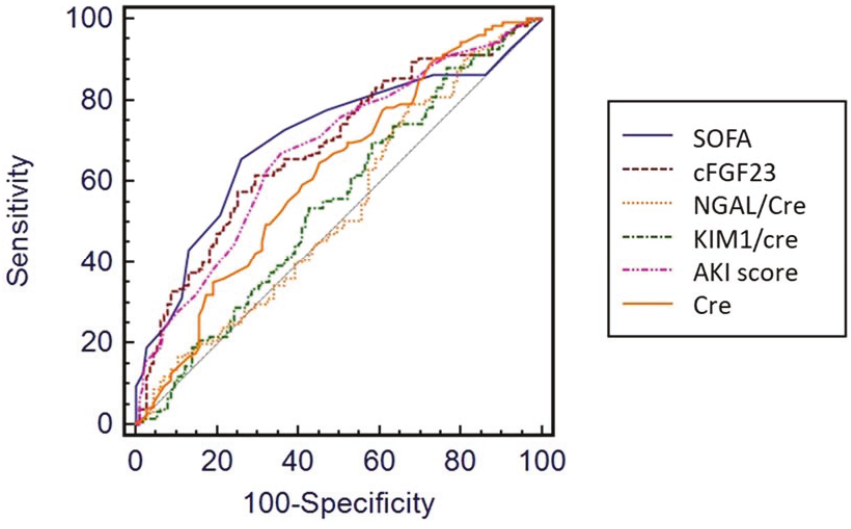
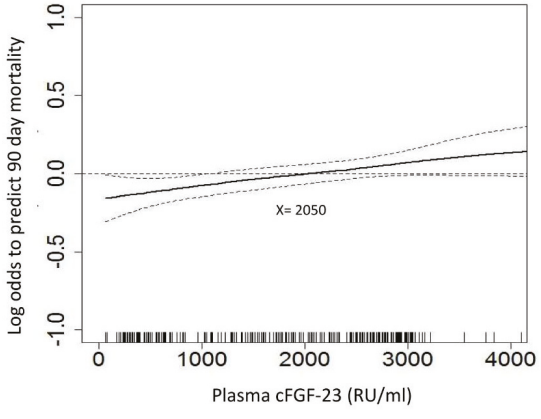


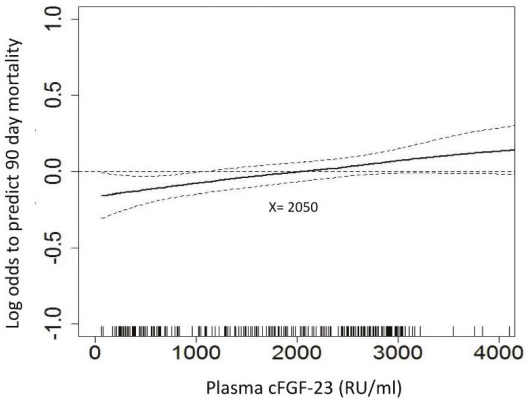
Figure 1. Comparisons of predictive powers for 90-day mortality among different variables. Note: the comparison was performed using the area under the receiver operator characteristic curves (AUROCs). Abbreviations: Cre, creatinine; cFGF-23, c-terminal fibroblast growth factor-23; KIM-1, Kidney Injury Molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; SOFA, Sequential Organ Failure Assessment; KDIGO, Kidney Disease Improving Global Outcomes; AKI, acute kidney injury.

The GAM plot showed a positive correlation between increased plasma cFGF-23 levels at start of dialysis and the log of the odds of 90-day mortality and composite outcome. After adjusting all variables listed in Table 1 for nonlinear effects, plasma cFGF-23, at a cut-off value of 2050 RU/mL by the GAM model, demonstrated independently good prediction of both 90-day mortality (Figure 2A) and 90-day composite outcome (Figure 2B).



(**A**)

Figure 2. *Cont.*



(**B**)

Figure 2. Generalized additive model (GAM) plot for the probability of (**A**) 90-day mortality, and (**B**) 90-day composite outcome against serum cFGF-23 levels at initiation of dialysis. Note: The GAM plot was incorporated with the subject-specific (longitudinal) random effects expressed as the logarithm of the odds (logit). The probability of outcome events was constructed with cFGF-23 levels averaging zero over the range of the data, i.e., cFGF-23 = 2050 ng/mL. All the relevant covariates, including characteristics, comorbidities, laboratory data, at intensive care unit (ICU) admission, etiology of acute kidney injury (AKI), indication for dialysis, dialysis modality, SOFA score, and plasma cFGF-23 at dialysis, and some of their interactions, such as interventions listed in Table 1, were put on a selected variable list to predict the outcome of interest.

3.4. Plasma cFGF-23 and Outcome

Using a cut-off value of 2050 RU/mL, patients were divided in a "high" and a "low" cFGF-23 group. Subjects with high cFGF-23 had lower baseline sCr, but higher phosphate concentrations at dialysis initiation, higher in-hospital and 90-day mortality, lower dialysis weaning rate and higher composite outcome results (Table 2).

Table 2. Clinical characteristics of patients with high versus low plasma cFGF-23 levels.

Serum cFGF23 Categories	Low cFGF-23	High cFGF-23	*p*
	(*n* = 116)	(*n* = 141)	
Patient characteristics			
Age (years)	65.8 ± 16.0	65.7 ± 17.2	0.973
Gender (male)	77 (66.4%)	90 (63.8%)	0.695
Baseline creatinine (mg/dL)	2.2 ± 1.9	1.8 ± 1.3	0.039
eGFR (MDRD) (mL/min/1.73 m^2)	54.4 ± 42.5	56.5 ± 39.8	0.690
Comorbidities			
Diabetes mellitus	33 (43.4%)	82 (45.3%)	0.891
Cirrhosis	1 (0.9%)	8 (5.7%)	0.044
COPD	7 (6.0%)	8 (5.7%)	0.999
CAD	27 (23.3%)	27 (19.1%)	0.445
CVA	12 (10.3%)	12 (8.5%)	0.670

Table 2. *Cont.*

Serum cFGF23 Categories	Low cFGF-23 (*n* = 116)	High cFGF-23 (*n* = 141)	*p*
Congestive heart failure			0.265
0	32 (27.6%)	35 (24.8%)	
I	37 (31.9%)	63 (44.7%)	
II	27 (23.3%)	24 (17.0%)	
III	15 (12.9%)	16 (11.3%)	
IV	0 (0%)	8 (5.5%)	
Laboratory data at ICU admission			
BUN (mg/dL)	48.3 ± 36.1	47.8 ± 31.4	0.897
pH	7.4 ± 0.1	7.4 ± 0.1	0.354
FiO2	0.5 ± 0.2	0.5 ± 0.2	0.609
SBP	126.1 ± 29.2	116.7 ± 27.0	0.008
GCS	11.9 ± 4.3	11.9 ± 4.2	0.984
SOFA	8.2 ± 3.6	9.6 ± 3.3	0.001
APACHE II	15.9 ± 6.0	16.6 ± 6.4	0.405
MODS	5.7 ± 3.5	6.1 ± 3.8	0.328
Etiology of AKI			
Shock	66 (56.9%)	84 (59.6%)	0.704
Sepsis	40 (34.5%)	58 (41.1%)	0.303
Rhabdomyolysis	7 (6.0%)	2 (1.4%)	0.083
Drug-induced	2 (1.7%)	1 (0.7%)	0.591
Pigmentation	5 (4.3%)	1 (0.7%)	0.094
Contrast	17 (14.7%)	20 (14.2%)	0.999
Others	12 (10.3%)	14 (9.9%)	0.999
At initiating dialysis			
Admission to dialysis (days)	35.5 ± 34.1	42.6 ± 45.4	0.163
Mechanical ventilation	78 (67.2%)	107 (75.9%)	0.128
Emergency Surgery	45 (38.8%)	55 (39.0%)	0.999
IABP	13 (11.2%)	14 (9.9%)	0.839
Urine output (mL/24 h)	650.9 ± 642.9	542.9 ± 892.8	0.277
AKI risk prediction score	21.5 ± 6.7	23.5 ± 6.9	0.021
Body weight (kg)	67.2 ± 15.4	66.5 ± 13.3	0.728
IE	7.14 ± 11.5	9.1 ± 17.4	0.310
SOFA	10.6 ± 4.3	11.2 ± 3.6	0.218
APACHE II	17.8 ± 6.7	11.8 ± 6.2	0.980
MODS	7.8 ± 4.4	8.4 ± 3.8	0.222
Phosphate, mg/dL	4.1 ± 1.7	4.9 ± 1.7	0.021
25 OH Vit D, ng/mL	11.0 ± 5.8	12.5 ± 5.6	0.617
1,25 diOH Vit D, pg/mL	29.7 ± 6.9	25.0 ± 5.5	0.149
Kidney function marker			
BUN (mg/dL)	81.2 ± 45.8	83.4 ± 48.4	0.714
Creatinine (mg/dL)	4.2 ± 2.4	4.1 ± 2.3	0.677
Urine KIM1 (ng/mL)	5.9 ± 5.9	6.1 ± 5.7	0.800
Urine KIM1/Cre	0.13 ± 0.18	0.14 ± 0.14	0.715
Urine NGAL (ng/mL)	196.5 ± 86.1	198.2 ± 85.0	0.916
Urine NGAL/Cre	7.0 12.9	6.8 ± 9.4	0.877
Urine cFGF-23/Cre	523.4 ± 747.2	1173.3 ± 1077.6	<0.001
Plasma iFGF-23 (pg/mL)	257.6 ± 243.0	325.50 ± 542.3	0.536

Table 2. *Cont.*

Serum cFGF23 Categories	Low cFGF-23 (*n* = 116)	High cFGF-23 (*n* = 141)	*p*
Indication for dialysis			
Azotemia	56 (48.3%)	67 (47.5%)	0.999
Fluid overload	48 (41.4%)	63 (44.7%)	0.615
Electrolyte disorders	7 (60%)	11 (7.8%)	0.631
Metabolic acidosis	22 (19.0%)	24 (17.0%)	0.745
Oliguria	73 (62.9%)	93 (66.0%)	0.694
Uremic complication	7 (6.0%)	5 (3.5%)	0.386
Dialysis modality			0.011
CVVH	44 (37.9%)	31 (22.0%)	
IHD	21 (18.1%)	41 (29.1%)	
SLED	51 (44.0%)	69 (48.9%)	
Outcomes of interest			
Hospital length of stay (days)	49.0 ± 43.0	59.4 ± 55.5	0.101
Duration of hospital dialysis (days)	39.9 ± 34.4	39.0 ± 45.5	0.862
Hospital mortality	42 (36.2%)	82 (58.2%)	<0.001
Composite outcome at discharge	69 (59.5%)	104 (73.8%)	<0.001
90-day mortality	45 (38.8%)	90 (63.8%)	<0.001
90-day weaning from dialysis	47 (40.5%)	29 (20.6%)	<0.001
90-day composite outcome	69 (59.5%)	112 (79.4%)	<0.001

Abbreviations: AKI, acute kidney injury; APACHE; Acute Physiology and Chronic Health Evaluation, BMI, body mass index; CABG, coronary artery bypass graft; Cre, creatinine; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; Cre, creatinine; CVA, cerebrovascular accident; CVVH, continuous venovenous hemofiltration; eGFR, estimated glomerular filtration rate; FGF-23, Fibroblast growth factor-23; GCS, Glasgow Coma Scale; IABP: intra-aortic balloon pump; IE, inotropic equivalent; ICU, intensive care unit; IHD, intermittent hemodialysis; KIM-1, Kidney Injury Molecule-1; LVEF, Left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MODS, Multiple Organ Dysfunction Syndrome; NGAL, neutrophil gelatinase-associated lipocalin; SLED, sustained low efficiency dialysis; SOFA, Sequential Organ Failure Assessment; Vit D, vitamin D.

A high cFGF-23 level represented an independent risk factor for in-hospital mortality (OR, 1.80, $p = 0.049$), composite outcome at discharge (OR, 1.80, 95% CI = 1.01–3.24; $p = 0.043$), 90–day mortality (OR, 2.19, 95% CI = 1.20–4.00; $p = 0.011$), and 90-day composite outcome (OR, 2.39, 95% CI = 1.31–4.35; $p = 0.005$) after adjusting for age, gender, baseline eGFR, and factor interaction with cFGF-23 and SOFA score. Importantly, no interaction was observed between the cFGF-23 level and underlying diabetes mellitus, baseline eGFR, age, and AKI risk predicting score at dialysis initiation (all $p > 0.05$) (Table 3).

Table 3. Logistic regression model for mortality and composite outcomes at hospital discharge and 90 days after discharge. Significant risks were shown.

Independent Variables	Hospital Mortality			Composite Outcome at Discharge		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (per year)	1.03	1.01–1.04	0.007	1.03	1.01–1.04	0.004
SOFA (per score)	1.26	1.15–1.39	<0.001	1.12	1.03–1.22	0.011
High cFGF-23	1.80	1.01–3.24	0.043	1.80	1.01–3.19	0.045
	90-Day Mortality			90-Day Composite Outcome		
Age (per year)	1.03	1.01–1.05	0.001	1.03	1.01–1.05	0.001
SOFA (per score)	1.30	1.17–1.44	0.037	1.17	1.07–1.27	<0.001
High cFGF-23	2.19	1.20–4.00	0.011	2.39	1.31–4.35	0.005

Abbreviations: cFGF-23, c-terminal fibroblast growth factor-23; CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment. All the univariate significant and non-significant relevant covariates, including age, sex, baseline comorbidities, indication for dialysis, etiology of AKI, kidney function profile (e.g., baseline eGFR and candidate biomarkers), cFGF-23 and SOFA score at dialysis initiation, dialysis modality, and some of their interactions were put on the variable lists to be selected (Table 1).

Cox proportional hazard regression analysis revealed that patients undergoing RRT who displayed high cFGF-23 levels had a higher 90-day mortality during the follow-up period with an adjusted HR of 1.76 (95% CI, 1.22–2.53; $p = 0.020$) as compared with patients with lower cFGF-23 values (Figure 3A). There was no interaction of the baseline comorbidities with high cFGF-23 to predict 90-day composite outcome. (Table S2) Taking mortality as a competing risk factor for dialysis, high cFGF-23 levels also predicted less weaning from dialysis in surviving patients (HR, 0.62, $p = 0.032$) (Figure 3B).

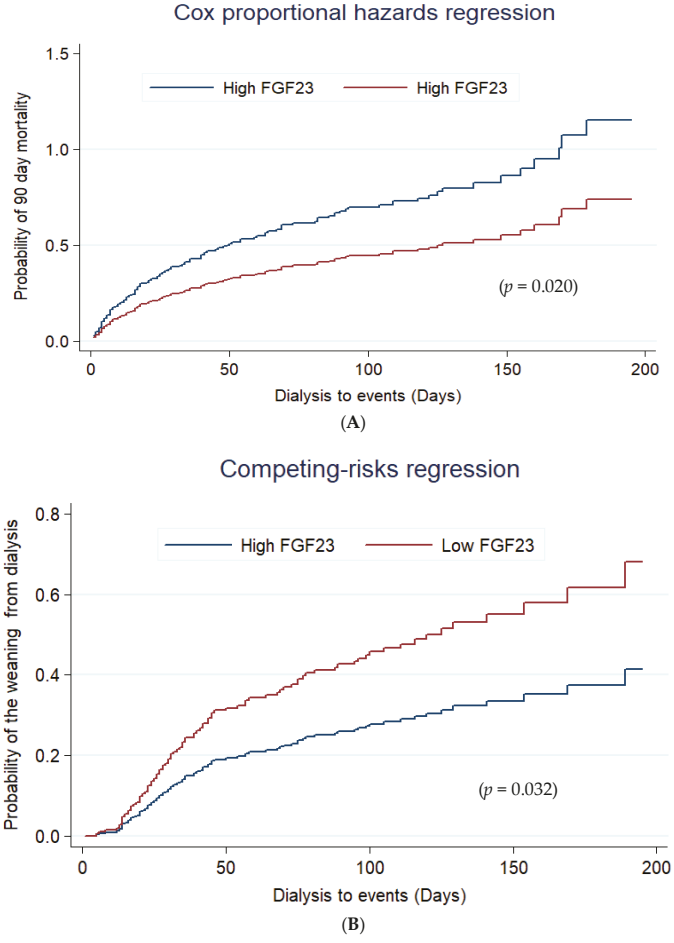


Figure 3. Cox proportional hazard plots stratified by serum cFGF-23 level for assessing probability of 90-day mortality (**A**) and the weaning from dialysis (**B**) by competing analysis and with mortality as a risk factor. Abbreviations: cFGF-23, c-terminal fibroblast growth factor-23; Using a cut-off value of 2050 RU/mL of cFGF-23 at initializing dialysis, patients were divided in a "high" and a "low" cFGF-23 group; all the relevant covariates, including characteristics, comorbidities, laboratory data, at ICU admission, etiology of AKI, indication for dialysis, dialysis modality, SOFA score, and plasma cFGF-23 at dialysis, and some of their interactions, such as interventions listed in Table 1, were put on a selected variable list to predict the outcome of interest.

The relationship of cFGF-23 with these variables was also underscored by a GAM analysis adjusted for SOFA score, gender, and age, which showed that cFGF-23 levels correlated with iFGF-23 ($p = 0.013$) and SOFA score ($p < 0.001$), but not with sCr ($p = 0.116$), phosphate ($p = 0.591$), 25-hydroxy Vit D ($p = 0.485$) and 1, 25 dihydroxy vit D ($p = 0.638$) concentrations at initiating RRT (Figure S1).

3.5. Addition of cFGF-23 to AKI Risk Predicting Score at Start of Dialysis

Adding cFGF-23 to the AKI risk predicting score at dialysis initiation significantly increased risk stratification (total NRI = 0.148; 95% CI = 0.057–0.239; $p = 0.002$) for detection of 90-day mortality. This effect was primarily determined by death (NRI event = 0.068, 95% CI = 0.043–0.087; $p = 0.025$) and survival (NRI event = 0.069; 95% CI = 0.039–0.097; $p = 0.029$). Similarly, the total IDI was significant. (0.051, 95% CI = 0.024–0.079; $p < 0.001$) (Figures S2 and S3).

4. Discussion

At initializing dialysis, the discriminative power of AKI biomarkers for 90-day mortality is fair. At dialysis initiation, the discrimination of cFGF-23 is better than NGAL, KIM-1, iFGF-23 and creatinine predicting patients' outcome. With mortality as competing risk, higher cFGF-23 levels also predicted lesser kidney recovery in survivors. More importantly, cFGF-23 had better predictive power than creatinine-adjusted urine NGAL and its integration into the AKI risk predicting score significantly enhanced the accuracy of risk stratification. At a cut-off level above 2050 RU/mL, cFGF-23 could predict of AKI mortality after adjusting for different clinical and disease severity parameters. Thus, cFGF-23 could be used as an early determinant of prognosis in ICU patients subjected at initializing RRT and also as an early determinant of the timing of dialysis initiation.

An increasing body of evidence has shown that cFGF-23 levels are increased in patients with AKI [11,14,29–32]. No significant interaction was observed between cFGF-23 and baseline CKD, sepsis grading in predicting mortality. The SOFA score was independently associated with increased cFGF-23 levels, which underpins the potential use of cFGF-23 in a critical care setting. We dare suggest that a higher plasma cFGF-23 not only corresponds with more severe AKI, but also reflects a higher degree of systemic inflammation.

Several mechanisms may explain increased FGF-23 levels in AKI: (1) increased production by osteocytes and possibly osteoblasts, that escapes regulation by parathyroid hormone, vitamin D signaling, and dietary phosphate restriction [33,34]; (2) increased ectopic production of FGF-23 by damaged renal tubules [33,35]; (3) tubular dysfunction resulting in FGF-23 resistance [36]; (4) and decreased clearance of circulating FGF-23 [14]. Whilst circulating FGF-23 levels rise rapidly during AKI [14] and a causal role for FGF-23 in the pathogenesis of left ventricular hypertrophy has previously been unveiled, suggesting that chronically elevated FGF-23 levels contribute directly to cardiac mortality in patients with CKD [37].

The ideal circumstances for whether and when to start RRT remain unclear [4]. We found significantly elevated cFGF-23 levels at the start of dialysis in non-survivors, whilst other structural and functional renal biomarkers failed to discriminate. Elevated plasma cFGF-23 was related to the degree of organ failure at initializing RRT [33]. In fact, high cFGF-23 concentrations predicted worse outcome equally well as the SOFA score in critically ill patients with advanced AKI [38]. Moreover, in patients without AKI, plasma cFGF-23 levels were significantly higher in the more severely ill patients [14]. This underscores that high cFGF-23 levels are correlated with increased systemic inflammation and/or stress secondary to illness or major surgery [33]. Although both serum and urine cFGF-23 could predict AKI mortality after ICU admission [12], many patients were oliguric at initializing dialysis, that will highlight the role of serum cFGF-23. In surviving patients, high cFGF-23 levels also predicted a lesser possibility for RRT withdrawal. Early prediction of renal recovery is likely to be helpful with regard to post-discharge care after critical illness and subsequent progression to CKD and ESRD.

Taken together, the ability of cFGF-23 to predict adverse outcomes might be related more to the systemic inflammatory status than to tubular damage. Based on our findings, a prognostic model can

be constructed that allows to predict individual mortality risk as well as potential kidney recovery in surviving patients before starting RRT. The addition of cFGF-23 to a clinical AKI risk predicting score resulted in greater discrimination, and enhanced the ability to anticipate a higher number of subsequent deaths. Given the lack of appropriate or reliable biomarkers in patients receiving RRT, plasma cFGF-23 tentatively may serve as a novel outcome-specific marker in critical care nephrology. In patients with augmented plasma cFGF-23 concentration to arrive 2050 RU/mL, the clinician should evaluate the traditional AKI risk score or parameters to decide commencing dialysis.

Whether the cFGF-23 assay provides comparable sensitivity to that for iFGF-23 in patients with different stages of AKI or illness severity is still debated [13]. Although measurements obtained with iFGF-23 and cFGF-23 assays reflect the same circulating moiety, it has been suggested that the levels of iFGF23 also increased in patients who developed severe AKI, but the magnitude was lower than cFGF23 [13]. This is also supported by the present study showing that a plasma cFGF-23 concentration exceeding 2050 RU/mL at initializing RRT was significantly associated with worse patient outcome at a higher discriminative power than iFGF-23. The levels of adjusted urine cFGF23 also increased in patients who did not survive, but the magnitude was lower than serum cFGF23.

Several limitations of our study must be highlighted. Our cFGF-23 cutoff value was somewhat higher than that in other AKI studies [11–15], probably because most patients already had advanced AKI when admitted to the ICU. Furthermore, the predicting power of cFGF-23 in patients without AKI but with high inflammation status needs further validation. Finally, the exact mechanism underlying increased cFGF-23 concentrations in AKI patients as well as possible other intrinsic biological effects of cFGF-23 in this particular population remain to be explored. As previously studies few biomarkers were ever validated and they could only modestly predictive of renal recovery [8]; we do acknowledge also that the AUCs of cFGF-23 were relatively modest in AKI-D patients with critical status, however adding cFGF-23 to a parsimonious model augmented prediction of mortality and kidney recovery.

5. Conclusions

At initializing dialysis, the discriminative power of AKI biomarkers for 90-day mortality is fair. Our study showed that cFGF-23, measured at initiation of RRT in critical patients with AKI, may be a novel and distinct marker for predicting 90-day mortality after discharge and less weaning from RRT in survivors. Its predictive discrimination was superior to other established biomarkers of kidney injury, in particular creatinine, NGAL and Kim-1. Adding cFGF-23 to the traditional AKI risk predicting score may allow better risk stratification and enhance prognostic power. cFGF-23 could further be used as a surrogate marker to decide the best timing to initiate RRT.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/8/202/s1, Figure S1: Scatter plots with an adjusted spline of cFGF23 with (A) iFGF23 ($p = 0.013$), (B) phosphate ($p = 0.591$) (C) creatinine ($p = 0.116$) (D) 25 OH Vitamin D ($p = 0.485$) and (E) 1,25 OH, Vitamin D ($p = 0.638$) (F) KDIGO-AKI score ($p = 0.820$) (G) SOFA ($p < 0.001$) at initiation of dialysis, Figure S2: Decision curve analysis (DCA) plot to assess 90 day mortality using cFGF-23 in addition to AKI risk prediction score, Figure S3: The correlation of AKI risk predicting score and AKI risk predicting score with cFGF-23 predicting 90 day mortality, Table S1: p value comparison of the receiver operating characteristic (ROC) curve for discriminative ability, Table S2: Interaction of baseline co-morbidity with high cFGF-23 to predict 90-day composite outcome.

Author Contributions: V.-C.W., C.-C.S., S.-C.J.C., H.-H.L. and T.-S.C. conceived the review topic, analysis and interpretation and wrote the manuscript. H.D.S., N.-H.C., C.-H.W. and P.M.H. revised and approved the final version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AKI	acute kidney injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
AUROC	area under the receiver operator characteristic curve
CKD	chronic kidney disease
ESRD	end-stage renal disease
ICU	intensive care unit
KIM-1	Kidney Injury Molecule-1
MODS	Multiple Organ Dysfunction Score
NGAL	neutrophil gelatinase-associated lipocalin
RRT	renal replacement therapy
RU	relative units
sCr	serum creatinine
SOFA	Sequential Organ Failure Assessment

References

1. Shiao, C.C.; Wu, P.C.; Huang, T.M.; Lai, T.S.; Yang, W.S.; Wu, C.H.; Lai, C.F.; Wu, V.C.; Chu, T.S.; Wu, K.D.; et al. Long-term remote organ consequences following acute kidney injury. *Crit. Care* **2015**, *19*, 438. [CrossRef] [PubMed]
2. Wu, V.C.; Shiao, C.C.; Chang, C.H.; Huang, T.M.; Lai, C.F.; Lin, M.C.; Chiang, W.C.; Chu, T.S.; Wu, K.D.; Ko, W.J.; et al. Long-term outcomes after dialysis-requiring acute kidney injury. *Biomed. Res. Int.* **2014**, *2014*, 365186. [CrossRef] [PubMed]
3. Wald, R.; Bagshaw, S.M. The timing of renal replacement therapy initiation in acute kidney injury: Is earlier truly better? *Crit. Care Med.* **2014**, *42*, 1933–1934. [CrossRef] [PubMed]
4. Klein, S.J.; Brandtner, A.K.; Lehner, G.F.; Ulmer, H.; Bagshaw, S.M.; Wiedermann, C.J.; Joannidis, M. Biomarkers for prediction of renal replacement therapy in acute kidney injury: A systematic review and meta-analysis. *Intensive Care Med.* **2018**, *44*, 323–336. [CrossRef] [PubMed]
5. Kumpers, P.; Hafer, C.; Lukasz, A.; Lichtinghagen, R.; Brand, K.; Fliser, D.; Faulhaber-Walter, R.; Kielstein, J.T. Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. *Crit. Care* **2010**, *14*, R9. [CrossRef] [PubMed]
6. Zarbock, A.; Kellum, J.A.; Schmidt, C.; Van Aken, H.; Wempe, C.; Pavenstadt, H.; Boanta, A.; Gerss, J.; Meersch, M. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The Elain Randomized Clinical Trial. *JAMA* **2016**, *315*, 2190–2199. [CrossRef] [PubMed]
7. Lin, C.Y.; Chang, C.H.; Fan, P.C.; Tian, Y.C.; Chang, M.Y.; Jenq, C.C.; Hung, C.C.; Fang, J.T.; Yang, C.W.; Chen, Y.C. Serum interleukin-18 at commencement of renal replacement therapy predicts short-term prognosis in critically ill patients with acute kidney injury. *PLoS ONE* **2013**, *8*, e66028. [CrossRef] [PubMed]
8. Pike, F.; Murugan, R.; Keener, C.; Palevsky, P.M.; Vijayan, A.; Unruh, M.; Finkel, K.; Wen, X.; Kellum, J.A. Biomarker Enhanced Risk Prediction for Adverse Outcomes in Critically Ill Patients Receiving RRT. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 1332–1339. [CrossRef] [PubMed]
9. Consortium, A. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat. Genet.* **2000**, *26*, 345–348.
10. Berndt, T.; Kumar, R. Phosphatonins and the regulation of phosphate homeostasis. *Annu. Rev. Physiol.* **2007**, *69*, 341–359. [CrossRef] [PubMed]
11. Ali, F.N.; Hassinger, A.; Price, H.; Langman, C.B. Preoperative plasma FGF23 levels predict acute kidney injury in children: Results of a pilot study. *Pediatr. Nephrol.* **2013**, *28*, 959–962. [CrossRef] [PubMed]
12. Leaf, D.E.; Jacob, K.A.; Srivastava, A.; Chen, M.E.; Christov, M.; Juppner, H.; Sabbisetti, V.S.; Martin, A.; Wolf, M.; Waikar, S.S. Fibroblast Growth Factor 23 Levels Associate with AKI and Death in Critical Illness. *J. Am. Soc. Nephrol.* **2017**, *28*, 1877–1885. [CrossRef] [PubMed]
13. Leaf, D.E.; Christov, M.; Juppner, H.; Siew, E.; Ikizler, T.A.; Bian, A.; Chen, G.; Sabbisetti, V.S.; Bonventre, J.V.; Cai, X.; et al. Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery. *Kidney Int.* **2016**, *89*, 939–948. [CrossRef] [PubMed]

14. Christov, M.; Waikar, S.S.; Pereira, R.C.; Havasi, A.; Leaf, D.E.; Goltzman, D.; Pajevic, P.D.; Wolf, M.; Juppner, H. Plasma FGF23 levels increase rapidly after acute kidney injury. *Kidney Int.* **2013**, *84*, 776–785. [CrossRef] [PubMed]
15. Donate-Correa, J.; de Fuentes, M.M.; Mora-Fernandez, C.; Navarro-Gonzalez, J.F. Pathophysiological implications of fibroblast growth factor-23 and Klotho and their potential role as clinical biomarkers. *Clin. Chem.* **2014**, *60*, 933–940. [CrossRef] [PubMed]
16. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.S.; Chen, Y.W.; Chen, Y.M.; Hu, F.C.; Lin, Y.H.; Tsai, P.R.; Wu, K.D. Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: Effect on postoperative outcomes. *J. Am. Coll. Surg.* **2007**, *205*, 266–276. [CrossRef] [PubMed]
17. Wu, V.C.; Ko, W.J.; Chang, H.W.; Chen, Y.W.; Lin, Y.F.; Shiao, C.C.; Chen, Y.M.; Chen, Y.S.; Tsai, P.R.; Hu, F.C.; et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive Care Med.* **2008**, *34*, 101–108. [CrossRef] [PubMed]
18. Shiao, C.C.; Wu, V.C.; Li, W.Y.; Lin, Y.F.; Hu, F.C.; Young, G.H.; Kuo, C.C.; Kao, T.W.; Huang, D.M.; Chen, Y.M.; et al. Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. *Crit. Care* **2009**, *13*, R171. [CrossRef] [PubMed]
19. Wu, V.C.; Wang, C.H.; Wang, W.J.; Lin, Y.F.; Hu, F.C.; Chen, Y.W.; Chen, Y.S.; Wu, M.S.; Lin, Y.H.; Kuo, C.C.; et al. Sustained low-efficiency dialysis versus continuous veno-venous hemofiltration for postsurgical acute renal failure. *Am. J. Surg.* **2010**, *199*, 466–476. [CrossRef] [PubMed]
20. Huang, T.M.; Wu, V.C.; Young, G.H.; Lin, Y.F.; Shiao, C.C.; Wu, P.C.; Li, W.Y.; Yu, H.Y.; Hu, F.C.; Lin, J.W.; et al. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. *J. Am. Soc. Nephrol.* **2011**, *22*, 156–163. [CrossRef] [PubMed]
21. Demirjian, S.; Chertow, G.M.; Zhang, J.H.; O'Connor, T.Z.; Vitale, J.; Paganini, E.P.; Palevsky, P.M. Network VNARFT. Model to predict mortality in critically ill adults with acute kidney injury. *Clin. J. Am. Soc. Nephrol.* **2011**, *6*, 2114–2120. [CrossRef] [PubMed]
22. Wu, V.C.; Huang, T.M.; Lai, C.F.; Shiao, C.C.; Lin, Y.F.; Chu, T.S.; Wu, P.C.; Chao, C.T.; Wang, J.Y.; Kao, T.W.; et al. Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. *Kidney Int.* **2011**, *80*, 1222–1230. [CrossRef] [PubMed]
23. Lin, Y.F.; Ko, W.J.; Wu, V.C.; Chen, Y.S.; Chen, Y.M.; Hu, F.C.; Shiao, C.C.; Wu, M.S.; Chen, Y.W.; Li, W.Y.; et al. A modified sequential organ failure assessment score to predict hospital mortality of postoperative acute renal failure patients requiring renal replacement therapy. *Blood Purif.* **2008**, *26*, 547–554. [CrossRef] [PubMed]
24. Shiao, C.C.; Ko, W.J.; Wu, V.C.; Huang, T.M.; Lai, C.F.; Lin, Y.F.; Chao, C.T.; Chu, T.S.; Tsai, H.B.; Wu, P.C.; et al. U-curve association between timing of renal replacement therapy initiation and in-hospital mortality in postoperative acute kidney injury. *PLoS ONE* **2012**, *7*, e42952. [CrossRef] [PubMed]
25. Wu, V.C.; Lo, S.C.; Chen, Y.L.; Huang, P.H.; Tsai, C.T.; Liang, C.J.; Kuo, C.C.; Kuo, Y.S.; Lee, B.C.; Wu, E.L.; et al. Endothelial progenitor cells in primary aldosteronism: A biomarker of severity for aldosterone vasculopathy and prognosis. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3175–3183. [CrossRef] [PubMed]
26. Wu, V.C.; Lai, C.F.; Shiao, C.C.; Lin, Y.F.; Wu, P.C.; Chao, C.T.; Hu, F.C.; Huang, T.M.; Yeh, Y.C.; Tsai, I.J.; et al. Effect of diuretic use on 30-day postdialysis mortality in critically ill patients receiving acute dialysis. *PLoS ONE* **2012**, *7*, e30836. [CrossRef] [PubMed]
27. Hin, L.Y.; Lau, T.K.; Rogers, M.S.; Chang, A.M. Dichotomization of continuous measurements using generalized additive modelling—Application in predicting intrapartum caesarean delivery. *Stat. Med.* **1999**, *18*, 1101–1110. [CrossRef]
28. Wu, V.C.; Chang, C.H.; Wang, C.Y.; Lin, Y.H.; Kao, T.W.; Lin, P.C.; Chu, T.S.; Chang, Y.S.; Chen, L.; Wu, K.D.; et al. Risk of Fracture in Primary Aldosteronism: A Population-Based Cohort Study. *J. Bone Miner. Res.* **2017**, *32*, 743–752. [CrossRef] [PubMed]
29. Zhang, M.; Hsu, R.; Hsu, C.Y.; Kordesch, K.; Nicasio, E.; Cortez, A.; McAlpine, I.; Brady, S.; Zhuo, H.; Kangelaris, K.N.; et al. FGF-23 and PTH levels in patients with acute kidney injury: A cross-sectional case series study. *Ann. Intensive Care.* **2011**, *1*, 21. [CrossRef] [PubMed]
30. Leaf, D.E.; Wolf, M.; Waikar, S.S.; Chase, H.; Christov, M.; Cremers, S.; Stern, L. FGF-23 levels in patients with AKI and risk of adverse outcomes. *Clin. J. Am. Soc. Nephrol.* **2012**, *7*, 1217–1223. [CrossRef] [PubMed]

31. Leaf, D.E.; Waikar, S.S.; Wolf, M.; Cremers, S.; Bhan, I.; Stern, L. Dysregulated mineral metabolism in patients with acute kidney injury and risk of adverse outcomes. *Clin. Endocrinol.* **2013**, *79*, 491–498. [CrossRef] [PubMed]
32. Brown, J.R.; Katz, R.; Ix, J.H.; de Boer, I.H.; Siscovick, D.S.; Grams, M.E.; Shlipak, M.; Sarnak, M.J. Fibroblast growth factor-23 and the long-term risk of hospital-associated AKI among community-dwelling older individuals. *Clin. J. Am. Soc. Nephrol.* **2014**, *9*, 239–246. [CrossRef] [PubMed]
33. Neyra, J.A.; Moe, O.W.; Hu, M.C. Fibroblast growth factor 23 and acute kidney injury. *Pediatr. Nephrol.* **2015**, *30*, 1909–1918. [CrossRef] [PubMed]
34. Shimada, T.; Muto, T.; Urakawa, I.; Yoneya, T.; Yamazaki, Y.; Okawa, K.; Takeuchi, Y.; Fujita, T.; Fukumoto, S.; Yamashita, T. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. *Endocrinology* **2002**, *143*, 3179–3182. [CrossRef] [PubMed]
35. Spichtig, D.; Zhang, H.; Mohebbi, N.; Pavik, I.; Petzold, K.; Stange, G.; Saleh, L.; Edenhofer, I.; Segerer, S.; Biber, J.; et al. Renal expression of FGF23 and peripheral resistance to elevated FGF23 in rodent models of polycystic kidney disease. *Kidney Int.* **2014**, *85*, 1340–1350. [CrossRef] [PubMed]
36. Hassan, A.; Durlacher, K.; Silver, J.; Naveh-Many, T.; Levi, R. The fibroblast growth factor receptor mediates the increased FGF23 expression in acute and chronic uremia. *Am. J. Physiol. Renal Physiol.* **2016**, *310*, F217–F221. [CrossRef] [PubMed]
37. Faul, C.; Amaral, A.P.; Oskouei, B.; Hu, M.C.; Sloan, A.; Isakova, T.; Gutierrez, O.M.; Aguillon-Prada, R.; Lincoln, J.; Hare, J.M.; et al. FGF23 induces left ventricular hypertrophy. *J. Clin. Investig.* **2011**, *121*, 4393–4408. [CrossRef] [PubMed]
38. Chang, C.H.; Fan, P.C.; Chang, M.Y.; Tian, Y.C.; Hung, C.C.; Fang, J.T.; Yang, C.W.; Chen, Y.C. Acute kidney injury enhances outcome prediction ability of sequential organ failure assessment score in critically ill patients. *PLoS ONE* **2014**, *9*, e109649. [CrossRef] [PubMed]

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Acute Kidney Injury Adjusted for Parenchymal Mass Reduction and Long-Term Renal Function after Partial Nephrectomy

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Abstract: We sought to evaluate the association of postoperative acute kidney injury (AKI) adjusted for parenchymal mass reduction with long-term renal function in patients undergoing partial nephrectomy. A total of 629 patients undergoing partial nephrectomy were reviewed. Postoperative AKI was defined by the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria, by using either the unadjusted or adjusted baseline serum creatinine level, accounting for renal parenchymal mass reduction. Estimated glomerular filtration rates (eGFRs) were followed up to 61 months (median 28 months) after surgery. The primary outcome was the functional change ratio (FCR) of eGFR calculated by the ratio of the most recent follow-up value, at least 24 months after surgery, to eGFR at 3–12 months after surgery. Multivariable linear regression analysis was performed to evaluate whether unadjusted or adjusted AKI was an independent predictor of FCR. As a sensitivity analysis, functional recovery at 3–12 months after surgery compared to the preoperative baseline was analyzed. Median parenchymal mass reduction was 11%. Unadjusted AKI occurred in 16.5% (104/625) and adjusted AKI occurred in 8.6% (54/629). AKI using adjusted baseline creatinine was significantly associated with a long-term FCR ($\beta = -0.129 \pm 0.026$, $p < 0.001$), while unadjusted AKI was not. Adjusted AKI was also a significant predictor of functional recovery ($\beta = -0.243 \pm 0.106$, $p = 0.023$), while unadjusted AKI was not. AKI adjusted for the parenchymal mass reduction was significantly associated with a long-term functional decline after partial nephrectomy. A creatinine increase due to remaining parenchymal ischemic injury may be important in order to predict long-term renal functional outcomes after partial nephrectomy.

Keywords: acute kidney injury; partial nephrectomy; parenchymal mass reduction; ischemia

1. Introduction

Acute kidney injury (AKI) frequently occurs after partial nephrectomy, with an incidence of up to 54% [1,2]. Furthermore, renal function gradually declines and chronic renal insufficiency may develop after partial nephrectomy [3]. A new baseline estimated glomerular filtration rate (eGFR) after early postoperative recovery following partial nephrectomy can impact survival after nephrectomy [4]. As a postoperative AKI is associated with the development of chronic kidney disease (CKD) [5], the AKI after a nephrectomy could also be associated with poor long-term renal function. However, the potential impact of an AKI after a partial nephrectomy on long-term renal function has been debated.

Several studies investigated the impact of AKI after radical or partial nephrectomies, with controversy resulting [2,6–8]. Studies of radical nephrectomy reported that AKIs are associated with new-onset CKD [7,8], while studies of partial nephrectomy reported inconsistent results [2,6].

Furthermore, there remains uncertainty regarding how to diagnose AKI after partial nephrectomy. An AKI is diagnosed by the degree of serum creatinine elevation according to clinical criteria, such as the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [9]. However, an AKI after nephrectomy is different from other surgeries, because postoperative serum creatinine elevation could be due to the parenchymal mass reduction by surgical resection as well as ischemic injury of the remaining renal nephrons [2,4,10]. Therefore, conventional criteria which do not consider the parenchymal mass reduction by partial nephrectomy could overestimate the incidence and severity of AKIs. In light of that, a recent study proposed new criteria for AKI after partial nephrectomy, which use an adjusted creatinine measurement as a postoperative baseline to determine AKI. Adjusted baseline creatinine was determined as the projection of the creatinine value after correcting it for the creatinine elevation due to the effect of parenchymal mass reduction [2]. There was a significant association between the renal functional recovery after surgery and AKI, determined by their proposed criteria, using adjusted baseline creatinine, but not for the AKIs determined by conventional criteria. However, another study using similar methodology reported no association between AKIs adjusted for parenchymal mass reduction and long-term renal function after partial nephrectomy [6].

As such, the diagnosis of AKI and the influence of AKI on long-term renal function after partial nephrectomy, are still not clear. Therefore, we attempted to investigate the relationship between AKI after partial nephrectomy and long-term renal outcomes in our cohort. To evaluate AKI adjusted for the parenchymal mass reduction, we compared the association between AKI and postoperative long-term renal function by using both AKIs determined by unadjusted and adjusted baseline serum creatinine, accounting for parenchymal mass reduction. Previous studies investigated the long-term renal function after partial nephrectomy by measuring functional recovery and functional change ratio (FCR) (Figure 1) [2,6]. These outcomes measure the ratio of glomerular filtration rate (GFR) at different time points after surgery. We compared long-term renal function regarding two outcomes of functional recovery and FCR.

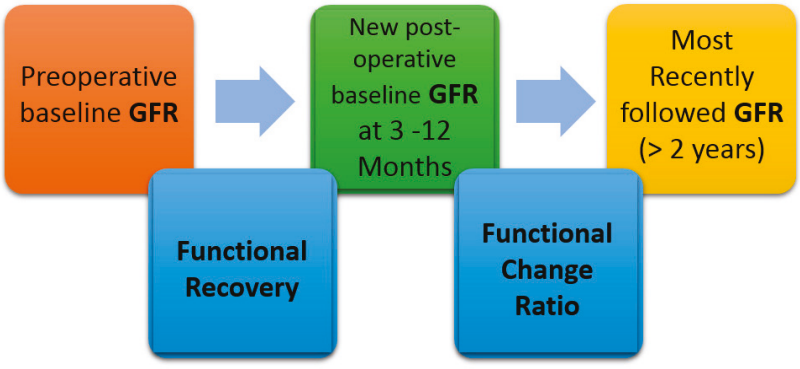

Figure 1. Study outcomes and time points of measurement. Functional recovery was measured as the ratio of glomerular filtration rate (GFR) at 3–12 months to preoperative baseline GFR. Functional change ratio was calculated as the ratio of most recent GFR to a new postoperative baseline GFR at 3–12 months. Preoperative baseline GFR was used as a baseline to calculate the outcome of functional recovery and a new post-operative baseline GFR at 3–12 months was used as a baseline to calculate the outcome of functional change ratio.

2. Materials and Methods

2.1. Study Population

This single-center retrospective observational study was approved by the institutional review board of Seoul National University Hospital (1904-060-1026). Written informed consent was waived due to the retrospective nature of the present study. We reviewed electronic medical records of the patients who were ≥18 years old; had a renal mass and underwent partial nephrectomy, regardless of surgical techniques; and had a contralateral kidney between 2010 and 2014. Among the 639 patients who underwent partial nephrectomy, 629 patients were included in the final analysis, after excluding the patients without a preoperative, computed tomography (CT), coronal reconstruction image (n = 10).

2.2. Surgical and Anesthesia Procedure

Partial nephrectomies by open, laparoscopic and robot-assisted techniques were included in our analysis. Decisions regarding the type of surgical approach and use of warm versus cold ischemia were made based on the tumor characteristics. Surgical resection was performed after clamping the main renal artery or arteries. The renal vein was clamped selectively. Saline ice slush was used for cold ischemia. Anesthesia was induced and maintained by sevoflurane, desflurane or total intravenous anesthesia with propofol and remifentanil. All patients received an intraoperative 20 g mannitol infusion within 30 min before vascular clamping. For significant surgical bleeding, hydroxyethyl starch was administered to expand the intravascular volume and red blood cells were transfused to maintain the intraoperative hematocrit >24%.

2.3. Patient Data and Outcome Measurements

Demographic, baseline characteristics and surgery-related parameters that were known to be associated with renal function after nephrectomy were extracted from our electronic medical records (Table 1) [1,2,6,11–13]. Serum creatinine values measured 3 to 60 months after surgery were collected. GFR estimates were based on the equation in [14].

Table 1. Patient characteristics and perioperative parameters according to acute kidney injury adjusted for parenchymal mass reduction.

Characteristic	Adjusted AKI	No AKI	p-Value
Patient population, n	54 (8.6)	575 (91.4)	
Demographic data			
Age, yr	61 (51–67)	54 (46–65)	0.020
Female, n	3 (5.6)	176 (30.6)	<0.001
Body-mass index, kg/m^2	24.2 (22.5–26.7)	24.6 (22.6–26.7)	0.599
Background medical status			
Hypertension, n	27 (50.0)	202 (35.1)	0.030
Diabetes mellitus, n	9 (16.7)	75 (13.0)	0.409
Cerebrovascular accident, n	1 (1.9)	14 (2.4)	0.781
Angina pectoris, n	2 (3.7)	4 (0.7)	0.087
Preoperative hemoglobin, g/dL	14.0 (11.1–15.2)	14.1 (12.9–15.0)	0.147
Preoperative serum albumin level, g/dL	4.3 (3.9–4.5)	4.5 (4.2–4.6)	0.001
Preoperative proteinuria, n	8 (14.8)	27 (4.7)	0.007
Unilateral kidney, n	8 (14.8)	51 (8.9)	0.147
Operation and anesthesia details			
Surgery type, n			0.965
Laparoscopic	1 (1.9)	31 (5.4)	
Robot-assisted	6 (11.1)	122 (21.2)	
Open	47 (87.0)	422 (73.4)	
Clinical stage, n			<0.001

Table 1. *Cont.*

Characteristic	Adjusted AKI	No AKI	*p*-Value
T1a/T1b	35 (64.8)/12 (22.2)	496 (86.3)/62 (10.8)	
T2a/T2b	3 (5.6)/2 (3.7)	14 (2.4)/2 (0.3)	
T3a/T3b/T3c	1 (1.9)/1 (1.9)/0	1 (0.2)/0/0	
N 0/1	51 (94.4)/3 (5.6)	571 (99.3)/4 (0.7)	0.016
M 0/1	51 (94.4)/3 (5.6)	567 (98.6)/8 (1.4)	0.060
R.E.N.A.L. score	7 (7–8)	6 (5–7)	<0.001
Low (4–6)	9 (16.7)	390 (67.8)	
Intermediate (7–9)	42 (77.8)	179 (31.1)	
High (10–12)	3 (5.6)	6 (1.0)	
Tumor maximal diameter, cm	2.5 (2.0–4.0)	2.3 (1.5–3.5)	0.038
Operation time, min	150 (120–206)	140 (107–180)	0.113
Warm ischemia, *n*	51 (94.4)	548 (95.3)	0.736
Cold ischemia, *n*	3 (5.6)	27 (4.7)	0.736
Renal ischemic time, min	30 (24–42)	24 (17–30)	<0.001
Warm ischemic time, min	28 (24–42)	24 (18–30)	<0.001
Cold ischemic time, min	38 (30–38)	31 (17–39)	0.387
Estimated parenchymal volume preservation, %	89 (85–90)	89 (88–90)	0.623
Anesthesia technique			0.113
Total intravenous agent, *n*	50 (92.6)	483 (84.0)	
Inhalational agent, *n*	4 (7.4)	92 (16.0)	
Intraoperative vasopressor use, *n*	7 (16.3)	66 (12.0)	0.467
Bleeding and transfusion amount			
pRBC transfusion, *n*	10 (18.5)	20 (3.5)	<0.001
Estimated blood loss, mL	300 (200–600)	200 (100–350)	<0.001
Input and output during surgery			
Crystalloid administration, mL	1150 (800–1700)	1200 (800–1700)	0.653
Colloid administration, mL	0 (0–500)	0 (0–400)	0.486

Data are presented as median (interquartile range) or number (%). AKI = acute kidney injury; R.E.N.A.L. = radius, exophytic/endophytic properties, nearness of tumor to collecting system or sinus, anterior/posterior, hilar, location relative to polar lines; pRBC = packed red blood cell.

The primary outcome was a long-term FCR of GFR, which was defined as the most recent GFR/new baseline GFR after surgery [7]. New baseline GFR was defined as the latest value available during 3–12 months. Renal function is expected to recover a little after the sudden drop following partial nephrectomy, and the recovering GFR was defined as the new baseline GFR. This period of 3–12 months was chosen because individual follow-up duration varied and according to a previous study [6]. The most recent GFR collected was the GFR of at least 24 months after surgery. One secondary outcome was functional recovery from renal ischemia [2]. Functional recovery was calculated as the ratio of the percentage of function saved to the percent of parenchymal volume saved. The percentage of function saved was determined as the ratio of eGFR at 3–12 months after nephrectomy to the preoperative baseline eGFR. The summary and time points for these outcomes are shown in Figure 1. Outcome definitions and time points were selected to be the same as previous studies to compare results in the same time period [2,6].

Postoperative unadjusted AKI was defined by the creatinine criteria of KDIGO, which was determined according to the maximal change in serum creatinine level during the first seven postoperative days (stage 1, stage 2 and stage 3: 1.5–1.9, 2: 2–2.9 and a more than three-fold increase of preoperative baseline serum creatinine, respectively) [9,15]. The most recent serum creatinine level measured before surgery was used as the baseline. Adjusted AKI was defined by using the concept of previous studies [2,4], which set a new baseline adjusted creatinine after removing the contribution of parenchymal mass reduction and compared the postoperative peak serum creatinine level to the new baseline. We calculated the baseline adjusted creatinine by using the percentage of functional volume preservation (PFVP) based on the measurements on the preoperative CT image (Figure 2) [16,17]. The

details of our calculation were described in Supplemental Text S1. By using the adjusted baseline, adjusted AKI was determined again using the same KDIGO criteria.

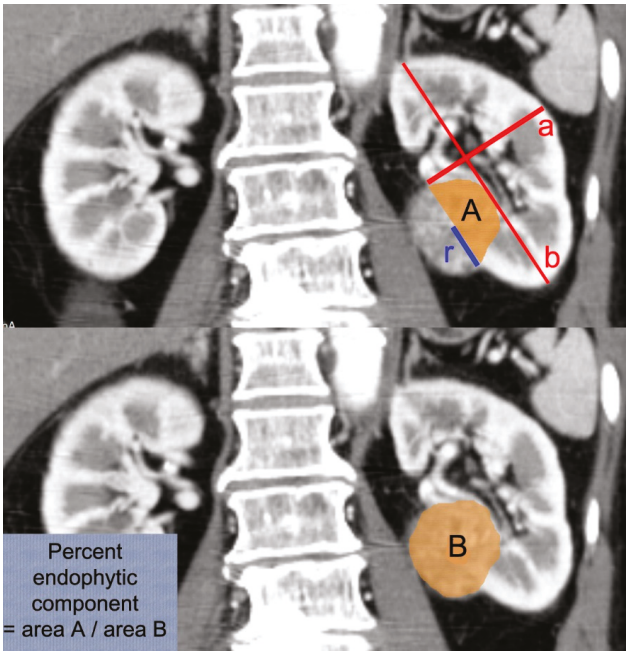

Figure 2. Measurements of the study. Kidney volume was estimated as cylindrical volume using the short (**a**) and long diameter (**b**) of the kidney on the three-dimensional computerized tomography (CT) image. The tumor volume was estimated as a ball with its radius of maximal tumor radius (r). Percent endophytic component was measured as a percentage ratio of endophytic tumor area (**A**) to whole tumor area (**B**) on the CT image where the maximal tumor area was observed.

2.4. Statistical Analysis

SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and STATA/MP version 15.1 (StataCorp, College Station, TX, USA) were used to analyze the data. For all analyses, $p < 0.05$ was considered statistically significant. The Kolmogorov-Smirnov test was used to determine the normality of the data. All following analyses were performed separately for adjusted and unadjusted AKIs.

Firstly, baseline patient and surgical characteristics were compared between patients with and without adjusted AKIs. Mann–Whitney tests were used for continuous variables, and the chi-square test or Fisher's exact test was used to compare incidence variables according to their expected counts.

Secondly, we performed a multivariable linear regression analysis to elucidate significant predictors of the long-term FCR from the new baseline GFR after surgery to the most recent follow-up. Unadjusted and adjusted AKI stages were entered alternatively as a covariate to evaluate the association between AKI and FCR. Neither stepwise variable selection nor univariable screening was performed.

Thirdly, multivariable linear regression was performed to identify independent risk factors of the functional recovery during 3–12 months after partial nephrectomy. Unadjusted and adjusted AKI stages were considered the potential predictor alternatively.

Fourthly, univariable Spearman correlation analyses were performed to assess the relationships between the stages of adjusted AKIs and the longitudinal FCR.

3. Results

Demographics and perioperative parameters are compared between adjusted AKI and no-AKI in Table 1 and between unadjusted AKI and no-AKI in supplemental Table S1. Baseline renal function is compared in supplemental Table S2. The incidence of unadjusted AKI was 16.5% (n = 104/629) (stage 1: n = 88 (14.0%); stage 2 or 3: n = 16 (2.5%)). The incidence of adjusted AKI was 8.6% (n = 54/629) (stage 1: n = 40 (6.4%); stage 2 or 3: n = 14 (2.2%)). Among all patients, only 19 patients (3.0%) required any renal replacement therapy during the postoperative hospital stay.

The median patient age was 54 years and the median parenchyma volume preservation was 89%. The median follow-up times for renal function were 27 and 28 months for patients with and without adjusted AKI (up to 61 months). The median FCR was 1.0 in patients without AKIs; and 0.92, 0.79 and 0.45 for patients with stage 1, 2 and 3 adjusted AKIs, respectively. The median functional recovery was 99% in patients without AKI; and 93%, 81% and 67% for patients with stage 1, 2 and 3 adjusted AKIs. There was no immediate postoperative mortality in our retrospective cohort. During the whole follow-up period, there were 17 (2.7%) cases of mortality from any cause and 13 (2.1%) cases of mortality from renal cell carcinoma.

Table 2 shows the results of multivariable linear regression analysis for FCR after partial nephrectomy. Postoperative adjusted AKI was identified as an independent risk factor for FCR of the most recent follow-up ($\beta = -0.129 \pm 0.026$, $p < 0.001$), while unadjusted AKI was not. Performance of our multivariable prediction in terms of R^2 was 0.10 and there was no significant multicollinearity between covariates. Figure 3 shows the distribution of FCR across the adjusted AKI stages. There was a significant correlation between FCR and adjusted AKI stages ($p < 0.001$, correlation coefficient −0.241).

Table 2. Multivariable linear regression analysis of functional change ratio after partial nephrectomy.

Variable	$\beta \pm$ Standard Error	p-Value	VIF
Age, per 10 yr	0.003 ± 0.009	0.741	1.48
Male	−0.014 ± 0.024	0.556	1.34
Body-mass index, kg/m^2	0.008 ± 0.003	0.107	1.16
Hypertension	−0.011 ± 0.022	0.622	1.28
Diabetes mellitus	0.016 ± 0.030	0.608	1.14
Preoperative hemoglobin concentration, g/dL	0.014 ± 0.007	0.051	1.56
Preoperative albumin level, g/dL	0.065 ± 0.026	0.011	1.41
Preoperative proteinuria	−0.147 ± 0.054	0.007	1.23
Preoperative estimated glomerular filtration rate, mL/min/1.73 m^2	0.001 ± 0.001	0.160	1.13
Surgery type, open versus minimal invasive surgery	−0.014 ± 0.023	0.555	1.20
Renal ischemia time, per 10 min	−0.026 ± 0.009	0.008	1.21
Ischemia type (cold)	0.036 ± 0.047	0.444	1.06
Maximal diameter of renal mass, cm	−0.005 ± 0.007	0.410	1.16
Adjusted acute kidney injury grade *	−0.129 ± 0.026	<0.001	1.10
OR unadjusted acute kidney injury grade	−0.011 ± 0.020	0.573	1.32

VIF = variance inflation factor. * Adjusted acute kidney injury was determined based on adjusted baseline creatinine value accounting for parenchymal mass reduction. Functional change ratio was determined as the ratio of most recent glomerular filtration rate (GFR) (at least 24 months after surgery) to GFR at 3 to 12 months.

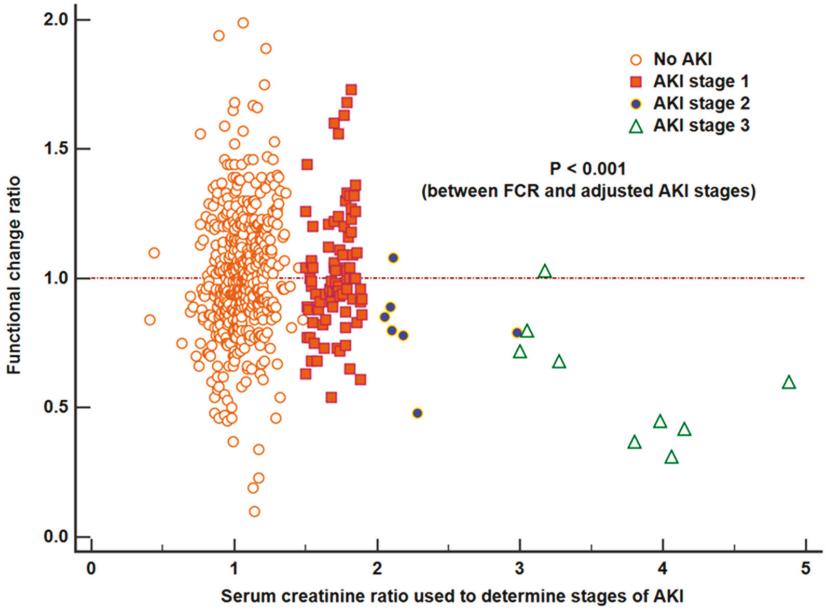

Figure 3. Distribution of long-term functional change ratio (FCR) across the different serum creatinine ratios used to determine acute kidney injury (AKI) stages. There was a significant correlation between FCR and adjusted AKI stages ($p < 0.001$).

As a sensitivity analysis, the association between functional recovery from ischemia at 3–12 months after partial nephrectomy was evaluated (Table 3). In the multivariable linear regression analysis, adjusted AKI stage was significantly associated with subsequent functional recovery ($\beta = -0.243 \pm 0.106$, $p = 0.023$), while unadjusted AKI stage classified by the standard criteria failed to associate.

Table 3. Multivariable linear regression analysis of functional recovery from ischemia at 3–12 months after partial nephrectomy.

Variable	$\beta \pm$ Standard Error	p-Value	VIF
Age, per 10 yr	−0.019 ± 0.049	0.706	1.48
Male	−0.186 ± 0.130	0.152	1.31
Body-mass index, kg/m^2	−0.024 ± 0.017	0.162	1.17
Hypertension	−0.027 ± 0.122	0.826	1.27
Diabetes mellitus	−0.073 ± 0.166	0.663	1.14
Preoperative hemoglobin concentration, g/dL	0.020 ± 0.041	0.631	1.55
Preoperative albumin level, g/dL	0.130 ± 0.136	0.338	1.29
Preoperative estimated glomerular filtration rate, mL/min/1.73 m^2	0.001 ± 0.003	0.726	1.25
Renal ischemia time, per 10 min	−0.057 ± 0.048	0.236	1.17
Ischemia type (cold)	0.774 ± 0.262	0.003	1.06
Maximal diameter of renal mass, cm	−0.230 ± 0.037	<0.001	1.23
Adjusted acute kidney injury stage *	−0.243 ± 0.106	0.023	1.28
OR unadjusted acute kidney injury stage	−0.177 ± 0.118	0.137	1.15

VIF = variance inflation factor. Functional recovery was calculated as the ratio of the percentage of function saved to the percentage of parenchymal volume saved. * Adjusted acute kidney injury was determined based on adjusted baseline creatinine value accounting for parenchymal mass reduction. Percent function saved was determined as the ratio of estimated glomerular filtration rate (eGFR) at 3–12 months after nephrectomy to preoperative baseline eGFR.

4. Discussion

We evaluated the association between AKI after partial nephrectomy, and long-term renal function. To account for the nephron mass reduction when diagnosing AKI, we determined AKI in two ways: using either unadjusted or adjusted baseline creatinine. Adjusted AKI after partial nephrectomy was a significant predictor of long-term FCR, but was not for unadjusted AKI. This significant association was consistent for both outcomes of FCR of at least two years after surgery and functional recovery of 3–12 months after partial nephrectomy.

AKI may be important for the long-term renal function only when it reflects true acute ischemic injury of the remaining renal nephrons. Efforts to reduce this ischemic injury may mitigate long-term renal dysfunction, thereby improving patient outcomes.

Partial nephrectomy has been regarded as standard therapy for patients with localized renal cancer [18]. Nevertheless, using the conventional diagnostic criteria of AKI, the incidence of AKI after partial nephrectomy was reported to be as high as 39%–54% [1,2]. Renal functional decline after partial nephrectomy is due to incomplete recovery of the remaining kidney from ischemic insult and parenchymal volume loss due to renal resection [4,19]. In surgeries other than nephrectomy, AKI is closely associated with the development of CKD and increased mortality [5,20,21]. However, for partial nephrectomy, this association has not been clearly ascertained. Previous studies reported varying results [2,6–8], possibly due to the difficulty there is to diagnose the pure renal parenchymal injury, and different study outcomes measuring long-term renal function at a varying intervals from nephrectomy.

Therefore, accurate diagnosis of AKI after partial nephrectomy is important, to evaluate the true impact of AKI on long-term renal function after nephrectomy. However, conventional AKI criteria simply compare the preoperative baseline creatinine level with postoperative values, not considering the aforementioned two components [2,9]. Although both of those two components could contribute to the long-term renal outcomes, our analysis indicated that the ischemic injury of the remaining kidney is more important for long-term renal prognosis.

We estimated PFVP according to a previous method which measures the renal volume on the CT images using a cylinder volume ratio method [16]. Although this is a simple and easy estimation of kidney volume, this could be inaccurate. We calculated adjusted baseline serum creatinine and eGFR by using this estimated PFVP under the assumption that endophytic components of the kidney lose functioning nephrons due to surgical resection. However, previous studies of partial nephrectomy used volumetric analysis using pre and postoperative CT images, which could be more accurate [2,6,22]. The spherical cap surface model used only the preoperative CT image to measure PFVP like our study [17]. However, they calculated the volume of normal parenchyma removed during surgery, which was not considered in our calculation. Although not available in our data, the surgeon's visual assessment of parenchymal preserved volume was reported to be strongly associated with measured values [23]. Preoperative assessment of PFVP based on preoperative imaging provided similar predictive capacity to the surgeon's assessment [24]. Our study results should be interpreted under these limitations.

There have been two studies investigating the association between AKI and long-term renal function after partial nephrectomy [2,6]. Both studies used a volumetric analysis of pre and postoperative CT images. Zhang et al. defined adjusted AKI according to projected serum creatinine as a new baseline and reported a significant association between AKI using a creatinine-adjusted baseline, and early renal functional recovery after partial nephrectomy [2]. This study used functional recovery at 3–12 months after partial nephrectomy and the preoperative baseline. The median parenchymal mass reduction was 11% and cold ischemia was used 53% of the time. However, in another study, which evaluated FCR at least after 12 months after partial nephrectomy compared to the postoperative, new baseline at 3–12 months after surgery, reported no significant association between adjusted AKI stages and FCR [6]. The median parenchymal mass reduction was 20% and cold ischemia was used 47% of the time. Although adjusted AKI was used in both studies, varying follow-up duration and different baseline of renal function could yield different results. Different sizes of the tumors, degrees of parenchymal resection, the incidence of cold ischemia, ischemic time and tumor complexity, could

influence long-term renal function after partial nephrectomy. A patient cohort with shorter ischemic time and higher incidence of cold ischemia may lead to relatively good long-term renal function, and a population with a longer ischemic time and low incidence of cold ischemia may yield poor long-term renal function, which could discriminate the influence of AKI. We used the same outcomes as those two studies for a valid comparison.

For the patients undergoing unilateral radical nephrectomy, there have been only two studies, which reported a significant association between postoperative AKI and progressive CKD [7,8]. The incidence of AKI was rather high, up to 49.1%, and the association was strong, with a three to four-fold higher risk, although CKD was defined differently between the two studies. Further prospective studies are required to validate this association.

Although functional recovery after partial nephrectomy is mainly determined by parenchymal volume preservation [22], we demonstrated that ischemic insult of the remaining kidney could also affect the functional outcome substantially if ischemic time is prolonged. Efforts have been made to reduce renal injury after partial nephrectomy. The effects of pharmacological agents, such as mannitol and dopamine, have been questioned [25,26]. Cold ischemia is known to be effective in restoring renal function after partial nephrectomy [27]. However, cold ischemia was not significant in the present study, possibly due to its low incidence in our cohort. Recently, zero ischemia partial nephrectomy or selective arterial clamping has been suggested [28,29]. Remote ischemic conditioning using transient limb ischemia was suggested to reduce short-term renal functional impairment after a laparoscopic partial nephrectomy [30,31]. A previous pilot study reported combined treatment of ketorolac and remote ischemic conditioning in patients undergoing partial nephrectomy reduced the incidence of AKI [32]. Hydrogen sulfide was effective in attenuating prolonged warm renal ischemia-reperfusion injury in a previous animal study [33]. However, the incidence of AKI and CKD after partial nephrectomy was still high. Further studies for these interventions may consider the outcome of AKI based on adjusted creatinine.

Most of the significant predictors for new-onset CKD are consistent with previous studies. Although unmodifiable, preoperative proteinuria is a known predictor [1,11,34], which was consistent with our results. Renal ischemic time [1,34,35] should be reduced and cold ischemia can be applied during renal mass resection to reduce renal injury, despite existing controversy [4,36,37].

This study has several limitations. Firstly, our study was a retrospective study of a single tertiary care center. Unknown and unmeasured biases could have affected our results. Open and minimally invasive surgeries are mixed in our population. Missing values of long-term renal function jeopardize the validity of our results. Secondly, as mentioned earlier, our estimation of adjusted baseline creatinine or eGFR has limitations. Further studies are required to support our results with validated volumetric analysis. Thirdly, we included patients who have bilateral kidneys in our analysis. Although all patients underwent partial nephrectomy, the adjustment of baseline creatinine could be more inaccurate in a patient with bilateral kidneys compared to one with a single kidney.

5. Conclusions

By using baseline creatinine corrected for parenchymal mass reduction based on our simple measurements on preoperative CT, AKI adjusted for the renal parenchymal mass reduction was a significant predictor of long-term renal function for at least two years after surgery, while unadjusted AKI was not. We demonstrated this association by using two different outcomes that previous studies used. Our study suggests the prognostic implication of acute injury of remaining renal parenchyma during partial nephrectomy, in regard to long-term renal function. Efforts to reduce the remaining renal parenchymal injury may contribute to mitigate the risk of long-term deterioration in renal function after partial nephrectomy. However, prospective trials with validated renal volume measurements are required.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/9/1482/s1, Supplemental Text S1. Calculation of adjusted preoperative estimated glomerular filtration rate and adjusted serum creatinine in partial nephrectomy. Supplemental Table S1. Patient characteristics and perioperative parameters according to acute kidney injury using unadjusted preoperative baseline creatinine. Supplemental Table S2. Comparison of baseline renal function and the rates of surgical complications between those with and without adjusted acute kidney injury.

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References

1. Rajan, S.; Babazade, R.; Govindarajan, S.R.; Pal, R.; You, J.; Mascha, E.J.; Khanna, A.; Yang, M.; Marcano, F.D.; Singh, A.K.; et al. Perioperative factors associated with acute kidney injury after partial nephrectomy. *Br. J. Anaesth.* **2016**, *116*, 70–76. [CrossRef] [PubMed]
2. Zhang, Z.; Zhao, J.; Dong, W.; Remer, E.; Li, J.; Demirjian, S.; Zabell, J.; Campbell, S.C. Acute Kidney Injury after Partial Nephrectomy: Role of Parenchymal Mass Reduction and Ischemia and Impact on Subsequent Functional Recovery. *Eur. Urol.* **2016**, *69*, 745–752. [CrossRef] [PubMed]
3. Weight, C.J.; Larson, B.T.; Fergany, A.F.; Gao, T.; Lane, B.R.; Campbell, S.C.; Kaouk, J.H.; Klein, E.A.; Novick, A.C. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. *J. Urol.* **2010**, *183*, 1317–1323. [CrossRef] [PubMed]
4. Mir, M.C.; Ercole, C.; Takagi, T.; Zhang, Z.; Velet, L.; Remer, E.M.; Demirjian, S.; Campbell, S.C. Decline in renal function after partial nephrectomy: Etiology and prevention. *J. Urol.* **2015**, *193*, 1889–1898. [CrossRef] [PubMed]
5. Chawla, L.S.; Eggers, P.W.; Star, R.A.; Kimmel, P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **2014**, *371*, 58–66. [CrossRef] [PubMed]
6. Zabell, J.; Isharwal, S.; Dong, W.; Abraham, J.; Wu, J.; Suk-Ouichai, C.; Palacios, D.A.; Remer, E.; Li, J.; Campbell, S.C. Acute Kidney Injury after Partial Nephrectomy of Solitary Kidneys: Impact on Long-Term Stability of Renal Function. *J. Urol.* **2018**, *200*, 1295–1301. [CrossRef]
7. Cho, A.; Lee, J.E.; Kwon, G.Y.; Huh, W.; Lee, H.M.; Kim, Y.G.; Kim, D.J.; Oh, H.Y.; Choi, H.Y. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol. Dial. Transplant.* **2011**, *26*, 3496–3501. [CrossRef]
8. Garofalo, C.; Liberti, M.E.; Russo, D.; Russo, L.; Fuiano, G.; Cianfrone, P.; Conte, G.; De Nicola, L.; Minutolo, R.; Borrelli, S. Effect of post-nephrectomy acute kidney injury on renal outcome: A retrospective long-term study. *World J. Urol.* **2018**, *36*, 59–63. [CrossRef]
9. Thomas, M.E.; Blaine, C.; Dawnay, A.; Devonald, M.A.; Ftouh, S.; Laing, C.; Latchem, S.; Lewington, A.; Milford, D.V.; Ostermann, M. The definition of acute kidney injury and its use in practice. *Kidney Int.* **2015**, *87*, 62–73. [CrossRef]
10. Chapman, D.; Moore, R.; Klarenbach, S.; Braam, B. Residual renal function after partial or radical nephrectomy for renal cell carcinoma. *Can. Urol. Assoc. J.* **2010**, *4*, 337–343. [CrossRef]
11. Tachibana, H.; Kondo, T.; Takagi, T.; Okumi, M.; Tanabe, K. Impact of preoperative proteinuria on renal functional outcomes after open partial nephrectomy in patients with a solitary kidney. *Investig. Clin. Urol.* **2017**, *58*, 409–415. [CrossRef] [PubMed]
12. Martín, O.D.; Bravo, H.; Arias, M.; Dallos, D.; Quiroz, Y.; Medina, L.G.; Cacciamani, G.E.; Carlini, R.G. Determinant factors for chronic kidney disease after partial nephrectomy. *Oncoscience* **2018**, *5*, 13–20. [PubMed]

13. Kim, N.Y.; Hong, J.H.; Koh, D.H.; Lee, J.; Nam, H.J.; Kim, S.Y. Effect of Diabetes Mellitus on Acute Kidney Injury after Minimally Invasive Partial Nephrectomy: A Case-Matched Retrospective Analysis. *J. Clin. Med.* **2019**, *8*, 468. [CrossRef] [PubMed]
14. Levey, A.S.; Bosch, J.P.; Lewis, J.B.; Greene, T.; Rogers, N.; Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* **1999**, *130*, 461–470. [CrossRef] [PubMed]
15. Shin, S.R.; Kim, W.H.; Kim, D.J.; Shin, I.W.; Sohn, J.T. Prediction and Prevention of Acute Kidney Injury after Cardiac Surgery. *BioMed Res. Int.* **2016**, *2016*, 2985148. [CrossRef] [PubMed]
16. Simmons, M.N.; Fergany, A.F.; Campbell, S.C. Effect of parenchymal volume preservation on kidney function after partial nephrectomy. *J. Urol.* **2011**, *186*, 405–410. [CrossRef]
17. Ding, Y.; Kong, W.; Zhang, J.; Dong, B.; Chen, Y.; Xue, W.; Liu, D.; Huang, Y. Spherical cap surface model: A novel method for predicting renal function after partial nephrectomy. *Int. J. Urol.* **2016**, *23*, 667–672. [CrossRef] [PubMed]
18. Campbell, S.; Uzzo, R.G.; Allaf, M.E.; Bass, E.B.; Cadeddu, J.A.; Chang, A.; Clark, P.E.; Davis, B.J.; Derweesh, I.H.; Giambarresi, L.; et al. Renal Mass and Localized Renal Cancer: AUA Guideline. *J. Urol.* **2017**, *198*, 520–529. [CrossRef]
19. McIntosh, A.G.; Parker, D.C.; Egleston, B.L.; Uzzo, R.G.; Haseebuddin, M.; Joshi, S.S.; Viterbo, R.; Greenberg, R.E.; Chen, D.Y.T.; Smaldone, M.C.; et al. Prediction of significant estimated glomerular filtration rate decline after renal unit removal to aid in the clinical choice between radical and partial nephrectomy in patients with a renal mass and normal renal function. *BJU Int.* **2019**. [CrossRef]
20. Coca, S.G.; Singanamala, S.; Parikh, C.R. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int.* **2012**, *81*, 442–448. [CrossRef]
21. Chertow, G.M.; Burdick, E.; Honour, M.; Bonventre, J.V.; Bates, D.W. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J. Am. Soc. Nephrol.* **2005**, *16*, 3365–3370. [CrossRef] [PubMed]
22. Mir, M.C.; Campbell, R.A.; Sharma, N.; Remer, E.M.; Li, J.; Demirjian, S.; Kaouk, J.; Campbell, S.C. Parenchymal volume preservation and ischemia during partial nephrectomy: Functional and volumetric analysis. *Urology* **2013**, *82*, 263–268. [CrossRef] [PubMed]
23. Tobert, C.M.; Takagi, T.; Liss, M.A.; Lee, H.; Derweesh, I.H.; Campbell, S.C.; Lane, B.R. Multicenter Validation of Surgeon Assessment of Renal Preservation in Comparison to Measurement with 3D Image Analysis. *Urology* **2015**, *86*, 534–538. [CrossRef] [PubMed]
24. Klingler, M.J.; Babitz, S.K.; Kutikov, A.; Campi, R.; Hatzichristodoulou, G.; Sanguedolce, F.; Brookman-May, S.; Akdogan, B.; Capitanio, U.; Roscigno, M.; et al. Assessment of volume preservation performed before or after partial nephrectomy accurately predicts postoperative renal function: Results from a prospective multicenter study. *Urol. Oncol.* **2019**, *37*, 33–39. [CrossRef] [PubMed]
25. Cosentino, M.; Breda, A.; Sanguedolce, F.; Landman, J.; Stolzenburg, J.U.; Verze, P.; Rassweiler, J.; Van Poppel, H.; Klingler, H.C.; Janetschek, G.; et al. The use of mannitol in partial and live donor nephrectomy: An international survey. *World J. Urol.* **2013**, *31*, 977–982. [CrossRef] [PubMed]
26. O'Hara, J.F.; Hsu, T.H., Jr.; Sprung, J.; Cywinski, J.B.; Rolin, H.A.; Novick, A.C. The effect of dopamine on renal function in solitary partial nephrectomy surgery. *J. Urol.* **2002**, *167*, 24–28. [CrossRef]
27. Mir, M.C.; Takagi, T.; Campbell, R.A.; Sharma, N.; Remer, E.M.; Li, J.; Demirjian, S.; Stein, R.; Kaouk, J.; Campbell, S.C. Poorly functioning kidneys recover from ischemia after partial nephrectomy as well as strongly functioning kidneys. *J. Urol.* **2014**, *192*, 665–670. [CrossRef]
28. Hung, A.J.; Cai, J.; Simmons, M.N.; Gill, I.S. "Trifecta" in partial nephrectomy. *J. Urol.* **2013**, *189*, 36–42. [CrossRef]
29. Paulucci, D.J.; Rosen, D.C.; Sfakianos, J.P.; Whalen, M.J.; Abaza, R.; Eun, D.D.; Krane, L.S.; Hemal, A.K.; Badani, K.K. Selective arterial clamping does not improve outcomes in robot-assisted partial nephrectomy: A propensity-score analysis of patients without impaired renal function. *BJU Int.* **2017**, *119*, 430–435. [CrossRef]
30. Huang, J.; Chen, Y.; Dong, B.; Kong, W.; Zhang, J.; Xue, W.; Liu, D.; Huang, Y. Effect of remote ischaemic preconditioning on renal protection in patients undergoing laparoscopic partial nephrectomy: A 'blinded' randomised controlled trial. *BJU Int.* **2013**, *112*, 74–80. [CrossRef]
31. Hur, M.; Park, S.K.; Shin, J.; Choi, J.Y.; Yoo, S.; Kim, W.H.; Kim, J.T. The effect of remote ischemic preconditioning on serum creatinine in patients undergoing partial nephrectomy: A study protocol for a randomized controlled trial. *Trials* **2018**, *19*, 473. [CrossRef] [PubMed]

32. Kil, H.K.; Kim, J.Y.; Choi, Y.D.; Lee, H.S.; Kim, T.K.; Kim, J.E. Effect of Combined Treatment of Ketorolac and Remote Ischemic Preconditioning on Renal Ischemia-Reperfusion Injury in Patients Undergoing Partial Nephrectomy: Pilot Study. *J. Clin. Med.* **2018**, *7*, 470. [CrossRef] [PubMed]
33. Zhu, J.X.; Kalbfleisch, M.; Yang, Y.X.; Bihari, R.; Lobb, I.; Davison, M.; Mok, A.; Cepinskas, G.; Lawendy, A.-R.; Sener, A. Detrimental effects of prolonged warm renal ischaemia-reperfusion injury are abrogated by supplemental hydrogen sulphide: An analysis using real-time intravital microscopy and polymerase chain reaction. *BJU Int.* **2012**, *110*, E1218–E1227. [CrossRef] [PubMed]
34. Porpiglia, F.; Renard, J.; Billia, M.; Musso, F.; Volpe, A.; Burruni, R.; Terrone, C.; Colla, L.; Piccoli, G.; Podio, V.; et al. Is renal warm ischemia over 30 min during laparoscopic partial nephrectomy possible? One-year results of a prospective study. *Eur. Urol.* **2007**, *52*, 1170–1178. [CrossRef] [PubMed]
35. Funahashi, Y.; Hattori, R.; Yamamoto, T.; Kamihira, O.; Kato, K.; Gotoh, M. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. *Eur. Urol.* **2009**, *55*, 209–215. [CrossRef] [PubMed]
36. Lane, B.R.; Russo, P.; Uzzo, R.G.; Hernandez, A.V.; Boorjian, S.A.; Thompson, R.H.; Fergany, A.F.; Love, T.E.; Campbell, S.C. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. *J. Urol.* **2011**, *185*, 421–427. [CrossRef] [PubMed]
37. Lee, H.; Song, B.D.; Byun, S.S.; Lee, S.E.; Hong, S.K. Impact of warm ischaemia time on postoperative renal function after partial nephrectomy for clinical T1 renal cell carcinoma: A propensity score-matched study. *BJU Int.* **2018**, *121*, 46–52. [CrossRef] [PubMed]

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Utility of Novel Cardiorenal Biomarkers in the Prediction and Early Detection of Congestive Kidney Injury Following Cardiac Surgery

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Abstract: Acute Kidney Injury (AKI) in the context of right ventricular failure (RVF) is thought to be largely congestive in nature. This study assessed the utility of biomarkers high sensitivity cardiac troponin T (hs-cTnT), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and neutrophil gelatinase-associated lipocalin (NGAL) for prediction and early detection of congestive AKI (c-AKI) following cardiac surgery. This prospective nested case-control study recruited 350 consecutive patients undergoing elective cardiac surgery requiring cardiopulmonary bypass. Cases were patients who developed (1) AKI (2) new or worsening RVF, or (3) c-AKI. Controls were patients free of these complications. Biomarker levels were measured at baseline after anesthesia induction and immediately postoperatively. Patients with c-AKI had increased mean duration of mechanical ventilation and length of stay in hospital and in the intensive care unit ($p < 0.01$). For prediction of c-AKI, baseline NT-proBNP yielded an area under the curve (AUC) of 0.74 (95% CI, 0.60–0.89). For early detection of c-AKI, postoperative NT-proBNP yielded an AUC of 0.78 (0.66–0.91), postoperative hs-cTnT yielded an AUC of 0.75 (0.58–0.92), and Δhs-cTnT yielded an AUC of 0.80 (0.64–0.96). The addition of baseline creatinine to Δhs-cTnT improved the AUC to 0.87 (0.76–0.99), and addition of diabetes improved the AUC to 0.93 (0.88–0.99). Δhs-cTnT alone, or in combination with baseline creatinine or diabetes, detects c-AKI with high accuracy following cardiac surgery.

Keywords: cardiac surgery; biomarkers; right heart failure; congestive acute kidney injury; venous congestion

1. Introduction

Right ventricular failure (RVF) is associated with significant morbidity and mortality following cardiac surgery [1,2]. Acute RVF is present in up to 50% of patients with postoperative hemodynamic instability [3] and is associated with difficult separation from cardiopulmonary bypass (CPB) [4], up to 75% increase in operative mortality as well as poor late survival [5,6]. Acute kidney injury (AKI) is a common sequela of RVF, which further complicates the management of RVF and portends a worsening prognosis. AKI occurs in up to 30% of cardiac surgical patients, of whom 1–2% require renal

replacement therapy [7,8]. Management of perioperative AKI is primarily focused on maintenance of renal perfusion pressure and treatment of hypovolemia [9,10]. However, in the presence of RVF, AKI worsens with fluid administration and improves only with fluid removal [2]. This congestive form of AKI (c-AKI) is both difficult to diagnose and treat, especially as the cause of c-AKI is often not readily apparent and it is difficult to diagnose using current clinical criteria. Current diagnosis of AKI relies on measures of glomerular filtration such as serum creatinine, which is insensitive and lags behind actual renal injury; leading to delayed diagnosis and unfavourable outcomes [11,12]. Hemodilution, especially during the immediate postoperative period, may further confound creatinine-based diagnosis of AKI [13]. The paucity of early predictive biomarkers is one purported reason for the failure of recent prevention and treatment clinical trials for cardiac surgery induced AKI [14].

The pathogenesis of cardiac surgery induced AKI is multifactorial including many interrelated, and largely non-modifiable, injury pathways. However, venous congestion-induced AKI may potentially be reversed through diuretic and vasodilator based preventative and early treatment strategies. Contrary to popular belief [15], central venous pressure (CVP) is a poor indicator of circulating blood volume and fluid responsiveness [16,17]. Hence, there remains a need for better identification of patients who are most likely to benefit from early decongestive therapy.

Cardiac and renal biomarkers such as high sensitivity cardiac troponin T (hs-cTnT), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and neutrophil gelatinase-associated lipocalin (NGAL) are excellent prognosticators in patients with RVF and/or AKI [18–25]. These biomarkers provide direct cellular insight into cardiorenal physiology and may enable early identification of patients who are already in a congestive state prior to development of clinical consequences of venous congestion. However, the timing and pattern of release of these biomarkers are unknown in the setting of c-AKI with an acutely failing right ventricle (RV). An in-depth understanding of these biomarker patterns may enable identification of high-risk patients for intensive monitoring and early treatment. The objective of this study was to evaluate the utility of NT-proBNP, hs-cTnT, and NGAL for prediction and early detection of c-AKI following cardiac surgery.

2. Methods

The research ethics board of the University of Ottawa Heart Institute (UOHI) approved this prospective nested case-control study (protocol #: 2015049401H). Written informed consent was obtained from all participants prior to enrolment.

2.1. Patients

We recruited 350 consecutive consenting patients aged 18 years or older, who underwent major elective cardiac surgery requiring CPB at UOHI between 29 September 2015 and 21 February 2017. Exclusion criteria included end stage renal disease (glomerular filtration rate [GFR] <15 mL/min or dialysis dependence), history of renal transplantation, solitary kidney, emergent operative status, off pump procedures, procedures involving circulatory arrest, heart transplantation, and left ventricular assist device implantation.

2.2. Outcomes

The primary outcome was c-AKI, defined by AKI in the presence of postoperative RVF (definition of c-AKI is detailed in Supplemental Table S1). The secondary outcomes were non-congestive AKI, RVF, duration of mechanical ventilation, intensive care unit (ICU) and hospital lengths of stay and in-hospital mortality. AKI was defined by the Acute Kidney Injury Network (AKIN) criteria [26] as >50% relative or >26 μmol/L absolute rise in serum creatinine above preoperative value within 48 h of surgery, or new onset dialysis. Postoperative RVF was defined as new or worsening RVF satisfying published criteria A and/or B [27,28] post separation from CPB and until postoperative day 2 (Supplemental Table S1). Pulmonary artery catheterization is practiced routinely for patients undergoing cardiac surgery at our institution.

A. Combined Clinical and Echocardiographic: [28,29]

   i. Difficult separation from CPB, characterized by

      1. Concurrent use of ≥1 vasopressor and ≥1 inotrope or ≥1 pulmonary vasodilator (i.e., nitric oxide or epoprostenol); or
      2. More than one CPB weaning attempt; or
      3. Mechanical support device (i.e., RV assist device); and

   ii. >20% relative reduction in RV fractional area change measured by two-dimensional echocardiography.

B. Hemodynamic criteria:

   i. CVP >18 mmHg or cardiac index <1.8 L/min/m^2, in the absence of elevated left atrial and pulmonary capillary wedge pressure >18 mmHg, tamponade, ventricular arrhythmias, or pneumothorax; and
   ii. RV stroke work index <4 g·min^{-1}·m^2. RVSWI = 0.136 × SVI × (mPAP − RAP); where SVI = stroke volume index = stroke volume/body surface area, mPAP = mean pulmonary artery pressure, and RAP = right atrial pressure.

2.3. Cases and Controls

Cases were defined as patients with postoperative RVF, c-AKI or non-congestive AKI. Controls were patients who were free of these complications during the follow up period. Controls were 1:1 matched to the cases based on age and sex. All patients received routine standard of care during the study period.

2.4. Study Procedures

All patients were followed prospectively until hospital discharge. Baseline patient characteristics, operative data and postoperative outcomes were recorded by trained research staff. The attending anesthesiologist recorded baseline RV function, and whether difficulty was encountered with CPB separation. Baseline RV function was recorded from the most recent echocardiogram within 90 days of surgery in patients with stable cardiac disease, and during the index surgical admission or intraoperatively prior to CPB in patients who presented acutely.

2.5. Biomarkers

Biomarkers were sampled at baseline immediately following anesthesia induction and postoperatively within 1 h of arrival to the ICU. In addition, serum creatinine was measured at least daily during the first 2 postoperative days. Biomarker samples were centrifuged and plasma supernatants stored at −80 °C until analysis. Plasma hs-cTnT (Roche Diagnostics, Indianapolis, IN, USA) and NT-proBNP (Roche Diagnostics) were measured using commercially available US food and Drug Administration-approved electrochemiluminescence immunoassays with a Roche Cobas e411 anaylzer. Manufacturer's normal reference value for hs-cTnT and NT-proBNP are <13.5 pg/mL (99th percentile) and <300 pg/mL, respectively [23,30]. NGAL levels were measured using a commercially available ELISA kit (Bioporto Diagnostics, Copenhagen, Denmark) and using a mean reference value in healthy volunteers of 35.4 (95% CI, 18.9–46.5) ng/mL [31].

2.6. Statistical Analysis

Statistical analyses and graphic representation were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and Graphpad Prism 6.0 (Graphpad Software, San Diego, CA, USA). Categorical characteristics were compared using X^2 or Fisher's exact test for categorical variables where

appropriate. Continuous variables were compared using Student's *t* test or Wilcoxon rank sum test depending on normality of distribution. An analysis of variance (ANOVA) was used to compare hospital and ICU stay and ventilation duration between groups. Log transformed NGAL, NT-proBNP, and hs-cTnT were used because their distributions were not normal. A two-way, repeated measure ANOVA was used to compare the effects of time (pre-versus post surgery) and AKI/RVF status for all variables. A Bonferroni correction was used for post hoc pairwise comparison of means. We used conditional logistic regression to assess the association between individual biomarker levels and c-AKI, with and without adjustment for baseline estimated GFR (eGFR), diabetes, and surgery type. These covariates were selected *a priori* based on the strength of their known association with AKI and RVF in cardiac surgical patients [21,32]. As cases were already matched to controls based on age and sex, these covariates were not included in the model. Measure of association was odds ratio (OR) with associated 95% confidence interval (CI). In addition, linear regression was used to assess the association between biomarker levels and continuous outcomes such as length of hospital/ICU stay and duration of mechanical ventilation. The Pearson correlation coefficient was reported as measure of correlation. Area under (AUC) the receiver operator characteristic (ROC) curve was used to assess the ability of individual biomarkers to discriminate between patients who developed each of the outcomes vs. those who did not. Youden's index was used to identify the optimal ROC cutoff. We also evaluated the incremental value of these biomarkers when added to the clinical model using the method of Delong, Delong, and Clarke-Pearson [33]. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient Characteristics

A total of 350 patients were enrolled in the study, from whom 89 cases were identified and age-sex matched to 89 controls (Supplemental Table S2). Of the cases, 36 (40.5%) developed postoperative RVF, 35 (39.3%) developed non-congestive AKI, and 18 (20.2%) developed c-AKI. Baseline characteristics of c-AKI cases and controls are shown in Table 1. Compared to matched controls, c-AKI patients were more likely to have pre-existing renal insufficiency, diabetes, and to undergo more complex surgery with longer CPB and aortic crossclamp durations. In addition, there was a trend towards higher baseline CVP and lower cardiac index in c-AKI patients. There were no differences in baseline left ventricle ejection fraction (LVEF) between c-AKI and controls.

Table 1. Characteristics of patients with congestive acute kidney injury (c-AKI) vs. controls.

	Control (n = 89)	c-AKI (n = 18)	p-Value
Baseline Characteristics			
Male	61 (68.5%)	11 (61.1%)	0.54
Age (years)	66.0 (63.8–68.2)	67.1 (61.1–73.2)	0.57
Body Mass Index (kg/m^2)	28.5 (27.4–29.7)	30.5 (27.3–33.6)	0.35
eGFR (mL/min/1.73 m^2)	89.8 (83.4–96.1)	75.2 (60.6–89.7)	0.03
Serum Creatinine (µmol/L)	84.3 (79.5–89.1)	100.7 (87.3–114.1)	0.009
Cardiac Index (L/min/m^2)	2.18 (2.03–2.33)	1.93 (1.66- 2.19)	0.08
Central Venous Pressure (mmHg)	13.9 (12.9–14.9)	16.6 (14.1–19.1)	0.06
Left Ventricle Ejection Fraction (%)	53.1 (51.4–54.9)	49.6 (44.3–54.8)	0.14
Comorbidities			
Hypertension	57 (64%)	12 (67%)	0.83
Diabetes	20 (22%)	12 (67%)	0.0002
COPD	8 (9%)	1 (6%)	1.0
Pre-existing Right Heart Dysfunction	1 (1.1%)	1 (6%)	0.31
Coronary Artery Disease	57 (64%)	11 (61%)	0.81
Medications			
ASA	54 (61%)	11 (62%)	0.97
Beta Blocker	59 (66%)	11 (62%)	0.67
ACE Inhibitor	50 (56%)	8 (44%)	0.36
Lipid Lowering agents	55 (62%)	11 (62%)	0.96

Table 1. *Cont.*

	Control (n = 89)	c-AKI (n = 18)	p-Value
Intraoperative Characteristics			
Surgery Type			0.0006
CABG	43 (48%)	5 (28%)	
Single Valve	33 (37%)	3 (17%)	
Combined CABG/Valve/Other	13 (15%)	10 (56%)	
Cardiopulmonary Bypass Duration (min)	89.1 (82.1–96.0)	141.1 (114.5–167.7)	0.0002
Aortic Cross Clamp Duration (min)	64.6 (58.4–70.8)	102.1 (78.8–125.4)	0.003
Postoperative characteristics			
Length of Hospital Stay (days)	11.8 (9.5–14.1)	23.3 (14.2–32.4)	0.0001
Length of Intensive Care Unit Stay (days)	2.1 (1.3–2.8)	6.1 (3.4–8.8)	<0.0001
Mechanical Ventilation Duration (hours)	9.7 (3.6–15.7)	63.0 (1.23–124.7)	<0.0001

eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ASA, acetylsalicylic acid; ACE, angiotensin-converting-enzyme; Data presented are expressed as n (%) or mean (95% confidence interval).

3.2. Biomarker Analysis Pre and Post Cardiac Surgery

Patients who developed c-AKI had significantly higher baseline NT-proBNP levels compared to controls (Figure 1A). In patients who developed non-congestive AKI, baseline NT-proBNP, NGAL, and hs-cTnT were significantly higher than controls (Figure 1A–C). Following surgery, NT-proBNP remained relatively unchanged while hs-cTnT and NGAL increased 2–2.5 fold in all groups (Figure 1B,C). The magnitude of postoperative increase in hs-cTnT was highest in the c-AKI group. Postoperatively, NGAL increased in those who developed RVF but remained relatively unchanged in the AKI, c-AKI, and control groups.

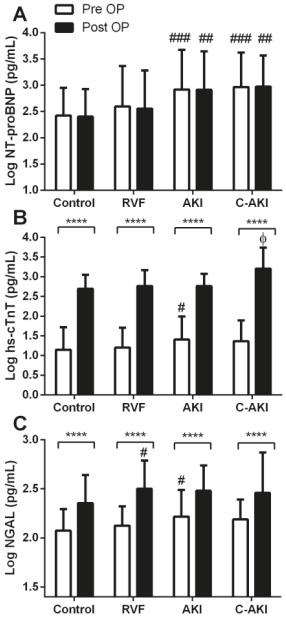

Figure 1. Baseline and postoperative biomarker levels in patients who developed congestive acute kidney injury (c-AKI) vs. controls. **** Within group differences (baseline vs. postoperative) $p < 0.0001$. # Significantly different than control $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$. Φ Significantly different than control, right ventricular failure (RVF), and AKI, $p < 0.05$.

3.3. Hemodynamics Pre and Post Cardiac Surgery

Compared to controls, patients who developed c-AKI had significantly lower cardiac index at all time points (Figure 2A). Conversely, CVP decreased postoperatively from baseline in both c-AKI and control groups but remained higher in c-AKI patients throughout the postoperative period (Figure 2B). This trend was particularly evident on postoperative day 2 where CVP in c-AKI patients remained >1.5 fold higher than in the controls ($p < 0.001$).

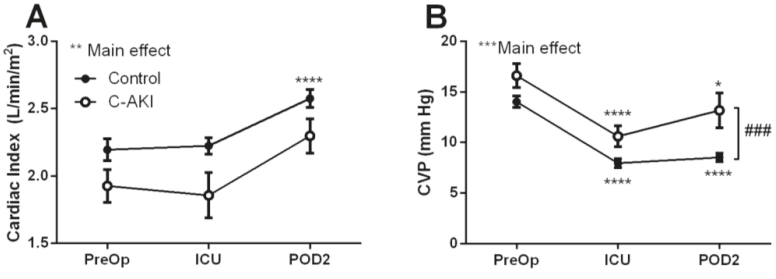

Figure 2. Cardiac index (**A**) and central venous pressure (**B**) in patients who developed congestive acute kidney injury (c-AKI) vs. controls. Hemodynamic variables were assessed preoperatively, upon admission to the intensive care unit and on postoperative day two. * Significantly different than baseline levels, $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. ### Significant difference between c-AKI and control, $p < 0.001$.

In patients with non-congestive AKI, a similar trend was observed where CVP was significantly elevated compared to controls throughout the follow up period (Supplemental Figure S1A). No significant differences in hemodynamic profiles were observed for patients who developed RVF vs. controls (Supplemental Figure S1B,D).

3.4. Biomarker and Hemodynamic Correlation

A weak positive relationship was observed between baseline log hs-cTnT and CVP ($r = 0.21$, $p = 0.006$). However, log NT-proBNP and log NGAL levels did not correlate with CVP at baseline. At baseline, cardiac index was inversely correlated with log NT-proBNP ($r = -0.2$, $p = 0.01$) and log hs-cTnT ($r = -0.19$, $p = 0.01$). In addition, there were weak-moderate inverse correlations between baseline eGFR and log hs-cTnT ($r = -0.27$, $p = 0.0002$), log NT-proBNP ($r = -0.37$, $p < 0.0001$), and log NGAL ($r = -0.28$, $p < 0.0001$). Postoperatively, a positive correlation was observed between log NT-proBNP and CVP ($r = 0.20$, $p = 0.007$), but no correlations were found between cardiac index and biomarkers.

3.5. Performance of Biomarkers vs. Traditional Parameters for c-AKI Prediction and Detection

3.5.1. Prediction of c-AKI

Higher baseline CVP was associated with c-AKI after multivariable adjustment (adjusted OR 1.20, 95% CI 1.04–1.38 for each 1 mmHg increase in CVP) (Table 2).

Table 3 and Figure 3 summarize the AUCs for individual biomarkers and traditional parameters for prediction of c-AKI. Of the baseline biomarkers, NT-proBNP had the highest AUC for predicting c-AKI (0.74, 95% CI 0.60–0.89). However, the clinical model alone (based on baseline eGFR, diabetes and surgery type) had an AUC of 0.83 (0.72–0.94), and the addition of NT-proBNP to the clinical model did not significantly improve the AUC ($p = 0.39$, Table 3). The optimal cut-off of baseline NT-proBNP for c-AKI prediction was >476 pg/mL (sensitivity 77%, specificity 72%) (Table 4).

Table 2. Association between cardiorenal biomarkers and congestive acute kidney injury.

	Unadjusted		Adjusted [a]	
	OR (95% CI)	***p* Value**	**OR (95% CI)**	***p* Value**
Baseline				
NGAL	1.37 (1.05–1.78)	0.02	1.19 (0.88–1.61)	0.25
NT-proBNP	1.17 (1.06–1.29)	0.001	1.10 (0.97–1.24)	0.12
hs-cTnT	1.06 (0.98–1.15)	0.15	0.99 (0.87–1.11)	0.81
CVP	1.12 (1.01–1.25)	0.03	1.20 (1.04–1.38)	0.01
Postoperative				
NGAL	1.11 (0.93–1.33)	0.25	1.02 (0.83–1.26)	0.86
NT-proBNP	1.21 (1.09–1.34)	0.0005	1.13 (1.00–1.29)	0.05
hs-cTnT	1.26 (1.10–1.45)	0.0009	1.22 (1.05–1.42)	0.008
CVP	1.17 (1.03–1.32)	0.01	1.15 (0.98–1.35)	0.09
Change (Postoperative–Baseline)				
ΔNGAL	1.23 (0.96–1.57)	0.09	1.26 (0.93–1.71)	0.13
ΔNT-proBNP	0.99 (0.96–1.03)	0.85	0.99 (0.94–1.05)	0.84
Δhs-cTnT	1.15 (1.07–1.24)	0.0002	1.25 (1.09–1.44)	0.001
ΔCVP	1.00 (0.91–1.10)	0.94	0.93 (0.83–1.04)	0.20

eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; hs-cTNT, high sensitivity cardiac troponin T; CVP, central venous pressure; OR, odds ratio; CI, confidence interval. [a] Biomarker models were adjusted for eGFR, diabetes and type of cardiac surgery. Baseline and postoperative biomarker levels were log transformed. Odds ratios were expressed per 0.1 unit increase in log-transformed baseline and postoperative biomarker levels and per 100 pg/mL increase for Δbiomarker levels.

Table 3. Areas under the Receiver-Operating Curve for the prediction of congestive acute kidney injury.

	Unadjusted AUC (95% CI) Biomarker Only	**[a] Adjusted AUC (95%CI) Biomarker + Clinical Model**
Clinical Model	-	0.83 (0.72, 0.94)
Baseline		
NGAL	0.67 (0.51–0.82)	0.84 (0.73–0.95)
NT-proBNP	0.74 (0.60–0.89)	0.84 (0.75–0.94)
hs-cTnT	0.67 (0.53–0.81)	0.82 (0.71–0.94)
CVP	0.64 (0.50–0.78)	0.88 (0.80–0.96)
Postoperative		
NGAL	0.60 (0.43–0.77)	0.83 (0.72–0.94)
NT-proBNP	0.78 (0.66–0.91)	0.86 (0.76–0.96)
hs-cTnT	0.75 (0.58–0.92)	0.88 (0.80–0.96)
CVP	0.68 (0.55–0.81)	0.87 (0.80–0.95)
Change (Postoperative-Baseline)		
ΔNGAL	0.61 (0.42–0.79)	0.82 (0.72–0.93)
ΔNT-proBNP	0.69 (0.54–0.85)	0.83 (0.71–0.94)
Δhs-cTnT	0.80 (0.64–0.96)	* 0.94 (0.89–0.99)
ΔCVP	0.49 (0.34–0.63)	0.84 (0.72–0.96)
Combined Model		
ΔHs-cTnT + Preoperative Creatinine	0.87 (0.76–0.99)	-
ΔHs-cTnT + Diabetes	0.93 (0.88–0.99)	-

eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; hs-cTNT, high sensitivity cardiac troponin T; CVP, central venous pressure; AUC, area under the receiver operative characteristic curve; CI, confidence interval. * Significantly improves AUC of the clinical model $p < 0.05$. [a] Biomarker models were adjusted for eGFR, type of cardiac surgery and diabetes.

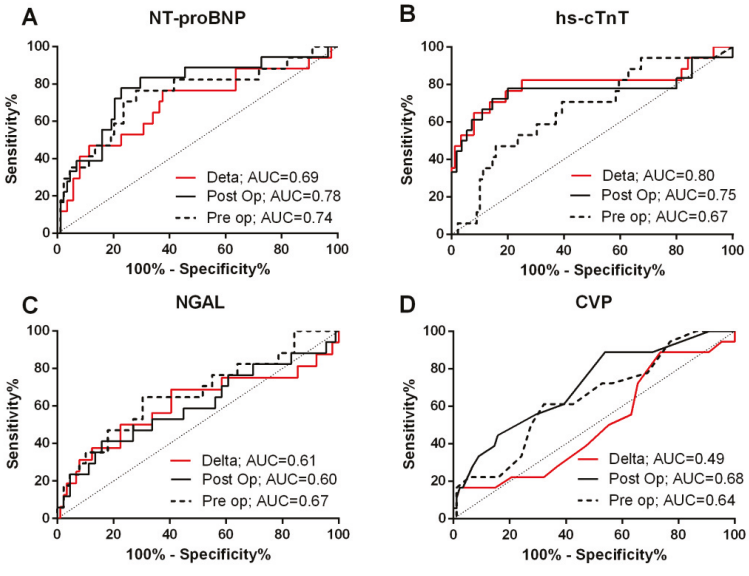

Figure 3. Receiver operating characteristic curves for N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) (**A**), high sensitivity cardiac troponin T (hs-cTnT) (**B**), neutrophil gelatinase-associated lipocalin (NGAL) (**C**), and central venous pressure (**D**). Dotted lines are for baseline assessments, black lines are for postoperative assessments, and red lines are for change in levels (post-preoperative). AUC, area under the curve.

Table 4. Cutoff values for predicting congestive acute kidney injury.

	Cutoff	Sensitivity	Specificity
Baseline			
NGAL (pg/mL)	140.2	64.7	69.7
NT-proBNP (pg/mL)	476.0	76.5	71.9
hs-cTnT (pg/mL)	25.0	47.1	84.3
CVP	15.5	61.1	67.8
Postoperative			
NGAL (pg/mL)	440.9	41.2	84.3
NT-proBNP (pg/mL)	599.5	72.2	79.5
hs-cTnT (pg/mL)	1089.0	66.7	84.1
CVP	10.5	44.4	84.3
Change (Postoperative-Baseline)			
ΔNGAL (pg/mL)	181.7	50.0	77.5
ΔNT-proBNP (pg/mL)	−38.8	76.5	62.5
Δhs-cTnT (pg/mL)	730.9	82.4	75.0
ΔCVP	−9.5	88.9	26.4

NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; hs-cTNT, high sensitivity cardiac troponin T; CVP, central venous pressure.

3.5.2. Early Detection of c-AKI

After adjusting for eGFR, diabetes, and type of surgery, postoperative NT-proBNP and hs-cTnT remained robust in detecting c-AKI (Table 2). Of note, postoperative CVP was not associated with c-AKI after risk adjustment.

ROC analysis (Table 3, Figure 3) revealed postoperative NT-proBNP and hs-cTnT as parameters with the highest AUCs for early detection of c-AKI after multivariable adjustment. Specifically, AUC for postoperative NT-proBNP was 0.78 (0.66–0.91) alone (optimal cutoff 599.5 pg/mL, sensitivity 72.2%, specificity 79.5%) and 0.86 (0.76–0.96) after risk adjustment (Table 3). AUC for postoperative hs-cTnT was 0.75 (0.58–0.92) alone (optimal cutoff 1089.0 pg/mL, sensitivity 66.7%, specificity 84.1%) and 0.88 (0.80–0.96) after risk adjustment. Postoperative NGAL alone and CVP alone only yielded moderate AUCs for detecting c-AKI (0.60 for NGAL and 0.68 for CVP).

3.5.3. Perioperative Changes in Biomarker Levels

Change in hs-cTnT levels between baseline and the postoperative period was associated with c-AKI (Tables 2 and 3). Δhs-cTnT alone yielded an AUC of 0.8 (0.64–0.96) for c-AKI detection, and was the only biomarker that significantly increased the AUC of the clinical model. Specifically, the AUC was 0.87 (0.76–0.99) when Δhs-cTnT was combined with baseline creatinine, 0.93 (0.88–0.99) when combined with diabetes status, and 0.94 (0.89–0.99) when combined with the full clinical model (Table 3). The optimal cutoff of Δhs-cTnT for detecting c-AKI was > 730.9 pg/mL (sensitivity 82%, specificity 75%; Table 4). In contrast, the ability of ΔCVP to detect c-AKI was no better than a coin toss (AUC 0.49, 95% CI 0.34–0.63).

3.6. Sample Size Calculation

A post-hoc sample size calculation was performed to validate our findings in light of the size of our cohort. An AUC of 0.70 for biomarker prediction of post cardiac surgery AKI has been deemed clinically meaningful [34]. We conservatively chose a null hypothesis AUC of 0.75. To detect an AUC of 0.93 in our Δhs-cTnT + diabetes model, our observed 18 c-AKI cases and 89 controls yielded a 86% power using a two-sided *z*-test at an alpha of 0.05.

3.7. Secondary Outcomes

Supplemental Table S3 summarizes the AUCs of biomarkers and CVP in predicting non-congestive AKI and postoperative RVF. At baseline, all three biomarkers had moderate accuracy for predicting non-congestive AKI (AUC 0.67 to 0.70). Postoperatively, NT-proBNP detected non-congestive AKI with moderate accuracy (AUC 0.72). ΔBiomarker levels and ΔCVP detected non-congestive AKI poorly (AUC ranging from 0.44–0.57). In contrast, none of the parameters predicted or detected RVF well (AUC 0.48–0.62).

During follow up, 3 (1.7%) patients died (2 c-AKI and 1 control) and 3 patients (1.7%) developed severe AKI requiring renal replacement therapy (2 c-AKI and 1 non-congestive AKI). Compared to controls, patients who developed c-AKI had significantly longer hospitalization, ICU length of stay and duration of mechanical ventilation (Table 1, Figure 4). Non-congestive AKI was associated longer periods of ICU stay and mechanical ventilation compared to controls. In contrast, there were no differences in observed outcomes for patients who developed postoperative RVF alone (Figure 4).

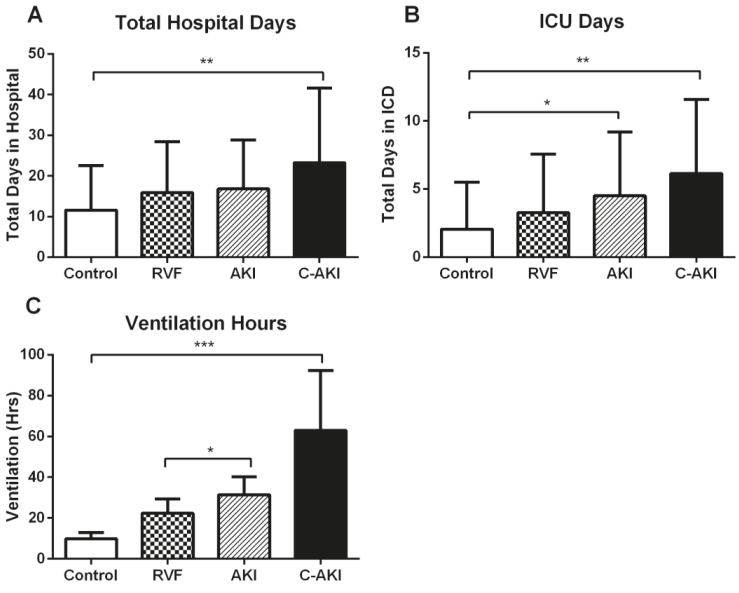

Figure 4. Lengths of stay in hospital (**A**) and ICU (**B**) and duration of mechanical ventilation (**C**) in patients who developed postoperative acute kidney injury (AKI), right ventricular failure (RVF), congestive AKI (c-AKI), and controls. Data expressed mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4. Discussion

This prospective nested case-control study found cardiac biomarkers hs-cTnT and NT-proBNP to be stronger predictors of c-AKI following cardiac surgery than the renal biomarker NGAL. Four major findings were derived from this study. (1) We identified the novel concept of c-AKI as a cardiorenal syndrome in the context of RVF. C-AKI was associated with prolonged mechanical ventilation and length of stay in hospital and ICU; (2) A single measurement of NT-proBNP or hs-cTnT predicted and detected c-AKI with high accuracy. In contrast, traditional measure of venous congestion such as ΔCVP had an AUC for c-AKI that was analogous to a coin flip. Specifically, baseline and postoperative NT-proBNP yielded AUCs of 0.74 and 0.78, postoperative hs-cTnT yielded an AUC of 0.75, and baseline and postoperative CVP yielded AUCs of 0.64 and 0.68, respectively; (3) Δhs-cTnT alone yielded an AUC of 0.80 for c-AKI, and the addition of diabetes increased the AUC to 0.93; (4) Neither the cardiorenal biomarkers, clinical variables, nor CVP were able to predict postoperative RVF well.

4.1. A New AKI Phenotype

Our study is novel in our definition and characterization of a congestive subtype of AKI. We found that c-AKI was associated with a higher burden of postoperative morbidity and healthcare cost than non-congestive AKI or RVF alone. The etiology of cardiac surgery-associated AKI is multifactorial involving many non-modifiable risk factors such as ischemic-reperfusion injury, inflammation and oxidative stress [14]. Unlike other AKI subtypes, c-AKI is potentially preventable and treatable, although it is often difficult to detect at an early stage. Our findings offer new insights on the role of biomarkers in the prediction and early detection of c-AKI and represent a critical first step towards characterizing postoperative c-AKI. Determining whether a biomarker-guided approach can complement current prediction, prevention and timely management strategies in the perioperative period is an important area for future investigation.

4.2. Venous Congestion and CVP

Our study is the first to prospectively characterize postoperative c-AKI with serial cardiac and renal biomarkers. Although several studies have evaluated the utility of similar biomarkers for AKI risk stratification in cardiac surgery cohorts [14,18,21,32,35], none have focused on c-AKI, which is truly a cardiorenal syndrome [15]. AKI in the context of RVF results from a complex series of cardiorenal interactions. This interaction has been believed to be primarily due to renal hypoperfusion [36], but recent evidence suggests venous congestion as a primary contributor [2,15,16,37,38]. Transrenal perfusion pressure is calculated as the mean arterial pressure minus the CVP. Clinically, in patients with acute decompensated heart failure and volume overload, the combination of low systemic pressure with elevated CVP may impair renal perfusion [15,39,40]. In a study of 145 patients admitted with acute decompensated heart failure, and using CVP as a surrogate for systemic venous congestion, Mullens et al. demonstrated that patients with low CVP (<8 mmHg) experienced significantly less decline in renal function compared to those with high CVP (>24 mmHg), independent of their cardiac index [38]. Similarly, we demonstrated that patients who developed postoperative c-AKI had elevated CVP at baseline that persisted into the postoperative period. In further support of a congestive etiology, those who developed c-AKI had LVEFs that were statistically similar to the controls and may benefit from perioperative decongestive strategies. The success of such strategies requires accurate and timely identification of venous congestion, as accumulating evidence suggests a poor correlation between CVP and circulating blood volume and an inability of CVP or ΔCVP to predict fluid responsiveness (ROC AUC value of 0.56) [16,17]. Our study corroborates these findings. Specifically, CVP detected c-AKI poorly (AUC = 0.64 for baseline CVP and AUC = 0.49 for ΔCVP). In contrast, biomarkers of cardiac function and distention (NT-proBNP) and myocardial injury (hs-cTnT) were superior to CVP for predicting and detecting c-AKI.

4.3. Congestive AKI and Cardiorenal Biomarkers

NT-proBNP and hs-cTnT are well-established prognosticators in stable and acute decompensated heart failure. NT-proBNP is a prohormone secreted by the atria and ventricles in response to volume and pressure overload. In patients with pulmonary hypertension, NT-proBNP has been shown to increase in proportion to the degree of RV distension and wall stress; whereas hs-cTnT levels increase in proportion to the severity of RV dysfunction [24,25,41]. Several studies have evaluated whether baseline and postoperative BNP could predict cardiac surgery-associated AKI with mixed results (AUC range 0.60 to 0.86) [21,34,35]. To our knowledge, only two studies have evaluated the relationship between hs-cTnT and AKI in the perioperative setting [32,34]. One study reported similar hs-cTnT and NT-proBNP changes in a pediatric cohort to those observed in our adult cohort. In addition, these authors found baseline and postoperative biomarker levels were weakly predictive of AKI (AUC for hs-cTnT: Baseline 0.57, post 0.62; AUC for NT-proBNP: Pre 0.53, post 0.57) [34]. Our study adds to this knowledge by evaluating the same biomarkers to predict RVF, c-AKI, and non-congestive AKI in adult patients. We demonstrate NT-proBNP and hs-cTnT as excellent potential biomarkers for postoperative c-AKI, but poor predictors of isolated RVF. This observation may be explained by two mechanisms. First, potential etiologies for perioperative RVF are diverse, including myocardial ischemia due to poor myocardial preservation [42], graft occlusion, or air emboli [43]. Some of these events are unanticipated complications of CPB and surgery and cannot be predicted using biomarkers or conventional means [44,45]. Second, c-AKI is the end organ manifestation of longer and more severe episodes of perioperative RVF. In our study, there was a positive correlation between hs-cTnT and CPB duration ($r = 0.44$, $p < 0.0001$). Higher postoperative hs-cTnT levels (and thus higher Δhs-cTnT) were likely secondary to complex surgery requiring prolonged CPB with prolonged myocardial ischemia that was possibly compounded by suboptimal myocardial preservation. In addition, prolonged RV ischemia and infarction leading to end organ complications are more likely with complex cardiac procedures. Future studies are needed to fully elucidate mechanisms responsible for hs-cTnT release in c-AKI and congestive states.

4.4. Secondary Outcomes

In the cardiac surgical setting, elevated pre and postoperative NT-proBNP and hs-TnT levels have been shown to be associated with prolonged ICU length of stay, mechanical ventilation, and postoperative inotropic support [35,46–49]. We showed higher preoperative hs-cTnT and postoperative NT-proBNP were associated with increased duration of mechanical ventilation and hospital and ICU stay.

4.5. Clinical Implications

Our findings have important implications for the optimization of patients who may be at high-risk for developing postoperative c-AKI. This is especially important, as unlike its non-congestive counterpart, c-AKI, may improve with diuretic, vasodilator therapies, and inotropic support [16,38]. Although both baseline and postoperative NT-proBNP levels were associated with c-AKI, baseline biomarker level may be of greater practical importance as it allows for a greater window of opportunity for preoperative optimization by postponing non-emergent surgery for decongestive therapy. We in addition demonstrated a high AUC of 0.93 (95% CI 0.88–0.99) when combining Δhs-cTnT and diabetes for the early detection of c-AKI in the immediate postoperative period, days before the confirmation of c-AKI by serum creatinine using the traditional AKIN definition. When adjusted for diabetes, each 100 pg/mL increase in Δhs-cTnT is associated with a 23% increased odds of c-AKI (adjusted OR 1.23, 95% 1.10–1.38). In addition, 37% of diabetic patients who had Δhs-cTnT values above the cutoff developed c-AKI, where as none of the non-diabetic patients with Δhs-cTnT values below cutoff developed c-AKI. This simple model helps to efficiently identify a high-risk group that is most likely to benefit from future clinical trials of intensive perioperative monitoring and targeted therapy including fluid restriction, decongestion, and inotropic support. The feasibility of these biomarker-guided trials is enhanced by the availability of NT-proBNP and hs-cTnT as accurate and affordable point of care assays that could be easily and rapidly implemented at the bedside or preoperative assessment clinics [50,51]. Significant progress has been made in the development of these point of care assays, with newer generations demonstrating comparable diagnostic accuracy as high sensitivity core-laboratory assays [50,51].

4.6. Study Limitations

This study has several limitations. Firstly, it is single center in nature. However, we recruited a representative sample of patients undergoing all major cardiac surgery, and our sample size was similar to that from other studies in the field. Secondly, c-AKI was a relatively rare event, and the small event rate limited our ability to explore the additive predictive value of biomarkers in more comprehensive clinical models. Thirdly, the number of patients experiencing dialysis or death in our study was low, limiting our ability to evaluate the association of biomarkers with these outcomes.

5. Conclusions

Our study findings support hs-cTnT and NT-proBNP as potential biomarkers for prediction of a highly morbid subtype of postoperative AKI that occurs with RVF. Baseline and postoperative NT-proBNP, postoperative hs-cTnT, and Δhs-cTnT had excellent AUCs for the prediction and early detection of c-AKI. Importantly, the addition of diabetes status to Δhs-cTnT further increased accuracy for detecting c-AKI. Our findings provide novel insights into cardiorenal physiology in the perioperative setting and may be used to monitor response to goal-directed decongestive therapy in clinical trials to mitigate c-AKI. In addition, the relatively rare incidence of postoperative c-AKI identified in our study highlights the importance of using biomarker models (i.e., Δhs-cTnT + diabetes) to identify high-risk patients for future interventional studies.

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References

1. Skhiri, M.; Hunt, S.A.; Denault, A.Y.; Haddad, F. Evidence-based management of right heart failure: A systematic review of an empiric field. *Rev. Esp. Cardiol.* **2010**, *63*, 451–471. [CrossRef]
2. Gambardella, I.; Gaudino, M.; Ronco, C.; Lau, C.; Ivascu, N.; Girardi, L.N. Congestive kidney failure in cardiac surgery: The relationship between central venous pressure and acute kidney injury. *Interact. Cardiovasc. Thorac. Surg.* **2016**, *23*, 800–805. [CrossRef] [PubMed]
3. Costachescu, T.; Denault, A.; Guimond, J.-G.; Couture, P.; Carignan, S.; Sheridan, P.; Hellou, G.; Blair, L.; Normandin, L.; Babin, D.; et al. The hemodynamically unstable patient in the intensive care unit: Hemodynamic vs. transesophageal echocardiographic monitoring. *Crit. Care Med.* **2002**, *30*, 1214–1223. [CrossRef] [PubMed]
4. Denault, A.Y.; Haddad, F.; Jacobsohn, E.; Deschamps, A. Perioperative right ventricular dysfunction. *Curr. Opin. Anaesthesiol.* **2013**, *26*, 71–81. [CrossRef] [PubMed]
5. Maslow, A.D.; Regan, M.M.; Panzica, P.; Heindel, S.; Mashikian, J.; Comunale, M.E. Precardiopulmonary bypass right ventricular function is associated with poor outcome after coronary artery bypass grafting in patients with severe left ventricular systolic dysfunction. *Anesth. Analg.* **2002**, *95*, 1507–1518. [CrossRef] [PubMed]
6. Haddad, F.; Denault, A.Y.; Couture, P.; Cartier, R.; Pellerin, M.; Levesque, S.; Lambert, J.; Tardif, J.-C. Right ventricular myocardial performance index predicts perioperative mortality or circulatory failure in high-risk valvular surgery. *J. Am. Soc. Echocardiogr.* **2007**, *20*, 1065–1072. [CrossRef] [PubMed]
7. Thiele, R.H.; Isbell, J.M.; Rosner, M.H. AKI associated with cardiac surgery. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 500–514. [CrossRef] [PubMed]
8. Karkouti, K.; Wijeysundera, D.N.; Yau, T.M.; Callum, J.L.; Cheng, D.C.; Crowther, M.; Dupuis, J.-Y.; Fremes, S.E.; Kent, B.; Laflamme, C.; et al. Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. *Circulation* **2009**, *119*, 495–502. [CrossRef] [PubMed]
9. Thomson, R.; Meeran, H.; Valencia, O.; Al-Subaie, N. Goal-directed therapy after cardiac surgery and the incidence of acute kidney injury. *J. Crit. Care* **2014**, *29*, 997–1000. [CrossRef]
10. Pearse, R.; Dawson, D.; Fawcett, J.; Rhodes, A.; Grounds, R.M.; Bennett, E.D. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit. Care* **2005**, *9*, R687–R693. [CrossRef]
11. Waikar, S.S.; Bonventre, J.V. Creatinine kinetics and the definition of acute kidney injury. *J. Am. Soc. Nephrol.* **2009**, *20*, 672–679. [CrossRef] [PubMed]
12. Shiao, C.-C.; Wu, V.-C.; Li, W.-Y.; Lin, Y.-F.; Hu, F.-C.; Young, G.-H.; Kuo, C.-C.; Kao, T.-W.; Huang, D.-M.; Chen, Y.-M.; et al. Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. *Crit. Care* **2009**, *13*, R171. [CrossRef] [PubMed]
13. Karkouti, K.; Beattie, W.S.; Wijeysundera, D.N.; Rao, V.; Chan, C.; Dattilo, K.M.; Djaiani, G.; Ivanov, J.; Karski, J.; David, T.E. Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J. Thorac. Cardiovasc. Surg.* **2005**, *129*, 391–400. [CrossRef] [PubMed]
14. Devarajan, P. Neutrophil gelatinase-associated lipocalin: A promising biomarker for human acute kidney injury. *Biomark. Med.* **2010**, *4*, 265–280. [CrossRef]
15. Ronco, C.; McCullough, P.; Anker, S.D.; Anand, I.; Aspromonte, N.; Bagshaw, S.M.; Bellomo, R.; Berl, T.; Bobek, I.; Cruz, D.N.; et al. Cardio-renal syndromes: Report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur. Heart J.* **2010**, *31*, 703–711. [CrossRef]

16. Aronson, D.; Abassi, Z.; Allon, E.; Burger, A.J. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. *Eur. J. Heart Fail.* **2013**, *15*, 637–643. [CrossRef]
17. Marik, P.E.; Baram, M.; Vahid, B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* **2008**, *134*, 172–178. [CrossRef]
18. Bulluck, H.; Maiti, R.; Chakraborty, B.; Candilio, L.; Clayton, T.; Evans, R.; Jenkins, D.P.; Kolvekar, S.; Kunst, G.; Laing, C.; et al. Neutrophil gelatinase-associated lipocalin prior to cardiac surgery predicts acute kidney injury and mortality. *Heart* **2018**, *104*, 313–317. [CrossRef]
19. Daniels, L.B.; Barrett-Connor, E.; Clopton, P.; Laughlin, G.A.; Ix, J.H.; Maisel, A.S. Plasma neutrophil gelatinase-associated lipocalin is independently associated with cardiovascular disease and mortality in community-dwelling older adults: The Rancho Bernardo Study. *J. Am. Coll. Cardiol.* **2012**, *59*, 1101–1109. [CrossRef]
20. Lindberg, S.; Pedersen, S.H.; Mogelvang, R.; Jensen, J.S.; Flyvbjerg, A.; Galatius, S.; Magnusson, N.E. Prognostic utility of neutrophil gelatinase-associated lipocalin in predicting mortality and cardiovascular events in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J. Am. Coll. Cardiol.* **2012**, *60*, 339–345. [CrossRef]
21. Patel, U.D.; Garg, A.X.; Krumholz, H.M.; Shlipak, M.G.; Coca, S.G.; Sint, K.; Thiessen-Philbrook, H.; Koyner, J.L.; Swaminathan, M.; Passik, C.S.; et al. Preoperative serum brain natriuretic peptide and risk of acute kidney injury after cardiac surgery. *Circulation* **2012**, *125*, 1347–1355. [CrossRef] [PubMed]
22. Song, D.; de Zoysa, J.R.; Ng, A.; Chiu, W. Troponins in acute kidney injury. *Ren. Fail.* **2012**, *34*, 35–39. [CrossRef] [PubMed]
23. Januzzi, J.L.; van Kimmenade, R.; Lainchbury, J.; Bayes-Genis, A.; Ordonez-Llanos, J.; Santalo-Bel, M.; Pinto, Y.M.; Richards, M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: An international pooled analysis of 1256 patients: The International Collaborative of NT-proBNP Study. *Eur. Heart J.* **2006**, *27*, 330–337. [CrossRef] [PubMed]
24. Blyth, K.G.; Groenning, B.A.; Mark, P.B.; Martin, T.N.; Foster, J.E.; Steedman, T.; Morton, J.J.; Dargie, H.J.; Peacock, A.J. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. *Eur. Respir. J.* **2007**, *29*, 737–744. [CrossRef] [PubMed]
25. Nagaya, N.; Nishikimi, T.; Okano, Y.; Uematsu, M.; Satoh, T.; Kyotani, S.; Kuribayashi, S.; Hamada, S.; Kakishita, M.; Nakanishi, N.; et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J. Am. Coll. Cardiol.* **1998**, *31*, 202–208. [CrossRef]
26. Ricci, Z.; Cruz, D.N.; Ronco, C. Classification and staging of acute kidney injury: Beyond the RIFLE and AKIN criteria. *Nat. Rev. Nephrol.* **2011**, *7*, 201–208. [CrossRef] [PubMed]
27. Holman, W.L. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): What have we learned and what will we learn? *Circulation* **2012**, *126*, 1401–1406. [CrossRef]
28. Denault, A.Y.; Bussières, J.S.; Arellano, R.; Finegan, B.; Gavra, P.; Haddad, F.; Nguyen, A.Q.N.; Varin, F.; Fortier, A.; Levesque, S.; et al. A multicentre randomized-controlled trial of inhaled milrinone in high-risk cardiac surgical patients. *Can. J. Anaesth. J.* **2016**, *63*, 1140–1153. [CrossRef]
29. Rudski, L.G.; Lai, W.W.; Afilalo, J.; Hua, L.; Handschumacher, M.D.; Chandrasekaran, K.; Solomon, S.D.; Louie, E.K.; Schiller, N.B. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J. Am. Soc. Echocardiogr.* **2010**, *23*, 685–713, quiz 786–788.
30. Giannitsis, E.; Kurz, K.; Hallermayer, K.; Jarausch, J.; Jaffe, A.S.; Katus, H.A. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin. Chem.* **2010**, *56*, 254–261. [CrossRef]
31. Bolignano, D.; Lacquaniti, A.; Coppolino, G.; Donato, V.; Campo, S.; Fazio, M.R.; Nicocia, G.; Buemi, M. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 337–344. [CrossRef] [PubMed]
32. Omar, A.S.; Mahmoud, K.; Hanoura, S.; Osman, H.; Sivadasan, P.; Sudarsanan, S.; Shouman, Y.; Singh, R.; AlKhulaifi, A. Acute kidney injury induces high-sensitivity troponin measurement changes after cardiac surgery. *BMC Anesthesiol.* **2017**, *17*, 15. [CrossRef] [PubMed]
33. DeLong, E.R.; DeLong, D.M.; Clarke-Pearson, D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* **1988**, *44*, 837–845. [CrossRef] [PubMed]

34. Bucholz, E.M.; Whitlock, R.P.; Zappitelli, M.; Devarajan, P.; Eikelboom, J.; Garg, A.X.; Philbrook, H.T.; Devereaux, P.J.; Krawczeski, C.D.; Kavsak, P.; et al. Cardiac biomarkers and acute kidney injury after cardiac surgery. *Pediatrics* **2015**, *135*, e945–e956. [CrossRef] [PubMed]
35. Elíasdóttir, S.B.; Klemenzson, G.; Torfason, B.; Valsson, F. Brain natriuretic peptide is a good predictor for outcome in cardiac surgery. *Acta Anaesthesiol. Scand.* **2008**, *52*, 182–187. [CrossRef] [PubMed]
36. Schrier, R.W.; Bansal, S. Pulmonary hypertension, right ventricular failure, and kidney: Different from left ventricular failure? *Clin. J. Am. Soc. Nephrol.* **2008**, *3*, 1232–1237. [CrossRef] [PubMed]
37. Firth, J.D.; Raine, A.E.; Ledingham, J.G. Raised venous pressure: A direct cause of renal sodium retention in oedema? *Lancet* **1988**, *331*, 1033–1036. [CrossRef]
38. Mullens, W.; Abrahams, Z.; Francis, G.S.; Sokos, G.; Taylor, D.O.; Starling, R.C.; Young, J.B.; Tang, W.H.W. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J. Am. Coll. Cardiol.* **2009**, *53*, 589–596. [CrossRef]
39. Liang, K.V.; Williams, A.W.; Greene, E.L.; Redfield, M.M. Acute decompensated heart failure and the cardiorenal syndrome. *Crit. Care Med.* **2008**, *36*, S75–S88. [CrossRef]
40. Liu, P.P. Cardiorenal syndrome in heart failure: A cardiologist's perspective. *Can. J. Cardiol.* **2008**, *24*, 25B–29B. [CrossRef]
41. Daquarti, G.; March Vecchio, N.; Mitrione, C.S.; Furmento, J.; Ametrano, M.C.; Dominguez Pace, M.P.; Costabel, J.P. High-sensitivity troponin and right ventricular function in acute pulmonary embolism. *Am. J. Emerg. Med.* **2016**, *34*, 1579–1582. [CrossRef] [PubMed]
42. Allen, B.S.; Winkelmann, J.W.; Hanafy, H.; Hartz, R.S.; Bolling, K.S.; Ham, J.; Feinstein, S. Retrograde cardioplegia does not adequately perfuse the right ventricle. *J. Thorac. Cardiovasc. Surg.* **1995**, *109*, 1116–1126. [CrossRef]
43. Kevin, L.G.; Barnard, M. Right ventricular failure. *Contin. Educ. Anaesth. Crit. Care Pain* **2007**, *7*, 89–94. [CrossRef]
44. Aissaoui, N.; Salem, J.-E.; Paluszkiewicz, L.; Morshuis, M.; Guerot, E.; Gorria, G.M.; Fagon, J.-Y.; Gummert, J.; Diebold, B. Assessment of right ventricular dysfunction predictors before the implantation of a left ventricular assist device in end-stage heart failure patients using echocardiographic measures (ARVADE): Combination of left and right ventricular echocardiographic variables. *Arch. Cardiovasc. Dis.* **2015**, *108*, 300–309. [PubMed]
45. Matthews, J.C.; Koelling, T.M.; Pagani, F.D.; Aaronson, K.D. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. *J. Am. Coll. Cardiol.* **2008**, *51*, 2163–2172. [CrossRef] [PubMed]
46. Brynildsen, J.; Petäjä, L.; Pettilä, V.; Nygård, S.; Vaara, S.T.; Linko, R.; Okkonen, M.; Hagve, T.-A.; Soininen, L.; Suojaranta-Ylinen, R.; et al. The predictive value of NT-proBNP and hs-TnT for risk of death in cardiac surgical patients. *Clin. Biochem.* **2018**, *53*, 65–71. [CrossRef] [PubMed]
47. Cuthbertson, B.H.; Croal, B.L.; Rae, D.; Gibson, P.H.; McNeilly, J.D.; Jeffrey, R.R.; Smith, W.C.; Prescott, G.J.; Buchan, K.G.; El-Shafei, H.; et al. N-terminal pro-B-type natriuretic peptide levels and early outcome after cardiac surgery: A prospective cohort study. *Br. J. Anaesth.* **2009**, *103*, 647–653. [CrossRef]
48. Domanski, M.J.; Mahaffey, K.; Hasselblad, V.; Brener, S.J.; Smith, P.K.; Hillis, G.; Engoren, M.; Alexander, J.H.; Levy, J.H.; Chaitman, B.R.; et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *JAMA* **2011**, *305*, 585–591. [CrossRef]
49. Mohammed, A.A.; Agnihotri, A.K.; van Kimmenade, R.R.J.; Martinez-Rumayor, A.; Green, S.M.; Quiroz, R.; Januzzi, J.L. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. *Circulation* **2009**, *120*, 843–850. [CrossRef]
50. Wilke, P.; Masuch, A.; Fahron, O.; Zylla, S.; Leipold, T.; Petersmann, A. Diagnostic performance of point-of-care and central laboratory cardiac troponin assays in an emergency department. *PLoS ONE* **2017**, *12*, e0188706. [CrossRef]
51. Fellner, S.; Hentze, S.; Kempin, U.; Richter, E.; Rocktäschel, J.; Langer, B. Analytical evaluation of a BNP assay on the new point-of-care platform respons® IQ. *Pract. Lab. Med.* **2015**, *2*, 15–21. [CrossRef] [PubMed]

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