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Impact of Clinical Aspects and Pathophysiology Mechanisms of Acute Kidney Injury on Outcomes of Patients Affected by COVID-19—A Retrospective Cohort Study

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Abstract: Introduction: COVID-19, caused by the SARS-CoV-2 virus, has been associated with oligosymptomatic cases or severe acute respiratory syndrome, with multiple organ failure and death. One of the most significant events for clinical outcomes is Acute Kidney Injury (AKI). It is known that AKI in COVID-19 is multifactorial, and the main mechanisms are cytokine storm, metabolic stress, use of nephrotoxic drugs, rhabdomyolysis, viral tropism to kidney tissues, and multiple organ failure. However, little is known about the impact of AKI clinical presentation and pathophysiological mechanisms on the outcome of patients affected by COVID-19. Objectives: To identify AKI clinical presentation and etiology, also known as phenotypes, and pathophysiological mechanisms, also known as subphenotypes, in patients affected by COVID-19 and associate them with death. This cohort and retrospective study evaluate the medical records of patients with SARS-CoV-2 infection admitted to a tertiary public hospital from 1 June 2020, to 31 July 2021, from admission to clinical outcome (hospital discharge or death). Clinical and laboratory data were analyzed during the hospitalization. Renal function was estimated by urine output and serum creatinine; therefore, the diagnosis and AKI classification were based on the 2012 KDIGO criteria. The occurrence of AKI was the inclusion criterion. According to clinical and laboratory presentations, we recognized two phenotypes of AKI (the direct and indirect impact of SARS-CoV-2 on the kidney) and several pathophysiological mechanisms. Subphenotypes of the direct impact of SARS-CoV-2 on kidneys were associated with Kidney Viral Tropism, Cytokine Storm, COVID-19-Related Multiple Organ Failure, and Mixed (more than one mechanism associated with COVID-19). Subphenotypes of indirect impact of SARS-CoV-2 on kidney phenotypes were Ischemic, Nephrotoxic due to rhabdomyolysis, and Septic. Univariate and multivariate analyses were performed to identify risk factors associated with death. Result: In total, 372 patients were included; 55.6% were male, 82.3% were Caucasians, and the mean age was 61.4 years. The majority of patients were admitted to the ICU (88.2%) and required mechanical ventilation (86.3%). AKI was predominantly KDIGO 3 (65.6%). When classifying our patients' AKI in two kidney phenotypes based on their clinical presentation, the direct impact of the SARS-CoV-2 phenotype was predominant (71,5%) and associated with higher mortality (83.8 vs. 46.3%, $p = 0.001$). Among the AKI pathophysiological mechanisms, Mixed—synergism of viral mechanisms—was the most prevalent (23.4%), followed by Viral Tropism (19.9%), Multiple Organ Failure—MOF (18%), Septic (15.6%), Ischemic (12.9%), and Cytokine Storm (10.2%). Mortality was high (73.1%). Logistic regression identified APACHE II, ATN-ISS, and the direct impact of SARS-CoV-2 on the kidney as factors associated with death, while ischemic AKI was associated with lower mortality. Conclusions: We can conclude that APACHE II and ATN-ISS scoring are clinical predictions of hospital mortality in COVID patients with AKI, as well as AKI etiology involving the direct impact of SARS-CoV-2 on the kidney, while ischemic pathophysiological mechanisms of AKI are associated with lower mortality.

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1. Introduction

In 2019, the World Health Organization declared COVID-19 a new pandemic [1]. The SARS-CoV-2 virus causes the disease and has been associated with asymptomatic and mild infections, severe acute respiratory syndrome, multiple organ dysfunction, and death. The severity of the cases was related to several factors, the main one being Acute Kidney Injury (AKI) [2–10].

Concerning AKI in COVID-19, it is known that it is an extremely relevant condition due to its high incidence and contribution to the clinical outcome. A study by Chan L. et al. carried out in 2021 [5] found that AKI is diagnosed in 46% of COVID-19 hospitalized patients, with 19% requiring dialysis. The importance of AKI for the clinical outcomes of patients is noteworthy. In-hospital mortality is outstanding among patients with AKI associated with COVID-19 and is reported as 50% among patients in this group, as opposed to the 8% mortality of those patients with COVID-19 who did not develop it [5,6,9,10].

According to a review study by Menez and Parikh from 2021 [11], the impact of SARS-CoV-2 on kidney tissues can be divided into direct and indirect. The former is direct endothelial damage due to virus entry into cells, local inflammation, and glomerular collapse. The latter are sepsis, the use of nephrotoxic drugs, and rhabdomyolysis, in addition to exacerbated systemic inflammation and oxidative stress [12–14], also known as cytokine storms [9]. However, the authors were unable to conclude from the currently available literature whether viral tropism to kidney cells may cause AKI.

Regarding kidney viral tropism in COVID-19 through the receptors and protein factors expressed therein, the study by Su H., 2020 [13] analyzed a cohort of 26 patients, 9 of whom had been diagnosed with AKI. They underwent necropsy and identified, using electron microscopy, viral particles with a diameter between 65 and 136 nm with preserved spikes of 20 to 25 nm, proving the possibility of direct viral tropism to kidney tissue.

Still on this topic, another post-mortem study, now in a cohort of 63 patients, carried out by Braun F. in 2021 [3], showed the presence of viral RNA in the kidneys of 60% of patients, which was associated with the existence of comorbidities, advanced age, and more premature death—facts of extreme clinical relevance. Moreover, patients who did not have AKI presented viral RNA in the kidney at a lower frequency than the ones who went through AKI (72%). Therefore, it is inferred that viral tropism in the kidneys may be associated with the development of AKI and, accordingly, with higher mortality rates.

Among patients with AKI, the majority presented proteinuria, hematuria, and leukocyturia [5,6,15–17]. Despite the lack of specific clinical studies on the topic of pathophysiology, different laboratory presentations of AKI may be related to different pathophysiologic mechanisms.

Recently published papers have suggested that the approach to AKI requires review from a broader perspective to incorporate clinical realities, ranging from risk assessment to diagnosis, and revision of the classification, including nomenclature. They have recommended renaming AKI according to cause (phenotype) and mechanism (subphenotype) to facilitate identifying patients at high risk of death and triaging them for appropriate therapy. Targeted AKI management will only be possible if different phenotypes and subphenotypes of AKI are recognized based on causality and related pathophysiology [18,19].

There is no doubt that the pathophysiology of AKI associated with COVID-19 is multifactorial and may impact fatal outcomes. However, no studies in the current literature have recognized, evaluated, or compared the phenotype and subphenotype of COVID-19-associated AKI and clinical outcomes.

2. Objectives

To identify AKI etiology and its possible pathophysiological mechanisms in patients affected by COVID-19 admitted to wards and ICUs and determine whether there is an association between them and unfavorable clinical outcomes, such as the need for dialysis and death.

3. Methodology

3.1. Patients and Methods

This project is an observational, longitudinal, and retrospective cohort study that evaluated the medical records of patients diagnosed with SARS-CoV-2 infection admitted to a public, tertiary, and reference hospital for COVID-19 during the first and second waves of the pandemic in the country (from 1 June 2020 to 31 July 2021), from admission to outcome (hospital discharge or death). The study included hospitalized patients with COVID-19 who developed AKI. The diagnosis of COVID-19 was carried out using the polymerase chain reaction (PCR) technique following standardized procedures validated by the São Paulo State Department of Health. The diagnosis of AKI followed the KDIGO 2012 (Kidney Disease Improving Global Outcomes) criteria, which defines AKI as an increase of 0.3 mg/dL in serum creatinine in 48 h, a 1.5-to-1.9-fold increase in creatinine serum within 7 days, or a reduction of urine output to less than 0.5 mL/kg/h for 6 to 12 h [20].

Clinical and laboratory data were collected during the hospitalization. Kidney function was assessed daily by measuring serum creatinine and checking urine output. For proteinuria or hematuria detection, the semi-quantitative dipstick test was used; data were requested at admission in all patients and during the hospital stay in those patients without proteinuria at admission. Patients without a midstream (type 1) urine test collected at the time of hospital admission, those with an altered midstream (type 1) urine test at the time of hospital admission, and patients using nephrotoxic drugs during hospitalization were excluded.

According to clinical and laboratory presentations, we recognized two AKI etiologies (direct and indirect impact of SARS-CoV-2 on the kidneys) and several possible AKI pathophysiological mechanisms (subphenotypes). Pathophysiological mechanisms of the direct impact of SARS-CoV-2 on kidneys were associated with Kidney Viral Tropism, Cytokine Storm, COVID-19 Multiple Organ Failure (MOF), and Mixed (more than one mechanism associated with COVID-19). Subphenotypes of indirect impact of SARS-CoV-2 on kidney were Ischemic, Nephrotoxic due to rhabdomyolysis, and Septic. The definitions of the possible pathophysiological mechanisms were based on clinical presentation and laboratory tests due to the lack of kidney histopathological information in Brazil during the pandemic period because necropsies were not allowed. They are described below:

- Ischemic: when an ischemic insult (dehydration or hypotension) related to renal ischemia-reperfusion syndrome is identified, generating acute tubular necrosis [21]. It is associated with the presence of clinical signs of dehydration, hypotension, or requiring vasoactive drugs (with progression of the vasoactive drug weaning order after clinical measures) at the time of AKI diagnosis. They are related to conditions with no substantial changes in midstream (type 1) urine findings.
- Septic: a septic condition of fever, impaired consciousness, and multiple organ failure, including kidneys, with positive blood cultures for pathogens compatible with this condition. It is usually accompanied by significant neutrophilia with a left shift [20].
- Nephrotoxic due to rhabdomyolysis: when musculoskeletal cells lysis occurs due to COVID-19, releasing nephrotoxic content [22]. It is diagnosed when creatine phosphokinase (CPK) exceeds 5000 IU at the time of the AKI diagnosis. Due to its manifestation elucidated throughout the study, this etiology of AKI is no longer considered in isolation and is now included in the Mixed etiology of AKI since patients who develop AKI due to rhabdomyolysis, as demonstrated by our preliminary analyses, suffer from this condition in synergism with other AKI COVID-19-associated etiologies.

- Associated with Cytokine Storm [14–16]: a subtype of multiple organ failure that occurs when there is a defective immune response, mainly with intense production of IL-6, IL-8, αTNF, type I, and III interferon. It is diagnosed in the presence of a fever higher than 39 degrees Celsius for more than 12 h throughout the day, for 48 h consecutive to the diagnosis of AKI.
- Associated with COVID-19 Multiple Organ Failure: a condition in which there is failure of two or more organ systems, including the kidneys, concomitantly or sequentially [12–14]. It is diagnosed when, concomitantly with AKI, there is a need for mechanical ventilation and vasoactive drug escalation with great difficulty in the weaning order. Furthermore, laboratory parameters compatible with MOF may occur concomitantly.
- Associated with Kidney Viral Tropism: when the renal tubules and podocytes are directly affected by the entry of the SARS-CoV-2 virus [15–17]. Identified with a midstream (type 1) urine test, the presence of hematuria, proteinuria, leukocyturia, epithelial cell sediment, and casts is assessed. It is usually identified when there is new hematuria or a large increase in previously mild hematuria at the time of AKI diagnosis, with no systemic factors indicating overlapping etiologies.
- Mixed: when there is more than one mechanism associated with COVID-19. Example: Viral Tropism and Cytokine Storm [23].

3.2. Data Management and Statistical Analysis

Based on the study protocol, data were entered into an electronic spreadsheet, and any typing errors were eliminated. The analysis was carried out using IBM SPSS 20 or Sigma Stat 3.5. Measures of frequency, central tendency, and dispersion were calculated for categorical or continuous variables, respectively, with death established as the outcome variable. The chi-square test was used for comparison of categorical variables; the t-test was used to compare parametric variables between two groups; and ANOVA was followed by the Newman–Keuls test for multiple comparisons between groups.

Afterward, multivariate analysis was performed by constructing a logistic regression model with odds ratio (OR) calculations, including in the model all independent variables that showed association with the outcome, with $p \leq 0.05$. The Kolmogorov-Smirnov test was applied to verify data normality, and collinear variables were excluded from this analysis. Kaplan-Meier curves and log-rank tests were used to compare the survival time of patients during the study period according to AKI etiologies (direct and indirect impact of SARS-CoV-2 on the kidney).

4. Results

Data from 372 AKI patients hospitalized with AKI due to COVID-19 were evaluated. The majority (88.3%) were admitted to the intensive care unit (ICU) and required mechanical ventilation (86.3%), with a mean age of 61.4 ± 10.8 years. Regarding the morbid history of these patients, hypertension was the most frequent comorbidity (68%), followed by obesity (36.5%), diabetes (39.5%), dyslipidemia (25.9%), and chronic kidney disease (14.8%). Mortality was 73.1%. Most patients presented with AKI KDIGO 3 (64.8%) and required dialysis (65.1%) as shown in Table 1.

According to univariate analysis, the factors associated with death were: use of vasoactive drugs (81.6 vs. 58%; $p < 0.001$), need for mechanical ventilation (81.6 vs. 59%; $p < 0.001$), need for dialysis (84.3 vs. 38% $p < 0.001$), ICU admission (79.6 vs. 67% $p < 0.001$), hematuria (76.3 vs. 44%; $p = 0.015$), proteinuria (75.6 vs. 43%; $p = 0.015$), AKI KDIGO 3 (82.6 vs. 42%; $p < 0.001$), dyslipidemia (61.5 vs. 37%; $p = 0.004$), age (62.72 vs. 57.8 years; $p = 0.004$), ATN-ISS (0.786 vs. 0.595; $p < 0.001$), and shorter length of stay (18.1 vs. 30, 3 days; $p < 0.001$). Patients with AKI etiology involving the direct impact of SARS-CoV-2 on kidneys presented higher mortality than patients with AKI etiology involving the indirect impact of SARS-CoV-2 on kidneys (83.8 vs. 46.3%, $p < 0.001$), as shown in Table 1.

Table 1. Analysis of patients hospitalized with COVID-19 and AKI, according to clinical outcome.

	General n = 372	Death n = 272 (73.1)	Hospital Discharge n = 100 (26.95)	*p*-Value
ICU [n, (%)]	328 (88.2)	261 (79.6)	67 (67)	0.0001
VAD [n, (%]	316 (84.9)	258 (81.6)	58 (58)	0.0001
MV [n, (%)]	321 (86.3)	262 (81.6)	59 (59)	0.0001
Dialysis [n, (%)]	242 (65.1)	204 (84.3)	38 (38)	0.0001
HTU [n, (%)]	186 (50)	142 (76.3)	44 (44)	0.005
PTU [n, (%)]	176 (47.3)	133 (75.6)	43 (43)	0.047
KDIGO 3 [n, (%)]	241 (64.8)	199 (82.6)	42 (42)	0.0001
DLP [n, (%)]	96 (25.9)	59 (61.5)	37 (37)	0.002
CKD [n, (%)]	55 (14.8)	35 (63.6)	20 (20)	0.086
APACHE	18.6 (12.2–25.1)	19.7 (5.3–34.1)	14.4 (8.3–20.5)	0.0001
SOFA	7.9 (4.2–11.7)	8.58 (5.08–12.08)	5.41 (1.91–8.91)	0.0001
AGE	61.4 (46.6–76.2)	62.72 (48.7–76.7)	57.8 (41.15–74.45)	0.004
length of stay (days)	21.4 (4.8–37.9)	18.1 (4.5–31.6)	30.3 (10.05–50.55)	0.0001
ATN-ISS	0.74 (0.54–0.94)	0.786 (0.64–0.93)	0.595 (0.453–0.737)	0.0001
phenotype direct impact of SARS-CoV-2 on kidney	266 (71.5)	223 (83.8)	43 (16.2)	<0.001
indirect impact of SARS-CoV-2 on kidney	106 (28.5)	49 (46.3)	57 (53.7)	

APACHE: Acute Physiology and Chronic Health Evaluation; ATN-ISS: acute tubular necrosis index-specific prognostic; CKD: Chronic Kidney Disease; CPK: creatine phosphokinase, originating mainly from skeletal muscle degradation; HTU: hematuria; KDIGO: Kidney Disease Improving Global Outcomes; MV: Mechanical Ventilation; PTU: proteinuria; SOFA: Sequential Organ Failure Assessment; VAD: vasoactive drug.

Concerning AKI etiology, the most frequent was the direct impact of SARS-CoV-2 on the kidney (71.5%), while the indirect impact of SARS-CoV-2 on the kidney occurred in 106 patients (28.5%).

Figure 1 shows the distribution of possible pathophysiological mechanisms for AKI. The most frequent was mixed (23.4%), followed by AKI associated with viral tropism (19.9%), MOF (18.0%), septic (15.6%), ischemic (12.9%), and the least prevalent, Cytokine Storm (10.2%).

Possible pathophysiological mechanisms of AKI in patients with COVID-19 were also associated with death. Mortality in COVID-19 patients with AKI associated with Mixed etiology, Cytokine Storm, and MOF subphenotypes was similar (90.8, 89.5, and 88.1%, respectively), and mortality was higher in COVID-19 patients with AKI associated with Viral Tropism (68.9%), Septic (55.2%), and Ischemic (35.4%, $p < 0.001$), as shown in Table 2.

Table 2. Analysis of the possible pathophysiological mechanisms of AKI in patients hospitalized with COVID-19 and AKI, according to the outcome.

	Cytokine Storm n = 38	Viral Tropism n = 74	MOF n = 67	Septic n = 58	Ischemic n = 48	Mixed COVID n = 87	*p*-Value
Death (%)	34 (89.5) [a]	51 (68.9) [b]	59 (88.1) [a]	32 (55.2) [b]	17 (35.41) [b]	79 (90.8) [a]	0.0001

a ≠ b; $p < 0.05$, MOF: Multiple Organ Dysfunction.

Logistic regression identified APACHE II, ATN-ISS, and the AKI etiology involving the direct impact of SARS-CoV-2 on the kidney as factors associated with death, while the possible ischemic pathophysiological mechanism of AKI was associated with lower mortality, as shown in Table 3. The Kolmogorov-Smirnov test was applied to check data normality. Some variables were excluded from this analysis due to collinearity (vasoactive

drugs that require mechanical ventilation were collinear with APACHE and ATN-ISS; proteinuria was collinear with hematuria).

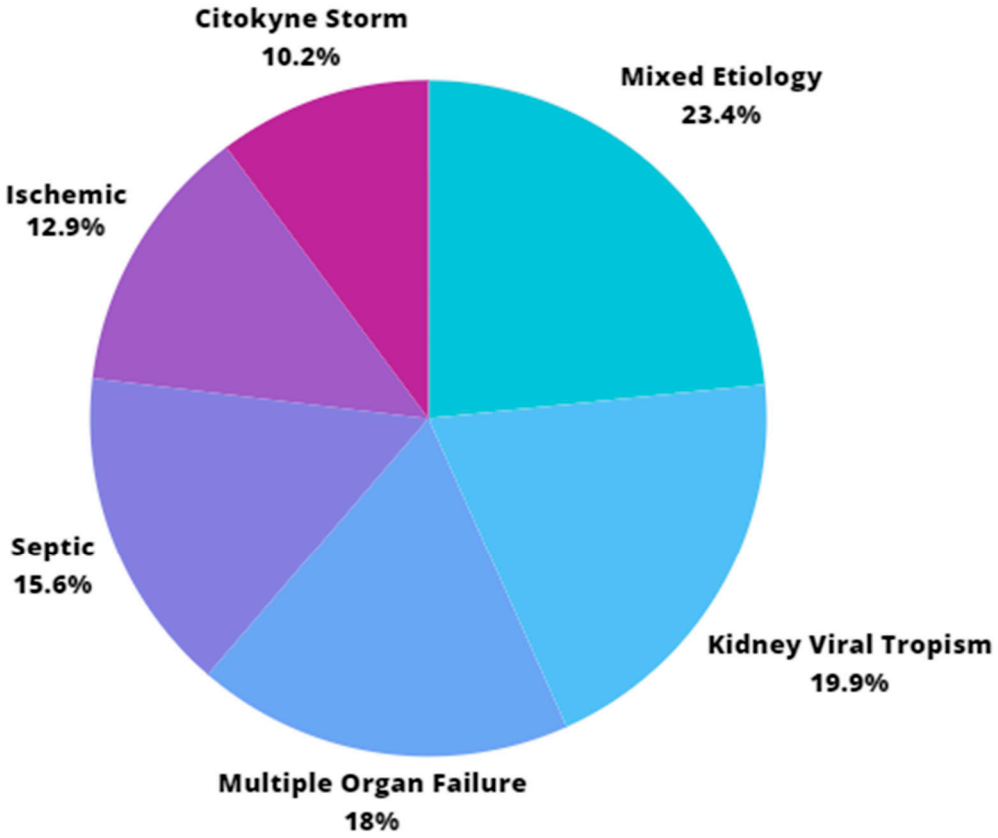

Figure 1. Analysis of the incidence of possible different pathophysiological mechanisms of AKI in patients with COVID-19.

Table 3. Logistic regression for the death of hospitalized patients with COVID-19 and AKI.

VARIABLES	ODDS RATIO	CI-95%	*p* Value
APACHE II	1.777	1.08–1.28	<0.001
HTU	2.117	0.65–6.86	0.211
DLP	0.442	0.17–1.16	0.098
ATN-ISS	17.972	1.09–295.7	0.043
DIALYSIS	0.929	0.31–2.75	0.895
AKI ETIOLOGY INVOLVING DIRECT IMPACT OF SARS-CoV-2 ON KIDNEY	1.780	1.7–13.44	0.003
ISCHEMIC PATHOPHYSIOLOGICAL MECHANISM OF AKI	0.876	0.81–0.98	0.046

APACHE II: Acute Physiology and Chronic Health Evaluation, ATN-ISS: Acute Tubular Necrosis Index Specific Prognostic, DLP: Dyslipidemia, HTU: Hematuria.

Finally, the survival curve of patients with AKI due to etiology involving directly the action of SARS-CoV-2 (Cytokine Storm, Viral Kidney Tropism, Multiple Organ Failure Related to COVID-19, and Mixed) was lower than that of patients with classic mechanisms of AKI concomitantly with COVID-19 (Septic and Ischemic), as shown in Figure 2 (log-rank < 0.001).

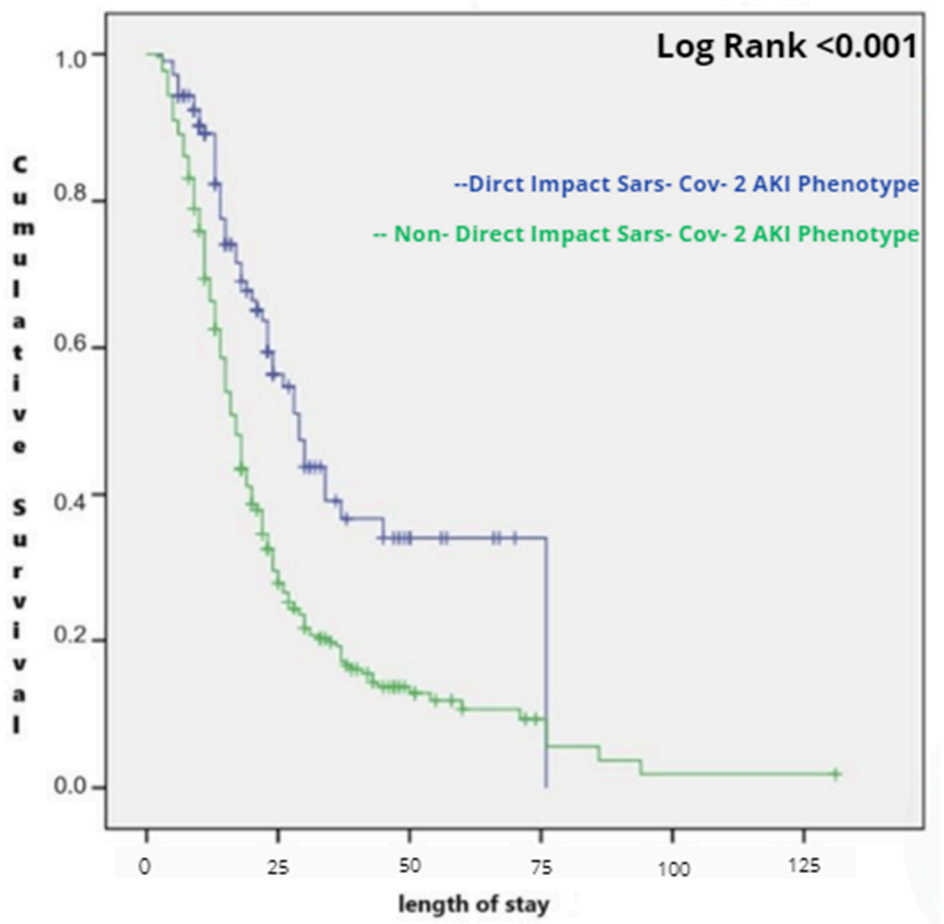

Figure 2. Kaplan–Meier survival analysis: The impact of the direct vs. indirect impact of the SARS-CoV-2 AKI etiology on days to death.

5. Discussion

This retrospective cohort study aimed to identify the etiology and possible pathophysiological mechanisms of AKI in COVID-19 patients and evaluate their impact on the patient's clinical outcome. Patients were admitted to a public university hospital in the inland of São Paulo, Brazil, which is a reference for 28 municipalities in the region with more than 2 million inhabitants. During this period, 372 patients diagnosed with COVID-19 and AKI were hospitalized, with a mean age of 61.4 ± 10.8 years; 88.2% were admitted to the ICU; and 86.3% required mechanical ventilation. AKI was predominantly KDIGO 3 (65.6%), most patients underwent dialysis, and mortality was high (73.1%). National and international studies [7,24–26] corroborate our results. It has been reported that in-hospital mortality is 50% among patients who develop AKI, as opposed to 8% mortality among those who do not develop it. Among patients requiring dialysis, mortality in Brazil ranged from 63.4 to 67% [7,25,26].

It is well known that AKI in COVID-19 is multifactorial. However, no previous study has aimed to assess the impact of its etiology and possible pathophysiological mechanisms on death.

Recently published papers have suggested that the approach to AKI requires review from a broader perspective to incorporate clinical realities, ranging from risk assessment to diagnosis, and revision of the classification, including nomenclature. They recommended renaming AKI according to cause (phenotype) and mechanism (subphenotype) to facilitate identifying patients at high risk of death and triaging them for appropriate therapy. Targeted management of AKI will only be possible if different phenotypes and subphenotypes of AKI are recognized based on causality and related pathophysiology [10–20].

According to Rodrigues [18], there is no genetic AKI phenotype. Although the phenotype is defined by a specific precipitant or exposure, this occurs in a context of risk and on a background of genetic predisposition and comorbidity. The subphenotype depends on the pathophysiological mechanisms activated in an individual patient and will include both nonspecific and specific pathways of stress or injury. Identification of such subphenotypes may predict responses to treatments based on cellular mechanisms of injury and their impact on prognosis.

Although this classification may be relevant, unfortunately, in this study, the recognition of the pathophysiological mechanisms involved was only based on clinical presentation and laboratory tests because necropsies were not allowed in Brazil during the pandemic period [27].

In clinical and laboratorial presentations, we recognized two phenotypes (direct and indirect impact of SARS-CoV-2 on the kidneys) and several possible pathophysiological mechanisms related to the direct impact of SARS-CoV-2 on the kidney (Kidney Viral Tropism, Cytokine Storm, COVID-19 Multiple Organ Failure, and Mixed) and indirectly related to the impact of SARS-CoV-2 on the kidney (Ischemic, Nephrotoxic due to Rhabdomyolysis, and Septic).

Our results show that the direct impact of SARS-CoV-2 on kidneys is more frequently associated with mortality. Among the possible pathophysiological mechanisms of AKI, our results show that Mixed—synergism of viral mechanisms—was the most prevalent, followed by Viral Tropism, MOF, Septic, Ischemic, and Cytokine Storm. In univariate analysis, the mortality rate was higher in patients with AKI related to Cytokine Storm, MOF, and Mixed and lower in patients with AKI related to Kidney Viral Tropism, Sepsis, and Ischemia.

Logistic regression identified APACHE II, ATN-ISS, and the direct impact of SARS-CoV-2 on the kidney as factors associated with death. On the other hand, the possible ischemic pathophysiological mechanism of AKI was associated with lower mortality.

Our data corroborate previous and recent literature that has shown that scoring systems like APACHE II, SOFA, and ATN-ISS predict outcomes and evaluate clinical performance [28–31]. Several specific prognostic indexes for AKI have been studied, and most of them are difficult to reproduce and studied retrospectively. Liaño, in 1993, analyzed the influence of risk factors in the prognosis of acute tubular necrosis (ATN) and carried out a study with a protocol containing data on demographics, causes of ATN, diuresis, the need for dialysis, and clinical conditions—the ATN-ISS, which showed a greater capacity for discrimination than the APACHE II in both the ICU and non-ICU groups in different studies, including Brazilian research.

Compared to other scoring systems, APACHE II has a sensitivity of 89.9% and a specificity of 97.6%; SOFA has 90.1% sensitivity and 96.6% specificity; and the ATN-ISS score has 94.2% sensitivity and 91.0% specificity [30–32].

The Kaplan-Meier Survival Analysis showed that patients with possible pathophysiological mechanisms of AKI directly associated with SARS-CoV-2, namely, Cytokine Storm, Viral Kidney Tropism, COVID-19-Related Multi-Organ Failure, and Mixed, not only presented higher mortality when compared to patients with AKI related to the indirect impact of the virus (Sepsis and Ischemia), but also reached this outcome earlier.

Our results highlight the importance of expanding the prognostic analysis in patients with severe COVID-19, considering not only the classic AKI scores but also the AKI etiology and pathophysiological mechanisms involved.

The present study has limitations, such as the fact that it was carried out at a single center. Another difficulty is the absence of necropsies in Brazil during the pandemic period, with no kidney histopathological information on the patients evaluated; therefore, the diagnosis of AKI etiology relies primarily on clinical and laboratory findings. Furthermore, there is a major limitation regarding the availability of data, such as the midstream (type 1) urine test, either due to the lack of collection material or the absence of a protocol in the service. In our study, 35 patients from the total of 433 evaluated did not have a midstream

urine test on admission or before hospital admission and, therefore, were excluded from the study, as it would not be possible to assess whether urinary changes in the proteinuria and/or hematuria type were due to COVID at the time of AKI or were chronic changes in these patients. This partially explains the current number of 372 patients and may erroneously reduce the incidence of AKI due to viral tropism and mixed etiology.

Despite these limitations, to the best of our knowledge, this is the only study that aimed to evaluate AKI etiologies and the possible pathophysiological mechanisms involved in COVID-19 hospitalized patients, providing insights into their impact on clinical outcomes. Finally, there are many factors affecting the prognosis of patients, and we need to perform a propensity analysis to further explore this issue.

6. Conclusions

We can conclude that APACHE II and ATN-ISS scoring are clinical predictions of hospital mortality in COVID patients with AKI, as well as AKI etiology involving the direct impact of SARS-CoV-2 on the kidney, while ischemic pathophysiological mechanisms of AKI are associated with lower mortality. However, AKI subphenotypes must be further clarified by specific biomarkers or a renal biopsy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available at UNESP repository.

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

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