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Renal Artery Resistive Index as an Early Cardiovascular–Renal Biomarker in Preterm Neonates: Differential Associations with Hypertension and Acute Kidney Injury

Dwi Oktari Erfanti ^{1,2}, Tetty Yuniati ¹, Fiva Aprilia Kadi ¹ , Aris Primadi ¹, Ahmedz Widiasta ¹, Dwi Prasetyo ¹, Harry Galuh Nugraha ³ and Johaness Edy Siswanto ^{4,5,*}

¹ Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung 40161, Indonesia

² Department of Child Health, Universitas Padjadjaran Hospital, Sumedang 45360, Indonesia

³ Department of Radiology, Universitas Padjadjaran Hospital, Sumedang 45360, Indonesia

⁴ Department of Neonatology, Harapan Kita National Women and Children Health Centre, Jakarta 11420, Indonesia

⁵ Faculty of Medicine, Universitas Pelita Harapan, Tangerang 15811, Indonesia

* Correspondence: johaness.siswanto@lecturer.uph.edu

Abstract

Background: Renal artery resistive index (RI) may reflect renal–vascular adaptation in preterm neonates, but its ability to distinguish early hypertension from acute kidney injury (AKI) remains uncertain. **Methods:** This prospective cohort study enrolled preterm neonates born at 28–34 weeks' gestation at Dr. Hasan Sadikin Hospital, Indonesia. Renal Doppler ultrasonography was performed at 72 h of life to measure the RI of the right and left renal arteries. Blood pressure was assessed during the first postnatal week using repeated non-invasive oscillometric measurements. AKI was defined according to neonatal Kidney Disease: Improving Global Outcomes criteria. Associations between RI, early-onset hypertension, and AKI were evaluated using bivariate analyses, receiver operating characteristic curves, and exploratory adjusted logistic regression. **Results:** Of 113 eligible infants, 77 completed follow-up evaluation. Higher RI values were associated with early-onset hypertension in univariable analyses for both the right ($p = 0.010$) and left ($p = 0.038$) RI. RI thresholds > 0.94 for the right renal artery and > 0.87 for the left renal artery were associated with increased risk of hypertension. RI values did not differ significantly between infants with and without AKI. Exploratory adjusted analyses showed attenuation of side-specific associations, whereas the higher bilateral RI value suggested a modest hypertension-related signal. **Conclusions:** In this cohort of clinically stable surviving preterm neonates, renal artery RI showed a clearer association with early-onset hypertension than with AKI classified using the study's operational KDIGO approach. RI may provide adjunctive physiological information regarding vascular impedance and early cardiovascular–renal adaptation, but it should not be interpreted as a specific or stand-alone biomarker of hypertension or kidney injury. These findings are hypothesis-generating and require validation in larger multicenter cohorts using serial renal and hemodynamic assessments.

Keywords: renal artery; resistive index; hypertension; acute kidney injury; Doppler ultrasonography; preterm neonates



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1. Introduction

Renal artery resistive index (RI) is a Doppler-derived hemodynamic parameter calculated as $(\text{peak systolic velocity} - \text{end-diastolic velocity}) / \text{peak systolic velocity}$. It reflects downstream vascular impedance within the intrarenal circulation and enables non-invasive assessment of renal blood flow. Renal artery RI is age- and maturation-dependent. Although values of approximately 0.50–0.70 are commonly cited in general renal Doppler interpretation, higher values have been reported in newborn infants, particularly preterm neonates during early postnatal transition, because of immature vascular compliance and evolving renal and systemic hemodynamics [1–4]. More recent evidence indicates that RI is also affected by systemic vascular compliance, pulse pressure, and cardiovascular hemodynamics, supporting its interpretation as an integrated cardiovascular–renal parameter rather than a purely intrarenal resistance index [5,6].

Beyond its traditional renal applications, RI is increasingly recognized as an integrated hemodynamic marker influenced not only by intrarenal vascular resistance but also by systemic hemodynamic load, arterial compliance, pulse pressure, and downstream vascular impedance. Consequently, RI may provide a broader assessment of cardiovascular–renal interactions rather than reflecting isolated renal perfusion alone [5–7]. This evolving concept raises the possibility that RI may function as an early cardiovascular–renal biomarker during neonatal transition.

Neonatal hypertension affects a small but clinically important proportion of infants admitted to neonatal intensive care units and may remain under-recognized because of rapid circulatory transition, measurement variability, and limited normative blood pressure data in preterm infants [8–11]. Accurate recognition requires standardized blood pressure measurement and interpretation within the infant's gestational age, postnatal age, clinical status, and treatment exposure [9,10]. Blood pressure rises more rapidly in preterm than in term infants, especially among those born before completion of nephrogenesis. Reduced nephron endowment and immature renal autoregulation may increase susceptibility to systemic vascular stress and contribute to early cardiovascular programming, consistent with Barker's developmental hypothesis [12]. Recent population-based evidence further demonstrates that children born preterm have an increased risk of persistent childhood hypertension, emphasizing that vascular programming may begin during the early neonatal period [13,14].

Acute kidney injury (AKI) represents another major complication of prematurity and may result from hemodynamic instability, sepsis, nephrotoxic exposure, or impaired renal perfusion. Although KDIGO criteria provide a standardized framework for neonatal AKI diagnosis, early detection remains challenging because serum creatinine and urine output often change only after substantial renal injury has occurred [15]. Consequently, Doppler ultrasonography has been proposed as a rapid, bedside, non-invasive modality to assess renal perfusion and complement conventional biochemical assessment [7,16].

Despite these advances, evidence regarding the clinical significance of RI in preterm neonates remains limited. Most previous studies have primarily evaluated RI as a marker of renal perfusion or AKI, whereas its potential role as an integrated cardiovascular–renal biomarker has received considerably less attention. Furthermore, clinically meaningful RI thresholds for hypertension risk stratification have not been established in low- and middle-income settings such as Indonesia. Therefore, this study aimed to (i) evaluate the associations between right and left renal artery RI and the incidence of early-onset hypertension and AKI in preterm neonates, and (ii) determine RI cut-off values that may support early hypertension risk stratification in this vulnerable population.

2. Materials and Methods

2.1. Study Population

Preterm neonates with a gestational age of 28–34 weeks admitted to the Neonatology Unit of Dr. Hasan Sadikin Hospital, Bandung, were consecutively recruited into this prospective cohort. Written informed consent was obtained from parents or legal guardians prior to enrollment. Infants with major congenital anomalies or presenting in hemodynamic shock at the time of assessment were excluded. The final study population comprised clinically stable preterm neonates suitable for renal Doppler evaluation, serial biochemical monitoring, and blood pressure assessment during the early postnatal period.

2.2. Study Measures and Outcomes

Acute kidney injury (AKI) was classified using an operational application of the neonatal Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on the measurements available in the study protocol. The first serum creatinine measurement was obtained at approximately 24 h of postnatal age and was treated as the initial available creatinine value rather than as a definitive neonatal baseline. A second serum creatinine measurement was obtained after 72 h of life, together with urine-output assessment during the corresponding observation period. The study protocol did not specify a narrower uniform sampling interval beyond 72 h for the second measurement. AKI classification incorporated changes in serum creatinine and documented urine output. Because serum creatinine during the first postnatal day may still reflect maternal creatinine and because only two scheduled creatinine measurements were available, this operational classification carries a risk of misclassification, particularly among infants with delayed physiological creatinine decline or early oliguria.

Renal Doppler ultrasonography was performed once infants reached more than 72 h of life, a timing chosen to minimize transitional circulatory variability. Examinations were carried out by pediatric radiologists using a Philips EPIQ Elite ultrasound system equipped with an mL26-8 high-frequency linear-array transducer (Philips, Amsterdam, The Netherlands), with conventional sampling of interlobar or arcuate arteries, appropriate angle correction, and minimization of motion artifacts. Right and left renal artery resistive index (RI) values were obtained according to established neonatal Doppler protocols.

Blood pressure was measured non-invasively using a Nihon Kohden automated oscillometric monitor (Nihon Kohden Corporation, Tokyo, Japan) and an appropriately sized neonatal cuff. Measurements were obtained while the infant was resting and clinically undisturbed whenever possible. At each assessment, three consecutive blood-pressure readings were taken at two-minute intervals, and this measurement procedure was repeated during the first postnatal week to minimize the influence of transient physiological variation and measurement error. Early-onset hypertension was defined as systolic blood pressure above the 95th percentile for gestational age, postnatal or postmenstrual age, birth weight, and sex, using published neonatal normative blood-pressure data and clinical interpretation summarized in contemporary neonatal hypertension references [8,9]. Classification was based on the set of three consecutive measurements and was not made from a single isolated elevated reading.

The primary outcomes were early-onset hypertension and AKI as defined by KDIGO criteria. The primary exposure variables were right and left renal artery RI values obtained during the first Doppler examination.

2.3. Statistical Analyses

Baseline characteristics were summarized using descriptive statistics. Categorical variables were expressed as frequencies and percentages, while continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Normally distributed variables were reported as mean $\pm$ standard deviation (SD), whereas non-normally distributed variables were reported as median (range).

Group comparisons employed chi-square or Fisher's exact tests for categorical variables, and independent *t*-tests or Mann–Whitney U tests for continuous variables, depending on data distribution. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory performance of right and left renal artery RI for early-onset hypertension. The area under the curve (AUC), associated *p*-value, sensitivity, and specificity were reported for each threshold. The selected thresholds corresponded to the criterion values generated in the original ROC analysis. Because the archived statistical output did not specify whether the criterion was selected using the Youden index or another optimization method, no specific cut-off selection algorithm was attributed retrospectively. Confidence intervals for the AUC estimates were not available in the archived ROC output. AKI-related analyses were evaluated using group comparisons and exploratory adjusted models, given the absence of significant RI–AKI associations in the primary analyses.

Exploratory multivariable logistic regression analyses were additionally performed to assess whether RI–outcome associations persisted after adjustment for selected clinically relevant covariates. Right and left RI were modelled separately to maintain consistency with side-specific hypertension analyses. An additional patient-level sensitivity model was constructed using the higher RI value between the right and left kidneys. Candidate covariates were selected a priori based on clinical relevance and included gestational age, late-onset sepsis, and mechanical ventilation.

Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. Given the sample size and number of outcome events, multivariable models were interpreted as exploratory and supportive rather than confirmatory. Statistical significance was set at a two-sided *p*-value < 0.05 . All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Study Population and Baseline Characteristics

A total of 113 preterm neonates fulfilled the initial inclusion criteria. Of these, 36 infants died before follow-up laboratory evaluation or Doppler ultrasound could be completed, resulting in 77 infants being included in the final analysis. Accordingly, the analytical cohort represents infants who survived and were clinically stable enough to complete the required Doppler, biochemical, urine-output, and blood-pressure assessments. Complete and consistently recorded baseline and illness-severity data were not available for all infants who died before completion of the study assessments; therefore, a formal comparison between included and excluded infants was not performed.

The baseline characteristics of the study population are presented in Table 1. Among the 77 preterm neonates included in the final analysis, 45 infants were male (58.4%) and 32 were female (41.6%). The median gestational age was 33 weeks, with a range of 28 to 34 weeks. The mean birth weight was 1597.3 ± 380.1 g. Spontaneous delivery occurred in 42 infants (54.5%), while 35 infants (45.5%) were delivered by cesarean section. Hypertension was identified in 41 infants (53.2%), and AKI based on KDIGO criteria was present in 19 infants (24.7%).

Table 1. Characteristics of preterm neonates included in the final analysis. Baseline demographic and clinical characteristics of the 77 preterm neonates included in the final analysis are presented.

Characteristics	Value
Sex, <i>n</i> (%)	
Male	45 (58.4)
Female	32 (41.6)
Gestational age, weeks	
Median (range)	33 (28–34)
Birth weight, g	
Mean $\pm$ SD	1597.3 $\pm$ 380.1
Mode of delivery, <i>n</i> (%)	
Spontaneous delivery	42 (54.5)
Cesarean section	35 (45.5)
Hypertension, <i>n</i> (%)	
Yes	41 (53.2)
No	36 (46.8)
AKI by KDIGO criteria, <i>n</i> (%)	
Positive	19 (24.7)
Negative	58 (75.3)

Note: Data are presented as *n* (%) for categorical variables, median (range) for gestational age, and mean $\pm$ SD for birth weight. Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; SD, standard deviation.

3.2. Renal Artery RI and Early-Onset Hypertension

The relationship between renal artery resistive index and early-onset hypertension is shown in Table 2. Infants with hypertension had higher RI values in both renal arteries compared with those without hypertension. The median right renal artery RI was 0.89 in infants with hypertension and 0.80 in those without hypertension, with a statistically significant difference ($p = 0.010$). Similarly, the median left renal artery RI was 0.85 in infants with hypertension and 0.81 in those without hypertension, which was also statistically significant ($p = 0.038$). These findings indicate that increased renal vascular resistance was significantly associated with early-onset hypertension in this cohort.

Table 2. Association between renal artery resistive index and early-onset hypertension. Right and left renal artery RI values were compared between preterm neonates with and without early-onset hypertension.

Renal Artery RI	Hypertension Positive (<i>n</i> = 41)	Hypertension Negative (<i>n</i> = 36)	<i>p</i> -Value
Right renal artery RI, median (range)	0.89 (0.64–1.00)	0.80 (0.54–1.00)	0.010
Left renal artery RI, median (range)	0.85 (0.50–1.00)	0.81 (0.52–1.00)	0.038

Note: Data are presented as median (range). *p*-values were calculated using the Mann–Whitney test. Abbreviation: RI, resistive index.

3.3. Renal Artery RI and Acute Kidney Injury

The association between renal artery RI and AKI based on KDIGO criteria is presented in Table 3. The mean right renal artery RI was 0.86 ± 0.12 among infants with AKI and

0.84 ± 0.10 among those without AKI. The mean left renal artery RI was 0.84 ± 0.13 in infants with AKI and 0.83 ± 0.10 in those without AKI. Neither comparison reached statistical significance, with p -values of 0.432 for right renal artery RI and 0.807 for left renal artery RI. These findings suggest that renal vascular resistance, as measured by RI, did not differ significantly between infants with and without early AKI based on KDIGO criteria.

Table 3. Association between renal artery resistive index and acute kidney injury by KDIGO criteria. Right and left renal artery RI values were compared between preterm neonates with and without AKI based on KDIGO criteria.

Renal Artery RI	AKI Positive ($n = 19$)	AKI Negative ($n = 58$)	p -Value
Right renal artery RI, mean $\pm$ SD	0.86 ± 0.12	0.84 ± 0.10	0.432
Left renal artery RI, mean $\pm$ SD	0.84 ± 0.13	0.83 ± 0.10	0.807

Note: Data are presented as mean $\pm$ SD. p -values were calculated using the independent t -test. Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RI, resistive index; SD, standard deviation.

3.4. ROC-Derived RI Thresholds for Early-Onset Hypertension

ROC analysis demonstrated modest discriminatory performance for both renal artery RI measurements (Figure 1). For the right renal artery RI, the AUC was 0.656 ($p = 0.006$). A threshold of >0.94 yielded a sensitivity of 31.7% and a specificity of 94.4%. When this threshold was applied categorically, 13 of 15 infants (86.7%) with $RI > 0.94$ had hypertension, compared with 28 of 62 infants (45.2%) with $RI \leq 0.94$ ($p = 0.004$; RR 1.92, 95% CI 1.37–2.69), as shown in Table 4. For the left renal artery RI, the AUC was 0.618 ($p = 0.034$). A threshold of >0.87 yielded a sensitivity of 46.3% and a specificity of 77.8%. When applied categorically, 19 of 27 infants (70.4%) with $RI > 0.87$ had hypertension, compared with 22 of 50 infants (44.0%) with $RI \leq 0.87$ ($p = 0.027$; RR 1.60, 95% CI 1.08–2.38), as shown in Table 5. These AUC values indicate only modest discrimination, and the limited sensitivities preclude interpretation of the thresholds as screening cut-offs.

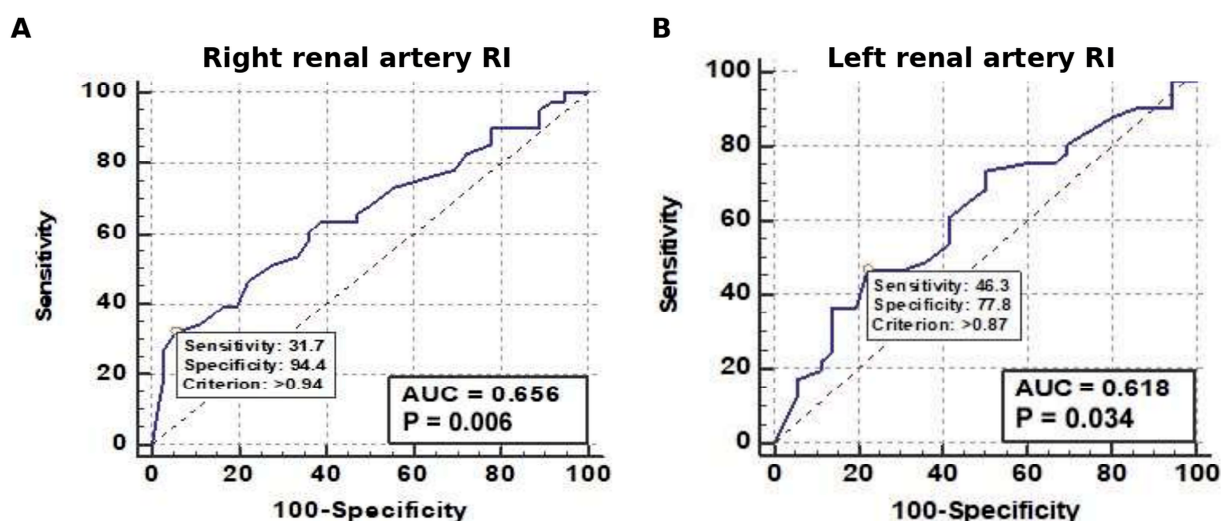


Figure 1. Receiver operating characteristic curves of renal artery resistive index for early-onset hypertension. (A) Right renal artery RI: AUC 0.656, $p = 0.006$, threshold > 0.94 , sensitivity 31.7%, and specificity 94.4%. (B) Left renal artery RI: AUC 0.618, $p = 0.034$, threshold > 0.87 , sensitivity 46.3%, and specificity 77.8%. The purple solid line represents the ROC curve, whereas the dashed diagonal line represents the line of no discrimination (AUC = 0.5).

Table 4. Association between right renal artery resistive index cut-off and early-onset hypertension. The distribution of early-onset hypertension was evaluated according to the right renal artery RI cut-off value of >0.94 .

Right Renal Artery RI	Hypertension Positive, <i>n</i> (%)	Hypertension Negative, <i>n</i> (%)	<i>p</i> -Value
RI > 0.94	13 (86.7)	2 (13.3)	0.004
RI ≤ 0.94	28 (45.2)	34 (54.8)	

Note: Data are presented as *n* (%). The categorical *p*-value was calculated using the chi-square test. RR: 1.92; 95% CI: 1.37–2.69. ROC metrics: AUC 0.656 ($p = 0.006$), sensitivity 31.7%, and specificity 94.4% at RI > 0.94 . Abbreviations: CI, confidence interval; RI, resistive index; RR, relative risk.

Table 5. Association between left renal artery resistive index cut-off and early-onset hypertension. The distribution of early-onset hypertension was evaluated according to the left renal artery RI cut-off value of >0.87 .

Left Renal Artery RI	Hypertension Positive, <i>n</i> (%)	Hypertension Negative, <i>n</i> (%)	<i>p</i> -Value
RI > 0.87	19 (70.4)	8 (29.6)	0.027
RI ≤ 0.87	22 (44.0)	28 (56.0)	

Note: Data are presented as *n* (%). The categorical *p*-value was calculated using the chi-square test. RR: 1.60; 95% CI: 1.08–2.38. ROC metrics: AUC 0.618 ($p = 0.034$), sensitivity 46.3%, and specificity 77.8% at RI > 0.87 . Abbreviations: CI, confidence interval; RI, resistive index; RR, relative risk.

3.5. Exploratory Multivariable Analysis

Exploratory adjusted logistic regression analyses were performed to evaluate the association between renal artery RI and hypertension after adjustment for gestational age, late-onset sepsis, and mechanical ventilation. The results are presented in Table 6. In the side-specific models, right renal artery RI showed a positive but attenuated association with hypertension, although this did not reach statistical significance (adjusted OR 1.04; 95% CI: 0.99–1.10; $p = 0.090$). Left renal artery RI was not independently associated with hypertension after adjustment (adjusted OR 1.02; 95% CI: 0.98–1.08; $p = 0.321$). In the patient-level sensitivity model, the higher bilateral RI value showed a modest association with hypertension after adjustment (adjusted OR 1.07; 95% CI: 1.00–1.13; $p = 0.042$).

Table 6. Exploratory multivariable logistic regression models for early-onset hypertension. Exploratory adjusted logistic regression models were used to evaluate the association between renal artery RI and early-onset hypertension.

Model, Variable	Adjusted OR	95% CI	<i>p</i> -Value
Model 1: Right renal artery RI			
Right renal artery RI, per 0.01 increase	1.04	0.99–1.10	0.090
Gestational age, per week	0.77	0.58–1.02	0.073
Late-onset sepsis	2.13	0.45–10.21	0.342
Mechanical ventilation	1.20	0.28–5.12	0.802
Model 2: Left renal artery RI			
Left renal artery RI, per 0.01 increase	1.02	0.98–1.08	0.321
Gestational age, per week	0.74	0.56–0.99	0.044
Late-onset sepsis	2.02	0.43–9.46	0.374
Mechanical ventilation	1.27	0.31–5.29	0.742

Table 6. *Cont.*

Model, Variable	Adjusted OR	95% CI	p-Value
Model 3: Higher bilateral RI value			
Higher right-or-left RI, per 0.01 increase	1.07	1.00–1.13	0.042
Gestational age, per week	0.78	0.58–1.04	0.088
Late-onset sepsis	2.18	0.45–10.64	0.337
Mechanical ventilation	1.18	0.27–5.15	0.824

Note: Three separate logistic regression models were constructed. Model 1 included right renal artery RI, Model 2 included left renal artery RI, and Model 3 included the higher value of the two side-specific RI measurements. All models were adjusted for gestational age, late-onset sepsis, and mechanical ventilation. RI estimates are expressed per 0.01-unit increase. These analyses were exploratory and should be interpreted as hypothesis-generating rather than confirmatory. Abbreviations: CI, confidence interval; OR, odds ratio; RI, resistive index.

Overall, the observed association between renal artery RI and early-onset hypertension was driven primarily by the univariable and cut-off-based analyses. Neither right nor left RI remained statistically significant in the side-specific adjusted models. The higher bilateral RI model retained a modest association, but this exploratory result should be interpreted cautiously and not as confirmatory evidence of an independent effect. Adjusted analyses for AKI under the study's operational neonatal KDIGO classification did not show significant associations for right renal artery RI, left renal artery RI, or the higher bilateral RI value, consistent with the univariable results presented in Table 3. Because AKI occurred in only 19 infants, the multivariable estimates for this outcome were considered underpowered and were not emphasized in the main results.

4. Discussion

Preterm birth accounts for nearly 10% of global deliveries and remains a major contributor to neonatal morbidity and mortality, particularly in low- and middle-income countries (LMICs) such as Indonesia [17]. Among the diverse sequelae that follow prematurity, systemic hypertension is increasingly recognized as an early manifestation of altered cardiovascular programming, while acute kidney injury (AKI) contributes to short- and medium-term neonatal complications [8,13–15]. These conditions are not isolated neonatal events, but rather reflect disrupted maturation of renal, vascular, and neurohormonal systems. Identifying early, physiologically meaningful markers of vascular load in preterm infants is therefore a critical clinical priority.

The principal hypertension-related findings arose from the univariable comparisons and ROC-derived cut-off analyses. After adjustment for gestational age, late-onset sepsis, and mechanical ventilation, the side-specific associations were attenuated and no longer statistically significant. Right RI retained only a directional association, whereas left RI showed no independent association. Although the higher bilateral RI model retained a modest statistical signal, this exploratory model should not be interpreted as definitive evidence of an independent relationship. In contrast, no significant association was observed between RI and AKI under the study's operational KDIGO classification. These results should therefore be interpreted as hypothesis-generating rather than as confirmatory evidence of an independent RI-hypertension association.

Taken together, the findings indicate that renal artery RI showed a clearer association with early-onset hypertension than with AKI under the operational classification used in this cohort. This pattern should not be interpreted as establishing RI as a predominantly vascular biomarker or as excluding a relationship with kidney injury. RI is a Doppler-derived measure of vascular impedance influenced by both systemic and local factors, including arterial compliance, pulse pressure, heart rate, systemic hemodynamic load, renal

perfusion, downstream resistance, and renal autoregulation. The absence of a significant RI–AKI association may also reflect potential AKI misclassification, survivor selection bias, the clinically stable composition of the final cohort, the timing of Doppler assessment, and limited statistical power. The observed pattern should therefore be considered hypothesis-generating rather than mechanistically definitive.

4.1. Mechanistic Interpretation of the RI–Hypertension Relationship

Preterm birth interrupts nephrogenesis and leaves the kidney with reduced nephron endowment, immature microvasculature, and limited autoregulatory reserve [12,18]. These developmental features increase susceptibility to changes in systemic perfusion and vascular load. Higher postnatal RI may therefore reflect reduced vascular compliance and microvascular immaturity during early adaptation, consistent with Doppler studies in preterm infants [3].

RI is influenced not only by intrarenal resistance but also by pulse pressure, arterial compliance, downstream impedance, heart rate, and systemic hemodynamics [5–7,19]. Because these variables change rapidly after birth [4], neonatal RI is best interpreted as an integrated measure of systemic and intrarenal vascular conditions rather than as an isolated measure of renal perfusion.

Prematurity-related alterations in nephron mass, tubuloglomerular feedback, and renal perfusion may also activate the renin–angiotensin–aldosterone and sympathetic systems, providing a plausible link between elevated RI and early hypertension [5,6]. However, the present study cannot determine the relative contributions of systemic vascular load, local renal hemodynamics, or autoregulatory responses. These mechanisms may be particularly relevant in resource-limited settings where sepsis, nephrotoxic exposure, and intermittent hemodynamic instability are common, but they remain hypothesis-generating.

4.2. RI Thresholds and Early Vascular Risk

Right renal artery RI > 0.94 and left renal artery RI > 0.87 were associated with early-onset hypertension in the unadjusted cut-off analyses. The right-sided threshold had higher specificity and a larger unadjusted risk estimate, but the adjusted right-sided association was not statistically significant. The observed side-to-side difference therefore does not establish independent or biological superiority and may reflect sampling variability, anatomy, or technical factors.

RI values in this cohort were higher than ranges commonly cited for older children and adults. This may reflect prematurity, early postnatal timing, immature vascular compliance, and transitional hemodynamics; neonatal RI should therefore be interpreted in an age- and maturity-specific context rather than against a universal threshold of 0.70. Previous pediatric studies also link higher RI with hypertension, pulse pressure, and cardiovascular remodeling [5,6,20].

The proposed thresholds showed only modest discrimination and limited sensitivity, were derived from a single-center cohort, and have not been externally validated. They should therefore be regarded as exploratory research thresholds rather than diagnostic or screening cut-offs. The higher bilateral RI model likewise represents an exploratory statistical signal whose physiological meaning requires confirmation in independent, multicenter cohorts.

4.3. Interpretation of the RI–AKI Relationship

No significant association was detected between renal artery RI and AKI under the study's operational neonatal KDIGO classification. This finding requires caution because the first serum creatinine value was obtained at approximately 24 h, when maternal creatinine may still contribute, and only one further scheduled measurement was obtained after

72 h. Variable postnatal creatinine decline in preterm infants may therefore have resulted in AKI misclassification [15].

The timing of Doppler assessment may also have reduced sensitivity to transient perfusion abnormalities, and the clinically stable survivor cohort excluded many of the sickest infants. Together with only 19 AKI events and the multifactorial nature of neonatal AKI, these factors may have obscured a relationship between RI and kidney injury. The negative result should therefore not be interpreted as evidence that such a relationship is absent.

RI should not be used as a stand-alone diagnostic marker for AKI. Associations reported in critically ill children and neonates appear strongest in severe illness, sepsis, extracorporeal support, or marked hemodynamic compromise [21–25], suggesting that its performance may be context-dependent. Future studies should combine serial Doppler measurements with frequent creatinine assessment, standardized urine-output monitoring, and biomarkers such as NGAL, cystatin C, and KIM-1 [26].

4.4. Clinical Implications for Neonatal Practice

Renal artery RI can be obtained at the bedside with conventional Doppler ultrasonography without ionizing radiation or additional blood sampling. In selected preterm infants, it may provide complementary physiological information when interpreted alongside repeated blood-pressure measurements, renal function, urine output, and the overall hemodynamic condition. Its incremental value beyond standardized blood-pressure assessment remains unproven.

This potential adjunctive role may be relevant in low- and middle-income settings, where access to NGAL, cystatin C, KIM-1, and other emerging biomarkers is limited, whereas Doppler ultrasonography is increasingly incorporated into routine neonatal imaging. RI may therefore be feasible as part of an integrated assessment, but it should not replace established clinical and biochemical evaluation.

The findings do not support universal RI screening or management decisions based on the proposed thresholds. RI assessment should remain restricted to research or carefully selected clinical contexts until larger multicenter studies determine its reproducibility, added predictive value, and relationship with short- and long-term cardiovascular and renal outcomes.

4.5. Strengths, Limitations, and Future Directions

This study has several strengths. To our knowledge, it is among the first prospective studies to directly compare the associations of renal artery RI with both early-onset hypertension and KDIGO-defined AKI within the same cohort of preterm neonates. Standardized Doppler examinations, repeated blood pressure measurements, and predefined AKI criteria provided a consistent framework for evaluating the differential clinical significance of RI during the early postnatal period. Furthermore, by integrating ROC analysis with exploratory multivariable modeling, this study offers preliminary evidence supporting the potential role of RI in early hypertension risk stratification.

Several limitations should be acknowledged. First, 36 of the 113 initially eligible infants died before completion of follow-up laboratory evaluation and renal Doppler ultrasonography. Consequently, the final analytical cohort comprised infants who survived and were clinically stable enough to complete the study assessments. This introduces potential survivor selection bias and limits the generalizability of the findings, particularly to critically ill, hemodynamically unstable, or extremely vulnerable preterm infants. Because the infants with the greatest illness severity were not represented in the final analysis, the association between renal artery RI and AKI may have been attenuated. The findings

should therefore be interpreted as applying primarily to clinically stable surviving preterm neonates rather than to the full spectrum of preterm infants admitted to intensive care. Second, AKI classification was based on two scheduled serum creatinine measurements, the first obtained at approximately 24 h and the second after 72 h. The early creatinine value may still reflect maternal renal function, and the physiological decline in serum creatinine is variable in preterm neonates. Together with the limited temporal resolution provided by only two measurements, this may have resulted in AKI misclassification and reduced sensitivity for detecting evolving or transient AKI. Accordingly, the absence of a significant RI–AKI association should be interpreted cautiously. Third, this was a single-center study with a moderate sample size, and the limited number of AKI events may have reduced statistical power to detect weaker associations. Blood pressure was assessed only during the early neonatal period, precluding evaluation of longer-term cardiovascular outcomes. In addition, Doppler examinations were performed at a single postnatal time point; therefore, serial changes in RI during neonatal adaptation could not be assessed. In addition, the archived ROC output did not provide 95% confidence intervals for the AUC estimates or document the specific optimization algorithm used to select the criterion values; these thresholds should therefore be interpreted as exploratory. The primary hypertension-related findings were driven mainly by unadjusted analyses. The attenuation of the side-specific associations after covariate adjustment raises the possibility of confounding and limits causal interpretation. Finally, the multivariable analyses were exploratory and should be interpreted as hypothesis-generating rather than confirmatory. Because complete, harmonized baseline and illness-severity data were not available for all excluded infants, the magnitude and direction of this selection bias could not be quantified through a formal included-versus-excluded comparison.

Future multicenter studies involving larger and more diverse neonatal populations are warranted to validate the proposed RI thresholds and determine their reproducibility across different clinical settings. Longitudinal investigations incorporating serial Doppler assessments together with emerging renal biomarkers and long-term cardiovascular follow-up may further clarify the role of RI within an integrated cardiovascular–renal monitoring strategy for preterm infants.

Overall, our findings support a cautious, integrated interpretation of renal artery RI as a physiological measure of vascular impedance influenced by both systemic and intrarenal conditions. In this cohort, RI showed a clearer association with early-onset hypertension than with operationally classified AKI; however, this pattern is hypothesis-generating and does not establish RI as a hypertension-specific biomarker or exclude a relationship with neonatal kidney injury. Further studies using serial Doppler measurements, more robust AKI ascertainment, and broader neonatal populations are required before clinical implementation.

5. Clinical Implications

The present findings suggest that renal artery resistive index (RI) may provide complementary physiological information in the hemodynamic assessment of selected high-risk preterm neonates, particularly when interpreted alongside repeated blood-pressure measurements and the overall clinical context. Its incremental clinical value beyond standardized blood-pressure assessment has not yet been established, and RI should not be regarded as a hypertension-specific biomarker. This cautious use is consistent with contemporary neonatal hypertension literature emphasizing standardized measurement, clinical context, and longitudinal follow-up [9–11,14].

Renal artery RI should not be interpreted in isolation or used as a stand-alone diagnostic test. Rather, it should be considered together with serial blood-pressure measurements,

serum creatinine, urine output, AKI assessment, and the infant's overall clinical and hemodynamic status. Such integrated interpretation is important because RI is a measure of vascular impedance influenced by both systemic and local renal factors, and the present findings do not establish a specific biological mechanism.

Accordingly, RI values above the proposed thresholds should not independently trigger a diagnosis, additional investigation, alteration of fluid or hemodynamic management, pharmacological treatment, or any other clinical intervention. The thresholds should currently be regarded only as exploratory research findings. Clinical decisions should continue to rely on standardized repeated blood-pressure measurements, renal-function assessment, urine output, and the infant's overall clinical and hemodynamic status. External validation is required before these thresholds can be considered for clinical risk-stratification protocols.

6. Conclusions

In this prospective cohort of clinically stable surviving preterm neonates, higher right and left renal artery RI values were associated with early-onset hypertension in univariable and cut-off-based analyses, whereas no significant association was detected with AKI under the study's operational KDIGO classification. The hypertension-related findings were driven primarily by the unadjusted analyses; side-specific associations were attenuated and no longer statistically significant after adjustment. The higher bilateral RI model retained only a modest exploratory signal and should not be interpreted as confirmatory evidence of an independent effect.

These findings should be interpreted in light of potential AKI misclassification, survivor selection bias, the clinically stable composition of the final cohort, the timing of Doppler assessment, and limited statistical power. Renal artery RI is best regarded as an adjunctive physiological measure of vascular impedance influenced by both systemic and local renal factors. The present findings do not establish RI as a hypertension-specific biomarker or exclude a potential relationship with neonatal kidney injury.

The proposed RI thresholds should be regarded as hypothesis-generating and should not yet be used for routine screening or therapeutic decision-making. Validation in larger multicenter cohorts with serial Doppler assessment, more frequent renal-function measurements, and long-term cardiovascular and renal follow-up is required before clinical implementation.

Author Contributions: D.O.E. conceived and designed the study, supervised participant recruitment, coordinated data collection, performed the initial statistical analysis, and drafted the first version of the manuscript. T.Y., F.A.K., A.P., A.W. and D.P. contributed to clinical data acquisition, patient follow-up, data validation, and interpretation of neonatal hemodynamic findings. H.G.N. contributed to Doppler ultrasonography procedures, imaging quality assurance, and interpretation of renal Doppler measurements. T.Y. and A.P. provided clinical supervision throughout the study. J.E.S. contributed to conceptual refinement, interpretation of Doppler RI findings, manuscript restructuring, scientific revision, and integration of the mechanistic and translational aspects of the study. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (Ethical Review Registration No. 04.24.112; Ethical Approval No. DP.04.03/D.XIV.6.5/112/2024, 5 April 2024).

Informed Consent Statement: Written informed consent was obtained from the parents or legal guardians of all participating neonates.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to ethical and confidentiality restrictions involving neonatal clinical data.

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

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