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Prognostic Performance of Immune-Metabolic Indices Compared with Severity Scores in Children Requiring Continuous Kidney Replacement Therapy for Acute Kidney Injury

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Abstract

Background

Acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT) is associated with substantial mortality in critically ill children. Although illness severity scores provide robust prognostic information, the prognostic value of readily available immune-metabolic indices in this population remains uncertain. We aimed to evaluate the prognostic performance of immune-metabolic indices measured at CKRT initiation and compare their performance with established severity scores.

Methods

This retrospective single-center cohort study included children younger than 18 years who underwent CKRT for KDIGO-defined AKI between January 2020 and December 2024. Lactate-to-albumin ratio (LAR), urea-to-creatinine ratio (UCR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) were calculated using laboratory values obtained within 24 hours before CKRT initiation. The primary outcome was 28-day mortality following CKRT initiation. Receiver operating characteristic (ROC) analysis and multivariable logistic regression were used to evaluate prognostic performance.

Results

Ninety patients were included, and 19 (21.1%) died within 28 days after CKRT initiation. Among the evaluated immune-metabolic indices, LAR demonstrated the strongest discriminative performance for 28-day mortality (AUC 0.779, 95% CI 0.659–0.898), closely approximating PELOD-2 (AUC 0.785) and PRISM III (AUC 0.790) scores. UCR and MLR also demonstrated significant discriminatory ability (AUC 0.721 and 0.719, respectively). In univariable analyses, LAR and UCR were significantly associated with mortality. However, neither biomarker remained independently associated with mortality after adjustment for PELOD-2 score.

Conclusions

LAR, UCR, and MLR were associated with 28-day mortality in critically ill children requiring CKRT for severe AKI. Although these biomarkers demonstrated discriminative performance approaching that of established severity scores, they did not provide independent prognostic information beyond PELOD-2 score. Immune-metabolic indices may therefore serve as complementary bedside markers of physiologic burden rather than substitutes for established severity-of-illness scores.

Introduction

Acute kidney injury (AKI) is a common and serious complication among critically ill children, affecting approximately one-quarter to one-third of patients admitted to pediatric intensive care units (PICUs) and contributing substantially to morbidity, mortality, prolonged hospitalization, and increased healthcare utilization [1]. In many cases, AKI develops as part of a broader syndrome of multiple organ dysfunction associated with conditions such as sepsis, severe inflammatory states, cardiac dysfunction, and postoperative critical illness. For children with severe AKI who fail conservative management, continuous kidney replacement therapy (CKRT) represents the preferred renal support modality because it allows gradual fluid removal and metabolic control while maintaining hemodynamic stability [2].

Despite advances in critical care and extracorporeal therapies, mortality among pediatric patients requiring CKRT remains high. Previous studies have consistently demonstrated that outcomes are influenced not only by kidney dysfunction itself but also by illness severity, fluid overload, hemodynamic instability, and the extent of accompanying organ failure [3, 4]. Although several clinical severity scores are available for risk stratification, there remains a need for simple, readily obtainable biomarkers that may provide additional prognostic information at the time of CKRT initiation.

Recently, increasing attention has been directed toward inflammation- and metabolism-based biomarkers derived from routinely available laboratory parameters. The lactate-to-albumin ratio (LAR), which integrates tissue hypoperfusion and systemic metabolic stress with nutritional and inflammatory status, has emerged as a promising prognostic indicator in critically ill children [5]. Recent evidence suggests that LAR is an independent predictor of in-hospital mortality in pediatric acute kidney injury and may serve as a promising tool for early risk stratification [6]. Similarly, inflammation-based indices have attracted growing interest in critically ill populations. The monocyte-to-lymphocyte ratio (MLR) and neutrophil-to-lymphocyte ratio (NLR) reflect systemic inflammatory activation and immune dysregulation and have been associated with AKI development and adverse outcomes in intensive care settings [7]. In pediatric patients receiving CKRT, preliminary evidence also supports the prognostic value of inflammation-related biomarkers for mortality prediction [8].

Another potentially useful biomarker is the urea-to-creatinine ratio (UCR), which reflects not only renal dysfunction but also neurohormonal activation, catabolic stress, and alterations in volume status. Elevated UCR has been associated with increased mortality independent of AKI in hospitalized patients and may therefore provide complementary prognostic information beyond traditional renal function markers [9].

Although these biomarkers have individually demonstrated prognostic utility in various critically ill populations, their role in children with severe AKI requiring CKRT remains insufficiently characterized. In particular, comparative data regarding the prognostic performance of LAR, UCR, MLR, and NLR in pediatric CKRT populations are scarce.

Given the scarcity of comparative data in pediatric CKRT populations, we aimed to evaluate the prognostic utility of routinely available immune-metabolic indices measured at CKRT initiation and to determine whether their predictive performance approached that of established severity scores.

Methods

Study Design and Patient Population

This retrospective single-center observational study was conducted in the PICU of a tertiary referral center between January 2020 and December 2024. All patients younger than 18 years of age who underwent CKRT during the study period were screened for eligibility.

The study was approved by the Institutional Ethics Committee (Approval No: E-46059653-050.04-317541412; approval date: 10 June 2026) and conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design and the use of anonymized clinical data, the requirement for written informed consent was waived by the ethics committee.

Patients were identified through institutional CKRT records. Children who fulfilled the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI and underwent CKRT during PICU admission were screened for eligibility. AKI diagnosis and staging were determined according to the KDIGO serum creatinine and urine output criteria [10].

Indications for CKRT included persistent oliguria or anuria, clinically significant fluid overload (typically > 10–20%), particularly in patients who remained unresponsive to diuretic therapy or in whom negative fluid balance could not be achieved, refractory metabolic acidosis, severe electrolyte disturbances, and progressive multiorgan dysfunction despite conventional management. Although strict institutional thresholds were not mandated, CKRT initiation was guided by established clinical indications and determined by the pediatric intensive care team according to the patient's overall clinical status, consistent with contemporary pediatric critical care practice.

Patients in whom CKRT was initiated primarily for indications other than the management of AKI were excluded. These included patients receiving CKRT for toxin removal in acute intoxications, metabolic support in isolated inherited metabolic disorders, refractory metabolic acidosis, or extracorporeal blood purification/systemic support in hyperinflammatory or multiorgan dysfunction states. In cases where the primary indication for CKRT was unclear, eligibility was determined by consensus review of the clinical records by two investigators. These patients were excluded because the primary therapeutic objective of CKRT was toxin clearance, metabolic control, or systemic support rather than the treatment of AKI, which could have introduced substantial clinical and pathophysiological heterogeneity.

Patients with hemolytic uremic syndrome (HUS) were included because they fulfilled KDIGO-defined AKI criteria requiring CKRT. Likewise, patients with sepsis-associated AKI, MIS-C/COVID-19-associated AKI, cardiorenal syndrome, hepatorenal syndrome, and primary renal diseases were retained.

Definitions

AKI was defined and staged according to the KDIGO serum creatinine and urine output criteria [10].

Sepsis was defined as sepsis-associated organ dysfunction in the presence of suspected or confirmed infection according to the international Surviving Sepsis Campaign pediatric guidelines [11].

Multisystem inflammatory syndrome in children (MIS-C) was defined according to the Centers for Disease Control and Prevention criteria [12].

Multiple organ dysfunction syndrome (MODS) was defined as dysfunction involving two or more organ systems according to contemporary pediatric consensus definitions [13].

Data Collection

Patient data were retrospectively obtained from electronic medical records and nursing documentation systems. Collected variables included age, sex, primary diagnosis, requirement for invasive mechanical ventilation (IMV), requirement for vasoactive/inotropic support, CKRT duration, PICU length of stay, and mortality status.

Clinical and laboratory parameters obtained within the 24 hours preceding CKRT initiation included mean arterial pressure (MAP), serum lactate, pH, bicarbonate, serum urea, serum creatinine, serum albumin, and complete blood count parameters.

Illness severity was assessed using the Pediatric Risk of Mortality III (PRISM III), calculated from the worst values obtained within the first 24 hours of PICU admission, and the Pediatric Logistic Organ Dysfunction-2 (PELOD-2) and Organ Failure Index (OFI) scores, calculated from the worst values obtained within the 24 hours preceding CKRT initiation. Because PELOD-2 score was calculated using physiologic variables obtained during the same time window as the immune-metabolic indices, it was selected as the reference severity score for multivariable analyses [14–16].

Calculation of Immune-Metabolic Indices

Immune-metabolic indices were calculated using laboratory values obtained within the 24 hours preceding CKRT initiation. The evaluated indices were:

- Lactate-to-albumin ratio (LAR)
- Urea-to-creatinine ratio (UCR)
- Neutrophil-to-lymphocyte ratio (NLR)
- Monocyte-to-lymphocyte ratio (MLR)

These indices were derived from routinely available laboratory parameters and required no additional testing. They were included because of their previously reported associations with systemic inflammation, metabolic stress, and disease severity in critically ill patients [5–9].

Outcomes

The primary outcome was all-cause 28-day mortality following CKRT initiation.

Secondary analyses evaluated the discriminative performance of immune-metabolic indices and illness severity scores for predicting 28-day mortality.

CKRT Protocol

CKRT was performed using the Prismaflex™ system (Baxter, Deerfield, IL, USA) according to institutional clinical protocols. Continuous veno-venous hemodialysis (CVVHD) or continuous veno-venous hemodiafiltration (CVVHDF) was selected based on individual patient characteristics and clinical indications. Anticoagulation strategies, fluid management, and treatment prescriptions were determined according to standard institutional practices and individualized when clinically necessary.

Statistical Analysis

The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection of histograms. Data are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as number (percentage).

Patients were classified according to 28-day survival status following CKRT initiation. Comparisons between survivors and non-survivors were performed using the Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of immune-metabolic indices and illness severity scores to predict 28-day mortality. Areas under the curve (AUCs) were calculated, and optimal cut-off values were determined using the Youden index.

Spearman correlation analysis was used to assess correlations among candidate predictors.

Variables associated with mortality in univariable analyses were further evaluated using multivariable logistic regression models. Separate multivariable models were constructed to account for potential associations between PELOD-2 score and immune-metabolic indices. Because immune-metabolic indices were measured at CKRT initiation, multivariable models were adjusted for PELOD-2 score, which more accurately reflects contemporaneous organ dysfunction. In contrast, PRISM III is derived from physiologic variables collected during the first 24 hours after PICU admission and therefore may not reflect disease severity at the time of biomarker assessment. Given the limited number of outcome events, parsimonious models were constructed to minimize overfitting. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

Patients with HUS were included in the primary analysis because they fulfilled KDIGO-defined AKI criteria. However, because HUS represents a distinct thrombotic microangiopathy phenotype with

pathophysiological features that differ from other AKI etiologies, an additional sensitivity analysis excluding patients with HUS was performed to assess the robustness of the primary findings.

Complete data were available for all variables included in the primary analyses; therefore, no imputation procedures were required.

All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 90 pediatric patients who underwent CKRT for KDIGO-defined AKI were included in the study. The median age was 49.5 months (IQR, 12.8–142.5), and 46 patients (51.1%) were male. The most common underlying diagnoses were renal diseases (33.3%), sepsis (30.0%), and hemolytic uremic syndrome (16.7%). Twenty-nine patients (32.2%) died during hospital stay, including 19 patients (21.1%) who died within 28 days after CKRT initiation. Baseline characteristics according to 28-day mortality are presented in Table 1.

Table 1
Baseline characteristics according to 28-day mortality

Sex, n (%)	**Survivors (n = 71)**	**Non-survivors (n = 19)**	**p**
Male	**37 (52.1)**	**9 (47.4)**	**0.713**
Female	**34 (47.9)**	**10 (52.6)**	
Age (months), median (IQR)	53 (16–148)	20 (4–78)	0.040
Primary diagnosis, n (%)	29 (40.8)	1 (5.3)	0.001
Renal diseases	15 (21.1)	12 (63.2)	
Sepsis	15 (21.1)	0	
HUS	6 (8.5)	4 (21.1)	
Cardiac diseases	5 (7.0)	1 (5.3)	
COVID/MIS-C	1 (1.4)	1 (5.3)	
Hepatorenal syndrome/Liver failure			
PICU length of stay, median (IQR)	12 (6–25)	7 (4–14)	0.037
Invasive mechanical ventilation, n (%)	32 (46.4)	19 (100)	**< 0.001**
Vasoactive/inotropic support, n (%)	27 (39.7)	17 (89.5)	**< 0.001**
KDIGO stage, n (%)	20 (28.2)	10 (52.6)	0.045
Stage 2	51 (71.8)	9 (47.4)	
Stage 3			
p value calculated using Fisher-Freeman-Halton exact test.			

Compared with survivors, non-survivors were younger and more frequently had sepsis as the primary diagnosis. Non-survivors also had shorter PICU stays and more frequently required invasive mechanical ventilation and vasoactive/inotropic support. KDIGO stage 2 AKI was more common among non-survivors, whereas stage 3 AKI predominated among survivors (Table 1).

Clinical, physiologic, and immune-metabolic parameters

At CKRT initiation, non-survivors exhibited significantly greater illness severity, with higher VIS, PRISM III, PELOD-2, and OFI scores compared with survivors. Non-survivors also demonstrated lower MAP, lower pH and bicarbonate levels, and higher lactate concentrations (Table 2).

Table 2
Clinical, physiologic, and immune-metabolic parameters at CKRT initiation according to 28-day mortality

VIS score	**Survivors (n = 71)**	**Non-survivors (n = 19)**	**p**
	0 (0–20)	**35 (12.5-137.5)**	**0.002**
MAP (mmHg)	70 (55-86.5)	52 (46–65)	0.006
PRISM III score	9 (6.75–14.25)	19 (11–25)	**< 0.001**
PELOD-2 score	4 (2–7)	9 (6–12)	**< 0.001**
OFI score	2 (1–3)	4 (3–5)	**< 0.001**
pH	7.27 (7.17–7.32)	7.07 (7.00-7.22)	**< 0.001**
HCO_3 (mmol/L)	16.0 (12.0-18.8)	13.7 (6.2–16.0)	0.026
Lactate (mmol/L)	1.65 (1.20–2.74)	3.4 (2.4-8.0)	**< 0.001**
Albumin (g/dL)	3.2 (2.8–3.6)	3.1 (2.7–3.6)	0.385
Urea (mg/dL)	91 (49–134)	62.5 (37–130)	0.242
Creatinine (mg/dL)	2.37 (0.96–3.4)	0.85 (0.45–1.91)	**0.002**
LAR	0.50 (0.36–0.98)	1.21 (0.78–2.51)	**< 0.001**
UCR	42.2 (27.3–58.3)	73.0 (42.6-112.5)	0.005
NLR	3.8 (1.7–6.2)	1.8 (1.3–3.9)	0.054
MLR	0.28 (0.20–0.49)	0.15 (0.02–0.32)	0.008

Abbreviations: VIS, vasoactive-inotropic score; MAP, mean arterial pressure; PRISM III, Pediatric Risk of Mortality III; PELOD-2, Pediatric Logistic Organ Dysfunction-2; OFI, Organ Failure Index; LAR, lactate-to-albumin ratio; UCR, urea-to-creatinine ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

Among the evaluated immune-metabolic indices, LAR and UCR were significantly higher in non-survivors, whereas MLR was significantly lower. NLR showed a trend toward significance. Interestingly, serum creatinine levels were significantly lower among non-survivors despite higher mortality rates (Table 2).

Receiver operating characteristic analysis

Receiver operating characteristic analysis was performed to evaluate the discriminative performance of severity scores and immune-metabolic indices for prediction of 28-day mortality (Table 3).

Table 3
Discriminative performance of severity scores and immune-metabolic indices for prediction of 28-day mortality

Variable	AUC (95% CI)	Optimal cut-off	Sensitivity (%)	Specificity (%)	p value
PELOD-2 score	0.785 (0.667–0.902)	≥ 7	73.7	72.1	**< 0.001**
PRISM III score	0.790 (0.678–0.902)	**≥ 19**	52.6	91.4	**< 0.001**
LAR	0.779 (0.659–0.898)	≥ 0.79	78.9	70.6	**< 0.001**
UCR	0.721 (0.577–0.865)	≥ 54.8	70.6	70.4	0.005
MLR	0.719 (0.557–0.880)	≤ 0.161	53.3	87.1	0.008

Abbreviations: AUC, area under the curve; CI, confidence interval; LAR, lactate-to-albumin ratio; UCR, urea-to-creatinine ratio; MLR, monocyte-to-lymphocyte ratio.

PRISM III demonstrated the highest overall discriminative performance (AUC 0.790, 95% CI 0.678–0.902), followed closely by PELOD-2 score (AUC 0.785, 95% CI 0.667–0.902) and LAR (AUC 0.779, 95% CI 0.659–0.898). Among the evaluated immune-metabolic indices, LAR showed the strongest prognostic performance, with an optimal cut-off value of 0.79 yielding 78.9% sensitivity and 70.6% specificity. UCR and MLR also demonstrated significant discriminatory ability, with AUC values of 0.721 and 0.719, respectively.

Correlation analysis

Moderate correlations were observed between PELOD-2 score and LAR ($r = 0.510$, $p < 0.001$) and between PELOD-2 score and UCR ($r = 0.446$, $p < 0.001$). No evidence of severe collinearity was identified among candidate predictors included in subsequent regression analyses (Supplementary Table S1).

Logistic regression analyses

In univariable logistic regression analyses, PELOD-2 score (OR 1.30, 95% CI 1.12–1.51; $p < 0.001$), PRISM III score (OR 1.15, 95% CI 1.06–1.24; $p = 0.001$), LAR (OR 2.22, 95% CI 1.33–3.71; $p = 0.002$), and UCR (OR 1.02, 95% CI 1.01–1.04; $p = 0.005$) were significantly associated with 28-day mortality. MLR demonstrated a borderline association with mortality (OR 0.04, 95% CI 0.002–1.01; $p = 0.051$) (Table 4).

Table 4
Univariable logistic regression analysis for 28-day mortality

Variable	OR (95% CI)	p value
PELOD-2 score	1.30 (1.12–1.51)	**< 0.001**
PRISM III score	1.15 (1.06–1.24)	0.001
LAR	2.22 (1.33–3.71)	0.002
UCR	1.02 (1.01–1.04)	0.005
MLR	0.04 (0.002–1.01)	0.051

Abbreviations: OR, odds ratio; CI, confidence interval; LAR, lactate-to-albumin ratio; UCR, urea-to-creatinine ratio; MLR, monocyte-to-lymphocyte ratio.

In multivariable models adjusted for PELOD-2 score, neither LAR nor UCR remained independently associated with mortality. In Model 1, PELOD-2 score remained significantly associated with mortality (adjusted OR 1.22, 95% CI 1.03–1.44; p = 0.021), whereas LAR lost statistical significance (adjusted OR 1.46, 95% CI 0.86–2.50; p = 0.163). Similarly, in Model 2, PELOD-2 score remained independently associated with mortality (adjusted OR 1.20, 95% CI 1.02–1.42; p = 0.028), whereas UCR was no longer significant (adjusted OR 1.01, 95% CI 0.996–1.029; p = 0.136) (Table 5).

Table 5
Multivariable logistic regression models for prediction of 28-day mortality

Model	Variable	Adjusted OR (95% CI)	p value
Model 1*	PELOD-2	1.22 (1.03–1.44)	0.021
	LAR	1.46 (0.86–2.50)	0.163
Model 2**	PELOD-2	1.20 (1.02–1.42)	0.028
	UCR	1.01 (0.996–1.029)	0.136

**Model 1 adjusted for PELOD-2 and LAR.*

***Model 2 adjusted for PELOD-2 and UCR.*

Abbreviations: OR, odds ratio; CI, confidence interval; PELOD-2, Pediatric Logistic Organ Dysfunction-2; LAR, lactate-to-albumin ratio; UCR, urea-to-creatinine ratio.

Sensitivity analysis

A sensitivity analysis excluding patients with HUS yielded similar findings (Supplementary Tables S2 and S3). The associations of LAR, UCR, and MLR with 28-day mortality remained significant after exclusion of HUS patients. Furthermore, the discriminative performance of LAR (AUC 0.766, 95% CI 0.641–0.890),

UCR (AUC 0.723, 95% CI 0.579–0.866), and MLR (AUC 0.706, 95% CI 0.541–0.871) remained largely unchanged, supporting the robustness of the primary findings across different AKI etiologies.

Discussion

In this study, we evaluated the prognostic value of immune-metabolic indices in critically ill children who underwent CKRT for KDIGO-defined AKI. The principal findings were that routinely available immune-metabolic indices were associated with 28-day mortality and demonstrated discriminative performance approaching that of established severity scores, although these associations largely reflected the burden of organ dysfunctionand were not independent of illness severity.

Children requiring CKRT for AKI represent one of the highest-risk populations in pediatric intensive care. The incidence of AKI in pediatric intensive care units has been reported to reach 27%, and KDIGO stage 2–3 AKI has been associated with increased 28-day mortality [1]. Previous studies have reported mortality rates ranging from 20% to 50% among children requiring CKRT and have emphasized that outcomes are influenced not only by the severity of kidney dysfunction but also by the burden of underlying disease and multiorgan dysfunction [2–4]. Consistent with these observations, non-survivors in our cohort exhibited higher VIS, PRISM III, PELOD-2, and OFI scores, as well as lower mean arterial pressure and higher lactate concentrations, supporting the concept that mortality in children receiving CKRT is driven primarily by overall illness severity and organ dysfunction rather than by the degree of kidney injury alone.

Among the evaluated immune-metabolic indices, LAR demonstrated the strongest prognostic performance. By integrating lactate, a marker of tissue hypoperfusion and metabolic stress, with albumin, a marker of inflammation, capillary leak, and nutritional status, LAR reflects several key pathophysiological processes involved in critical illness. Previous studies have demonstrated associations between elevated LAR values and mortality, multiorgan dysfunction, and adverse outcomes in critically ill pediatric populations [5, 17]. More recently, LAR has also been identified as an independent predictor of in-hospital mortality in children with AKI, showing strong discriminative performance for risk stratification [6]. Similarly, inflammation-based biomarkers have been reported to be associated with mortality in pediatric patients undergoing CKRT [8]. In the present study, LAR achieved an AUC that was remarkably close to those of PELOD-2 and PRISM III scores. However, despite its favorable discriminative performance, the prognostic information provided by LAR appeared to largely overlap with the severity of organ dysfunction as captured by PELOD-2 score. Nevertheless, the close similarity between the AUC values of LAR, PELOD-2, and PRISM III scores highlights the potential utility of LAR as a simple bedside risk-stratification tool.

MLR was also significantly associated with mortality, whereas NLR demonstrated only a borderline association. Importantly, mortality in our cohort was associated with lower rather than higher MLR values. This observation suggests that, in children requiring CKRT, MLR may reflect immune dysregulation and immune exhaustion rather than simply the intensity of the inflammatory response.

Leukocyte-derived indices such as MLR and NLR have increasingly been recognized as markers of systemic inflammation and immune dysregulation [7, 18]. Previous studies have reported associations between MLR and both AKI development and adverse outcomes; however, its prognostic value appears to vary across different patient populations and disease severities [19, 20]. In contrast, although NLR has been reported to predict AKI development and adverse outcomes in patients with sepsis, it did not reach statistical significance in the present study [21, 22].

One of the most intriguing findings of the present study was that elevated UCR values were associated with 28-day mortality despite significantly lower serum creatinine levels among non-survivors. In addition, KDIGO stage 2 AKI was more common among non-survivors, whereas stage 3 AKI predominated among survivors. At first glance, these findings appear paradoxical. However, they suggest that mortality among critically ill children receiving CKRT is determined more by circulatory failure, systemic inflammation, and multiorgan dysfunction than by the degree of kidney dysfunction itself, a concept that has been highlighted in previous pediatric CKRT cohorts [2–4]. The younger age of non-survivors may partially explain their lower creatinine concentrations because serum creatinine is strongly influenced by muscle mass and creatinine generation. In addition, children with sepsis and shock may require CKRT because of severe metabolic derangements or hemodynamic instability before marked creatinine elevation develops [3]. Elevated UCR may reflect not only impaired renal function but also increased urea generation associated with catabolic stress and neurohormonal activation [23]. Consistent with this concept, higher UCR values have been associated with adverse outcomes and increased mortality in critically ill patients [9]. Collectively, these findings support the notion that mortality risk in severe pediatric AKI requiring CKRT is more closely related to overall physiological derangement and multiorgan dysfunction than to creatinine elevation alone.

A key finding of the present study was that neither LAR nor UCR remained independently associated with mortality after adjustment for PELOD-2 score. Furthermore, moderate correlations were observed between PELOD-2 score and both biomarkers. These findings suggest that the prognostic information provided by immune-metabolic indices substantially overlaps with the information captured by established organ dysfunction scores. Rather than acting as independent determinants of outcome, these biomarkers may primarily represent biochemical manifestations of the severity of organ dysfunction. This interpretation is consistent with the observation that PELOD-2 and PRISM III scores demonstrated the highest predictive performance in our cohort and remained the most robust indicators of mortality risk.

From a clinical standpoint, immune-metabolic indices remain attractive because they are inexpensive, readily available, and easily calculated from routine laboratory parameters. The associations observed between LAR, UCR, MLR, and mortality suggest that these biomarkers may provide additional information regarding illness severity. Nevertheless, their loss of independent prognostic significance after adjustment for PELOD-2 scores indicates that they are best interpreted as complementary markers of organ dysfunction rather than alternatives to established severity scoring systems. Accordingly, these

indices may serve as readily available adjunctive markers that complement established severity scores and contribute to early risk stratification in critically ill children requiring CKRT.

Limitations

Several limitations should be considered when interpreting our findings. First, the retrospective single-center design inherently limits causal inference and may affect the generalizability of the results. Second, although the cohort represents a relatively large pediatric CKRT population, the modest number of mortality events may have limited the statistical power of multivariable analyses. Third, the study included patients with diverse AKI etiologies, reflecting real-world clinical practice but potentially introducing biological heterogeneity. Nevertheless, the consistency of the findings in sensitivity analyses excluding patients with HUS supports the robustness of the observed associations. Fourth, both CVVHD and CVVHDF modalities were utilized according to clinical indications, and the potential influence of treatment modality on outcomes was not specifically examined. Finally, immune-metabolic indices were assessed only once, at the time of CKRT initiation. Therefore, the prognostic significance of their temporal trajectories could not be evaluated, and because the interval between AKI diagnosis and CKRT initiation may have varied among patients, the performance of these biomarkers during earlier stages of AKI remains uncertain. Prospective multicenter studies involving larger cohorts and serial biomarker measurements are warranted to validate these findings and further clarify the prognostic role of immune-metabolic indices in pediatric patients requiring CKRT.

Conclusion

In conclusion, LAR, UCR, and MLR were associated with 28-day mortality in critically ill children requiring CKRT for severe AKI. Among the evaluated biomarkers, LAR demonstrated the strongest discriminative performance. However, neither LAR nor UCR remained independently associated with mortality after adjustment for PELOD-2, suggesting that these indices primarily reflect the severity of underlying organ dysfunction. These findings support their use as complementary bedside markers of physiologic burden rather than substitutes for established severity-of-illness scores.

Abbreviations

CKRT
continuous kidney replacement therapy
HUS
hemolytic uremic syndrome
MIS-C
multisystem inflammatory syndrome in children
PICU
pediatric intensive care unit
KDIGO

Kidney Disease: Improving Global Outcomes
IQR
interquartile range.

Declarations

Author Contributions: The authors confirm their contributions to the paper as follows: Concept/design: CD, EGS. Data analysis/interpretation: CD. Drafting article: EGS, KBG. Critical revision of article: FV, SG, statistics: CD. Data collection: KBG, AE. Literature search: FV and EGS. All authors reviewed the results and approved the final version of the manuscript.

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Institutional Review Board Statement:

The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Research Ethics Committee of XXX Training and Research Hospital, (Approval No: E-46059653-050.04-317541412; approval date: 10 June 2026).

Informed Consent Statement:

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study and the use of anonymized clinical data.

Data Availability Statement:

The datasets generated and/or analyzed during the current study are not publicly available due to institutional and patient privacy restrictions but are available from the corresponding author on reasonable request.

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References

1. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL (2017) AWARE Investigators. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med 376(1):11–20
2. Goldstein SL, Somers MJG, Baum MA et al (2005) Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 67(2):653–658

3. Cortina G, McRae R, Hoq M et al (2019) Mortality of critically ill children requiring continuous renal replacement therapy: effect of fluid overload, underlying disease, and timing of initiation. Pediatr Crit Care Med 20(4):314–322
4. Hayes LW, Oster RA, Tofil NM, Tolwani AJ (2009) Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care 24(3):394–400
5. Ray CC, Pollack MM, Gai J, Patel AK (2023) The association of the lactate-albumin ratio with mortality and multi-organ dysfunction in pediatric ICU patients. Pediatr Crit Care Med 24(9):760–766
6. Zhang R, Feng W, Feng K et al (2025) The relationship between lactate/albumin ratio and prognosis in children with acute kidney injury. PLoS ONE 20(8):e0329453
7. Ren J, Zhao Y, Yuan Y et al (2022) Monocyte-to-lymphocyte ratio: a potential novel predictor for acute kidney injury in the intensive care unit. Ren Fail 44(1):881–890
8. Evren G, Okur Acar S (2026) Inflammation-based prognostic markers in pediatric continuous renal replacement therapy. J Pediatr Acad 7(1):30–34
9. Van der Slikke EC, Star BS, de Jager VD et al (2020) A high urea-to-creatinine ratio predicts long-term mortality independent of acute kidney injury among patients hospitalized with an infection. Sci Rep 10:15272
10. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group (2013) Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 17(1):204. 10.1186/cc11454
11. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP et al (2020) Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 46(Suppl 1):10–67. 10.1007/s00134-019-05878-6
12. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J et al (2020) COVID-19–associated multisystem inflammatory syndrome in children — United States, March–July 2020. MMWR Morb Mortal Wkly Rep 69(32):1074–1080. 10.15585/mmwr.mm6932e2
13. Weiss SL, Carcillo JA, Leclerc F, Leteurtre S, Dugas MA, Wypij D et al (2022) Refining the pediatric multiple organ dysfunction syndrome. Pediatrics 149(1 Suppl 1):S13–S22. 10.1542/peds.2021-052888C
14. Pollack MM, Patel KM, Ruttimann UE (1996) PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 24(5):743–752
15. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F (2013) PELOD-2: an update of the Pediatric Logistic Organ Dysfunction score. Crit Care Med 41(7):1761–1773
16. Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M (1996) Epidemiology of sepsis and multiple organ dysfunction syndrome in children. Chest 109(4):1033–1037
17. Aygun F, Durak C, Varol F, Cokugras H, Camcioglu Y (2021) The lactate/albumin ratio is an effective predictor for mortality in critically ill children. Turk J Pediatr Dis 15(6):493–499. 10.12956/tchd.591883

18. Buonacera A, Stancanelli B, Colaci M, Malatino L (2022) Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. Int J Mol Sci 23(7):3636. 10.3390/ijms23073636
19. Luo X, Wan D, Xia R, Liao R, Su B (2023) Prognostic value of the baseline and early changes in monocyte-to-lymphocyte ratio for short-term mortality among critically ill patients with acute kidney injury. J Clin Med 12(23):7353. 10.3390/jcm12237353
20. Wang Z, Li J, Song H, Wei D, Zhao X (2022) Monocyte to lymphocyte ratio, a novel predictor of acute kidney injury after cardiac valve surgery. Heart Surg Forum 25(6):E833–E839. 10.1532/HSF.5111
21. Yilmaz H, Cakmak M, Inan O, Darcin T, Akcay A (2015) Can neutrophil-lymphocyte ratio be an independent risk factor for predicting acute kidney injury in patients with severe sepsis? Ren Fail 37(2):225–229. 10.3109/0886022X.2014.982477
22. Pan YH, Tsai HW, Lin HA, Chen CY, Chao CC, Lin SF et al (2024) Early identification of sepsis-induced acute kidney injury by using monocyte distribution width, red-blood-cell distribution width, and neutrophil-to-lymphocyte ratio. Diagnostics (Basel) 14(9):918. 10.3390/diagnostics14090918
23. Feinfeld DA, Bargouthi H, Niaz Q, Carvounis CP (2002) Massive and disproportionate elevation of blood urea nitrogen in acute azotemia. Int Urol Nephrol 34(1):143–145. 10.1023/A:1025983009957

Figures

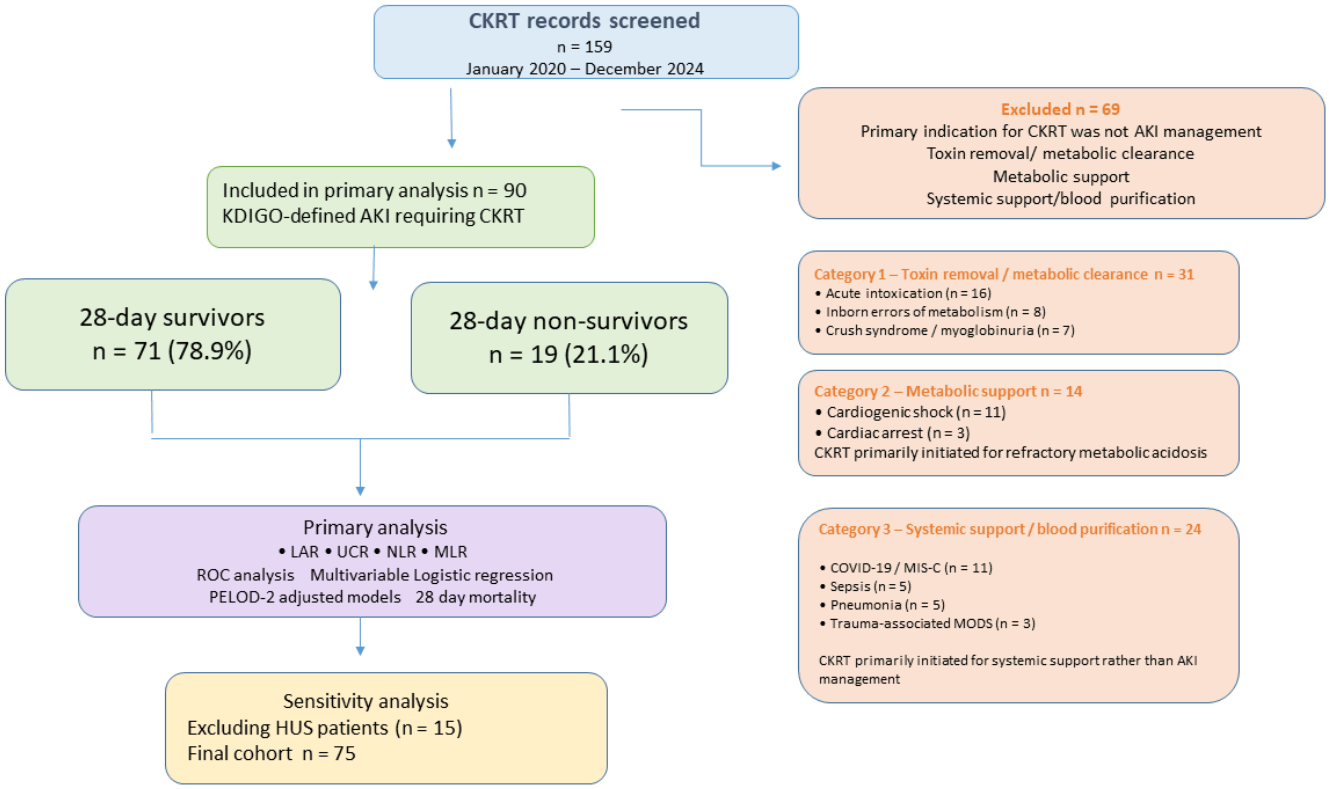


Figure 1

Study flowchart and patient selection process.

Flow diagram illustrating patient screening, eligibility assessment, exclusion criteria, and final cohort selection. A total of 159 children who underwent continuous kidney replacement therapy (CKRT) between January 2020 and December 2024 were screened. Patients in whom CKRT was initiated primarily for toxin removal, metabolic support, or extracorporeal blood purification rather than acute kidney injury (AKI) management were excluded. The final study cohort consisted of 90 children with KDIGO-defined AKI requiring CKRT. Sensitivity analyses were additionally performed after exclusion of patients with hemolytic uremic syndrome (HUS).

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