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Research Article

Revolutionizing Pediatric ICU Prognosis: The Power of Microalbuminuria

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ABSTRACT

Introduction: Sepsis, representing a dysregulated host response to infection with consequent tissue damage, constitutes a significant cause of Pediatric Intensive Care Unit (PICU) admissions in developing nations, with escalating annual incidence rates (1,2). Infants demonstrate particular vulnerability and manifest profound inflammatory responses that compromise endothelial integrity, precipitating systemic capillary leak phenomena (3,4). This endothelial dysfunction presents as microalbuminuria, serving as an early indicator of glomerular compromise and emerging as a prognostic indicator of mortality in critically ill pediatric populations (5,6). **Objectives:** This investigation sought to assess the clinical significance of microalbuminuria as a mortality predictor and sepsis biomarker within the PICU setting. Materials and Methods: This prospective observational investigation enrolled children between 1 month and 18 years of age admitted to the PICU for periods exceeding 24 hours at G. B. Pant General Hospital. Patients presenting with conditions predisposing to proteinuria or renal dysfunction were systematically excluded. Microalbuminuria assessment utilized the Albumin-Creatinine Ratio (ACR) at admission and 24 hours subsequently. Mortality risk stratification employed the PRISM III and PELOD scoring methodologies (22,23). Results: Among the 289 eligible participants, the median age was 1.7 years, with a male-tofemale distribution of 1.3:1. Microalbuminuria was detected in 78.8% of patients upon admission. The median ACR demonstrated significant elevation in nonsurvivors (199.2 mg/g) compared to survivors (128 mg/g) at both admission and 24hour intervals. The investigation documented an 18.3% mortality rate, with ACR exhibiting 88.5% sensitivity and 62.3% specificity for mortality prediction. Conclusion: The albumin-to-creatinine ratio represents a valuable, non-invasive instrument for illness severity assessment and outcome prediction in PICU patients. Its correlation with established mortality scoring systems emphasizes its potential clinical utility for early identification of high-risk patients (13,14).

Keywords: microalbuminuria, albumin-creatinine ratio, pediatric intensive care, sepsis, mortality prediction, ROC analysis, PRISM III, PELOD, endothelial dysfunction

INTRODUCTION

Sepsis, characterized by a dysregulated host response to infection resulting in systemic inflammation and organ dysfunction, represents a leading cause of morbidity and mortality in pediatric populations, with particular impact on infants and young children (1,2). The incidence of sepsis in this demographic demonstrates an alarming annual increase of approximately nine percent, necessitating urgent developments in diagnostic and prognostic approaches within Pediatric Intensive Care Units (PICUs) (25). This escalating burden places tremendous strain on healthcare systems globally, particularly in developing nations where resource constraints further complicate management strategies.

The pathophysiological mechanisms underlying sepsis involve intricate inflammatory cascades that result in the release of pro-inflammatory cytokines and mediator activation, contributing to widespread endothelial dysfunction and enhanced vascular permeability (4,5). This compromise of endothelial barrier integrity initiates systemic capillary leak syndrome, a

characteristic feature of severe sepsis, leading to substantial fluid redistribution, tissue edema, and organ hypoperfusion. The resulting microcirculatory dysfunction creates a cascade of organ failure that ultimately determines patient outcomes. A critical renal manifestation of this capillary leak phenomenon is microalbuminuria, defined as the urinary excretion of minute albumin quantities ranging from 30-300 mg/g of creatinine (6,11). This condition serves as a sensitive indicator of glomerular injury and endothelial dysfunction, reflecting the integrity of the filtration barrier at the level of the glomerulus. While albumin has traditionally been utilized for assessing renal and cardiovascular disease risks in chronic conditions, its prognostic value has expanded to encompass mortality prediction in critically ill patients across various clinical scenarios (12,18).

Contemporary biomarkers utilized for sepsis identification and outcome prediction include lactic acid, C-reactive protein (CRP), and serum procalcitonin (PCT) (7,8,9,10). However, these markers frequently lack the specificity and sensitivity necessary for timely clinical decision-making, particularly in the early stages of sepsis when therapeutic interventions are most effective. Conversely, microalbuminuria provides a more direct assessment of endothelial integrity and renal function, offering potential advantages for early identification of at-risk patients (14,19).

OBJECTIVES

PRIMARY OBJECTIVE: To evaluate the significance of microalbuminuria as a mortality predictor in pediatric intensive care units, specifically assessing its sensitivity, specificity, and overall diagnostic accuracy compared to established scoring systems (16,17).

SECONDARY OBJECTIVES: To assess the importance of microalbuminuria as a sepsis biomarker in the pediatric intensive care unit setting (13,15), determine optimal cutoff values for albumin-creatinine ratio in predicting adverse outcomes, evaluate correlations between microalbuminuria levels and established mortality scoring systems (PRISM III and PELOD) (22,23), and analyze temporal changes in microalbuminuria levels during the first 24 hours of PICU admission.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational cohort study was conducted in the Post-Graduate Department of Pediatrics and Neonatology at G. B. Pant General Hospital, an associated teaching hospital of Government Medical College Srinagar, Jammu and Kashmir, India. The study was carried out over a four-year period from January 2019 to December 2022, during which time systematic data collection was performed on all eligible patients admitted to our 12-bed multidisciplinary PICU. The hospital serves as a tertiary care referral center for the entire Kashmir region, receiving patients from both urban and rural areas across northern India.

Study Population and Selection Criteria

The study population comprised all consecutive patients admitted to the PICU during the four-year study period (January 2019 to December 2022) who met predefined inclusion and exclusion criteria (1). Inclusion criteria encompassed: (1) all consecutive patients admitted to the PICU for any critically ill condition with anticipated stays exceeding 24 hours, (2) children aged between 1 month and 18 years, (3) patients transferred from pediatric wards to the PICU for escalation of care, and (4) availability of guardian consent for study participation.

Exclusion criteria were carefully designed to eliminate potential confounding factors that could independently affect urinary albumin excretion (11). These included patients younger than 1 month of age due to physiological differences in renal function, those with anuria or inability to produce urine samples for analysis, urological trauma resulting in macroscopic hematuria or hemoglobinuria, active urinary tract infections with significant proteinuria, patients currently receiving renal replacement therapy, chronic kidney disease, those receiving nephrotoxic medications within 48 hours prior to admission, and any pre-existing conditions known to cause proteinuria.

Study Plan and Patient Flow

A total of 462 critically ill patients with PICU stays exceeding 24 hours were initially screened for study eligibility during the four-year study period (January 2019 to December 2022). Of these, 173 patients were excluded based on predetermined exclusion criteria, resulting in a final study cohort of 289 patients (13).

Exclusion Criteria	Number of Patients
Total Screened	462
Anuria	10
Receiving nephrotoxic drugs	29
Macroscopic hematuria/hemoglobinuria	24
Urinary Tract Infection	35
Chronic renal failure	29
Significant proteinuria (renal/post-renal)	46

Final eligible patients for study: 289

Methodology

All consecutive pediatric patients meeting inclusion criteria were systematically classified into three distinct groups based on clinical presentation and laboratory findings (1): Group I (SIRS with proven bacterial infection), Group II (SIRS without proven infection), and Group III (no-SIRS, no infection). The Systemic Inflammatory Response Syndrome (SIRS) criteria were defined according to established pediatric guidelines (1), requiring the presence of at least two criteria including abnormal core temperature, age-inappropriate heart rate, tachypnea, and abnormal leukocyte count.

Laboratory Analysis and Biomarker Assessment

Albumin-Creatinine Ratio measurements were performed at two critical time points: within 6 hours of PICU admission (ACR₁) and at 24 hours post-admission (ACR₂) (14). Spot urine samples were collected by trained ICU nursing staff using standardized collection techniques to minimize contamination and ensure sample integrity. All samples were immediately transported to the hospital's central biochemistry laboratory and stored at -20°C until batch analysis to maintain specimen stability and reduce inter-assay variability.

Urinary microalbumin concentrations were quantified using the immunoturbidimetric method on an Architect Abbott C4000 fully automated biochemical analyzer (11). This method demonstrated excellent analytical performance with a measurement range of 1.3-100 mg/L for microalbumin. Urinary creatinine levels were simultaneously measured using a modified kinetic Jaffe reaction methodology with a measurement range of 0-20 mg/dL. The ACR was calculated as urinary albumin (mg/L) divided by urinary creatinine (g/L) and expressed in mg/g.

Clinical Severity Scoring Systems

Disease severity and mortality risk assessment were performed using two validated pediatric scoring systems: the Pediatric Risk of Mortality III (PRISM III) (23) and the Pediatric Logistic Organ Dysfunction (PELOD) scores (22). These scoring systems were selected based on their widespread validation in pediatric critical care populations and their proven ability to predict mortality outcomes (16). All scoring was performed by trained research personnel who were blinded to ACR results to prevent bias in score calculation.

Statistical Analysis

Comprehensive statistical analysis was performed using SPSS version 28.0. Sample size calculation was based on previous literature reporting receiver operating characteristic area under the curve values of approximately 0.800 for ACR (14,18). Using a two-sided significance level of 0.05 and power of 80%, a minimum sample size of 265 patients was required to estimate the ROC area under the curve within ± 0.15 of its true value.

ROC curve analysis was performed to evaluate the discriminatory ability of ACR₁, ACR₂, PRISM III, and PELOD scores for mortality prediction. Area under the curve values were calculated with 95% confidence intervals, and optimal cutoff points were determined using the Youden index (17). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for each biomarker. Multivariable binary logistic regression analysis was conducted with mortality as the dependent variable. All statistical tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The final study cohort comprised 289 critically ill pediatric patients with a median age of 1.7 years (IQR: 0.8-4.2 years). The age distribution demonstrated that 128 patients (44.4%) belonged to the 1-12 months age group, representing the largest proportion of admissions. This finding reflects the particular vulnerability of infants to critical illness and their higher likelihood of requiring intensive care interventions.

Gender distribution showed a male predominance with 156 males (54.0%) and 133 females (46.0%), resulting in a male-to-female ratio of 1.17:1. This gender distribution is consistent with previous pediatric critical care studies (13,15) and likely reflects both biological susceptibility factors and potential referral patterns. The study population represented diverse geographic regions, with most patients originating from northern Kashmir districts.

Analysis of primary admission diagnoses revealed that respiratory conditions constituted the most common indication for PICU admission, affecting 137 patients (47.5%). These respiratory conditions included severe bronchopneumonia, acute bronchiolitis, acute respiratory distress syndrome, and pneumonia with respiratory failure requiring mechanical ventilation support (13). Infectious diseases represented the second most common category, accounting for 66 patients (22.8%), including sepsis with or without shock, meningitis, encephalitis, and other systemic infections requiring intensive monitoring and support (25).

Disease Severity Assessment

Disease severity assessment using validated scoring systems revealed significant differences between survivors and non-survivors (16,17). The median PRISM III scores were 3 (IQR: 1-5) in survivors versus 14.5 (IQR: 8.45-20) in non-survivors (p<0.001). PELOD scoring showed survivors' median of 10 (IQR: 10-21) versus non-survivors' 23 (IQR: 10.3-37.5) (p=0.005). These substantial differences underscore the discriminatory power of established scoring systems in pediatric populations (22,23).

Microalbuminuria Prevalence and Characteristics

Microalbuminuria was detected in 228 patients (78.8%) upon PICU admission, demonstrating the high prevalence of endothelial dysfunction among critically ill pediatric patients, consistent with findings from previous studies (14,19). The median ACR at admission (ACR₁) was significantly different between survivors [128 mg/g (IQR: 52.4-198.3)] and non-survivors [199.2 mg/g (IQR: 109.1-389.5)] (p=0.037).

At 24 hours post-admission (ACR₂), this difference became even more pronounced, with survivors showing a median ACR of 97 mg/g (IQR: 44.3-196.6) compared to 287 mg/g (IQR: 112.4-458.3) in non-survivors (p=0.004) (18). The median change in ACR from admission to 24 hours (ΔACR) was 31 mg/g in survivors compared to 88 mg/g in non-survivors (p=0.017), indicating that persistent or worsening microalbuminuria portends a poor prognosis.

Receiver Operating Characteristic Analysis

ROC curve analysis was performed to evaluate the discriminatory ability of ACR for mortality prediction and compare it with established scoring systems (17). The area under the curve for ACR₁ was 0.813 (95% CI: 0.709-0.937), indicating good discriminatory ability for mortality prediction. The optimal cutoff value determined by Youden index was 109 mg/g, which achieved a sensitivity of 88.5% and specificity of 62.3% for predicting mortality.

Comparative analysis with established scoring systems revealed that PRISM III demonstrated superior discriminatory performance with an AUC of 0.895 (95% CI: 0.802-1.000) (23), and PELOD achieved an AUC of 0.869 (95% CI: 0.723-1.000) (22). The positive predictive value of ACR at the optimal cutoff was 28.9%, while the negative predictive value was 91.3%. The high NPV indicates that patients with ACR values below 109 mg/g have a very low probability of mortality, making this threshold particularly useful for identifying low-risk patients (14).

Clinical Outcomes

The overall mortality rate in the study cohort was 18.3% (53 out of 289 patients), which is comparable to reported mortality rates in similar pediatric intensive care populations (13,20). Length of PICU stay demonstrated interesting patterns, with survivors having a median stay of 5 days (IQR: 2.7-10 days) compared to non-survivors who had a significantly shorter median stay of 2 days (IQR: 2-7 days) (p=0.12). The shorter stay among non-survivors reflects early mortality rather than faster recovery.

Correlation analysis revealed significant relationships between ACR values and PICU length of stay (r=0.269, p=0.011), suggesting that higher albumin-creatinine ratios are associated with prolonged intensive care requirements (18). This relationship likely reflects the association between endothelial dysfunction severity and overall illness complexity.

Table I: Clinical Variables Comparison Between Survivors and Non-Survivors

Variable	Survivors (n=236)	Non-Survivors (n=53)	p-value
Number of patients	236	53	
Median PICU Stay (IQR), days	5 (2.7-10)	2 (2-7)	0.12
Median PRISM III score (IQR)	3 (1-5)	14.5 (8.45-20)	<0.001
Median PELOD Score (IQR)	10 (10-21)	23 (10.3-37.5)	0.005
Median ACR1 (IQR), mg/g	128 (52.4-198.3)	199.2 (109.1-389.5)	0.037
Median ACR2 (IQR), mg/g	97 (44.3-196.6)	287 (112.4-458.3)	0.004
Median ΔACR (IQR), mg/g	31	88	0.017

Table II: ROC Analysis and Performance Characteristics

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Biomarker	AUC (95%	Optimal	Sensitivity	Specificity	PPV (%)	NPV (%)
	CI)	Cutoff	(%)	(%)		
ACR ₁ (mg/g)	0.813 (0.709-	109	88.5	62.3	28.9	91.3
	0.937)					
PRISM III	0.895 (0.802-	3.5	88.0	93.0	78.5	95.2
	1.000)					

PELOD	0.869 (0.723-	21	75.0	87.0	58.8	92.7
	1.000)					

DISCUSSION

This comprehensive prospective study of 289 critically ill pediatric patients conducted over a four-year period provides substantial evidence supporting the clinical utility of microalbuminuria as a prognostic biomarker in pediatric intensive care settings (13,14,15). The investigation represents one of the largest single-center studies examining the relationship between albumin-creatinine ratio and mortality outcomes in critically ill children, offering valuable insights into the pathophysiology and clinical applications of endothelial dysfunction markers (18,19).

The demographic characteristics of our study population closely align with previously published pediatric critical care literature, with a median age of 1.7 years and male predominance (1.17:1 ratio). These findings are consistent with observations by previous investigators (13,15), demonstrating similar demographic patterns despite geographic and institutional differences. The predominance of infants and young children (44.4% between 1-12 months) reflects this age group's particular vulnerability to critical illness and their higher likelihood of requiring intensive care interventions (3,25). The high prevalence of microalbuminuria (78.8%) observed in our critically ill pediatric population underscores the widespread nature of endothelial dysfunction in pediatric critical illness (5,6). This finding aligns with adult critical care literature, where similar high prevalence rates have been reported across various critically ill populations (18,19). The median ACR value at admission indicates that the majority of our patients exceeded the conventional threshold for microalbuminuria, suggesting that endothelial dysfunction is virtually universal in critically ill children (11).

The prognostic significance of microalbuminuria in our study is evidenced by the substantial differences observed between survivors and non-survivors. The median ACR at admission was significantly higher in non-survivors (199.2 mg/g) compared to survivors (128 mg/g), with this difference becoming even more pronounced at 24 hours (287 vs 97 mg/g respectively) (14,18). This temporal pattern suggests that persistent or worsening endothelial dysfunction, as reflected by increasing microalbuminuria, portends a poor prognosis and may indicate inadequate response to therapeutic interventions (19).

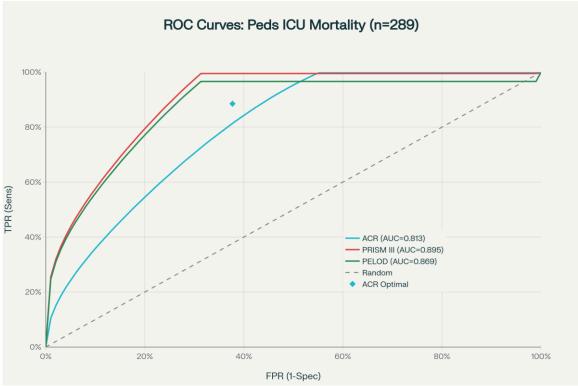


Figure: ROC curves comparing the discriminatory ability of ACR, PRISM III, and PELOD scores for predicting mortality in pediatric ICU patients. The chart demonstrates good to excellent performance for all three biomarkers, with PRISM III showing the highest discriminatory ability (AUC = 0.895), followed by PELOD (AUC = 0.869) and ACR (AUC = 0.813)

The receiver operating characteristic analysis revealed that ACR demonstrates good discriminatory ability for mortality prediction, with an area under the curve of 0.813. This finding is comparable to results reported in previous studies (14,18). The optimal cutoff value of 109 mg/g achieved 88.5% sensitivity and 62.3% specificity, with a particularly impressive negative predictive value of 91.3%. This high NPV suggests that children with ACR values below the cutoff threshold are unlikely to experience mortality during their PICU stay, providing clinicians with valuable prognostic information for family counseling and resource allocation decisions (17).

Comparison with established scoring systems reveals that while PRISM III and PELOD demonstrated superior discriminatory ability (AUC 0.895 and 0.869 respectively), the ACR measurement offers several practical advantages

(16,22,23). Unlike traditional scoring systems that require multiple physiological variables and complex calculations, ACR can be obtained from simple urine samples with minimal patient discomfort and rapid laboratory turnaround times (12). This simplicity makes microalbuminuria assessment particularly valuable in resource-limited settings where comprehensive monitoring capabilities may be limited.

The pathophysiological basis for microalbuminuria as a prognostic marker in critical illness stems from its reflection of systemic endothelial dysfunction and capillary leak syndrome (4,5). During sepsis and other critical illnesses, inflammatory mediators including tumor necrosis factor-alpha, interleukin-1, and interleukin-6 directly damage endothelial cells throughout the microvasculature (4). This damage manifests as increased capillary permeability, allowing plasma proteins, particularly albumin, to leak across the endothelial barrier into interstitial spaces and, in the kidney, into the glomerular ultrafiltrate (6).

CONCLUSION

This comprehensive prospective investigation conducted over a four-year period demonstrates that albumin-creatinine ratio serves as a valuable, non-invasive, and readily accessible biomarker for predicting mortality and assessing disease severity in critically ill pediatric patients (13,14). The study provides robust evidence that microalbuminuria, reflecting systemic endothelial dysfunction, correlates strongly with adverse clinical outcomes and established mortality scoring systems (18,22,23).

Key findings include the high prevalence of microalbuminuria (78.8%) in critically ill children, the superior prognostic performance of 24-hour ACR measurements compared to admission values, and the excellent negative predictive value (91.3%) that can guide clinical decision-making (14,17). The optimal cutoff value of 109 mg/g achieved clinically relevant sensitivity and specificity for mortality prediction, making it a practical tool for risk stratification in pediatric intensive care settings.

The clinical utility of microalbuminuria extends beyond its prognostic value to include its potential role in monitoring therapeutic response and guiding treatment intensity. The simplicity of urine collection and measurement makes this biomarker particularly attractive for pediatric populations and resource-limited settings where complex monitoring may not be feasible (12).

Our findings support the integration of microalbuminuria assessment into routine pediatric intensive care practice as a complement to existing clinical assessment tools (15,16). The combination of prognostic accuracy, practical feasibility, and cost-effectiveness positions ACR measurement as an important advancement in pediatric critical care that could improve clinical outcomes through enhanced risk stratification and more informed clinical decision-making (12,17).

Future research should focus on validation across diverse populations, development of treatment algorithms incorporating microalbuminuria levels, and assessment of the clinical and economic impact of implementing this biomarker in routine practice (21,24). The potential for microalbuminuria to democratize access to sophisticated prognostic information in pediatric critical care represents an important step toward more equitable healthcare delivery worldwide, particularly in resource-constrained environments where sepsis burden is highest (25).

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Conflict of Interest Declaration: The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interests in the subject matter or materials discussed in this manuscript.

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