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Research Article

Early Laboratory Predictors of Sepsis-Associated Acute Kidney Injury: Development and Validation of a Clinical Prediction Model

Muhammad Muzammil[1], Fatima Rehman[2], Memoona Fakhar[3], Muhammad Shoaib Kanwal[4], Sidra Hamayun[5], Roozina Shaikh[6]

[1]Associate professor, Nephrology Department, Bakhtwar Amin Medical & Dental College, Multan,
[2]Consultant Nephrologist, Nephrology Department, Govt. Nusrat Fateh Ali Khan DHQ Hospital, Faisalabad
[3]Senior registrar, Nephrology department, Multan Medical & Dental College, Multan.
[4]Senior Registrar Medicine Department, Multan Medical & Dental College, Multan.
[5]Associate professor Hematology, Pathology Department, Muhammad College of Medicine, Peshawar.
[6]Lecturer, Community medicine Department, Sindh Medical College, Jinnah Sindh Medical University. Karachi.
Email ID: [1]muzammil_2000@hotmail.com, [2]fatima.rehman.777@gmail.com,
[3]memoonafakhar@yahoo.com, [4]shoaibkanwal120@gmail.com, [5]drsidrafarooq4@gmail.com,
[6]rsheikh2002@hotmail.com
Corresponding Author: Muhammad Muzammil
Associate professor, Nephrology Department, Bakhtwar Amin Medical & Dental College, Multan.
Email ID: muzammil_2000@hotmail.com
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ABSTRACT

Objective: To identify early laboratory predictors of sepsis-associated acute kidney injury (SA-AKI) and develop a practical clinical prediction model using routinely available laboratory investigations among adult patients with sepsis admitted to tertiary care hospitals in Pakistan.

Methods: This prospective multicenter observational cohort study was conducted over 12 months in the Departments of Nephrology and General Medicine of tertiary care teaching hospitals in Pakistan. A total of 250 adult patients diagnosed with sepsis according to the Sepsis-3 criteria were enrolled consecutively. Demographic and clinical characteristics, along with routine laboratory investigations including complete blood count, serum creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), serum albumin, serum bicarbonate, and urine output, were recorded within 24 hours of admission. The primary outcome was the development of SA-AKI within seven days according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Independent predictors were identified using multivariable logistic regression. The predictive performance of the model was assessed using receiver operating characteristic (ROC) curve analysis, the Hosmer–Lemeshow goodness-of-fit test, and internal split-sample validation.

Results: Of the 250 enrolled patients, 92 (36.8%) developed SA-AKI. Higher serum creatinine, BUN, CRP, neutrophil-to-lymphocyte ratio, and lower serum albumin, serum bicarbonate, and urine output were independently associated with the development of SA-AKI ($p<0.05$). The final prediction model demonstrated good discrimination (AUC=0.85) and satisfactory calibration (Hosmer–Lemeshow p=0.58).

Conclusion: A prediction model based solely on inexpensive and routinely available laboratory investigations effectively identified septic patients at high risk of developing acute kidney injury. The model may facilitate early risk stratification and timely intervention in resource-limited tertiary care hospitals in Pakistan.

Keywords: Sepsis, acute kidney injury, clinical prediction model, routine laboratory tests, Pakistan, tertiary care hospitals.

INTRODUCTION

Sepsis is a life-threatening condition caused by a deregulated host response to infection and remains a leading cause of morbidity and mortality worldwide. Acute kidney injury (AKI) is one of its most common and serious complications, contributing to prolonged hospitalization and increased mortality [1]. Early identification of patients at risk of sepsis-associated acute kidney injury (SA-AKI) is therefore essential to enable timely intervention and improve clinical outcomes. [2]

Sepsis-associated acute kidney injury is now recognized as a distinct clinical entity rather than merely a consequence of renal hypo perfusion. The underlying pathophysiology involves a complex interaction of systemic inflammation, endothelial dysfunction, immune deregulations, micro vascular injury, oxidative stress, mitochondrial dysfunction, and tubular epithelial cell damage.[3] Approximately one-third to one-half of patients with sepsis develop AKI during hospitalization, and its occurrence is associated with prolonged hospital stay, increased requirement for renal replacement therapy, progression to chronic kidney disease, and significantly higher mortality.[4] Furthermore, patients with SA-AKI have poorer clinical outcomes than those with non-septic AKI, highlighting the importance of early recognition and intervention.[3, 4]

The burden of sepsis and its renal complications is particularly high in developing countries such as Pakistan, where infectious diseases remain a leading cause of hospital admissions.[5] Limited healthcare resources, delayed presentation, inadequate infection prevention practices, and restricted access to intensive care facilities contribute to unfavorable outcomes.[6] Although several novel biomarkers have been developed for the early detection of kidney injury, their routine use is limited in many public-sector hospitals because of high cost, limited availability, and the requirement for specialized laboratory facilities. Consequently, clinicians in resource-constrained settings continue to rely on routine laboratory investigations that are affordable, readily available, and rapidly obtainable for early risk assessment. [5, 6]

Although the KDIGO guidelines recommend serum creatinine and urine output for diagnosing AKI, both are relatively late markers of renal injury. [7] Routine laboratory parameters such as blood urea nitrogen (BUN), C-reactive protein (CRP), serum albumin, serum bicarbonate, and neutrophil-to-lymphocyte ratio (NLR) are inexpensive, widely available, and may facilitate early risk stratification of sepsis-associated AKI in resource-limited settings.[8,9]

Several prediction models for AKI have been proposed; however, most were developed in high-income countries and often incorporate advanced biomarkers, electronic health record integration, or complex computational algorithms that are difficult to implement in low-resource healthcare systems. [10] Moreover, evidence regarding early laboratory predictors of SA-AKI in the Pakistani population remains limited, and no widely accepted prediction model based exclusively on inexpensive and routinely available laboratory investigations has been validated in local tertiary care hospitals.[11,12] Therefore, the present multicenter study aimed to identify early laboratory predictors of sepsis-associated acute kidney injury and to develop and internally validate a practical clinical prediction model using routine laboratory investigations among adult patients admitted to three tertiary care hospitals in Pakistan. Such a model may facilitate early risk stratification, optimize clinical decision-making, and improve patient outcomes in resource-limited healthcare settings.

MATERIALS AND METHODS

This prospective multicenter observational cohort study was conducted over 12 months (January–December 2025) in the Departments of Nephrology and General Medicine of tertiary care teaching hospitals across Pakistan. The study aimed to identify early laboratory predictors of sepsis-associated acute kidney injury (SA-AKI) and develop an internally validated clinical prediction model using routinely available laboratory investigations. Ethical approval was obtained from the Institutional Review Boards of the participating hospitals and written informed consent was obtained from all participants or their legally authorized representatives.

Adult patients aged 18 years or older admitted to the emergency department, medical wards, or intensive care units with a diagnosis of sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were screened for eligibility. Sepsis was defined as suspected or documented infection accompanied by an increase of two or more points in the Sequential Organ Failure Assessment (SOFA) score. Consecutive non-probability sampling was employed to minimize selection bias, and eligible patients presenting within 24 hours of hospital admission were recruited. Patients were followed for seven days after admission or until discharge or death, whichever

occurred first, to determine the development of SA-AKI.

The sample size was calculated using the World Health Organization (WHO) sample size calculator for studies estimating prevalence. Assuming an anticipated frequency of sepsis-associated acute kidney injury of 35%, a confidence level of 95%, and an absolute precision of 6%, the minimum required sample size was 243 patients. To compensate for incomplete records and possible losses during follow-up, 250 patients were enrolled consecutively across the three participating centers.

Patients with chronic kidney disease stage IV or V (estimated glomerular filtration rate <30 mL/min/1.73 m²), maintenance hemodialysis or peritoneal dialysis, previous renal transplantation, obstructive uropathy, pregnancy, active malignancy receiving chemotherapy, end-stage liver disease, or incomplete clinical or laboratory records were excluded to minimize confounding factors that could independently influence renal function.

Table I. Eligibility criteria

Inclusion Criteria	**Exclusion Criteria**
Age ≥18 years	Chronic kidney disease stage IV–V
Sepsis diagnosed according to Sepsis-3 criteria	Maintenance dialysis
Admission within 24 hours	Previous renal transplantation
Informed consent	Obstructive uropathy
Baseline laboratory investigations available	Pregnancy
	Active malignancy receiving chemotherapy
	End-stage liver disease
	Incomplete clinical or laboratory records

Baseline demographic and clinical information was recorded using a standardized data collection form by trained physicians. Information included age, sex, body mass index, diabetes mellitus, hypertension, ischemic heart disease, source of infection, vital signs at admission, SOFA score, requirement for vasopressor support, mechanical ventilation, duration of hospital stay, and in-hospital outcome. The source of infection was categorized as pulmonary, urinary tract, abdominal, bloodstream, skin and soft tissue, or other documented sites based on clinical evaluation and microbiological findings.

Blood samples were obtained within 24 hours of admission before initiation of renal replacement therapy whenever applicable. Considering the resource limitations of public-sector hospitals in Pakistan, only routinely available laboratory investigations were included in the study. These comprised complete blood count, serum creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), serum albumin, serum bicarbonate, random blood glucose, and serum electrolytes. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from the complete blood count. Urine output was monitored hourly in intensive care patients and at six-hour intervals in ward patients. Laboratory analyses were performed in the respective hospital laboratories using standardized automated analyzers and quality control protocols.

The primary outcome was the development of sepsis-associated acute kidney injury within seven days of hospital admission. Acute kidney injury was diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as any one of the following: an increase in serum creatinine of ≥0.3 mg/dL within 48 hours, an increase in serum creatinine to ≥1.5 times the baseline value within seven days, or urine output of <0.5 mL/kg/hour for at least six consecutive hours. Patients fulfilling any of these criteria were classified as having SA-AKI, whereas the remaining patients were included in the non-SA-AKI group.

Potential predictors of SA-AKI were selected based on biological plausibility and published literature. Demographic characteristics, comorbid conditions, clinical variables, and laboratory parameters were initially analyzed using univariate analysis. Variables demonstrating a p-value <0.10 were subsequently entered into a multivariable

binary logistic regression model using the backward likelihood ratio method to identify independent predictors after adjustment for potential confounders. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were calculated for all significant variables. Regression coefficients of the independent predictors were used to develop a simplified clinical prediction model that could be applied at the bedside using routinely available laboratory investigations.

The predictive performance of the model was assessed by evaluating discrimination, calibration, and internal validity. Discrimination was determined using the receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was calculated to assess the ability of the model to distinguish patients who developed SA-AKI from those who did not. Calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test, while split-sample validation was performed by randomly allocating 70% of the study population to a derivation cohort for model development and the remaining 30% to a validation cohort for assessment of model performance.

Data were analyzed using SPSS version 26.0. Independent predictors of SA-AKI were identified using multivariable logistic regression. Model performance was assessed using ROC curve analysis and the Hosmer–Lemeshow goodness-of-fit test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 278 patients with sepsis were screened across the three participating tertiary care hospitals during the study period. Twenty-eight patients were excluded because they met one or more exclusion criteria, including advanced chronic kidney disease (n=10), maintenance dialysis (n=5), incomplete laboratory records (n=8), and other exclusion criteria (n=5). The remaining 250 patients were included in the final analysis. During the seven-day follow-up period**,** 92 patients (36.8%) developed sepsis-associated acute kidney injury (SA-AKI), whereas 158 (63.2%) did not.

The mean age of the study population was 56.4 ± 15.2 years, and 148 (59.2%) were male. Patients who developed SA-AKI were significantly older than those who did not (61.8 ± 14.3 vs. 53.2 ± 15.1 years; p<0.001). Diabetes mellitus and hypertension were also significantly more frequent among patients with SA-AKI. The mean SOFA score at admission was significantly higher in the SA-AKI group, and these patients more frequently required vasopressor support and mechanical ventilation during hospitalization (Table II).

Table II. Baseline demographic and clinical characteristics of the study population

Variable	SA-AKI (n=92)	Non-SA-AKI (n=158)	p-value
Age (years)	61.8 ± 14.3	53.2 ± 15.1	<0.001
Male gender, n (%)	58 (63.0)	90 (57.0)	0.356
Diabetes mellitus, n (%)	46 (50.0)	49 (31.0)	0.003
Hypertension, n (%)	41 (44.6)	48 (30.4)	0.024
SOFA score	7.6 ± 2.1	5.1 ± 1.8	<0.001
Vasopressor use, n (%)	39 (42.4)	27 (17.1)	<0.001
Mechanical ventilation, n (%)	31 (33.7)	22 (13.9)	<0.001

Routine laboratory investigations performed within 24 hours of admission demonstrated significant differences between the two groups. Patients who subsequently developed SA-AKI had significantly higher mean serum creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), total leukocyte count, and neutrophil-to-lymphocyte ratio (NLR) than those who did not develop AKI. Conversely, serum albumin, serum bicarbonate, hemoglobin concentration, platelet count, and urine output were significantly lower among patients with SA-AKI (Table III).

Table III. Comparison of admission laboratory parameters between study groups

Laboratory parameter	SA-AKI (n=92)	Non-SA-AKI (n=158)	p-value
Serum creatinine (mg/dL)	1.48 ± 0.39	0.94 ± 0.25	<0.001

Blood urea nitrogen (mg/dL)	34.9 ± 11.8	22.7 ± 8.6	<0.001
C-reactive protein (mg/L)	118 ± 46	82 ± 35	<0.001
Serum albumin (g/dL)	2.82 ± 0.49	3.48 ± 0.54	<0.001
Serum bicarbonate (mmol/L)	18.7 ± 3.8	22.9 ± 3.2	<0.001
Hemoglobin (g/dL)	10.2 ± 1.8	11.3 ± 1.7	<0.001
Total leukocyte count (×10⁹/L)	16.8 ± 5.4	13.2 ± 4.6	<0.001
Platelet count (×10⁹/L)	188 ± 74	214 ± 69	0.011
Neutrophil-to-lymphocyte ratio	11.6 ± 4.5	6.9 ± 2.8	<0.001
Urine output (mL/kg/hour)	0.52 ± 0.19	0.88 ± 0.24	<0.001

Variables that demonstrated a statistically significant association with SA-AKI on univariate analysis were considered for multivariable logistic regression analysis. Increasing age, diabetes mellitus, hypertension, higher SOFA score, vasopressor requirement, elevated serum creatinine, increased BUN, elevated CRP, higher NLR, hypoalbuminemia, lower serum bicarbonate, thrombocytopenia, and reduced urine output were all significantly associated with the development of SA-AKI (Table IV).

Table IV. Univariate analysis of factors associated with sepsis-associated acute kidney injury

Variable	Odds Ratio (95% CI)	p-value
Age (>60 years)	2.31 (1.35–3.96)	0.002
Diabetes mellitus	2.23 (1.30–3.82)	0.003
Hypertension	1.84 (1.05–3.20)	0.031
SOFA score	1.52 (1.31–1.76)	<0.001
Serum creatinine	3.78 (2.21–6.45)	<0.001
Blood urea nitrogen	1.07 (1.04–1.10)	<0.001
C-reactive protein	1.02 (1.01–1.03)	<0.001
Serum albumin	0.39 (0.25–0.62)	<0.001
Serum bicarbonate	0.87 (0.81–0.94)	<0.001
Neutrophil-to-lymphocyte ratio	1.20 (1.12–1.29)	<0.001
Urine output	0.09 (0.03–0.28)	<0.001

All variables that showed a significant association with SA-AKI on univariate analysis were entered into the multivariable logistic regression model. After adjustment for potential confounding factors, elevated serum creatinine, increased blood urea nitrogen (BUN), higher neutrophil-to-lymphocyte ratio (NLR), lower serum albumin, lower serum bicarbonate, and higher SOFA score remained independent predictors of sepsis-associated acute kidney injury. Among these variables, serum creatinine demonstrated the strongest association with SA-AKI (adjusted OR=3.41, 95% CI: 1.95–5.98, p<0.001), followed by hypoalbuminemia and higher SOFA score. Although CRP and age were significant on univariate analysis, they lost statistical significance after adjustment in the multivariable model, indicating that their effects were explained by other clinical and laboratory variables included in the analysis.

Table V. Multivariable logistic regression analysis for independent predictors of SA-AKI

Variable	Adjusted OR	95% CI	p-value
Serum creatinine	3.41	1.95–5.98	<0.001
Blood urea nitrogen	1.06	1.02–1.10	0.002
Serum albumin	0.42	0.24–0.73	0.002
Serum bicarbonate	0.89	0.82–0.97	0.008
Neutrophil-to-lymphocyte ratio	1.18	1.09–1.28	<0.001
SOFA score	1.39	1.17–1.66	<0.001

Based on the regression coefficients obtained from the final multivariable model, a simplified clinical prediction model was developed using the six independent predictors. Each predictor was assigned a weighted score proportional to its regression coefficient, and the cumulative score was used to estimate the probability of developing SA-AKI. Patients were subsequently stratified into low-, intermediate-, and high-risk categories according to their total prediction scores. The incidence of SA-AKI increased progressively across these risk groups, demonstrating the ability of the model to effectively discriminate between patients at different levels of risk. Only 11.2% of patients in the low-risk category developed SA-AKI compared with 35.5% in the intermediate-risk group and 81.4% in the high-risk group.

Table VI. Risk stratification using the clinical prediction model

Risk category	Prediction score	Number of patients	Developed SA-AKI n (%)
Low risk	0–3	98	11 (11.2)
Intermediate risk	4–6	93	33 (35.5)
High risk	≥7	59	48 (81.4)

The predictive performance of the clinical prediction model was evaluated using receiver operating characteristic (ROC) curve analysis. The model demonstrated good discriminatory ability with an area under the ROC curve (AUC) of 0.85 (95% CI: 0.80–0.90), indicating excellent accuracy in distinguishing patients who developed SA-AKI from those who did not. Calibration analysis using the Hosmer–Lemeshow goodness-of-fit test demonstrated good agreement between predicted and observed outcomes (χ^2=6.12, p=0.64), suggesting that the model adequately estimated the probability of SA-AKI across different risk categories. Internal validation using the split-sample approach produced similar findings, with an AUC of 0.83 in the validation cohort, indicating good reproducibility and stability of the model.

Table VII. Performance of the clinical prediction model

Performance indicator	Value
Area under ROC curve (AUC)	0.85 (95% CI: 0.80–0.90)
Sensitivity	82.6%
Specificity	79.1%
Positive predictive value	69.8%
Negative predictive value	88.4%
Overall diagnostic accuracy	80.4%
Hosmer–Lemeshow test	χ^2=6.12, p=0.64
AUC after internal validation	0.83

Overall, the developed prediction model demonstrated satisfactory discrimination, calibration, and internal validity using routinely available laboratory investigations. The model accurately identified septic patients at increased risk of developing acute kidney injury and may serve as a practical bedside tool for early risk stratification in resource-limited tertiary care hospitals.

DISCUSSION

The present multicenter study identified a combination of routinely available laboratory parameters, including serum creatinine, blood urea nitrogen (BUN), serum albumin, serum bicarbonate, neutrophil-to-lymphocyte ratio (NLR), and SOFA score, as independent predictors of sepsis-associated acute kidney injury (SA-AKI). These variables were incorporated into a simple clinical prediction model that demonstrated good discrimination (AUC = 0.85) and satisfactory calibration. The findings suggest that inexpensive laboratory investigations performed at hospital admission can effectively identify septic patients at high risk of developing AKI. Such an approach is particularly valuable in low-resource healthcare settings like Pakistan, where access to novel biomarkers and advanced diagnostic technologies remains limited.[13] Our findings support the growing evidence that early risk stratification using readily available clinical and

laboratory data may facilitate timely interventions and improve patient outcomes. [14]

The incidence of SA-AKI in the present study was 36.8%, which is consistent with previous reports indicating that approximately one-third to one-half of hospitalized patients with sepsis develop acute kidney injury. Differences in reported incidence across studies are largely attributable to variations in patient populations, disease severity, ICU admission rates, and diagnostic criteria.[15] Similar to previous investigations, older age, diabetes mellitus, hypertension, and greater illness severity were more common among patients who developed SA-AKI, emphasizing the contribution of pre-existing comorbidities and impaired physiological reserve to renal injury during sepsis.[16] These observations reinforce the importance of close monitoring of high-risk patients immediately after hospital admission.

Among the laboratory variables evaluated, elevated serum creatinine and BUN were the strongest predictors of SA-AKI. Although serum creatinine is a relatively late marker of kidney injury, even mild elevations at admission were independently associated with subsequent AKI in our cohort. Likewise, increased BUN may reflect impaired renal perfusion, enhanced protein catabolism, and systemic hypoperfusion commonly observed in septic patients. [17] Hypoalbuminemia also emerged as an independent predictor, possibly because reduced serum albumin reflects both poor nutritional status and increased vascular permeability secondary to systemic inflammation. Previous studies have similarly demonstrated that hypoalbuminemia is associated with greater disease severity, prolonged hospitalization, and increased mortality among critically ill patients with sepsis.[18]

Inflammatory markers also played an important role in predicting SA-AKI. Patients who developed AKI had significantly higher neutrophil-to-lymphocyte ratios and lower serum bicarbonate concentrations than those without AKI. The NLR is increasingly recognized as an inexpensive indicator of systemic inflammation and immune disregulation and has been associated with adverse outcomes in several critical illnesses.[19] Reduced serum bicarbonate reflects metabolic acidosis resulting from impaired tissue perfusion and renal dysfunction, both of which contribute to worsening organ failure during sepsis.[20] These laboratory parameters are routinely measured in tertiary care hospitals and therefore provide practical advantages over expensive biomarkers such as NGAL, KIM-1, TIMP-2, and IGFBP7, which remain unavailable in many resource-limited settings. [19, 20]

The clinical prediction model developed in this study demonstrated good diagnostic performance with an AUC of 0.85 and maintained satisfactory discrimination following internal split-sample validation. These findings indicate that the model is robust and has the potential to support bedside clinical decision-making using routinely available investigations. Unlike many recently developed prediction models that rely on machine learning algorithms, electronic health record integration, or costly biomarkers, the present model was specifically designed for implementation in tertiary care hospitals with limited resources.[21] Consequently, it may be more practical for routine use in Pakistan and other low- and middle-income countries where financial and technological constraints limit the widespread adoption of sophisticated prediction tools.[22] Nevertheless, external validation in larger and more diverse patient populations is necessary before widespread clinical implementation.

The present study has several strengths, including its multicenter design, prospective data collection, standardized diagnostic criteria, and use of inexpensive laboratory parameters that are universally available in routine clinical practice. However, certain limitations should be acknowledged. The study was conducted in three tertiary care hospitals, which may limit the generalizability of the findings to primary or secondary healthcare facilities. Novel renal biomarkers and long-term renal outcomes were not evaluated because of financial constraints. In addition, only internal validation was performed; therefore, external validation in independent cohorts is warranted. Despite these limitations, the study provides a practical and cost-effective prediction model that may facilitate early recognition of SA-AKI and improve the management of septic patients in resource-constrained healthcare settings.

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