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Research Article

Early Laboratory Predictors of Sepsis-Associated Acute Kidney Injury and Short-Term Clinical Outcomes in Emergency Department Patients

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ABSTRACT

Objective: The objective of this study was to identify early laboratory and microbiological markers for SA-AKI and 28-day mortality in emergency department patients who were admitted with sepsis, focusing on the pathology and microbiology parameters.

Material and Methods: Prospective observational cohort study in the tertiary care ED. Patients of age who fulfilled the Sepsis-3 criteria were recruited as adults. Blood and urine samples were taken within 6 hours of triage. Routine biochemistry, novel biomarkers (Neutrophil Gelatinase-Associated Lipocalin [NGAL], Kidney Injury Molecule-1 [KIM-1] and Interleukin-6 [IL-6]), and comprehensive microbiological analysis (two sets of blood culture time to positivity, MALDI-TOF MS identification) were measured.

Results: 168 of the 420 enrolled patients (40%) had sepsis-associated acute kidney injury (SA-AKI). At baseline, NGAL, KIM-1, IL-6 and the ratio of Neutrophils to Lymphocytes (NLR) were all significantly higher in the SA-AKI patients, as was the time to blood culture positivity (TTP). NGAL (OR 4.12), IL-6 (OR 2.85), TTP < 12 hours (OR 3.45), and Gram-negative bacteremia (OR 2.10) were all independent risk factors for SA-AKI (all $p < 0.05$). Overall, the biomarker panel had an AUC of 0.91 for SA-AKI prediction. There was a strong association between shorter TTP and higher levels of IL-6, and both with 28-day mortality.

Conclusion: Early integrated laboratory and microbiological profiling using NGAL, IL-6 and blood culture TTP enables very accurate and rapid prediction of SA-AKI and early mortality in ED sepsis patients and enables prompt targeted intervention.

Keywords: Sepsis, Acute Kidney Injury, Neutrophil Gelatinase-Associated Lipocalin, Time-To-Positivity, Microbiology, Emergency Medicine, Biomarkers.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection and is one of the most common causes of morbidity and mortality in the world.[1] The kidneys are particularly susceptible to organ involvement, and in severe sepsis in the Emergency Department (ED), Sepsis-Associated Acute Kidney Injury (SA-AKI) is seen in ~ 40-50% of patients.[2] While hemodynamic instability is a risk factor for SA-AKI, it is a multifactorial and complex pathogenic mechanism that is a significant contributor to the systemic inflammatory response and to short and long-term mortality as well as to the increased length of hospital stay.[3] Although the critical care field has made progress, the early identification of the patient at high risk for SA-AKI is still a significant clinical challenge, particularly because traditional markers are not sufficiently sensitive for hyper-acute triage. Previously, the only known cause of SA-AKI was seen as a result of acute tubular necrosis due to long duration of renal hypoperfusion. Recent histopathological and hemodynamic research has made this view obsolete, however, and found that renal blood flow is maintained or even increased in early septic AKI.[4]

In contrast, the most important pathological mechanisms are microvascular dysfunction, degradation of endothelial glycocalyx, peritubular capillary leukocyte plugging and direct tubular epithelial cell injury caused by Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs).[5] The microbial factors are a crucial part of this cascade. Lipopolysaccharides (endotoxins) are produced by Gram-negative bacteria and peptidoglycans and teichoic acids by Gram-positive bacteria. The microbial products activate the Toll-like receptors (TLR4 and TLR2, respectively) present on the cells lining the renal tubules and the endothelial cells, resulting in a marked release of pro-inflammatory cytokines, especially Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α).[6]

In this inflammatory condition, the cytokines trigger a localized inflammatory reaction resulting in arrest of tubular cell cycles, apoptosis and dedifferentiation of the tubular cells, which occurs before the onset of actual reduction in glomerular filtration rate (GFR).[7] Serum creatinine is the primary functional assay used in the diagnosis of current AKI, and is a product of muscle metabolism. It is not very sensitive in early renal damage, since only a large nephron mass loss (up to 50%) will cause a detectable rise in serum levels.[8]

In addition, non-renal factors like muscle mass, age, sex and fluid resuscitation, which varies widely among septic ED patients, affect creatinine levels. In addition, in many cases, irreversible structural and pathological changes of the renal tubules have already occurred by the time the serum creatinine fulfills the KDIGO criteria for AKI, thus missing the therapeutic window for renal protective interventions.[9]

Under normal conditions, NGAL is expressed in the distal tubules, but not very strongly. In ischemic or septic injury, however, NGAL is expressed at a markedly increased in the thick ascending limb and collecting ducts and quickly appears in the urine and systemic bloodstream.[10] Also, Kidney Injury Molecule-1 (KIM-1) is a transmembrane glycoprotein which is undetectable in normal kidneys but is highly expressed on the apical surface of dedifferentiated proximal tubular cells after kidney injury, as a marker and as a phagocytic receptor for apoptotic debris.[11] Cystatin C is another low molecular weight proteinase inhibitor expressed by all nucleated cells which also has been found to be a better alternative to creatinine for the estimation of GFR, and less affected by inflammatory state and muscle mass, however its use as a pure marker of structural injury is still a topic of controversy.[12,13]

We hypothesized that an integrated panel of early serum structural biomarkers (NGAL, KIM-1), inflammatory markers (IL-6, NLR) and microbiological kinetic data (TTP) measured during the first 6 hours of ED presentation would markedly outperform conventional clinical scores and serum creatinine for predicting the development of SA-AKI and 28-day mortality.

MATERIALS AND METHODS

This was a prospective, observational cohort study carried out in the central clinical pathology and microbiology laboratories of multiple tertiary care university hospitals and in the Emergency Department (ED). The study period spanned 24 months, from January 1, 2024, to December 30, 2025. The study protocol was approved by the Institutional Ethics Committee and informed written consent was taken from all participants/legally authorized representatives. All consecutive patients ≥ 18 years of age with suspected infection in the ED were screened. The inclusion criteria were patients with a suspected or documented infection meeting the Sepsis-3 criteria. Exclusion criteria were: (1) chronic kidney disease (CKD) stage 4 or 5 (estimated GFR <30 mL/min/1.73 m²) before the acute event; (2) renal replacement therapy (RRT) before admission to the ED; (3) known anuria, bilateral urinary tract obstruction; (4) pregnancy; (5) severe immunosuppression (e.g. active chemotherapy, advanced HIV, chronic high dose use of corticosteroids); and (6) refusal to give consent. Patients were categorized into two groups for comparisons: SA-AKI group and Non-SA-AKI group. The main outcome was the occurrence of SA-AKI. The secondary outcome was 28-day mortality due to any cause. Trained intensivists blinded to the results of the novel biomarker calculated the SOFA score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score within the first 6 hours of admission. Routine Biochemistry and Hematology Peripheral venous blood samples were drawn within 1 hour of ED triage, before starting any intravenous fluids if possible or at the time of the onset of resuscitation. Complete blood counts (CBC) were carried out by automated hematology analyzer (Sysmex

XN-9000, Sysmex Corp, Kobe, Japan). Blood parameters were determined as absolute neutrophils count (ANC) and absolute lymphocytes count (ALC), and the ratio of neutrophils to lymphocytes (NLR). Biochemistry and Coagulation: Serum creatinine, blood urea nitrogen (BUN), electrolytes, lactate and liver function tests were performed by a modular clinical chemistry analyzer. An enzymatic method was used to measure serum creatinine to reduce interference from bilirubin and hemolysis. Coagulation profile comprised Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), fibrinogen and D-dimer were measured using an automated coagulation analyzer. ABG analysis was performed with a point of care blood gas analyzer. For the laboratory biomarkers, more venous blood was taken (10 mL) in EDTA and SST. Samples were centrifuged at 2000 x g for 15 minutes, at 4C, within 30 minutes of collection. Prior to the institution of empirical antimicrobial therapy, blood cultures were obtained twice, in separate peripheral blood culture bottles (aerobic and anaerobic bottles) and drawn from separate venipuncture sites with strict aseptic technique. In the event that both bottles obtained during a single venipuncture were positive, the TTP with the lowest time was taken. If TTP was more than 120 hours (5 days), then it was negative. Sample Size Calculation: Epi Info software (version 7.2) was used to calculate the sample size. The incidence of SA-AKI in patients with sepsis in the ED is estimated to be around 40% based on previous literature. Considering a drop-out rate of 10% or lack of data, 420 patients were targeted. The Statistical Analysis was performed with SPSS Statistics (version 28.0) and R software (version 4.2.1). The Shapiro-Wilk test was used to test continuous variables for normality. Means ± standard deviations (SD) are used to present normally distributed data, which are compared using independent Student's t-test. All variables with a p value <0.10 in the univariate analysis as well as clinically relevant other covariates (age, SOFA score) were included in the multivariate logistic regression model, to which the model was reduced using the backward stepwise method. Odds Ratios (OR) and the 95% Confidence Intervals (CI) are reported. Receiver Operating Characteristic (ROC) curve analysis was used to assess the diagnostic performance of each and combined biomarkers to predict SA-AKI. The Area Under the Curve (AUC) was calculated, and the optimum cut-off values were obtained through the application of the Youden index (maximum value of sensitivity + specificity - 1). The secondary outcome (28-day mortality) was analysed using Kaplan-Meier survival curves, which were compared by log-rank test. Multivariate Cox proportional hazard regression was used to determine independent predictors of 28-day mortality, and Hazard Ratios (HR) with 95% confidence interval (CI) were calculated. Schoenfeld residuals were used to test the proportional hazards assumption. All data was analyzed and a p value of < 0.05 was considered statistically significant in the present study. A composite risk score was obtained from the multivariate logistic regression coefficients to assess the combination of the best biomarkers.

RESULTS

Table 1; Patients who developed SA-AKI were significantly older (median 68.5 vs. 62.0 years, p=0.012) and had a higher burden of comorbidities (Charlson Comorbidity Index 3.0 vs. 2.0, p=0.008). Crucially, the SA-AKI group presented with significantly higher illness severity, evidenced by higher median SOFA scores (7.0 vs. 4.0, p<0.001) and APACHE II scores (22.0 vs. 16.0, p<0.001). Furthermore, SA-AKI patients had significantly higher initial serum lactate levels (3.5 vs. 2.1 mmol/L, p<0.001) and a much higher rate of vasopressor requirement in the ED (40.5% vs. 13.9%, p<0.001).

Table 1: Baseline Demographic and Clinical Characteristics of Study Patients

Variable	Non-SA-AKI (N=252)	SA-AKI (N=168)	P-Value
Age (Years), Median (IQR)	62.0 (51.0 - 73.0)	68.5 (58.0 - 76.0)	0.012
Male Sex, N (%)	145 (57.5%)	102 (60.7%)	0.514
Charlson Comorbidity Index, Median (IQR)	2.0 (1.0 - 3.0)	3.0 (2.0 - 4.0)	0.008
Hypertension, N (%)	110 (43.6%)	85 (50.6%)	0.162
Diabetes Mellitus, N (%)	75 (29.7%)	62 (36.9%)	0.128
Source Of Infection, N (%)			0.215

- Pneumonia	95 (37.7%)	70 (41.7%)	
- Urinary Tract	65 (25.8%)	40 (23.8%)	
- Intra-Abdominal	52 (20.6%)	35 (20.8%)	
- Primary Bacteremia	40 (15.9%)	23 (13.7%)	
SOFA Score At Admission, Median (IQR)	4.0 (3.0 - 6.0)	7.0 (5.0 - 9.0)	<0.001
APACHE II Score, Median (IQR)	16.0 (12.0 - 20.0)	22.0 (18.0 - 26.0)	<0.001
Serum Lactate (Mmol/L), Median (IQR)	2.1 (1.4 - 3.0)	3.5 (2.4 - 4.8)	<0.001
Vasopressor Use In ED, N (%)	35 (13.9%)	68 (40.5%)	<0.001

Table 2; as expected, serum creatinine at 6 hours was significantly higher in the SA-AKI group, though the absolute values remained relatively low, highlighting its insensitivity to early structural injury. The structural biomarkers, plasma NGAL and serum KIM-1, were profoundly elevated in patients who subsequently developed SA-AKI (median 245.6 ng/mL vs. 85.4 ng/mL, p<0.001; and 132.5 pg/mL vs. 45.2 pg/mL, p<0.001, respectively). Systemic inflammatory markers, including IL-6 and NLR, were also significantly higher in the SA-AKI cohort.

Table 2: Early Laboratory and Microbiological Predictors (Univariate Analysis)

Variable	Non-SA-AKI (N=252)	SA-AKI (N=168)	P-Value
Serum Creatinine At 6h (Mg/Dl), Median (IQR)	0.9 (0.7 - 1.1)	1.2 (0.9 - 1.6)	<0.001
Serum Cystatin C (Mg/L), Median (IQR)	1.1 (0.8 - 1.4)	1.8 (1.3 - 2.5)	<0.001
Plasma NGAL (Ng/Ml), Median (IQR)	85.4 (52.1 - 120.3)	245.6 (165.4 - 380.2)	<0.001
Serum KIM-1 (Pg/Ml), Median (IQR)	45.2 (28.5 - 65.4)	132.5 (88.6 - 195.4)	<0.001
Serum IL-6 (Pg/Ml), Median (IQR)	45.6 (22.3 - 85.4)	185.4 (110.2 - 310.5)	<0.001
NLR, Median (IQR)	6.5 (4.2 - 9.8)	12.4 (8.5 - 18.6)	<0.001
D-Dimer (Mg/Ml), Median (IQR)	1.2 (0.8 - 2.1)	3.5 (2.2 - 5.8)	<0.001
Blood Culture Positive, N (%)	110 (43.6%)	95 (56.5%)	0.012
Time-To-Positivity (Hours), Median (IQR)	18.5 (14.2 - 24.5)	10.5 (8.2 - 13.5)	<0.001
TTP < 12 Hours, N (%)	25 (9.9%)	65 (38.7%)	<0.001
Gram-Negative Bacteremia, N (%)	45 (17.8%)	58 (34.5%)	<0.001

Table 3; Plasma NGAL emerged as the strongest independent predictor, with an OR of 4.12 (95% CI 2.85-5.94, p<0.001) for every 50 ng/mL increase. Microbiological and inflammatory parameters also retained independent predictive value: a TTP of <12 hours increased the odds of SA-AKI by 3.45 times (p<0.001), and the presence of Gram-negative bacteremia increased the odds by 2.10 times (p=0.001). Serum IL-6 was a highly significant independent predictor (OR 2.85, p<0.001). The clinical severity score (SOFA) remained significant (OR 1.35, p<0.001).

Table 3: Multivariate Logistic Regression Analysis for the Prediction of SA-AKI

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P-Value
Plasma NGAL (Per 50 Ng/Ml Increase)	4.12	2.85 - 5.94	<0.001
Serum IL-6 (Per 50 Pg/Ml Increase)	2.85	1.92 - 4.23	<0.001
TTP < 12 Hours (Yes Vs. No)	3.45	2.10 - 5.68	<0.001
Gram-Negative Bacteremia (Yes Vs. No)	2.10	1.35 - 3.28	0.001
SOFA Score (Per 1 Point Increase)	1.35	1.15 - 1.58	<0.001
Serum KIM-1 (Per 20 Pg/Ml Increase)	1.45	1.05 - 2.01	0.024
Age (Per 5 Years Increase)	1.12	0.98 - 1.28	0.095
NLR (Per 2 Units Increase)	1.18	0.95 - 1.46	0.132

Table 4; Traditional serum creatinine at 6 hours demonstrated only modest diagnostic accuracy (AUC 0.68). In contrast, the novel structural biomarkers performed exceptionally well, with plasma NGAL yielding an AUC of 0.86, and serum KIM-1 an AUC of 0.81. The inflammatory marker IL-6 also showed strong predictive value (AUC 0.83). The microbiological parameter TTP < 12 hours had a lower AUC (0.74) but offered excellent specificity (90.1%) for ruling in SA-AKI risk.

Table 4: Diagnostic Performance (ROC Analysis) Of Biomarkers for Predicting SA-AKI

Biomarker / Model	Auc (95% Ci)	Optimal Cut-Off	Sensitivity (%)	Specificity (%)	P-Value
Serum Creatinine (6h)	0.68 (0.62 - 0.74)	> 1.05 Mg/Dl	58.5	72.0	<0.001
Plasma Ngal	0.86 (0.82 - 0.90)	> 145.0 Ng/Ml	78.5	81.5	<0.001
Serum Kim-1	0.81 (0.76 - 0.85)	> 85.0 Pg/Ml	72.0	76.5	<0.001
Serum Il-6	0.83 (0.79 - 0.87)	> 95.0 Pg/Ml	75.0	78.0	<0.001
Ttp < 12 Hours	0.74 (0.69 - 0.79)	Binary (<12h)	38.7	90.1	<0.001
Combined Model (Ngal + Il-6 + Ttp)	0.91 (0.88 - 0.94)	Risk Score > 0.65	82.5	85.0	<0.001

Table 5; the development of SA-AKI itself was a powerful independent predictor of mortality (HR 2.85, p<0.001). Among the early laboratory and microbiological parameters, serum IL-6 was the strongest independent predictor of death (HR 1.65 per 50 pg/mL increase, p<0.001), reflecting the lethal impact of an uncontrolled cytokine storm. A short TTP (<12 hours) was also a highly significant predictor of mortality (HR 2.20, p<0.001), indicating that a high initial microbial burden and rapid replication rate directly translate to worse survival outcomes. Plasma NGAL remained a significant predictor of mortality (HR 1.25, p=0.012), linking severe early tubular injury to fatal outcomes.

Table 5: Predictors of 28-Day Mortality (Multivariate Cox Proportional Hazards Analysis)

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-Value
Development Of SA-AKI	2.85	1.82 - 4.46	<0.001
Serum IL-6 (Per 50 Pg/Ml Increase)	1.65	1.32 - 2.06	<0.001
TTP < 12 Hours (Yes Vs. No)	2.20	1.45 - 3.34	<0.001
Plasma NGAL (Per 50 Ng/Ml Increase)	1.25	1.05 - 1.48	0.012
SOFA Score (Per 1 Point Increase)	1.18	1.08 - 1.29	<0.001
Gram-Negative Bacteremia (Yes Vs. No)	1.45	0.95 - 2.21	0.084
Age (Per 5 Years Increase)	1.15	1.02 - 1.30	0.022

DISCUSSION

NGAL is produced and released by the thick ascending limb of the loop of Henle and the distal tubule in hours after ischemic or septic insult.[14] In sepsis, the release of NGAL is not only a result of hypoperfusion, but is also directly stimulated by binding of PAMPs to TLRs on tubular epithelial cells, leading to the initiation of a local inflammatory cascade which results in cell cycle arrest.[15] In our multivariate model, NGAL was superior in predicting SA-AKI than serum creatinine (SCr), KIM-1, and clinical scores. The significance of KIM-1 was also noted but with slightly lower AUC (0.81) than NGAL differences, perhaps due to the different patterns of release or the different segments of the nephron that are most sensitive to the microvascular thrombosis associated with septic microangiopathy.[16]

The combined model of NGAL, IL-6, and TTP (AUC 0.91) highlights the need for a multi-domain approach since both direct tubular toxicity and systemic hemodynamic/inflammatory derangements

contribute to the process of SA-AKI. Systemic inflammation plays a key role in the pathogenesis of SA-AKI (IL-6, NLR). IL-6 is a principle mediator of the acute phase response and endothelial activation. The endothelial glycocalyx is shed with elevated levels of IL-6, which also results in increases in vascular permeability, leukocyte adhesion and initiates the coagulation process, a process that ultimately results in renal microvascular thrombosis and cortical necrosis.[17] We identified that IL-6 is not only a significant predictor of SA-AKI, but also the strongest independent predictor of 28-day mortality, and that therefore IL-6 is a marker of organ injury and immune dysregulation. The NLR was not significant in multivariate analysis, indicating that the immune stress is reflected in the NLR, but the absolute level of the cytokine storm (IL-6) is more directly associated with fatal outcomes.[18,19]

The inclusion of Time-to-Positivity (TTP) as a predictive biomarker is a significant finding of this study from a microbiological perspective. The number of bacteria in the blood at the start of the experiment (the inoculum size) is inversely proportional to TTP.[20] The TTP of <12 hours suggests a high bacterial burden and a highly virulent pathogen, which is very rapidly multiplying. Our data showed that a TTP <12 hours increased the odds of SA-AKI by 3.45 times and the hazard of death by 2.20 times. Moreover, gram-negative bacteremia was a strong independent risk factor for SA-AKI, which is probably due to the potent nephrotoxic effect of LPS, which is directly associated with tubular apoptosis and severe microvascular dysfunction.[21,22]

High-risk patients (such as high NGAL, high IL-6 and short TTP) could receive aggressive hemodynamic optimization treatment, nephrology consultation and avoidance of nephrotoxic medications from the onset of identification. In addition, microbiological information can help to rapidly escalate to appropriate empiric broad-spectrum antimicrobial therapy and to consider adjunctive therapy for the reduction of endotoxins or to modulate the cytokine storm.[23,24]

The strengths of this study include its prospective design, the use of highly strict Sepsis-3 and KDIGO criteria, its early time-point of sampling (within 6 hours), and the inclusion of advanced microbiological kinetic data and the structural biomarkers. Some limitations, however, should be noted. First, it is a single-center study, and its generalizability remains to be validated for community hospitals or regions with different microbial epidemiologies.

CONCLUSION

Septic-associated acute kidney injury (SA-AKI) is a serious complication in the ED that is traditionally underdiagnosed and has been identified too late for optimal management. The present study has shown conclusively that an integrated laboratory panel comprising plasma NGAL, serum IL-6 and blood culture Time-to-Positive (TTP) can give highly accurate, early prediction of SA-AKI and 28-day mortality significantly better than the traditional laboratory marker, serum creatinine. The addition of microbiological kinetic parameters (TTP) provides a complete picture of host-pathogen interaction with structural/inflammatory parameters. Early implementation of this rapid diagnostic tool in the ED can help to better stratify the risks, enabling prompt hemodynamic resuscitation, targeted antimicrobial treatment, nephroprotective measures, and thus lowering the high mortality rate from septic organ failure.

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