DEKA IN MEDICINE

Original article

Serum IL-18 as a predictive biomarker for acute kidney injury in sepsis patients

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ABSTRACT

BACKGROUND: Sepsis is a syndrome that can result in multiorgan dysfunction, including acute kidney injury (AKI). AKI is a serious complication of sepsis, and its incidence ranges from 30% to 50%. Newer predictive biomarkers such as serum interleukin-18 (IL-18) are being evaluated as early diagnostic markers with potentially greater sensitivity than serum creatinine.

OBJECTIVES: To evaluate the usefulness of serum IL-18 levels as a predictive biomarker for AKI in patients with sepsis.

METHODS: The cross-sectional study was conducted at Dr. Saiful Anwar General Hospital and included 68 sepsis patients, 34 with AKI and 34 without AKI. The serum level of IL-18 was measured using the ELISA method. AKI diagnosis was made according to the KDIGO criteria. The Mann-Whitney test, Spearman correlation, and receiver operating characteristic (ROC) curve analysis were included in the statistical analysis.

RESULTS: The results showed that serum IL-18 levels were significantly greater in the AKI group compared with the non-AKI group (49.88 ± 50.87 vs. 19.89 ± 10.40; $p < 0.001$). A significant positive correlation was observed between serum IL-18 levels and the risk of AKI ($r = 0.505$; $p < 0.001$). ROC analysis revealed an area under the curve (AUC) of 0.792 with 82.4% sensitivity and 64.7% specificity at a cut-off value of 23.81 pg/mL. Logistic regression revealed that with each 1-unit increase in serum IL-18, a 7.3% increase in the risk of developing AKI was observed.

CONCLUSION: Serum IL-18 has good potential to serve as a predictive biomarker for AKI in sepsis patients, with reasonable diagnostic accuracy.

KEYWORDS: Interleukin-18; biomarker; predictor; acute kidney injury; sepsis.

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INTRODUCTION

Sepsis is an acute condition of organ dysfunction following a dysregulated host response to infection. Sepsis is among the leading causes of morbidity and mortality in the intensive care unit (ICU) worldwide.[1] According to statistics, mortality from sepsis in the ICU is 25.8% and up to 35.5% in general. Sepsis hospital prevalence varies by region, and the highest is in Europe (54.1%), followed by Africa (47.2%), Oceania (19.3%), Asia (19.2%), and the Americas (17.1%).[2] Sepsis mild organ dysfunction can potentially rapidly evolve into MODS, which affects life-critical systems such as the brain, heart, lungs, kidneys, liver, and others.[3] Under such circumstances, a hyper-release of pro-inflammatory cytokines—e.g., interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α)—can lead to microcirculatory disturbance and, further on, renal tissue injury and trigger acute kidney injury (AKI) through complex molecular pathways.[4] AKI is one of the most frequent and critical sepsis complications with a

reported prevalence of about 30–50% in sepsis.[5] Currently, diagnosis of AKI relies on elevated serum creatinine levels and/or reduced urine output, both of which are indicators of functional and not structural injury to the kidney.[6] To raise early diagnosis of AKI in septic patients, some novel biomarkers have been investigated, including pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-18, and matrix metalloproteinase-2, which may have improved diagnostic sensitivity.[7]

Numerous studies have demonstrated that serum IL-18 levels are significantly elevated in septic patients, particularly those who develop AKI.[8,9] IL-18 is a pro-inflammatory cytokine released in response to systemic stress and inflammation, common in sepsis.[4] A study reported a strong correlation between elevated serum IL-18 levels and increased mortality among ICU patients with AKI requiring renal replacement therapy. These findings suggest that IL-18 may play a role not only in the pathogenesis of AKI but also in patient prognosis.[10] Other studies have highlighted IL-18's potential as a predictive biomarker for AKI in septic patients due to its rapid detectability, relatively high diagnostic accuracy, and lower testing cost compared to other biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and kidney injury molecule-1 (KIM-1).[11,12] IL-18 is predominantly produced by proximal tubular epithelial cells in an inactive precursor form, which is later activated by caspase-1 into a bioactive form that circulates in the bloodstream. Thus, elevated serum IL-18 levels may reflect early renal tubular damage, even before reductions in filtration function are detected via serum creatinine.[13] However, serum IL-18 levels can also be influenced by other systemic inflammatory conditions, such as non-septic infections, autoimmune diseases, trauma, or malignancies.[14] Therefore, interpretation of IL-18 levels should be contextualized within a comprehensive clinical evaluation. Although the exact mechanisms by which IL-18 contributes to AKI in sepsis remain to be fully elucidated, several pathophysiological hypotheses have been proposed. IL-18 may exacerbate inflammation by activating immune responses, increasing vascular endothelial permeability, and inducing apoptosis in tubular epithelial cells. These processes collectively contribute to renal tissue injury and support IL-18's involvement in the development of AKI in septic patients.[15] Accordingly, this study aims to evaluate the effectiveness and predictive potential of serum IL-18 levels as a biomarker for AKI in sepsis patients. Additionally, it seeks to determine the diagnostic accuracy of IL-18 in identifying patients at high risk for AKI during the early stages of illness. A better understanding of IL-18's clinical relevance may ultimately enhance diagnostic strategies and therapeutic approaches for AKI in the context of sepsis.

METHODS

Study Design

The present study was a cross-sectional study with longitudinal survey design, conducted at Saiful Anwar General Hospital in Malang, Indonesia, from May to December 2024. The primary objective of the current study was to evaluate the effectiveness of serum IL-18 levels as a biomarker for the prognosis of AKI in sepsis patients. The study followed the reporting guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for transparent and quality reporting of data.[16]

Ethical issues

The research was approved by the Health Research Ethics Committee, Saiful Anwar General Hospital (approval number: 400/242/K.3/102.7/2024). All procedures complied with the principles of the Declaration of Helsinki.[17] Prior to enrollment, the objectives of the study, the risks, and potential benefits were clearly explained to all participants.

Informed written consent was obtained from every subject, reserving the right of withdrawal from them at any moment without penalty. There were no monetary rewards given to participants.

Table 1. Baseline characteristic of patients in our study

Variable	AKI (N = 34)	Non-AKI (N = 34)	p
Age (year)	58.12 ± 15.19	51.35 ± 19.55	0.116
Male (n %)	15 (22.1%)	13 (19.1%)	0.622
Female (n%)	19 (27.9%)	21 (30.9%)	0.622
GCS	12.18 + 3.48	11.12 + 2.63	0.163
Systolic Blood Pressure	109.88 + 31.44	105.47 + 26.61	0.534
Diastolic Blood Pressure	70.68 + 15.05	68.29 + 9.22	0.434
MAP	83.83 + 19.44	80.76 + 14.26	0.462
HR	97.41 + 18.37	105.97 + 23.31	0.097
RR	23.85 + 2.54	24.41 + 3.61	0.464
UOP	1.20 ± 0.63	1.14 ± 0.52	0.451
Mortality	19 (28.8%)	19 (28.8%)	0.774
Hb (g/dL)	12.15 ± 2.05	10.89 ± 2.26	0.005
WBC	22.501 ± 13.255	18.892 ± 10.795	0.200
PLT	252.173 ± 142.736	224.535 ± 135.667	0.146
ANC	19.49 ± 12.53	14.23 ± 11.75	0.066
PF Ratio	250.61 ± 130.73	205.88 ± 94.19	0.679
Urea (mg/dL)	117.85 ± 87.84	81.91 ± 48.69	0.040
Creatinine (mg/dL)	3.08 ± 2.35	1.52 ± 0.69	0.003
Procalcitonin	11.79 ± 19.67	10.19 ± 16.03	0.764
Albumin	4.03 ± 7.2	2.22 ± 0.56	0.162
Total Bilirubin (mg/dL)	3.85 ± 9.54	4.73 ± 8.02	0.616
IL-18	49.88 + 50.87	19.89 + 10.40	0.002
Random Blood Sugar	142.34 ± 85.11	138.68 ± 75.73	0.241
Lactate (mmol/L)	2.92 ± 1.75	4.86 ± 3.94	0.024

Note, data were presented as n (%) or mean ± SD or Median (IQR); GCS, Glasgow Coma Scale; MAP, Mean Arterial Pressure; HR, Heart Rate; RR, Respiratory Rate; UOP, Urine Output Production; Hb, Hemoglobin; WBC, White Blood Cell; PLT, Platelet; ANC, Absolute Neutrophil Count; PO2, Partial Pressure of Oxygen; FiO2, Fraction of Inspired Oxygen; PF Ratio, PaO2/FiO2 ratio; IL-18, Interleukin 18.

Participants and eligibility criteria

The participants were enlisted via consecutive sampling technique, with a minimum of 60 patients. Inclusion criteria were: (1) Kidney Disease: Improving Global Outcomes (KDIGO) guideline-defined AKI—defined by an increase in serum creatinine by greater than 0.3 mg/dL within 48 hours or greater than 1.5 times baseline within 7 days, or urine output less than 0.5 mL/kg/h for 6 hours;[18] and (2) Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis—defined by suspected infection with rapid SOFA score > 2 and SOFA score > 2.[1] Patients who were eligible were both men and women 18–60 years old with suspected infection, and no previous treatment or informed consent had been given. Exclusion was for autoimmune disease, chronic kidney disease, pregnancy, previous antibiotic therapy, and hemolysis, icterus, or lipemia in serum samples.

Data collection

Data were gathered from May until December 2024 at Saiful Anwar General Hospital, Malang. Clinical and laboratory parameters such as age, sex, Glasgow Coma Scale (GCS), diastolic and systolic blood pressure, mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), urine output, mortality, hemoglobin, white blood cell count (WBC), platelet count, absolute neutrophil count (ANC), PaO_2/FiO_2 ratio (PF ratio),

urea, creatinine, procalcitonin, albumin, total bilirubin, serum IL-18 level, random blood glucose, and lactate were parameters obtained. Serum IL-18 levels were measured by employing the Enzyme-Linked Immunosorbent Assay (ELISA) method with BT Lab® Human IL-18 ELISA kits. Venipuncture was performed to obtain blood, which was stored at –80°C until analysis. Secondary data such as SOFA scores, renal function, and patient demographics were retrieved from case records. Data collection was conducted by the study team (SWP, HS, and NA), and discrepancies were resolved by group discussion.

Covariates

The predictor in this case was serum IL-18 level, and the outcome of interest was AKI incidence among sepsis patients. AKI was defined by KDIGO criteria (rise in serum creatinine >0.3 mg/dL over 48 hours, >1.5 times baseline within 7 days, or urine output <0.5 mL/kg/h for >6 hours).[18] Sepsis was diagnosed by Sepsis-3 criteria (suspected infection with qSOFA >2 and SOFA >2).[1]

Statistical analysis

Categorical variables were presented as percentages and frequency (n%), while numerical data were reported as mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Normality was assessed by the Kolmogorov-Smirnov test. Group comparisons were made using the chi-square test for categorical data, independent t-test for continuous normally distributed data, and Mann–Whitney U test for non-normally distributed continuous data. The t-test or Mann–Whitney U test was used to compare the differences in IL-18 concentrations between the non-AKI and AKI groups, as appropriate. Correlation between IL-18 concentrations and incidence of AKI was evaluated using Spearman's correlation test. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (IBM® SPSS® Statistics, NY, USA).

RESULTS

Baseline characteristics of study population

A total of 68 participants who met the inclusion and exclusion criteria were enrolled in this study, which included 34 AKI patients and 34 non-AKI patients. Table 1 presents the baseline demographics of the participants. The patient age in the AKI group was 58.12 ± 15.19 years, whereas that of the non-AKI group was 51.35 ± 19.55 years. Female participation was 27.9% in the AKI group and 30.9% in the non-AKI group. The physiological parameters of systolic BP, diastolic BP, and MAP, and other clinical indicators such as RR, HR, and GCS in the two groups were comparable with no statistically significant variation ($p > 0.05$). Meanwhile, lab values showed significant variation in serum concentrations of IL-18, which had a mean of 49.88 ± 50.87 pg/mL for the AKI group and 19.89 ± 10.40 pg/mL for the non-AKI group ($p < 0.001$). Urea, creatinine, hemoglobin, ANC, albumin, and lactate-to-albumin ratio were also important variables that were different between the groups. Procalcitonin, total leukocyte count, and total bilirubin levels had no differences among the groups.

Correlation and variation of serum IL-18 levels with AKI incidence in sepsis patients

Kolmogorov–Smirnov normality test showed that serum IL-18 levels in both groups were not normally distributed; therefore, non-parametric statistical analysis was performed. Spearman correlation analysis (Figure 1A) demonstrated a marked positive correlation between serum concentrations of IL-18 and the development of AKI in septic individuals ($r = 0.505$; $p < 0.001$), indicating increased concentrations of IL-18 to

be associated with an increased risk of developing AKI. Moreover, the Mann–Whitney U test (Figure 1B) substantiated the data that serum IL-18 concentration was considerably elevated in AKI patients compared to patients without AKI ($p < 0.001$).

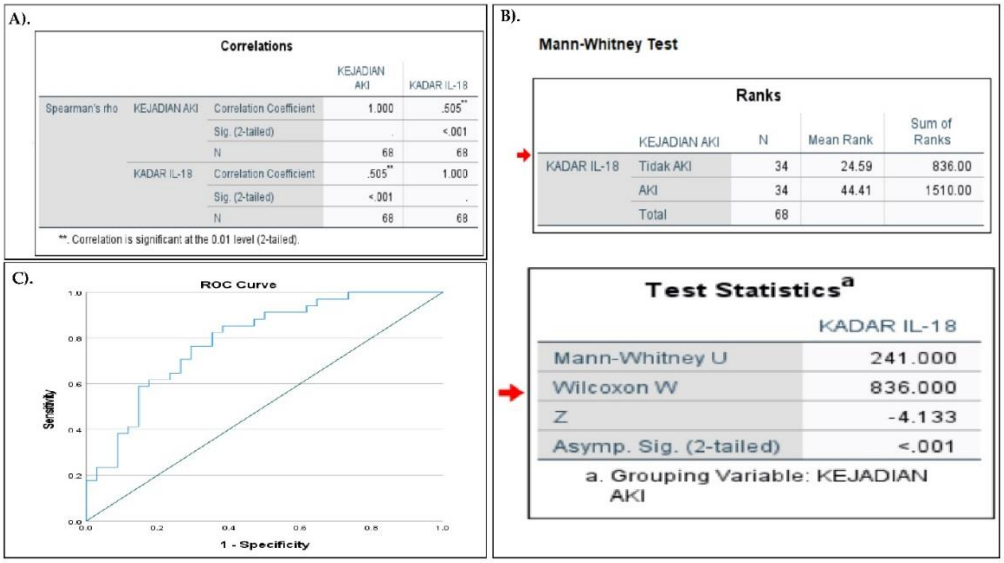

Figure 1. A). Serum IL-18 levels were significantly positively correlated with the incidence of AKI in sepsis, as demonstrated by the Spearman correlation test ($r = 0.505$; $p < 0.001$). B). The Mann–Whitney test revealed a significant difference in serum IL-18 levels between patients with AKI and those without AKI ($p < 0.001$). C). The ROC curve analysis of serum IL-18 levels for predicting AKI in sepsis patients showed an area under the curve (AUC) of 0.792 (95% CI: 0.685–0.898, $p < 0.001$), indicating good diagnostic performance.

Sensitivity and specificity of serum IL-18 for the prediction of AKI in sepsis patients

Receiver operating characteristic (ROC) curve analysis (Figure 1C) showed an area under the curve (AUC) of 0.792 (95% CI: 0.685–0.898; $p < 0.001$), which means that serum IL-18 is of good diagnostic accuracy in distinguishing AKI events among sepsis patients. Optimal cut-off value for serum IL-18 was 23.81 pg/mL with a sensitivity of 82.4% and specificity of 64.7%. Logistic regression analysis in subsequent part revealed that serum IL-18 is an independent predictor of AKI in septic patients ($p = 0.002$). Odds ratio (Exp(B)) was 1.073, indicating that every one-unit increase in serum IL-18 level was associated with 7.3% increased risk of AKI. Overall, the logistic regression model was 70.6% accurate in its prediction with a correct classification rate of 76.5% in the non-AKI group (26/34 cases) and 64.7% in the AKI group (22/34 cases).

DISCUSSION

This study shows a significant positive association between serum IL-18 levels and the incidence of AKI, with higher levels of IL-18 in AKI as compared to non-AKI individuals. These findings are similar to those in several previous studies. An animal model study demonstrated that IL-18 can induce renal ischemia-reperfusion injury that leads to acute tubular necrosis and intrarenal monocyte and neutrophil infiltration.[19] Also, in a meta-analysis, urinary IL-18 gave a pooled diagnostic odds ratio of 5.11 and an AUC of 0.77, which was better early diagnostic performance compared to serum creatinine.[20] Other research, however, found that urinary IL-18 did not show significant difference in children with or without AKI in non-critical conditions.[21] Furthermore, AUC values of 0.749 for urinary IL-18 and 0.742 for serum IL-18 were noted by one study as indicative of equivalent diagnostic precision in post-liver transplant AKI detection.[22] Our research thus conforms to and builds upon existing evidence relating to IL-18 as a biomarker for predicting AKI.

The underlying mechanisms that explain our findings are not fully elucidated. However, several biological explanations may support these results. IL-18 is produced as an inactive precursor by various organs, including macrophages, monocytes, and proximal tubular epithelial cells in the kidney. This precursor is subsequently activated into its mature 18.3 kDa form by Caspase-1.[13] IL-18 plays a critical role in the pathophysiology of AKI, particularly through mechanisms involving tubular injury and inflammation. Specifically, IL-18 can promote renal ischemia-reperfusion injury, resulting in acute tubular necrosis and immune cell infiltration.[23] The fact that IL-18 levels rise before the clinical onset of AKI supports its utility as an early detection biomarker, offering an advantage over serum creatinine, which increases later and reflects functional decline rather than direct tissue injury.[9] These pathophysiological insights may underlie the findings of our study.

This study presents several clinical implications. First, the significant elevation of serum IL-18 in sepsis patients who developed AKI, even before an increase in serum creatinine, highlights IL-18 as a potential early detection biomarker. This would allow for earlier and more targeted clinical intervention. Second, the strong positive correlation between IL-18 levels and AKI risk may help clinicians estimate the severity of sepsis and the likelihood of renal complications, aiding in more individualized and proactive management to prevent kidney failure progression. Third, since serum creatinine typically rises late, IL-18 could serve as an alternative or complementary biomarker for AKI diagnosis. A combination of IL-18 and serum creatinine might improve diagnostic sensitivity and specificity, particularly in the early phases of kidney dysfunction. Fourth, the findings may inform risk stratification in ICUs. Sepsis patients with elevated IL-18 could be classified as high-risk for AKI, thereby benefiting from closer monitoring and preventive interventions. Fifth, this study provides a strong rationale for future large-scale prospective trials and the development of biomarker-based clinical protocols. If validated, IL-18 could be incorporated into diagnostic algorithms for AKI among hospitalized sepsis patients.

Nevertheless, this study has several limitations. First, it employed a cross-sectional design, which only allows for associative rather than causal interpretation. It remains unclear whether elevated IL-18 levels cause AKI or merely reflect an inflammatory consequence of sepsis. Second, the sample size was relatively small (n = 68; 34 with and 34 without AKI), potentially limiting the statistical power and generalizability of the results. Small sample sizes also increase the risk of selection bias and variability in sensitivity/specificity estimates. Third, IL-18 levels were measured only once, without serial monitoring, thereby limiting our understanding of its dynamic changes throughout disease progression. Time-course analysis is essential to evaluate a biomarker's predictive utility accurately. Fourth, this study did not compare IL-18's diagnostic accuracy with other established AKI biomarkers such as NGAL, KIM-1, or cystatin C, which makes it difficult to assess IL-18's relative clinical value. Lastly, we did not fully evaluate potential confounding variables such as sepsis severity, hemodynamic status, baseline kidney function, or exposure to nephrotoxins, all of which could affect IL-18 levels and AKI development.

CONCLUSION

Overall, serum IL-18 level plays an important role as a predictor of AKI in septic patients. Elevated levels of IL-18 were closely correlated with the risk of AKI, as demonstrated by correlation analysis and difference in levels between AKI patients and non-AKI patients. The observed sensitivity and specificity confirm the promise of

IL-18 as a biomarker with the potential to identify sepsis patients at significant risk for the development of AKI. Furthermore, elevated levels of IL-18 were found to have odds for the development of AKI, particularly in the septic patients. Yet, further future research in bigger populations and more diverse settings is necessary to validate these findings and to assess the effectiveness of IL-18 as an AKI diagnostic biomarker in more diverse populations and diverse clinical settings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Participants had provided written informed consent prior to involve in the study. Our study had been approved by local ethical committee (No: 400/242/K.3/102.7/2024).

CONFLICTS OF INTEREST

We have no conflict of interest

FUNDING SOURCES

We have no source of funding

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AUTHOR CONTRIBUTION

Conceptualization: SWP, HS; Data Curation: SWP; Formal Analysis: SWP; Investigation: SWP; Project Administration: HS; Resources: HS, NS; Methodology: SWP, HS; Software: SWP; Visualization: SWP; Supervision: HS, NS; Validation: HS, NS; Writing – Original Draft Preparation: SWP; Writing – Review & Editing: HS, NS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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