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Neutrophil Gelatinase-Associated Lipocalin and Interleukin-18 in the Prediction of Acute Kidney Injury in Sepsis Patients

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Objective: We assessed the predictive value of blood neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) in predicting the onset of acute kidney injury (AKI) in sepsis patients in the intensive care unit (ICU).

Methods: In this retrospective analysis, we examined the medical records of sepsis patients admitted to the ICU. After ICU admission, blood samples were taken at 0 h, 6 h, 12 h, 24 h, and 48 h. Using an enzyme-linked immunosorbent assay, the concentrations of serum creatinine, NGAL, and IL-18 were determined.

Results: This study comprised a total of 197 participants, 104 of whom had AKI and 93 of whom did not. Blood concentrations of NGAL and IL-18 increased prior to serum creatinine levels. Between 6–48 hours after ICU administration, NGAL and IL-18 levels in the AKI group were considerably higher than those in the non-AKI group, and creatinine levels between the two groups were significantly different after 48 hours. Based on receiver operating characteristic (ROC) curve analysis, the area under the curve of NGAL and IL-18 for predicting AKI was 0.781 and 0.883, respectively.

Conclusion: Blood NGAL and IL-18 are potential biomarkers for the early prediction of AKI in sepsis patients in the ICU.

Keywords: acute kidney injury, intensive care unit, interleukin-18, neutrophil gelatinase-associated lipocalin sepsis

Introduction

Sepsis is a clinical syndrome characterized by life-threatening organ dysfunction induced by an inadequate response to infection. Sepsis is the leading cause of acute kidney injury (AKI), accounting for approximately 50% of AKI patients.[1] Approximately 10–50% of sepsis patients develop AKI, which is associated with a high mortality rate, a more complex hospitalization process, and an increased risk of sepsis-related infectious sequelae.[1–3]

Despite the development of clinical treatment methods for AKI in patients with sepsis, the mortality rate for this population remains high. Lack of reliable and specific biomarkers for early detection of AKI in sepsis patients is a key issue that delays optimal therapy and causes irreversible disease progression.[4] Currently, the clinical diagnosis of AKI in sepsis patients is usually based on serum creatinine levels and urine volume. Unfortunately, as a biomarker of AKI, serum creatinine does not increase until 48 hours after kidney injury.[5] As one of the clinical manifestations of AKI, the onset of oliguria is even more delayed than the increase in creatinine levels. Therefore, it is of the utmost importance to identify biomarkers for early detection of AKI in order to facilitate early intervention, evaluate intervention efficacy, and guide the treatment of AKI.[6]

Neutrophil gelatinase-associated lipocalin (NGAL), a protein expressed by neutrophils and certain epithelial cells, including renal tubules, is highly expressed in the kidney and secreted into the urine and plasma during ischemic or nephrotoxic kidney injury.[7,8] After injury, NGAL levels increase rapidly, making it a potential early and sensitive

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biomarker of kidney injury.[8] Interleukin-18 (IL-18) is mainly produced by antigen-presenting cells, macrophages, dendritic cells, $CD4^+$ T cells, and other T cells.[9] IL-18 plays an important role in lipopolysaccharide-induced AKI and is an important mediator of sepsis-induced organ failure.[10] Prior research has demonstrated that NGAL and IL-18 are significantly increased in critically ill patients after AKI.[11–14] NGAL and IL-18 have also been demonstrated to be early predictive biomarkers of AKI in children undergoing cardiac surgery.[15] However, the predictive value of NGAL and IL-18 for AKI in sepsis patients is limited. In this retrospective study, we explored the predictive value of NGAL and IL-18 levels in blood for AKI in sepsis-affected ICU patients.

Methods

Patients

We collected and reviewed the medical records of sepsis patients admitted to the intensive care unit (ICU) of Hengshui People's Hospital and diagnosed with sepsis between December 2017 and December 2019. According to the Third International Consensus Definitions for Sepsis and Septic Shock, the sepsis diagnosis criteria consisted of a change of at least 2 points in the sequential organ failure assessment (SOFA) score after infection.[16,17] This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hengshui People's Hospital. As this is a retrospective study, the clinical data of the patients involved are all based on the patient's past medical history and actual diagnosis and treatment data during hospitalisation. This study does not interfere with routine diagnosis and treatment, does not affect patients' medical rights, and does not increase additional risks to patients. Therefore, after discussion with the Ethics Committee of Hengshui People's Hospital, it was decided to waive the requirement for informed consent from patients. In addition, patients' clinical data will be used for scientific research and confidentiality will be ensured. The patient's consent was informed and obtained during hospitalisation.

Exclusion criteria included being younger than 18 years old; pregnant and lactating; an expected ICU hospitalization duration of less than 48 hours; suspected or confirmed chronic renal insufficiency (creatinine > 1.4 mg/dL, estimate glomerular filtration rate < 60 mL/min/1.73 m^2); intra-abdominal hypertension (IAH); a history of blood purification performed 24 hours prior to sample collection; and the absence of necessary medical records for this study.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) recommendations were used to diagnose AKI.[18] AKI may be diagnosed in patients with a serum creatinine increase of ≥ 26.5 μmol/L within 48 hours, 1.5 times the baseline serum creatinine value within one week, or a urine volume of < 0.5 mL/kg·h.

Procedure

Based on whether AKI occurred within 48 hours of ICU admission, patients were divided into AKI and non-AKI groups. Following ICU admission, blood samples were collected at 0 h, 6 h, 12 h, 24 h, and 48 h, respectively, to measure serum creatinine, NGAL, and IL-18 concentrations. Blood samples were collected and measured strictly according to the time point of each patient after admission. Blood collection was carried out by nurses with rich clinical experience, properly stored after blood collection, and timely sent to the laboratory for examination, which can minimize the bias in the process of blood sample taking and examination. All plasma NGAL measurements were performed independently by a single laboratory with no knowledge of clinical data. Using an enzyme-linked immunosorbent assay (ELISA), NGAL and IL-18 concentrations were measured. The concentration of serum creatinine (Scr) was measured using the picric acid method.

All patients were monitored with an electrocardiogram (ECG). The following parameters were measured: body temperature (T), heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), pulse oximeter oxygen saturation (SpO_2), and central venous pressure (CVP).

Statistical Analysis

SPSS v22.0 software (IBM Corp., Armonk, NY, US) was used for conducting statistical analysis. Normally distributed measurement data are presented as mean ± standard deviation. Independent samples were analyzed using the *t*-test, and multiple samples were analyzed using the chi-squared test. Non-normal parameters are represented by the median

(interquartile range), and the group difference was analyzed using the rank sum test. Using the chi-squared test and Fisher's exact probability method, the differences between categorical variables were analyzed.

Using MedCalc v15.2.2, receiver operating characteristic (ROC) curves were assessed to evaluate the predictive value of NGAL and IL-18 (MedCalc software, Mariakerke, Belgium). The evaluation results are presented as the area under the curve (AUC) and its 95% confidence interval (CI), and the cutoff value, sensitivity, and specificity were calculated, and the AUC values compared. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

In this study, we enrolled 197 eligible patients, including 104 patients with AKI (52.8%, AKI group) and 93 patients without AKI (47.2%, non-AKI group). Baseline characteristics are presented in Table 1. All the parameters at baseline were well balanced between both groups except for the central venous pressure (13±3 mmHg vs 10±2 mmHg, $P = 0.037$).

Comparison of Concentrations of Serum Creatinine, NGAL, and IL-18 Between the AKI Group and Non-AKI Group

Within 24 h of ICU admission, there were no significant differences in serum creatinine concentration levels between the AKI and non-AKI groups, however; the serum creatinine concentration levels in the AKI group was significantly higher than that in the non-AKI group (121.96±56.74 vs 65.69±19.73 μmol/L, $P = 0.001$; Table 2).

NGAL and IL-18 blood concentrations increased before serum creatinine levels (Table 2). Six hours after ICU admission, the blood NGAL level began to increase. At all the time points measured after ICU admission, the level of NGAL was higher in the AKI group than that in the non-AKI group (6 h, $P = 0.003$; 12 h, $P = 0.016$; 24 h, $P < 0.001$; 48 h, $P < 0.001$).

Blood IL-18 also started to increase at 6 h after the patients were admitted to the ICU (Table 2). At 6 h ($P = 0.046$), 12 h ($P = 0.039$), 24 h ($P = 0.014$), and 48 h ($P = 0.027$), the level of IL-18 in the AKI group was significantly higher than that in the non-AKI group. Blood IL-18 in the AKI group steadily increased over time, reaching a peak concentration at 24 h (6.78 ± 2.46 ng/mL) and then exhibited a decreasing trend.

Table 1 Baseline Characteristics

	AKI Group (n=104)	Non-AKI group (n=93)	P value
Male (%)	69 (66.3%)	58 (62.4%)	0.392
Age (y)	68.1±13.2	63.5±11.3	0.168
Weight (kg)	70.9±14.9	69.8±13.5	0.672
Body temperature (°C)	37.3±0.9	37.1±0.8	0.642
Heart rate (bpm)	105±23	111±28	0.328
Respiratory rate (times/minute)	22 (14, 26)	20 (16, 28)	0.121
Mean arterial pressure (mmHg)	80±18	85±12	0.062
SpO_2 (%)	97±3	96±4	0.098
Central venous pressure (mmHg)	13±3	10±2	0.037
Basal creatinine (μmol/L)	89.7±24.9	83.6±23.5	0.382
APACHE II	24±9	21±7	0.317
SOFA	12±3	11±3	0.436
Hypertension	61 (58.7%)	53 (56.9%)	0.813
Diabetes	31 (29.8%)	28 (30.1%)	0.963
Albuminuria	8 (7.7%)	6 (6.5%)	0.735
Need for vasopressor	56 (53.8%)	42 (45.2%)	0.224
Lactate level	1.4±0.5	1.1±0.3	0.462
Baseline eGFR	63.6±12.8	58.4±10.3	0.274
Use of renin- angiotensin- aldosterone system blockers	52 (50%)	46 (49.5%)	0.940

Notes: Data are n (%), mean±SD, or median (range).

Abbreviations: AKI, estimate glomerular filtration rate; SpO_2, pulse oximeter oxygen saturation; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; eGFR, estimate glomerular filtration rate.

Table 2 Comparison of Concentrations of Serum Creatinine, NGAL, and IL-18 Between AKI Group and Non-AKI Group After ICU Entry

	AKI group (n=104)	Non-AKI group (n=93)	P value
Serum creatinine (μmol/L)			
0 h	67.58±14.84	68.17±17.27	0.829
6 h	85.28±16.15	73.64±18.82	0.523
12 h	95.89±33.64	87.93±21.52	0.782
24 h	92.14±28.69	79.37±20.44	0.642
48 h	121.96±56.74	65.69±19.73	0.001
NGAL (ng/mL)			
0 h	73.36±12.67	66.46±8.69	0.168
6 h	196.83±23.49	102.47±13.86	0.003
12 h	104.37±26.85	62.28±17.95	0.016
24 h	318.38±29.71	48.46±10.63	<0.001
48 h	326.34±32.53	23.06±9.13	<0.001
IL-18 (ng/mL)			
0 h	0.83±0.41	0.73±0.31	0.692
6 h	3.69±1.28	2.48±0.98	0.046
12 h	5.26±1.96	3.63±1.28	0.039
24 h	6.78±2.46	2.69±1.18	0.014
48 h	3.42±1.03	1.03±0.36	0.027

Note: Data are mean±SD.
Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin-18.

Value of NGAL, IL-18 and Their Combined Indicator for AKI Prediction

We employed ROC curves based on blood NGAL and IL-18 at 6 h after ICU admission in both groups to predict the probability of AKI in sepsis, as we discovered that both NGAL and IL-18 began to rise in the AKI group 6 h after ICU admission.

Results showed that the AUC of NGAL was 0.781 (95% CI, 0.717–0.837). The sensitivity, specificity, and cut-off value of NGAL for predicting AKI in sepsis were 75.96%, 81.72%, and 190.25 ng/mL, respectively (Figure 1A). The AUC of IL-18 levels in blood was 0.883 (95% CI, 0.829–0.924), with a sensitivity, specificity, and a cut-off value of 85.58%, 69.89% and 2.9 ng/mL, respectively (Figure 1B). The AUC of IL-18 and NGAL combined indicator was 0.939

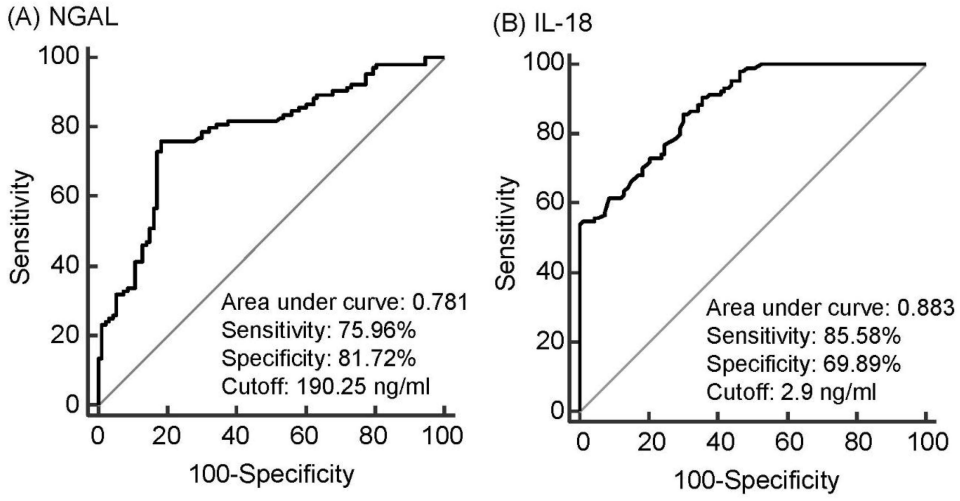

Figure 1 Receiver operating characteristic curve (ROC) of blood NGAL (**A**) and IL-18 (**B**) in predicting AKI in sepsis.
Abbreviations: NGAL, Neutrophil gelatinase-associated lipocalin; IL-18, Interleukin-18.

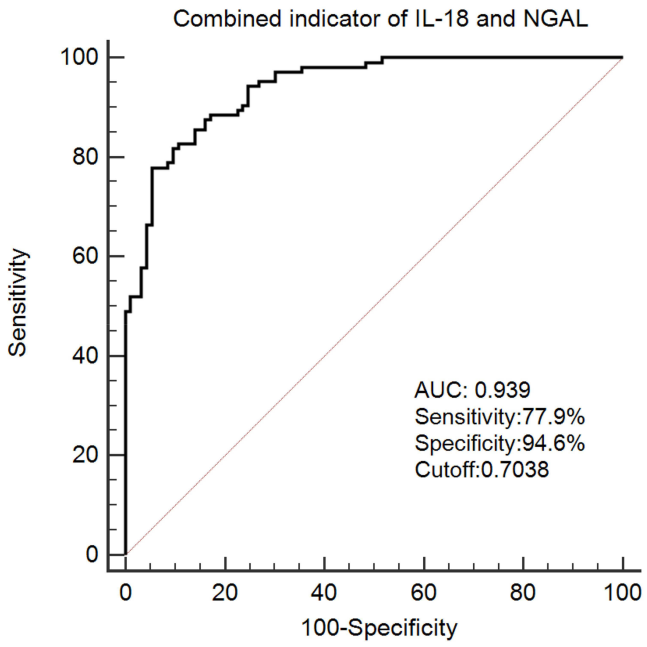

Figure 2 ROC of the combined indicator of IL-18 and NGAL in predicting AKI in sepsis.
Abbreviations: ROC, receiver operating characteristic; IL-18, Interleukin-18; NGAL, Neutrophil gelatinase-associated lipocalin; AKI, Acute kidney injury.

(95% CI, 0.896–0.968), with a sensitivity, specificity, and a cut-off value of 77.90%, 94.60% and 0.7038, respectively (Figure 2). The results demonstrated that NGAL, IL-18 and their combined indicator performed well for the diagnosis of AKI in sepsis patients 6 h after ICU admission.

Discussion

The results of this retrospective study revealed that the levels of NGAL and IL-18 in the AKI group were higher than those in the non-AKI group from 6 to 48 hours (or even more) after ICU admission. Blood NGAL and IL-18 concentrations increased before serum creatinine levels. The ROC analysis revealed that NGAL and IL-18 were potential biomarkers for the early prediction of AKI in sepsis patients 6 h after ICU admission.

Six hours after admission to the ICU, NGAL was significantly higher in the AKI group than in the non-AKI group; however, at that time, there was no significant difference in the serum creatinine level between the two groups. After 48 hours in the ICU, the serum creatinine level in the AKI group began to exceed that of the non-AKI group. This result demonstrated that NGAL can predict AKI in sepsis patients at least 42 hours before serum creatinine. This observation can be interpreted as follows: kidney, liver, stomach, and colon expressed modest quantities under normal physiological conditions. The expression of NGAL was induced if inflammation or epithelial cell damage occurred. A large number of inflammatory factors stimulate neutrophils to release NGAL during sepsis, resulting in an increase in NGAL concentration. The expression of NGAL continues to increase in AKI patients. However, the traditional indicator serum creatinine was frequently affected by age or clinical treatment, and its changes were often lagging. NGAL rapidly increases after the occurrence of AKI, particularly within 2 hours of renal injury, where significant changes in its levels may be observed. In contrast, traditional indicators such as serum creatinine often show significant elevations only after 24 to 72 hours. Therefore, NGAL can serve as an early warning indicator for AKI. The results of this study indicate that NGAL has high sensitivity and specificity in diagnosing AKI. This means that NGAL can more accurately identify patients with AKI, reducing the possibility of misdiagnosis and missed diagnosis.

In sepsis, IL-18 is closely related to the occurrence and development of AKI.[14] As a cytokine with multidirectional biological activity and function, IL-18 induces T cells and NK cells to produce interferon (INF)- γ, and plays a crucial role in anti-tumor immunity, antigenic microbial infection, and some autoimmune diseases.[19] IL-18, a powerful proinflammatory cytokine, is released into the blood when AKI occurs.[20] According to studies, the level of IL-18 in AKI

patients increased 24–48 hours earlier than serum creatinine after acute and critical illness, kidney transplantation, and heart surgery.[21–23] The results in our study, were consistent with previous findings. Between 6–48 hours after ICU admission, IL-18 in the AKI group was higher than that in the non-AKI group, and the difference was statistically significant, which supported the early predictive value of IL-18 for AKI in sepsis patients. IL-18 can not only be used for the diagnosis of AKI, but also for differentiating other types of renal impairment, such as chronic renal failure and malignant tumors. This aids doctors in more accurately determining the patient's etiology and condition, thereby formulating a more suitable treatment plan. Additionally, the level of IL-18 can predict the patient's short-term mortality. This is of great significance for assessing patient prognosis and formulating treatment strategies.

There are still some limitations to this study. Firstly, the most significant aspect is the retrospective nature of the study design. Secondly, we enrolled a relatively small number of patients from a single center, which may have introduced bias. Therefore, validation of these biomarkers in a large-scale, randomized, controlled, multicenter study is required.

Conclusions

In summary, NGAL and IL-18 hold significant importance as biomarkers for AKI. Compared to the existing gold standards, they offer advantages such as earlier prediction times, higher sensitivity and specificity, and a broader range of applications. These advantages render NGAL and IL-18 clinically invaluable in the diagnosis and treatment of AKI.

Abbreviations

AKI, acute kidney injury; NGAL, Neutrophil gelatinase-associated lipocalin; IL-18, Interleukin-18; SOFA, sequential organ failure assessment; IAH, intra-abdominal hypertension; KDIGO, the Kidney Disease: Improving Global Outcomes; ELISA, enzyme-linked immunosorbent assay; Scr, Serum creatinine; ECG, electrocardiogram; T, temperature; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; SpO2, pulse oximeter oxygen saturation; CVP, central venous pressure; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; ICU, intensive care unit; INF, interferon.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hengshui People's Hospital. As this is a retrospective study, the clinical data of the patients involved are all based on the patient's past medical history and actual diagnosis and treatment data during hospitalisation. This study does not interfere with routine diagnosis and treatment, does not affect patients' medical rights, and does not increase additional risks to patients. Therefore, after discussion with the Ethics Committee of Hengshui People's Hospital, it was decided to waive the requirement for informed consent from patients. In addition, patients' clinical data will be used for scientific research and confidentiality will be ensured. The patient's consent was informed and obtained during hospitalisation.

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Disclosure

The authors have no conflicts of interests to disclose.

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