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The impact of instant neutrophil gelatinase-associated lipocalin level on the severity of septic acute kidney injury

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Abstract. – OBJECTIVE: The clinical value of increased levels of neutrophil gelatinase-associated lipocalin (NGAL) in patients with septic acute kidney injury (AKI) is still unclear. This study aimed to assess the link between illness severity and NGAL in patients with septic AKI.

PATIENTS AND METHODS: This is a retrospective observational study that took place at the Fourth Hospital of Hebei Medical University, Shijiazhuang, China. The cohort included 365 patients who were admitted to the ICU during the 21-month period. Of them, 18 patients were diagnosed with sepsis (septic group). The average age of patients in the septic group was over 65, and 60.00% of them eventually progressed to septic AKI. Plasma NGAL (pNGAL) and urine NGAL (uNGAL) levels at defined time points were measured. AKI staging was done based on the Kidney Disease Improving Global Outcomes (KDIGO) classification. The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were determined. Patterns and associations between NGAL levels with SOFA scores and different stages of septic AKI were investigated.

RESULTS: Both pNGAL and uNGAL showed a positive correlation with SOFA and proved to be reliable predictors of the same. Furthermore, the accuracy of severe sepsis (SOFA ≥ 8) was 0.67 for pNGAL and 0.66 for uNGAL. Real-time detection of pNGAL and uNGAL indicated that they were good biomarkers of severe septic AKI. Area under the receiver operating characteristic (AUROC) for pNGAL and uNGAL were 0.72 (0.69-0.85), and 0.83 (0.71-0.95), respectively. However, only patients with KDIGO 3 AKI presented significantly elevated levels of pNGAL ($p < 0.05$). Furthermore, the uNGAL level at each stage of septic AKI was higher than that of the non-AKI period ($p < 0.01$).

CONCLUSIONS: In patients with septic AKI, levels of NGAL correlated with SOFA. Levels of pNGAL were good predictors of severe kidney injury and uNGAL levels could detect mild stages of AKI.

Key Words:
Acute kidney injury, Neutrophil gelatinase-associated lipocalin, SOFA score, Sepsis, Critically ill patients.

Abbreviations

AKI: NGAL, neutrophil gelatinase-associated lipocalin; septic AKI, acute kidney injury caused by sepsis; pNGAL, plasma NGAL; uNGAL, urine NGAL; AUROC, area under the receiver operator characteristic; AKI, acute kidney injury; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; APACHE II, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; RRT, renal replacement therapy.

Introduction

Despite current progress in the pathophysiology, definition, and management of sepsis, the short-term mortality rate of septic patients remains high, especially in developing countries[1], which further emphasizes the importance of timely decisions on the best treatment for this group of patients[2].

Sepsis often affects critically sick patients[3] and is associated with significantly worse prognosis compared to the general ICU population[4]. Therefore, it is crucial to rapidly stratify the risk of sepsis progression, which changes with time, especially during the early phase after admission. Sequential Organ Failure Assessment (SOFA) and APACHE II scores had the best accuracy in predicting multiple organ dysfunction/failure, duration of using a ventilator, and hospital mortality in adult septic patients[5,6]. Previous studies[6] showed that SOFA score is a reliable indicator of bad prognosis of patients with sepsis. Therefore, identifying effective biomarkers to evaluate SO-

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FA and APACHE II scores of early-stage septic patients after admission may further improve their prognosis.

In the past decade, studies[7,8] showed that neutrophil gelatinase-associated lipocalin (NGAL) is a promising indicator of sepsis and septic AKI[7] and may predict poor prognoses in patients with suspected sepsis[8]. However, NGAL levels in most studies[9,10] were measured only on admission or two days or more after the admission, which did not allow for monitoring the changes in NGAL levels with the progression of sepsis. We hypothesized that dynamic changes of NGAL in the beginning of sepsis be used to inform timely risk stratification adjustment and improve clinical therapy of septic patients. Therefore, this study aims to monitor and assess p- and u- NGAL levels in patients with severe sepsis within 72 hours of arrival in order to ascertain how they may be related to the SOFA score and various stages of AKI.

Patients and Methods

Study Population

This retrospective study was conducted in a high-volume hospital in Shijiazhuang, China. The study was conducted between March 2020 and December 2021, and the medical records of every patient admitted to the ICU were evaluated. Exclusion criteria were as follows: 1) age < 18, 2) inflammatory bowel disease, 3) required dialysis therapy, 3) history of renal diseases, 4) history of malignancy, 5) specimens were not obtained as scheduled, or the patient died within 72 hours after the admission.

Patients were grouped based on the Sepsis-3 criteria[11] that included (1) systolic blood pressure (SBP) ≤ 100 mmHg), (2) high respiratory rate (≥ 22 breaths per min), or (3) altered mental state (Glasgow coma scale < 15). The stage of AKI [no AKI (non-AKI), stage 1, stage 2, and stage 3] was assessed based on the KDIGO criteria, as described below[12].

Demographic data of all patients, comorbidities, and origin of infection were recorded at inclusion. Vital signs, blood parameters, urine output, and use of vasopressors or furosemide were obtained in real-time, and serial research blood and urine sampling collection were obtained over the first 72 hours as scheduled after the admission. SOFA score and APACHE II score (assesses disease severity based on current physiologic measurements, age, and previous health conditions) were calculated sequentially in accordance with the worst-case data. When available, basal serum creatinine levels were obtained from the measurements done one year preceding the onset of sepsis. In case of absent basal serum creatinine data, values were estimated according to the KDIGO guidelines[13]. Baseline urine output (0 hours after inclusion) was the amount of urine excreted by the hour during the first 6 hours after the admission.

Blood and Urine Sampling and Assays

Blood and urine samples were collected within the first 72 hours after the admission, centrifuged at 1,500 × g or 1,000 × g for 10 min, and stored at -80°C. NGAL was determined using an Enzyme-Linked Immunosorbent Assay (ELISA), and the dilution ratio was 1:100.

Defined Stage of AKI

Stage of AKI was categorized according to KDIGO guidelines at 0, 12, 24, 48, and 72 h after the admission. Patients were classified as non-AKI (without AKI), stage 1, stage 2, and stage 3 after inclusion according to the KDIGO classification.

Statistical Analysis

Results were presented as the median with a 95% confidence interval (CI), while categorical variables were presented as n (%). ANOVA or the Chi-square test was used, if necessary, to compare groups. Logistic regression models and the AUROC were used to assess the connections between the biomarker value at presentation and the clinical ratings of patients with septic shock. SPSS 16 (SPSS Inc., Chicago, IL, USA) was used for all analyses, and significance was determined by $p < 0.05$.

Results

Study Population

During the 21-month observation period, a total of 365 patients were admitted to the ICU. In accordance with the predetermined criteria, 18 of these patients were included in the septic group (Figure 1). Most patients were females (55.6%), and 61.1% of patients were older than 65. The etiology of sepsis was identified as intra-abdominal, ling, soft tissue, urinary tract, and coinfections in 13 (72.2%), 7 (38.89%), 1 (5.56%), 4 (22.22%), and 4 (22.22%) patients, respectively.

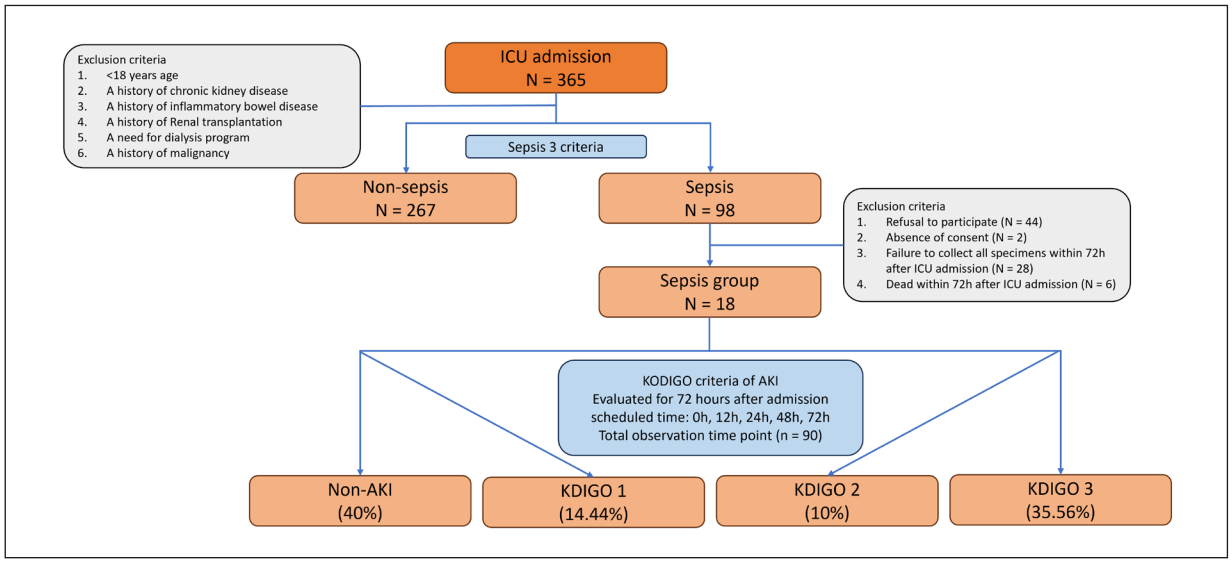

Figure 1. Flow chart of the enrolled patients.

The stages of AKI, SOFA, and APACHE scores were assessed at five-time points within the first 72 hours post-admission. Of total time points (5 per patient, total n = 90), 40.00% were Non-AKI (n = 36), and 60.00% were AKI (n = 54). Of them, according to the KDIGO criteria, 14.44% were stage 1 (KDIGO 1), 10.00% were stage 2 (KDIGO 2), and 35.56% were stage 3 (KDIGO 3). Moreover, vasopressors were required for 14.44% of the tracking time, and mechanical ventilation was required for 43.33% of the tracked time. Most APACHE score measurements were higher than 10 (97.78%), and most SOFA scores were higher than 7 (77.78%). As shown in Table I, APACHE and SOFA scores, as well as pNGAL and uNGAL showed significant differences between the four stages of septic AKI (APACHE $p = 0.02$, SOFA, pNGAL and uNGAL, all $p = 0.001$).

Table I. Demographic characteristics within 72 hours after ICU admission.

Parameter	Non-AKI	KDIGO 1	KDIGO 2	KDIGO 3	*p*-value
N	36	13	9	32	-
MAP (mmHg)	77 (58-102)	79 (69-91)	90 (86-95)	77 (57-114)	0.568
heart rate (bpm)	108 (51-160)	118 (82-146)	135 (117-160)	122 (98-151)	0.18
Lactate (mmol/l)	2.17 (0.90-4.60)	3.34 (2.20-5.50)	3.56 (1.60-6.70)	2.25 (0.90-8.50)	0.06
Mechanical ventilation [n(%)]	14 (40)	9 (53)	9 (60)	17 (55)	0.27
Bilirubin (mg/dL)	58.36 (11.21-160.17)	56.62 (16.33-119.98)	62.46 (21.09-173.23)	75.99 (17.14-186.15)	0.86
albumin (g/dL)	26.91 (1.3-33.2)	25.4 (20.3-33.2)	27.06 (24.2-34.0)	25.73 (20.7-30.4)	0.71
urine output (ml/kg/h)	88.42 (38.33-179.16)	76.17 (26.00-120.00)	70.13 (18.43-56.25)	60.44 (6.00-91.66)	0.04
creatinine (umol/l)	45.88 (18.80-89.00)	99.06 (85.40-122.50)	132.64 (68.20-185.00)	281.71 (209.30-407.60)	0.001
CRP (mg/L)	117.28 (48.0-158.8)	181.43 (174.4-188.4)	167.2 (133.4-186.1)	164.97 (141.2-177.1)	0.018
Platelet count (10^3/uL)	60.27 (14.0-123.0)	63.4 (40.0-92.0)	148.2 (65.0-311.0)	170.67 (55.0-381.0)	0.001
APACHE	17.1 (7.0-25.0)	17.86 (11.0-21.0)	17.4 (12.0-20.0)	22.56 (12.0-32.0)	0.02
SOFA	7.89 (4.0-14.0)	13 (11.0-15.0)	14.2 (7.0-19.0)	13.61 (4.0-24.0)	0.001
pNGAL	165.28 (72.16-263.68)	193.68 (84.74-278.12)	202.2 (130.64-339.52)	323.75 (192.60-533.35)	0.001
uNGAL	4.02 (0.07-8.22)	6.7 (4.01-9.06)	8.72 (6.82-10.03)	8.32 (5.21-10.52)	0.001

MAP = mean arterial pressure; CRP = C-reactive protein; APACHE = acute physiology and chronic health evaluation II; SOFA = sequential organ failure assessment; pNGAL = plasma neutrophil gelatinase-associated lipocalin; uNGAL = urine neutrophil gelatinase-associated lipocalin; Non-AKI = non acute kidney injury; KDIGO 1 = Kidney Disease Improving Global Outcomes stage 1; KDIGO 2 = Kidney Disease Improving Global Outcomes stage 2; KDIGO 3 = Kidney Disease Improving Global Outcomes stage 3.

Levels of pNGAL and uNGAL at Different Stages of Septic AKI

Levels of pNGAL and uNGAL were measured in septic patients at scheduled time points and represented as bar graphs in Figures 2A and 2B. The point-of-care testing of pNGAL and uNGAL stratified septic AKI within 72 hours after admission [pNGAL AUROC 0.82 (95% CI 0.69-0.95, $p < 0.001$), uNGAL area under the receiver operating characteristic curve (AUC-ROC) 0.83 (95% CI 0.71-0.95, $p < 0.001$)]. The cut-off levels for p- and u- NGAL were 232.76 and 5.12 ng/ml, respectively. To study the different prediction values of pNGAL and uNGAL, we evaluated them at different stages of septic AKI. We found that pNGAL concentrations were only significantly elevated during KDIGO 3 ($p < 0.001$) but not during KDIGO 2-3 relative to Non-AKI ($p > 0.05$). This suggested that pNGAL was an accurate predictor of serious septic AKI with the optimal cut-off level [AUC-ROC 0.91 (95% CI 0.83-0.99)]. Levels of uNGAL at each stage of septic AKI (KDIGO 1-3) were significantly higher than in Non-AKI patients (KDIGO 1 and KDIGO 2-3 both $p < 0.01$). However, no difference was found between uNGAL levels at KDIGO 3 and at milder stages of septic AKI ($p > 0.05$). The predictor value of NGAL (pNGAL and uNGAL) is shown in Figure 3A, 3B, and Table II.

Evaluating the Relationship Between NGAL and Clinical Condition of Septic Patients

For the in-time evaluation of a septic patient's condition, we obtained dynamic scores for APACHE and SOFA within 72 hours after admission and determined the changes over scheduled time points in patients with or without AKI (Figure 4). SOFA scores were higher in AKI patients compared to patients without AKI, since kidney injury is a major part of multiple organ function damage and results in the deterioration of septic patient condition scores. Furthermore, APACHE scores were higher in KDIGO 3 compared to Non-AKI and mild stages of AKI (KDIGO 1-2) (Non-AKI $p < 0.01$, KDIGO 1-2 $p < 0.05$). We found that pNGAL and uNGAL had different predictive values. While pNGAL showed a significant correlation with both APACHE and SOFA scores, uNGAL only positively correlated with the SOFA score ($r = 0.46$, $p < 0.001$) (Figure 5). Additionally, both pNGAL and uNGAL had a moderate level of diagnostic accuracy when categorizing patients with sepsis and multiple organ failure (SOFA ≥ 8). The AUC-ROC values for pNGAL and uNGAL were 0.67 and 0.66, respectively, and the cut-off values were 263.92 ng/ml and 7.39 ng/ml, respectively (Figure 6 and Table III).

Discussion

Our results showed that plasma and urine levels of NGAL correlated with SOFA and APACHE II scores of patients with septic AKI. Levels of pNGAL had a good predictive value for severe kidney injury, while uNGAL levels could detect mild stages of AKI.

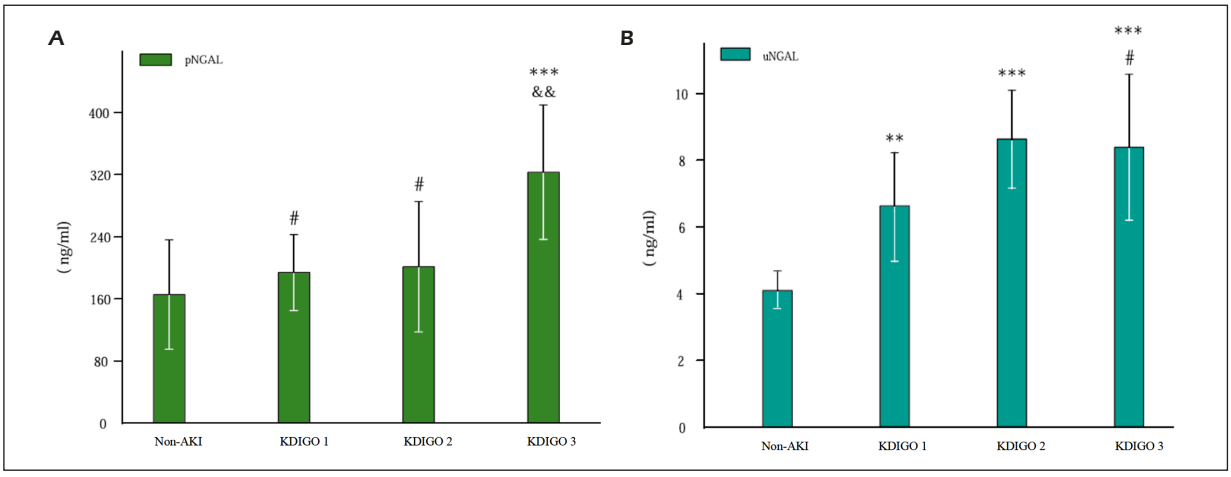

Figure 2. A, pNGAL in different stage of septic AKI. **B**, uNGAL in different stage of septic AKI. pNGAL: plasma neutrophil gelatinase-associated lipocalin; uNGAL: urine neutrophil gelatinase-associated lipocalin; AKI: acute kidney injury. ***$p < 0.001$, relative to Non-AKI, **$p < 0.01$, relative to Non-AKI. $^{\&\&}p < 0.01$.

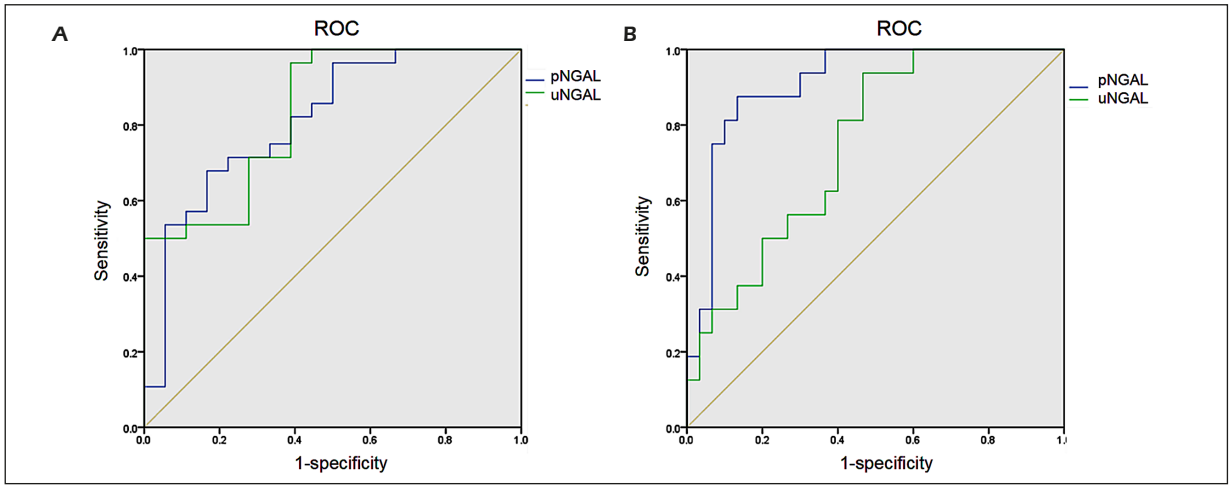

Figure 3. **A**, ROC curves of pNGAL and uNGAL in predicting septic AKI. **B**, ROC curves of pNGAL and uNGAL in predicting severe septic AKI. ROC: receiver operating characteristic; pNGAL: plasma neutrophil gelatinase-associated lipocalin; uNGAL: urine neutrophil gelatinase-associated lipocalin; AKI: acute kidney injury.

Table II. Diagnostic characteristics of pNGAL and uNGAL to predict septic AKI within 72 hours after admission.

Variables	Cutoff value	AUC-ROC
Compared to all non-AKI time		
pNGAL	> 232.76 ng/ml	0.82 (0.69-0.95)
uNGAL	> 5.12 ng/ml	0.83 (0.71-0.95)
Compared to all non-AKI and mild AKI time		
pNGAL	> 264.57 ng/ml	0.91 (0.83-0.99)
uNGAL	> 6.89 ng/ml	0.75 (0.61-0.89)

pNGAL = plasma neutrophil gelatinase-associated lipocalin; uNGAL = urine neutrophil gelatinase-associated lipocalin; AUC-ROC = area under the curve of the receiver operating characteristic; AKI = acute kidney injury.

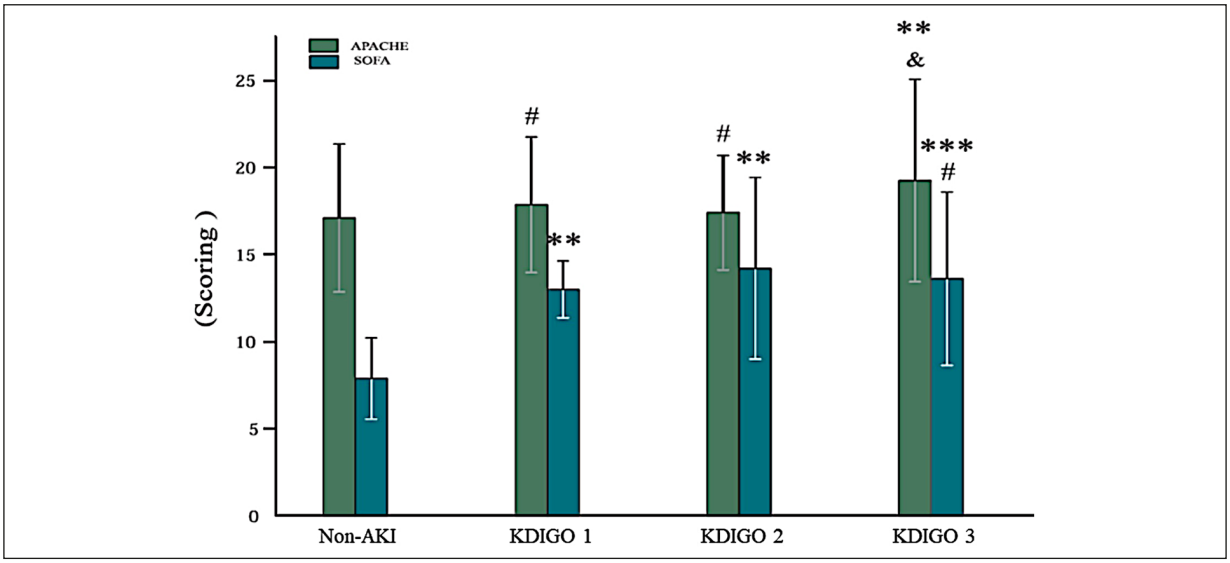

Figure 4. SOFA and APACHE scores in different stages of septic AKI. ***$p < 0.001$, relative to Non-AKI, **$p < 0.01$, relative to Non-AKI. $^{\&}p < 0.05$, relative to KDIGO1-2 times. $^{\#}p > 0.05$, relative to Non-AKI in APACHE scores, or relative to KDIGO1-2 times in SOFA scores. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; AKI: acute kidney injury; KDIGO 2: Kidney Disease Improving Global Outcomes stage 2.

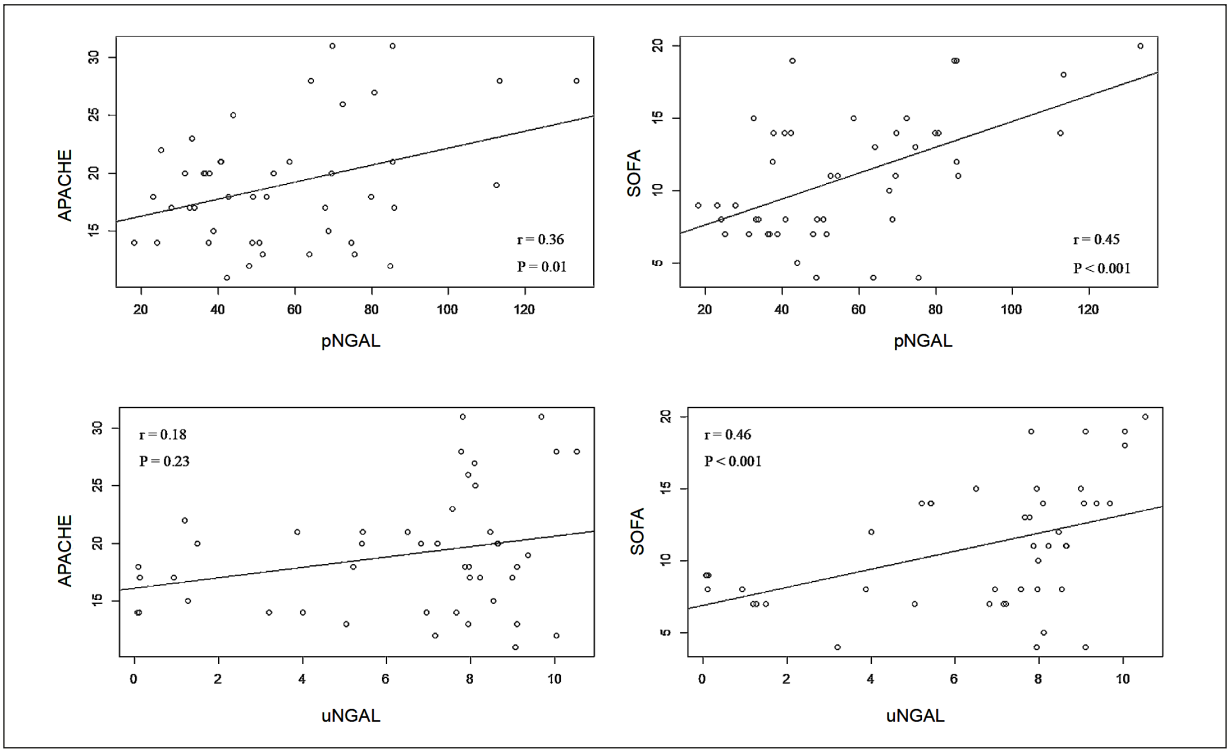

Figure 5. The relationships between NGAL with SOFA or APACHE. NGAL: neutrophil gelatinase-associated lipocalin; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

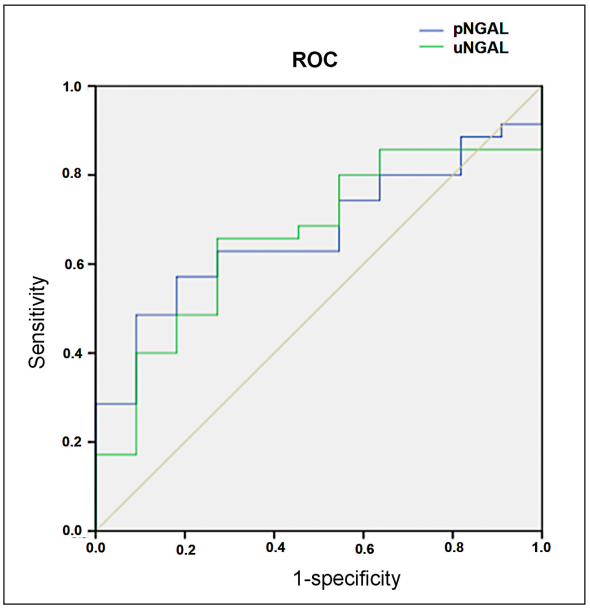

Figure 6. The predictive value of instant levels of pNGAL and uNGAL with SOFA of severe septic patients. pNGAL: plasma neutrophil gelatinase-associated lipocalin; uNGAL: urine neutrophil gelatinase-associated lipocalin; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

In the early stages of AKI, levels of NGAL, a member of the lipocalin superfamily, are increased in the urine and plasma, 24-48h earlier than the plasma creatinine peak. Therefore, a rise in pNGAL and uNGAL concentration may serve as an early indicator of renal failure[14]. While some studies[15,16] reported that NGAL is a useful biomarker for the early diagnosis of septic AKI, the clinical value of pNGAL and uNGAL levels is still unclear. A meta-analysis by Zhang et al[17] concluded that pNGAL and uNGAL had good predictive value for septic AKI (AUC = 0.86 and 0.90, respectively). However, the specificity of pNGAL was only 0.57, and 0.80 for uNGAL[17]. These results were similar to a Korean study[10], where the diagnostic accuracy of pNGAL was 0.881 for sensitivity, 0.474 for specificity, and 0.216 for positive predictive value. These results showed that pNGAL has a poor specificity and positive predictive value for septic AKI but a high sensitivity for the identification of AKI. Additionally, the ability of p- and u- NGAL levels alone to predict critically sick patients' requirement for renal

Table III. Diagnostic characteristics of pNGAL and uNGAL to predict SOFA within 72 hours after admission.

Variables	Cutoff value	AUC-ROC
SOFA < 8		
pNGAL	–	0.33 (0.17-0.49)
uNGAL	–	0.34 (0.17-0.51)
SOFA ≥ 8		
pNGAL	> 263.92 ng/ml	0.67 (0.51-0.83)
uNGAL	> 7.39 ng/ml	0.66 (0.49-0.83)

pNGAL = plasma neutrophil gelatinase-associated lipocalin; uNGAL = urine neutrophil gelatinase-associated lipocalin; AUC-ROC = area under the curve of the receiver operating characteristic; SOFA = sequential organ failure assessment.

replacement therapy (RRT) varied[18]. Therefore, the role of NGAL in septic AKI needs to be studied further.

Our results may provide a possible explanation for the difference, observed in previous reports[15-18]. We showed that real-time detection of pNGAL was a good indicator for septic AKI patients. However, pNGAL concentrations were only elevated significantly during KDIGO 3 of septic AKI, and not during KDIGO 1-2 of AKI, compared to non-AKI ($p > 0.05$). This suggested that while pNGAL is useful in predicting serious septic AKI, it should be used with caution when evaluating mild septic AKI cases.

A previous study[19] reported that uNGAL was able to predict severe AKI during hospitalization in critically ill adults independently, but the predictive value was moderate with an AUROC of 0.64 (95% CI 0.57-0.71). In the current study, instant uNGAL stratified septic AKI in critically ill patients within 72 hours, with an AUROC of 0.83.

NGAL is expressed in kidney, hepatic, lung, and gut epithelial cells in response to serious injury[20], especially when induced by infection. Therefore, changes in the levels of NGAL may indicate the occurrence and development of ischemia-reperfusion injury of kidneys, mucosal injury in Crohn's disease, bronchial inflammation in chronic obstructive pulmonary disease, and hematological disorders. Other studies[15,21] reported that NGAL was elevated significantly in bacterial infections and viral infections. This suggests the specificity of NGAL to detect septic AKI may be limited in critically ill patients, but its prediction value for critical illness might be useful. Therefore, the precise use of NGAL for diagnostic testing requires further study[22,23].

The current study showed that pNGAL and uNGAL moderately correlated with SOFA scores of sepsis patients. However, the use of NGAL alone is not sufficient to predict the risk. Therefore, the use of combinations of parameters (such as biomarker panel) may contribute significantly to the prognostic value of SOFA score. Moreover, as demonstrated before, there was a greater correlation between SOFA scores and uNGAL than with pNGAL[24]. The use of urine biomarkers can help patients avoid excessive blood loss. Therefore, biomarker panels, including uNGAL, may help improve early clinical judgement[20,23].

Conclusions

Levels of NGAL in blood and urine correlated with SOFA scores in patients with severe sepsis and may provide accurate information regarding the severity of sepsis. Plasma NGAL level was a good predictor of severe kidney injury, while urine NGAL levels detected mild stage septic AKI.

Conflict of Interest

We certify that none of our associations or business interests pose a conflict of interest with respect to the work that has been submitted.

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Authors' Contribution

MH participated in the study's design, carried out the experiments, and analyzed the data in addition to writing the article. LZ, XGL, and DHZ offered technical assistance. The research was created, planned, and executed under the direction of MYQ. YXW contributed ideas to the research and assisted in the rewriting of the paper. The final draft was authorized by all writers, who also reviewed and made contributions to the paper.

Ethics Approval
The study was approved by the Ethics Committee of The Hebei Medical University (No.: 2017-R217; Date: December 7th, 2017). The study was conducted in compliance of Helsinki Declaration and its latest amendments.

Informed Consent
Informed consent was obtained from all patients.

Data Availability
The data used to support the findings of this study are included in the article..

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