ORIGINAL RESEARCH

Early Diagnostic Value of Urinary NGAL in Acute Kidney Injury in Septic Patients

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ABSTRACT

Background • The aim of this study was to evaluate the predictive value of urinary neutrophil gelatinase-associated lipid (uNGAL) for the prediction of sepsis-associated acute kidney injury (SA-AKI).

Methods • From September to December 2012, 110 patients were prospectively enrolled from the intensive care units (ICUs) of 3 general hospitals. After being admitted to the ICU, the patients were continuously observed for 72 hours. According to the Kidney Disease Improving Global Outcomes (KDIGO) criteria for the diagnosis of acute kidney injury (AKI), the patients were divided into the AKI group (33 patients) and non-AKI group (77 patients). Per the sepsis diagnostic criteria, the patients were classified as septic (79 patients) and non-septic (31 patients). Serum creatinine and uNGAL of the patients were analyzed daily. The difference in uNGAL in septic and non-septic patients, patients with and without AKI, and septic patients with with and without AKI were compared. In addition, the difference in serum creatinine and uNGAL in patients with and without AKI were recorded and compared, and the sensitivity and specificity of uNGAL and sCr for the diagnosis of AKI in the ICU patients were evaluated using the receiver operating characteristic (ROC) curve.

Results • uNGAL levels were all significantly different in septic and non-septic patients ($P = .001$, $P = .028$, $P = .010$, respectively), patients with and without AKI ($P = .001$, $P = .042$, $P = .001$, respectively), septic patients with AKI and septic patients without AKI ($P = .003$, $P = .012$, $P = .001$, respectively) at 24, 48 and 72 hours after being admitted to the ICU, while the difference in sCr was not significant ($P = .169$) after 24 hours. The area under the ROC curve of uNGAL and sCr in patients admitted to the ICU at 24 hours were 0.828 (95% CI, 0.742 to 0.914) and 0.583 (95% CI, 0.471 to 0.695), respectively. The cutoff value of uNGAL was 170 ng/mL in patients admitted to the ICU at 24 hours, and the sensitivity and specificity were 0.778 and 0.784, respectively. The sensitivity of uNGAL was superior sCr.

Conclusion • uNGAL has relatively high sensitivity and specificity in predicting the occurrence of AKI in septic patients, which is superior to sCr and has certain clinical early diagnostic value. uNGAL could be used as an indicator for early diagnosis of AKI in septic patients in the ICU. (*Altern Ther Health Med.* 2022;28(7):120-124).

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INTRODUCTION

Acute kidney injury (AKI) is a syndrome characterized by a sudden loss of renal concentration and excretion function within hours to days, characterized by oliguria.[1] Although renal replacement therapy has made technological progress, it still incurs high morbidity and mortality.[2,3] AKI is common in hospitalized patients, especially in the intensive care unit (ICU), and sepsis is considered to be the most common cause of AKI in critically ill ICU patients.[4,5] According to an analysis from 409 hospitals in the United States where a large number of patients were admitted from 2004 to 2009, more than 40% of patients with sepsis had accompanying AKI, in accordance with the standard definition of sepsis-III.[6] The incidence of AKI increases with

increased sepsis severity. AKI occurs in 19% of patients with sepsis, 23% of patients with severe sepsis and 51% to 64% of patients with septic shock, and the mortality in AKI with sepsis increased significantly.[7] The main reason the incidence of AKI remains high is that it is difficult to diagnose and treat in the early stages. Therefore, early diagnosis of AKI is particularly important.[8]

The diagnosis of AKI currently is mainly based on an increase in serum creatinine (sCr) in the light of risk, injury, failure, loss and end-stage kidney disease, or according to Acute Kidney Injury Network (AKIN) standards.[9] In patients with sepsis-associated acute kidney injury (SA-AKI), sCr cannot reflect the glomerular filtration rate (GFR) accurately, because of the patients' unstable state. In addition, sCr can also be affected by renal tubular creatinine excretion and other non-renal factors, such as muscle mass, liver function and non-renal gastrointestinal excretion.[10-12] Moreover, Doi, et al.[13] found, in animal studies, that sepsis can lower sCR production significantly. A large number of patients with AKI lose their optimal treatment window because of the lack of early sensitive diagnostic indicators,[14] failing to correct the decrease in renal perfusion and reverse hemodynamic damage, finally leading to serious cell damage and acute tubular necrosis (ATN).[15] Therefore, looking for an effective marker that can fully reflect the pathophysiological changes of AKI has become the research trend.

Many clinical studies have proven that neutrophil gelatinase-associated lipid (NGAL) has a stronger ability to predict AKI than sCR in the early stages, and it can be detected in serum and urine within a short period of time (such as 2 hours) after the onset of AKI.[16-21] However, the implementation of the early diagnosis of AKI using NGAL in the ICU is still controversial,[22] because severe sepsis and septic shock are known to increase plasma NGAL levels in patients without AKI.[23,24] However, it is not clear whether sepsis could affect the specificity of urinary NGAL (uNGAL) as an early AKI marker.

In this study, uNGAL and sCR were evaluated to compare the difference in uNGAL levels between septic and non-septic patients, patients with and without AKI and septic patients with and without AKI. The difference in sCR and uNGAL between patients with and without AKI after 24 hours in the ICU were also compared. Our study aimed to explore the diagnostic value of uNGAL in the ICU patients who developed AKI.

MATERIALS AND METHODS

General Patient Data

From September to December 2012, 110 consecutive patients admitted to the ICU were enrolled in this prospective study. Among them, 59 patients were from Baoshan Branch Hospital of Shuguang Hospital, Affiliated with Shanghai University of Traditional Chinese Medicine, 27 were from Shanghai Pudong New Area People's Hospital and 24 patients were from Changzheng Hospital, Second Military Medical University.

This study was approved by the Ethics Committee of Baoshan Branch Hospital of Shuguang Hospital, Affiliated with Shanghai University of Traditional Chinese Medicine (Ethical No. IRB2018-YX-013). All patients signed informed consent forms before participating in the study. Urinary NGAL measurement is part of standard ICU protocol in these 3 hospitals.

Exclusion Criteria

Patients with (1) chronic renal insufficiency, (2) malignant tumor, (3) who died within 24 hours of being admitted to the ICU were not enrolled in the study.

Inclusion Criteria

Patients older than age 18 years with sepsis that met the diagnostic criteria for sepsis were included in the study.

In accordance with the new definition of "sepsis-3" published in 2016 in The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3),[25] the patients were divided into the non-sepsis group and the sepsis group. The diagnostic criteria of sepsis are as follows: a sequential organ failure assessment (SOFA) score of sequential organ failure caused by infection of ≥2 points, acute change; that is, sepsis = infection + SOFA ≥2.

According to the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI diagnosis, the patients were divided into the AKI group and the non-AKI group. AKI was defined as: (1) sCR increase ≥26.5 μmol/L within 48 h; (2) sCR increase of more than 1.5 times the baseline value within 7 days; (3) urine volume decrease of 0.5ml /kg/) that lasted for more than 6 hours.[26]

Data Collection

Patient baseline information including gender, age, body temperature, heart rate, respiratory rate and white blood cell count was obtained. Urine and blood samples were collected for 4 consecutive days: the day of admission to ICU, and 24, 48 and 72 hours after admission to the ICU.

Measurements

The method for collecting urine samples was as follows: in patients with or without an indwelling catheter, a sample of approximately 2 mL of mid-stream urine was collected. The urine sample was placed in a test tube free of pyrogen and endotoxins, and the supernatant was collected after centrifugation at 3000 RPM for 1 minute via 800D desktop low-speed centrifuge (Jiangsu Zhengyi Instrument Co, Ltd). The blood samples were sent to the hospital clinical laboratory for Cr measurement.

Urine samples were directly tested for uNGAL with a bedside NORMAN-2 scatter turbidimetry analyzer (Nanjing Norman Biotechnology Co., Ltd), and the immune-enhanced turbidimetric method was used. The reagents R1 and R2 were provided by Nanjing Norman Biotechnology Co., Ltd., and the sample was kept away from light and stored in a refrigerator at 2° to 8°C.

The detection method was as follows: 240 µL reagent R1 and 20 µL urine samples after centrifugation were obtained by pipette and mixed in a colorimetric cup. Then the colorimetric cup was pre-heated in the measurement channel of the scattering turbidimetric analyzer. Investigators took out the colorimetric cup and added 120 µL reagent R2, and then returned the colorimetric cup to the analyzer to test the uNGA level.

Statistical Analysis

All the data collected in this study were analyzed with IBM® SPSS 22.0 software. The measurement data were expressed as mean ± standard deviation (x ± s). The Shapiro-Wilk method combined with histogram was used to test whether the data were of normal distribution. Independent sample t-test was used for the 2 groups of data conforming to normal distribution. Otherwise, the Mann-Whitney non-parametric test was used to compare the difference between groups, and the chi-square test was used for counting data. The software was used to draw the ROC curve and calculate and analyze the area under the curve (AUC). The difference between the AUC and 0.5 was compared with a 95% CI. The sensitivity and specificity of the 2 groups were compared by chi-square test. All *P* values <.05 were considered statistically significant.

RESULTS

Demographic Characteristics

Among the 110 patients, there were 67 men and 43 women, age 33 to 96 years. There were 16 patients with cerebral hemorrhage and cerebral infarction, 26 with acute exacerbation of chronic obstructive pulmonary disease, severe multiple injuries (cerebral contusion and laceration, cervical fracture and high paraplegia, lung contusion and laceration). There were 39 patients with splenic rupture, multiple rib fractures, pelvic fractures and limb fractures; 12 with severe pneumonia;, 6 with severe electrolyte disturbance, 5 with acute severe pancreatitis; 3 with suppurative cholangitis; 2 with diabetic ketoacidosis complicated by pneumonia and urinary tract infection, and 1 patient with extensive intestinal adhesions.

There was no significant difference in gender ratio and age range in septic (n = 79) and non-septic (n = 31) patients in the ICU (*P* > .05). Patient demographic characteristics are shown in Table 1.

Table 1. Demographics of Non-Septic and Septic Patients in the ICU

Data	Non-Septic Patients (n = 31)	Septic Patients (n = 79)	*P* value
Gender (male /female)	20/11	47/32	.67
Age (years)	72.92 ± 13.98	73.7 ± 15.35	.614
T (°C)	36.9 ± 0.46	37.82 ± 1.03	.001
HR (n/min)	79.39 ± 5.89	108.85 ± 24.21	<.001
RR (n/min)	16.87 ± 2.40	23.7 ± 4.40	<.001
WBC (10^9/L)	7.28 ± 1.75	13.65 ± 6.39	<.001

Abbreviations: HR, heart rate; ICU, intensive care unit; R, respiratory rate; T, temperature; WBC, white blood cell count.

Table 2. Comparison of uNGAL in Septic and Non-Septic Patients (ng/mL)

Time	Non-Septic Patients (n = 31)	Septic Patients (n = 79)	*Z*	*P* value
0 h	276.06 ± 257.92	552.38 ± 622.93	-1.792	.073
24 h	226.45 ± 237.07	649.19 ± 603.55	-3.24	.001
48 h	230.45 ± 172.93	700.48 ± 703.05	-2.197	.028
72 h	282.97 ± 229.24	750.61 ± 698.72	-2.571	.010

Abbreviations: uNGAL, urinary neutrophil gelatinase-associated lipid.

Table 3. Comparison of sCr and uNGAL in Patients With and Without AKI

	Without AKI (n = 77)	With AKI (n = 33)	*Z*/*t*	*P* value
sCr @ 24 h (µmol/L)	73.74 ± 25.70	80.89 ± 24.69	*t* = -1.385	.169
uNGAL @ 0 h (ng/mL)	378.76 ± 433.42	749.43 ± 759.70	-1.889	.059
uNGAL @ 24 h (ng/mL)	356.66 ± 389.99	945.01 ± 739.64	-3.316	.001
uNGAL @ 48 h (ng/mL)	447.69 ± 499.21	992.67 ± 869.62	-2.032	.042
uNGAL @ 72h (ng/mL)	406.54 ± 402.81	1184.48 ± 829.28	-3.213	.001

Abbreviations: AKI, acute kidney injury; sCr, serum creatinine; uNGAL, urinary neutrophil gelatinase-associated lipid.

uNGAL Level in Septic and Non-septic Patients in the ICU

In comparing the uNGAL level in patients in the ICU with and without sepsis, we found that there was no significant difference in uNGAL levels in the 2 groups upon admission to the ICU (*P* = .073). However, the level of uNGAL in the septic patients was significantly higher than in the non-septic patients 24 to 72 hours after admission to the ICU (*P* < .05) as shown in Table 2.

uNGAL Level in Patients With and Without AKI

There was no significant difference in uNGAL levels in patients in the ICU with and without AKI (*P* = .059) on admission, but the difference in uNGAL levels between the 2 groups increased significantly after 24 hours. There was no significant difference in sCr levels between the 2 groups at the 24th hour (*P* = .169), as shown in Table 3.

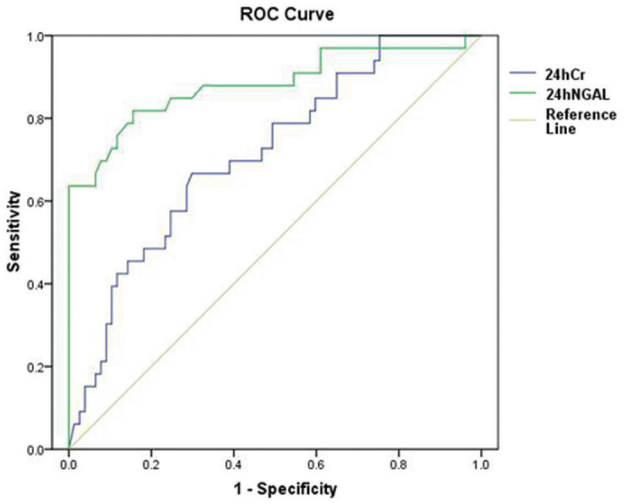
Comparison of uNGAL levels in septic patients in the ICU with and without AKI found no significant difference in uNGAL levels on admission to the ICU (*P* = .078). However,

Table 4. Comparison of uNGAL Septic Patients Without AKI and Septic Patients With AKI (g/mL)

Time	Septic Patients without AKI (n = 49)	Septic Patients with AKI (n = 30)	*Z*	*P* value
0 h	429.79 ± 516.81	815.31 ± 806.25	-1.764	.078
24 h	450.01 ± 450.79	1081.78 ± 732.65	-3.022	.003
48 h	487.34 ± 520.00	1163.01 ± 853.24	-2.506	.012
72 h	460.80 ± 442.38	1351.33 ± 796.10	-3.238	.001

Abbreviations: AKI, acute kidney injury; uNGAL, urinary neutrophil gelatinase-associated lipid.

Figure. Comparison of diagnostic value of uNGAL and sCr in AKI.



Abbreviations: AKI, acute kidney injury; sCr, serum creatinine; uNGAL, urinary neutrophil gelatinase-associated lipid.

there was a significant difference in the levels in the 2 groups at 24, 48 and 72 hours after admission to the ICU ($P = .003$, $P = .012$ and $P = .001$, respectively), as shown in Table 4.

Comparison of the Diagnostic Value of uNGAL and sCr in AKI

In order to study the predictive value of uNGAL as a marker for early diagnosis of AKI, the ROC curve was used to calculate AUC as shown in the Figure. The AUC of uNGAL was 0.828 (95% CI, 0.742-0.914), while 0.5 fell outside the 95% CI, and the difference was significant. The AUC of sCr was 0.583 (95% CI, 0.471-0.695), and 0.5 fell within 95% CI, which means the difference was not significant. When the cutoff value of uNGAL was 170 ng/mL, the sensitivity and specificity for diagnosing AKI were 0.778 and 0.784, respectively. When the cutoff value of sCr was 84 μ mol/L, the sensitivity and specificity of diagnosing AKI was 0.528 and 0.662, respectively. There was a significant difference in sensitivity between uNGAL and sCr ($\chi^2 = 8.134$; $P = .004$), but there was no significant difference in specificity ($\chi^2 = 0.26$; $P = .61$).

DISCUSSION

Sepsis is a heterogeneous syndrome with atypical and non-specific clinical signs. In the past, the diagnosis of AKI was mainly based on changes in urine volume and sCr. This study aimed to evaluate the predictive value of uNGAL in patients with sepsis secondary to acute renal injury. After observing 110 patients admitted to the ICU for 72 hours, we found that the uNGAL levels were significantly different in patients with and without AKI after admission to the ICU at 24 h ($P = .001$), while the difference in sCR was not significant ($P = .169$). NGAL levels may increase due to bacterial infection and systemic inflammation.[23] Because NGAL can be detected in serum and urine a short time after the occurrence of AKI (within 2 hours), it is also called troponin of the kidney.

In this study, uNGAL levels in critically ill patients in the ICU were compared in septic and non-septic patients. There was no significant difference in uNGAL levels on admission to the ICU, primarily because of the severity of their condition at that time. Although they did not meet the diagnostic criteria for sepsis, there was usually severe infection, shock or organ injury present, which can increase the level of plasma NGAL. When NGAL enters the kidneys via the blood, although plasma NGAL can be filtered freely through the glomeruli, it can be reabsorbed by megalin receptors in the proximal tubule by phagocytosis *in vivo*.[27] Despite the fact that sepsis or inflammation can lead to a high expression of plasma NGAL, uNGAL will not increase until AKI is present.[27] Therefore, there was no obvious abnormality in uNGAL levels in either group. This study also compared uNGAL levels from 24 to 72 hours after ICU admission, and the results showed that uNGAL levels in septic patients was significantly higher than in non-septic patients. This may be due to the fact that the longer a patient with sepsis stays in the ICU, the more the incidence of AKI increases with the severity of the sepsis.

In order to explore the possibility of uNGAL as a marker for early diagnosis of AKI in the ICU, uNGAL expression in patients with and without AKI were compared. There was no significant difference in uNGAL between patients with and without AKI upon admission to the ICU. The uNGAL levels in patients with AKI significantly increased 24 hours after admission to the ICU, but there was no significant difference in sCr levels at 24 hours. Furthermore, the results showed that there was no significant difference in uNGAL levels between patients with sepsis and AKI and patients without AKI upon admission to the ICU. The reason may be that both sepsis and AKI can lead to an increase in uNGAL levels. The increase in uNGAL upon admission to the ICU may be mainly caused by sepsis itself, and the effect of renal injury on the increase in uNGAL is not significant. However, with the gradual aggravation of renal injury, the reabsorption of plasma NGAL in renal tubules is decreased, while the level of uNGAL produced by the kidney itself is increased. Hence, the level of uNGAL in septic

patients without AKI changed little, and there would be a significant difference in uNGAL levels between the two.

Based on the above observation in septic and non-septic patients, patients with and without AKI, and septic and non-septic patients and AKI, there was a significant difference in uNGAL levels 24 hours after admission to the ICU, while there is no significant difference in sCr levels between patients with and without AKI. The ROC curve was also used to further analyze sCr and uNGAL levels 24 hours after ICU admission. Statistical analysis showed that when the area of uNGAL under the ROC curve is 0.828 (95% CI, 0.742-0.914), the cut-off value of uNGAL was 170 ng/mL, and the sensitivity and specificity for the diagnosis of AKI were 0.778 and 0.784, respectively; while the area of sCr under the ROC curve was only 0.583 (95% CI, 0.471-0.695), when the cutoff value of sCr was 84.3 μmol/L, and the sensitivity and specificity for the diagnosis of AKI were 0.528 and 0.662, respectively. There was a significant difference between these 2 kinds of sensitivities, but the specificity difference was not significant, which may be due to the small sample size. Nevertheless, our study suggests that the diagnostic value of uNGAL in the early stages of AKI was obvious compared with sCr.

Study Limitations

There were some study limitations, as follows: (1) The study was short, and the sample size limited. In addition, the standard deviation and the means were very close, indicating a high degree of data dispersion, which may be due to the small sample size. A prospective study with a larger sample size should be conducted to validate the value of uNGAL in the early diagnosis of AKI. (2) There are still some influencing factors such as infection and sepsis that would affect uNGAL levels. Cutoff levels and NGAL concentrations in patients with sepsis are generally considered higher than in patients after cardiac surgery, for example. It would be better to conduct the study with a larger sample size, and without possible interfering factors.

CONCLUSION

uNGAL has relatively high sensitivity and specificity in predicting the occurrence of AKI in patients with sepsis, which is a superior marker to sCr and has early diagnostic value. Therefore, it can be used as a marker for early diagnosis of AKI in septic patients in the ICU.

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AUTHOR CONTRIBUTIONS

Baisheng Hu, Da Li, and Yunxia Lu contributed equally to this paper and should be co-first authors.

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