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Urinary neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury in sepsis patients in the emergency department

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ABSTRACT

Background: Plasma neutrophil gelatinase-associated lipocalin (NGAL) is a useful biomarker for predicting acute kidney injury (AKI). The purpose of this study was to evaluate the diagnostic performance of urinary NGAL in predicting AKI in sepsis patients in the emergency department.
Methods: A total of 140 patients were enrolled. We compared serum procalcitonin and urinary NGAL concentrations between patients with local infection, sepsis, and septic shock, and between patients who did and did not develop AKI with sepsis. Receiver-operating characteristic curve analysis was used to evaluate the ability to predict AKI in sepsis patients.
Results: Both serum procalcitonin and urinary NGAL concentrations were significantly higher in the sepsis and septic shock groups than in the local infection group (both $p < 0.001$). In sepsis patients, serum procalcitonin and urinary NGAL concentrations were higher in AKI patients than in those without AKI ($p = 0.006$, $p < 0.001$, respectively). The area under the curve for predicting of AKI was higher for a urinary NGAL of 0.820 (95% confidence interval (CI) 0.721–0.895) than for a serum procalcitonin concentration of 0.76 (95% CI 0.597–0.800).
Conclusion: Urinary NGAL concentration may predict AKI in patients with sepsis in the emergency department.

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a deleterious host response to infection [1]. The kidney is one of the organs most commonly affected by sepsis, and 47% of acute kidney injury (AKI) cases are associated with sepsis [2]. AKI is a potentially fatal complication of sepsis and contributes to increased morbidity and mortality [3]. AKI is also associated with the development of chronic kidney disease. Doyle et al. [4] reported a relationship between AKI and short-term and long-term complications. The management of AKI is mainly supportive and aims to treat the underlying precipitating cause. Because AKI may be reversible, early detection of AKI is necessary to reduce the chance of further kidney damage and to ensure a favorable outcome in septic patients.

The diagnosis of AKI is based mainly on serum creatinine concentration and urine output [5]. However, these methods for diagnosing AKI are limited because it takes time to obtain urine output data or to detect the change of serum creatinine [6]. A few other biomarkers have been recently introduced for early prediction of the development of AKI. Neutrophil gelatinase-associated lipocalin (NGAL) has been investigated as a highly sensitive specific biomarker for AKI. NGAL concentration is usually detected within 2 to 4 h after renal injury, and elevation in its concentration can be detected before that of serum creatinine [7]. NGAL is also released by activated neutrophils, cells that exhibit antibacterial properties. NGAL may be a marker of inflammation and infection [8,9]. Therefore, it is controversy whether NGAL concentration can predict the occurrence of AKI accompanied by sepsis.

2. Methods

We conducted a retrospective study at a tertiary urban hospital in

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Seoul, South Korea. The institutional review board of our hospital approved this study. We reviewed all medical records of patients who visited our emergency department from June 2016 to December 2016, and included the data for all patients older than 18 years who were diagnosed with infective disease. The exclusion criteria were: 1) end-stage renal disease requiring hemodialysis, 2) refusal of further treatment, and 3) any malignant terminal cancer. Routine laboratory tests including measurement of serum procalcitonin and urinary NGAL concentrations were performed for patients with suspected infectious disease on presentation at the emergency department. Urinary NGAL concentration was measured using a chemiluminescent microparticle immunoassay and an Abbott Diagnostics Architect analyzer. The measurement range of the assay was 10–6000 ng/ml. Serum procalcitonin concentration was measured using an electrochemiluminescence immunoassay (Brahms GmbH) and the Roche Cobas e-System. The measurable range of the assay was 0.02–100 ng/ml. We also obtained detailed clinical data including the patient's age, gender, medical history, and comorbidities. All patients received proper treatment including fluid resuscitation and antibiotics according to the treatment guideline. All data were anonymized before analyses.

Sepsis was defined according to the Sepsis-3 criteria. The Sequential Organ Failure Assessment (SOFA) scoring system was used to evaluate organ dysfunction and failure [1]. The patients were classified into three groups according to the disease severity: local infection, sepsis, and septic shock groups. We set the local infection group as the control. The sepsis group included patients with a change from the baseline in the total SOFA score of ≥2 with an infection focus. The septic shock group included patients who developed sepsis with hypotension requiring vasopressor and a serum lactate concentration > 2 mmol/l despite adequate volume resuscitation. AKI was diagnosed using serum creatinine concentration and urine output according to the Kidney Disease: Improving Global Outcomes guidelines [5].

When reliable urine output data were missing, we used only the serum creatinine concentration. If the baseline creatinine concentration was not known, we calculated it based on the Modification of Diet in Renal Disease (MDRD) formula, and 75 ml/min/1.73 m^2 was considered normal. The highest AKI stage during the first 48 h after admission was recorded. The development of AKI was identified in patients with sepsis and septic shock, and this group was further classified into AKI and non-AKI subgroups.

All statistical analysis were performed using SPSS 19 (ver 19.0) and MedCalc 9. Data are presented as medians with interquartile ranges and as numbers with percentages. The Kruskal–Wallis test was used for multiple group comparisons, and the Mann–Whitney *U* test was used to compare urinary NGAL and serum procalcitonin concentrations between two groups. Receiver-operating characteristic (ROC) curve analysis was used to compare the diagnostic performance of urinary NGAL and serum procalcitonin concentrations in predicting AKI. A $p < 0.05$ was considered to be significant.

3. Results

A total of 217 patients' medical records were reviewed. Of these, 32 patients were excluded based on the exclusion criteria, and 45 patients who did not have a result for procalcitonin or urinary NGAL were excluded; 140 patients were finally included in this study. The median age was 75 (Interquartile range (IQR) 61.81) y and 67 (47.9%) were men. The baseline characteristics of the patients are presented in Table 1.

The plasma procalcitonin concentrations grouped according to the disease severity were 0.25 (IQR 0.1, 0.64) mg/dl in the local infection group, 1.67 (IQR 0.25, 13.45) mg/dl in the sepsis group, and 4.87 (IQR 2.21, 28.01) mg/dl in the septic shock group. The urinary NGAL concentrations were 39.6 (IQR 14.7, 200.8) ng/ml, 170.6 (IQR 43.95, 469.7) ng/ml, and 410.0 (IQR 138.7, 1317.5) ng/ml, respectively. Serum procalcitonin and urinary NGAL concentrations were higher in the sepsis and septic shock groups than in the local infection group (both $p < 0.001$) (Fig. 1).

Nineteen septic and septic shock patients developed AKI. The procalcitonin concentration was higher in the AKI group [10.53 (2.22, 28.01) mg/dl] than in the non-AKI group [1.65 (0.28, 6.65) mg/dl] ($p = 0.006$). Urinary NGAL concentration was also higher in the AKI group [909.3 (184.8, 2499.9) ng/ml] than in the non-AKI group [139.8 (38.67, 347.75) ng/ml] ($p < 0.001$) (Fig. 2). The median urinary NGAL concentration was significantly higher in the AKI group compared with the value used as a medical decision point (131.7 ng/ml).

The diagnostic accuracies according to the area under the ROC curve (AUC) value for serum procalcitonin for predicting the development of AKI was 0.706 (95% confidence interval (CI) 0.597–0.800) ($p = 0.004$). The optimal cutoff value for serum procalcitonin was 2.21 mg/dl, and the sensitivity and specificity were 62.1% and 78.9%, respectively. The AUC for urinary NGAL was 0.820 (95% CI 0.721–0.895) ($p < 0.001$). The optimal cutoff value for urinary NGAL was 359 ng/ml, and the sensitivity and specificity were 78.8% and 73.7%, respectively (p = NS) (Fig. 3).

4. Discussion

AKI is diagnosed mainly according to an increased serum creatinine concentration and decreased urine output in the current clinical setting [5]. However, the current method for diagnosing AKI has some limitations. The glomerular filtration rate in the kidney can increase in response to some physiological or pathological condition. It was termed as an augmented renal clearance when this phenomenon was seen in critically ill patients. Some inflammatory mediators may reduce systemic vascular resistance, which may increase renal blood flow. In addition, intravenous fluid or vasoactive drug administration can also increase renal blood flow. Consequently, these can cause an increase in glomerular filtration rate in patients. This may make it appear that the serum creatinine concentration does not temporarily increase despite the presence of renal injury occurring with sepsis. It can take about 24 to 48 h for an increased serum creatinine to appear after renal insult [10].

The diagnosis of AKI based on urine output also has limitations. Urine output is a good indicator of kidney dysfunction, and decreased urine output is associated with poor outcomes [11]. However, urine output can be normal until the appearance of severe renal dysfunction. In other words, both serum creatinine concentration and urine output may not accurately reflect renal insult itself but may only indicate excretory dysfunction in the kidney. Therefore, the extent of renal injury may not be clear in the early phase and the current tests may not provide a sensitive marker when a patient is first seen in the emergency department.

There is another problem with using the current criteria for diagnosing AKI. The creatinine-based AKI criterion requires the baseline creatinine level. If this is not known, clinicians must use the back-calculating method to estimate creatinine using the estimated glomerular filtration rate of the MDRD formula [12]. This estimation may not accurately identify true AKI incidence [13]. Moreover, urine output-based AKI criteria can be unreliable because it is sometimes difficult to obtain accurate hourly urine measurements in the emergency department.

A biomarker would offer clinical convenience as well as rapid diagnosis in the emergency department. Several biomarkers have been investigated for predicting AKI, and NGAL is a promising marker. It is upregulated after renal tubular injury such as ischemic stress, exposure to a nephrotoxin, or inflammation. NGAL can be detected within 3 h and its concentration peaks 6–12 h after renal injury [7]. In addition, the half-life of NGAL is usually at 10–20 min [14], which is shorter than that of creatinine (4 h) [15]; therefore, the NGAL concentration may change earlier than that of creatinine. Therefore, measuring the NGAL concentration may allow for the early detection of renal injury before the appearance of increased serum creatinine concentration or decreased urine output. Many studies have shown the role of NGAL in

Table 1
Baseline characteristics of the patients.

	All (140)	Local infection (55)	Sepsis (66)	Septic shock (19)	p-Value
Age (y)	75 (61–81)	65 (49–76)	78 (68.8–83)	79 (61–84)	< 0.001
Gender (m, %)	67 (47.9%)	23 (41.8%)	34 (51.5%)	10 (52.6%)	NS
AKI	19 (13.6%)	0	10 (15.2)	9 (47.4)	< 0.001
			Septic group		p-Value
			AKI (19)	Non-AKI (66)	
Age (y)			11 (57.9%)	33 (50%)	NS
Gender (m, %)			78 (61, 83)	78 (68.8, 83)	NS

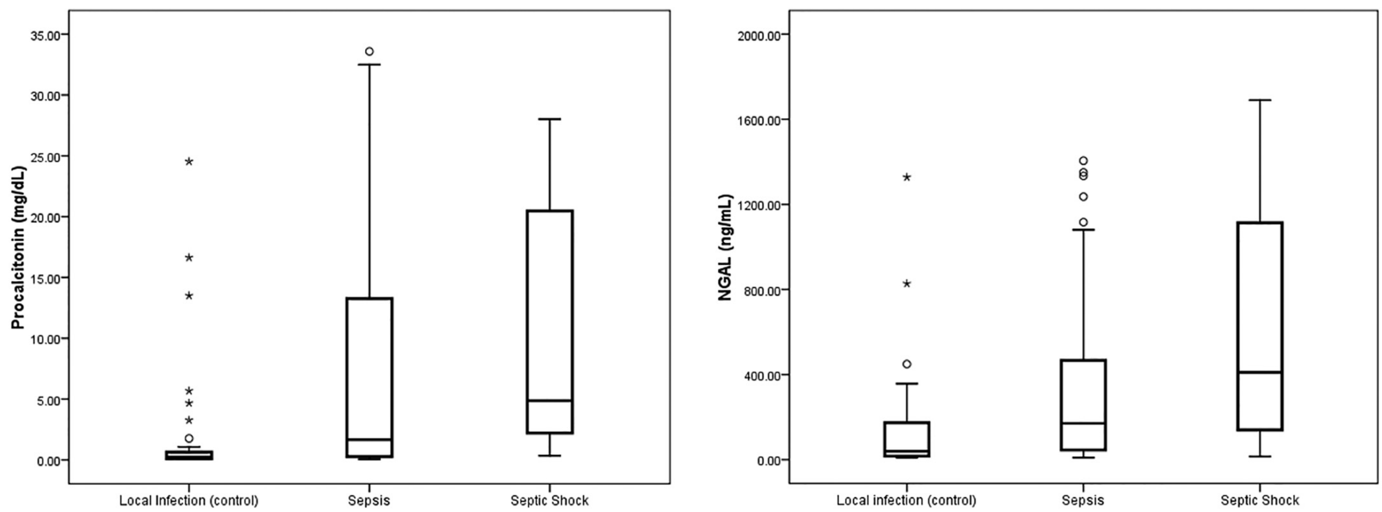

Fig. 1. Comparison of serum procalcitonin and urine NGAL categorized by disease severity.

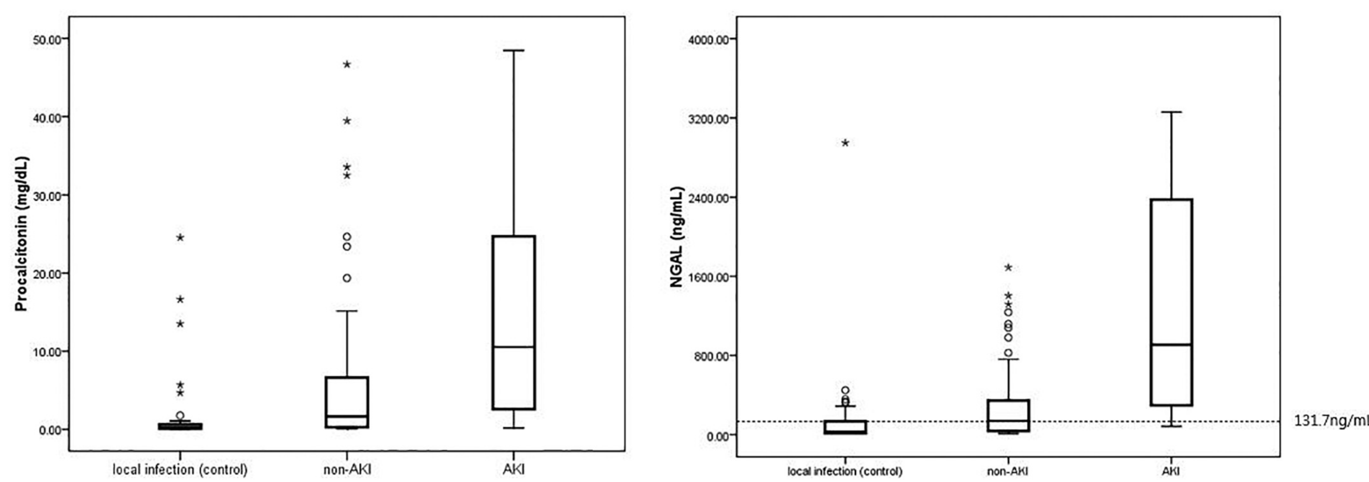

Fig. 2. Comparison of serum procalcitonin and urine NGAL between AKI group and non-AKI group of sepsis and septic shock patients.

various conditions that give rise to AKI, such as kidney transplantation or after cardiac surgery [16–18]. However, the evidence for an association between NGAL and AKI related to sepsis is inconsistent. NGAL was first identified in neutrophil granules, and it also secreted by activated neutrophils in response to infection, as its name implies [9]. Previous studies have demonstrated that NGAL concentration is increased during sepsis regardless of whether AKI does or does not occur [8]. This characteristic makes it difficult to use NGAL to identify AKI associated with sepsis. One study showed that NGAL was associated with renal tubular damage in sepsis, but it was not superior to serum creatinine concentration in the prediction of AKI and it did not have good performance for the prediction of clinical outcome in AKI with sepsis [19]. Another study showed that NGAL seems to be a useful predictor of AKI in patients with sepsis, although NGAL concentration did not differ significantly between AKI and non-AKI patient groups with sepsis [20]. More evidence is needed to validate the performance of NGAL concentration is predicting AKI with sepsis.

In our study, we found that urinary NGAL concentration was higher in the AKI than non-AKI group in patients with sepsis and that it had good predictive power for identifying AKI with sepsis. We compared

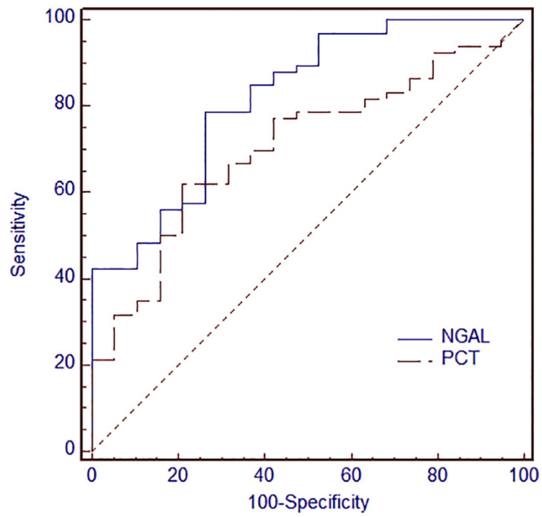

Fig. 3. Comparison of the receiver operating characteristic curve values between serum procalcitonin and urine NGAL for predicting the AKI of sepsis and septic shock patients.

serum procalcitonin concentration between patients who developed local infection, sepsis, and septic shock, and between the two subgroups of patients with sepsis (AKI and non-AKI). Procalcitonin is considered to be a good biomarker for identifying sepsis [21]. Serum procalcitonin concentrations differed significantly between the three groups, and its level was higher in the AKI than in the non-AKI subgroup. Similar results were obtained for NGAL. In the ROC curve analysis, the AUC for serum procalcitonin was 0.706, which was slightly lower than the 0.820 for urinary NGAL. Our data suggest that the increase in urinary NGAL concentration may be related to sepsis, as shown in other studies [8,9]. In addition, we found that urinary NGAL concentration could predict the development of AKI with sepsis even if this value may be confounded by the presence of infection.

Some patients were classified into the non-AKI group according to the classical diagnostic criteria despite having a high initial NGAL concentration. These outliers may have had some tubular cell injuries, but they would not have exhibited a decline in glomerular filtration rate. The cause of these outliers' infections related mainly to urinary tract infections. A Previous study has shown that the urinary NGAL concentration increases during a urinary tract infection [22]. The increased urinary NGAL concentration suggests that renal injury may have occurred. Additional renal damage will be accompanied by a decline in glomerular filtration rate and decreased urine output or increased serum creatinine concentration. Urinary NGAL can help identifying preclinical AKI from the high risk patients. It would be useful for clinicians to be able to identify these outliers early through an initial NGAL test, which would allow them to plan a therapeutic strategy to prevent further renal damage.

This study has some limitations. First, this study had a small sample size and was conducted at a single center, and the results may not be generalized to all patients with sepsis. Second, this study had a retrospective design and there may have been selection bias in the enrolment of patients. Third, we could not standardize the measurement of all data and there may have been differences in the timing of sample collection for urine output measurement between patients. Fourth, we measured urinary NGAL concentration only once at the emergency department and were unable to validate the additional predictive value of NGAL concentration. Fifth, this study was an observational study whose aim was to assess the performance of urinary NGAL concentration in predicting AKI development in patients with sepsis. Therefore, we could not identify any aggravating factors that contributed to, or protective factors that prevented against, the development of AKI in patients with sepsis.

One of the strengths of this study was that it was conducted in an emergency department. Usually, patients with sepsis are diagnosed in the emergency department initially. Although it is not clear when renal injury occurs to patients with sepsis, urinary NGAL concentration may be measured quickly in the emergency department in the early stage of sepsis in patients at high risk of AKI, and this may be helpful for predicting and monitoring their overall prognosis. Our study adds evidence about the ability of urinary NGAL concentration in the prediction of the development of AKI in sepsis patients.

5. Conclusion

Urinary NGAL concentration was associated with the severity of infection and had good performance for the prediction of AKI. Urinary NGAL concentration might be a useful biomarker for the early prediction of AKI in sepsis patients in the emergency department.

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