The value of urine neutrophil gelatinase-associated lipocalin in the prediction of septic acute kidney injury, dialysis need, and mortality in a cohort of Egyptian sepsis patients

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Aim
The aim of this study was to assess the role of urine concentrations of neutrophil gelatinase-associated lipocalin (NGAL) in the early diagnosis of septic acute kidney injury (AKI) in critically ill Egyptian adults.
Patients and Methods
The studied patients were categorized into three groups: sepsis–non-AKI; sepsis–AKI; and nonsepsis–non-AKI. Urine samples were collected daily for 5 days from the sepsis patients. For the sepsis–non-AKI patients urine NGAL levels were measured from samples taken on the admission day and on day 5. In the sepsis–AKI patients, urine NGAL levels were measured from samples taken on the admission day, from samples collected 24 h before the onset of AKI, and from those taken on the day of AKI onset. For nonsepsis–non-AKI patients, urine NGAL levels were measured from samples taken on the admission day only.
Results
Totally, 172 patients were studied: 61 in the sepsis–non-AKI group; 82 in the sepsis–AKI group; and 29 in the nonsepsis–non-AKI group. Urine NGAL was significantly higher in sepsis patients than in nonsepsis patients (14.8±4.2 and 5.5±2.6 ng/ml, respectively; $P<0.001$). In sepsis patients who developed AKI, urine NGAL preceded the rise in serum creatinine, and at its cutoff level of 33.1 ng/ml it predicted AKI with an area under the curve of 0.96, sensitivity of 99%, and specificity of 85%; at its cutoff level of 48.7 ng/ml, it predicted the need for dialysis with an area under the curve of 0.81, sensitivity of 84%, and specificity of 73%. Urine NGAL could not predict mortality among sepsis patients.
Conclusion
Urine NGAL predicted AKI well in critically ill septic patients and predicted their need for dialysis.

Keywords:
acute kidney injury prediction, neutrophil gelatinase-associated lipocalin, sepsis

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Introduction

Sepsis is considered a primary cause of morbidity and mortality in patients admitted to ICUs [1–3]. Acute kidney injury (AKI) occurs in ~51% of septic shock patients [4], with impact on morbidity and mortality [5,6].

Neutrophil gelatinase-associated lipocalin (NGAL), which is a member of the lipocalin superfamily expressed by neutrophils and various epithelial cells [7], is one of the most frequently investigated for early prediction of AKI [8].

We aimed to validate the use of urine NGAL in the early prediction of AKI development, dialysis need, and mortality in a cohort of adult Egyptian sepsis patients.

Patients and methods

This is a prospective cohort study that involved 172 patients admitted to a medical ICU between June 2013 and March 2015. It was performed after obtaining approval from the Medical Ethics Committee of Cairo University Hospitals, and in accordance with the Helsinki Declaration. Informed consent was obtained either from patients or from their family.

The patients included in the study were grouped into three groups. Group 1 included 61 patients with sepsis with no AKI; group 2 included 82 patients with sepsis and AKI; and group 3 included 29 nonsepsis, non-AKI patients (the control group).

In our study we excluded patients who were known to have chronic kidney disease, patients with AKI on

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admission, patients with prerenal and postrenal causes of AKI, patients with nonseptic AKI, and patients exposed to radiocontrast dye or nephrotoxic drugs (aminoglycoside, colistin, or amphotericin) within at least 1 week before ICU admission.

Sepsis and septic shock were diagnosed according to the guidelines of the International Sepsis Definitions Conference [9].

AKI was diagnosed according to Risk, Injury, Failure, Loss, and end stage renal disease (ESRD) (RIFLE) criteria. Urine output was closely monitored every hour, and daily assessment of serum creatinine and its change in relation to its baseline levels on admission (if normal) was carried out [10]. Chronic kidney disease was defined on the basis of the definition of National Kidney Foundation as kidney damage or glomerular filtration rate less than 60 ml/min/1.73 m^2 for 3 or more months, irrespective of the cause [11].

Demographic characteristics (age, sex, and body weight) and admission diagnosis of each patient were recorded. On admission, baseline creatinine and blood urea nitrogen levels, leukocyte count, C-reactive protein, and vital signs (heart rate, temperature, mean arterial blood pressure) were assessed for the evaluation of sepsis and AKI. Acute Physiology and Chronic Health Evaluation II score was used to evaluate severity of disease at admission [12].

The data collected included medications (vasoactive drugs, steroids antibiotics, nephrotoxic agents), length of ICU stay, and outcome.

Serum creatinine was assessed in spot blood samples obtained on admission and then reassessed daily at constant intervals (every 24 h) for 5 days in sepsis patients (groups 1 and 2).

Simultaneously, urine samples were collected on the day of admission from all involved patients by spontaneous voids or from inserted indwelling Foley catheters. Urine samples were collected daily for 5 days from sepsis patients (groups 1 and 2). In sepsis–AKI patients (group 2) sample collection was stopped at the onset of AKI.

Urine NGAL levels were assessed only in selected samples. In sepsis–non-AKI patients, urine NGAL levels were measured from samples taken on admission day and on day 5. In sepsis–AKI patients, urine NGAL levels were measured from samples taken on admission day, from samples collected 24 h before the onset of AKI (1 day before AKI), and from samples taken on the day of AKI onset. In nonsepsis–non-AKI patients, urine NGAL levels were measured from samples taken on the admission day only. The other urine samples were discarded.

After being centrifuged at 5000 bpm for 15 min, the urine and blood supernatant samples were frozen within 2 h of collection at −80°C. Urine NGAL levels were assessed with enzyme linked immunosorbent assay (Human Lipocalin-2/NGAL ELISA; Biovendor Research and Diagnostic Products, Czech Republic, Brno).

Statistical analysis

Data were statistically described in terms of mean±SD, frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between the study groups was done using the Student *t*-test for independent samples.

For comparing categorical data, the χ^2-test was performed. The exact test was used instead when the expected frequency was less than 5. Correlation between variables was determined using Pearson's moment correlation equation for linear relation. Accuracy was represented using the terms sensitivity and specificity. A *P* value less than 0.05 was considered statistically significant. All statistical calculations were performed using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, New York, USA) and statistical package for the social science (SPSS, version 15 for Microsoft Windows; SPSS Inc., Chicago, Illinois, USA).

Receiver operator characteristic (ROC) analysis was used to determine the optimum cutoff value for the studied diagnostic markers as follows: the best possible biomarker of a disease process would plot a point in the upper left corner of the ROC space, which would represent 100% sensitivity (all true positives detected) and 100% specificity (no false positives found).

An area under the curve (AUC) of 1.0 represents a perfect biomarker, whereas an AUC of 0.5 (as would be derived from the line of no discrimination) indicates a result that is no better than expected by random chance. An AUC of 0.75 or above is generally considered a good biomarker, and an AUC of 0.9 or above would represent an excellent biomarker.

Results

The demographic data of the involved patients, their admission diagnosis, comorbidities, and outcomes are summarized in Table 1. Out of the 143 sepsis patients,

Table 1 Demographic data, patients' criteria, and mortality

	Sepsis and no AKI (*N*=61) [*n* (%)]	Sepsis and AKI (*N*=82) [*n* (%)]	No sepsis and no AKI (*N*=29) [*n* (%)]	*P* value
Age (years)	58±8.1	59.4±8	53±11	0.21
Sex (male)	37 (60.1)	44 (53.7)	16 (55.1)	0.83
Diagnosis on admission				
Pneumonia	27 (44.2)	39 (47.5)	4 (13.7)	**0.027**
COPD exacerbations	8 (13)	9 (10.9)	3 (10.3)	0.75
Pulmonary embolism	2 (3)	1 (1.2)	2 (6.9)	**0.046**
Acute coronary syndrome	1 (1.5	2 (2.4)	8 (27.6)	**0.01**
GIT bleeding and shock	4 (6.5)	6 (7.3)	2 (6.9)	0.63
Diabetic ketoacidosis	5 (8.2)	5 (6.1)	2 (6.9)	0.72
Cerebrovascular stroke	5 (8.2)	4 (4.9)	1 (3.4)	0.051
Hepatic encephalopathy	4 (6.5)	6 (7.3)	1(3.4)	0.055
Cardiogenic shock	1 (1.5)	3 (3.6)	4 (13.7)	**0.012**
Infective endocarditis	1 (1.5)	2 (2.4)	1(3.4)	0.2
Malignancy	3 (4.9)	5 (6.1)	1 (3.4)	0.12
Comorbid diabetes mellitus	20 (32.7)	28 (34)	8 (27)	0.14
Comorbid hypertension	27 (44.2)	33 (40)	10 (34)	0.23
Baseline serum creatinine (mg/dl)	1.07±0.2	1.2±0.13	1.08±0.2	0.37
APACHE II score	26±6	32±7	16±5	**0.031**
Length of ICU stay	13±8	18±10	8±5	**0.001**
Mortality	22 (36)	36 (44)	4 (14)	**0.022**

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; GIT, gastrointestinal tract. Bold values are significant $P<0.05$.

pneumonia was the main source of sepsis (66 patients, 46%). During their ICU course, 63 (44%) patients developed septic shock, 82 (57.3%) patients developed AKI within their first 5 days of ICU stay, and 34 (41%) of the last group required dialysis. Patients with sepsis and AKI had significantly higher Acute Physiology and Chronic Health Evaluation II score, longer ICU stay, and higher mortality rate than did patients with sepsis and non-AKI (Table 1).

Initial neutrophil gelatinase-associated lipocalin values

In urine samples collected on the day of admission, urine NGAL was significantly higher in sepsis patients (groups 1 and 2) than in nonsepsis patients (group 3) (14.8±4.2 and 5.5±2.6 ng/ml, respectively; $P<0.001$) (Table 2). However, within these sepsis patients, urine NGAL on admission was not significantly different between patients who developed AKI in their first 5 days of ICU stay (group 2) and others who did not develop AKI (group 1) (16.8±4.3 and 13.5±4.6 ng/ml, respectively; $P=0.32$) (Table 3).

Neutrophil gelatinase-associated lipocalin and acute kidney injury development

At 5 days after admission, urine NGAL did not change significantly in those with sepsis who did not develop AKI (13.5±4.6 and 15.3±3.3 ng/ml, respectively; $P=0.081$) (Table 4).

However, sepsis patients who developed AKI within 5 days of admission had a significant progressive rise in urine NGAL values in samples collected 1 day before and on the day of AKI than on admission (16.8±4.3, 40.1±11.7, and 58.3+14.3, respectively; $P<0.001$) (Table 5).

The ROC curve analysis of urine NGAL values in samples collected 1 day before and on the day of AKI

Table 2 Urine neutrophil gelatinase-associated lipocalin on the day of admission in sepsis and control patients

	Sepsis patients (groups 1 and 2) (*n*=143)	Control (group 3) (*n*=29)	*P* value
Urine NGAL (ng/ml)	14.8±4.2	5.5±2.6	<**0.001**

NGAL, neutrophil gelatinase-associated lipocalin. Bold values are significant $P<0.05$.

Table 3 Urine neutrophil gelatinase-associated lipocalin on the day of admission in sepsis patients

	Sepsis and no AKI (group 1) (*n*=61)	Sepsis and AKI (group 2) (*n*=82)	*P* value
Urine NGAL (ng/ml)	13.5±4.6	16.8±4.3	0.32

AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4 Urine neutrophil gelatinase-associated lipocalin on the day of admission and on day 5 in sepsis–non-acute kidney injury patients

	On admission	Day 5	*P* value
Urine NGAL (ng/ml)	13.5±4.6	15.3±3.3	0.081

NGAL, neutrophil gelatinase-associated lipocalin.

Table 5 Urine neutrophil gelatinase-associated lipocalin in sepsis acute kidney injury patients on the day of admission 1 day before acute kidney injury and on the day of acute kidney injury onset

	On admission	24 h before sepsis	Day of sepsis	*P* value
Urine NGAL (ng/ml)	16.8±4.3	40.1±11.7	58.3+14.3	<**0.001**

NGAL, neutrophil gelatinase-associated lipocalin. Bold values are significant P<0.05.

onset showed that urine NGAL at its cutoff level of 33.1 ng/ml could efficiently predict the development of AKI in patients complaining of sepsis, with sensitivity of 99%, specificity of 85%, positive predictive value of 99%, and negative predictive value of 90% (Table 6 and Fig. 1).

Neutrophil gelatinase-associated lipocalin and serum creatinine

Urine NGAL was not correlated with serum creatinine on the day of admission in sepsis patients (in both who developed or did not develop AKI), nor with serum creatinine on follow-up samples, after 5 days in non-AKI patients, or on AKI onset in the AKI group (Table 7).

Neutrophil gelatinase-associated lipocalin and renal replacement therapy

The peak urine NGAL was significantly higher in patients who needed hemodialysis compared with that in those not receiving hemodialysis (53.6 vs. 46.1 ng/ml, respectively; *P*<0.001). The AUC of the peak urine NGAL for prediction of hemodialysis was 0.81 [95% confidence interval (CI): 0.62–0.82] with a cutoff level of 48.7 ng/ml and a sensitivity and specificity of 0.84 and 0.73, respectively.

Mortality prediction

The multivariate logistic regression analysis of the overall mortality showed that the development of septic shock [51 (35.7%) patients] [*P*=0.01, odds ratio (OR): 11, 95% CI: 2.1–91.5] and serum creatinine (*P*=0.005, OR: 9, 95% CI: 2.7–101) were the main independent predictors of mortality. However, the peak urine NGAL or its admission values could not predict mortality (*P*=0.31, OR: 6, 95% CI: 3.1–88.2) (*P*=0.17, OR: 3, 95% CI: 2.9–79.9).

Table 6 Validity of urine neutrophil gelatinase-associated lipocalin in the prediction of acute kidney injury

Variables	%
AUC	0.96
Best cut off	33.1
Sensitivity	99
Specificity	85
PPV	99
NPV	90

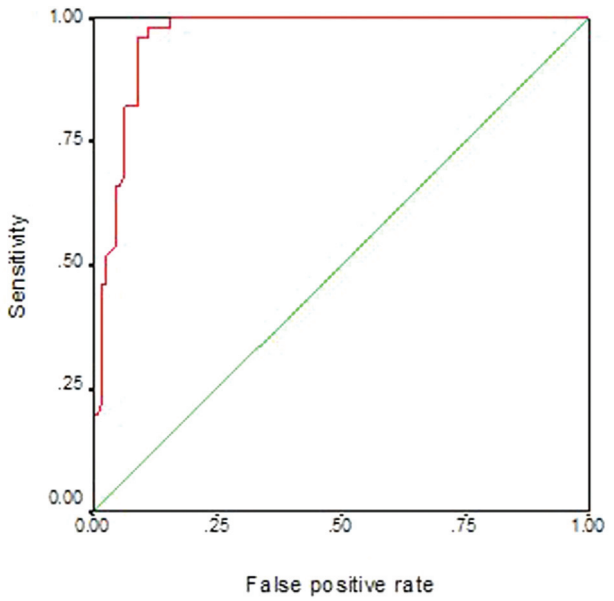
AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Table 7 Correlation between urine neutrophil gelatinase-associated lipocalin and serum creatinine

Serum creatinine	Urine NGAL
Sepsis–non-AKI	
On admission	0.345 (*P*=0.26)
After 5 days	0.18 (*P*=0.19)
Sepsis and AKI	
On admission	0.41 (*P*=0.47)
At AKI onset	0.56 (*P*=0.06)

AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin.

Figure 1



The receiver operator characteristic curve showing the performance of urine neutrophilgelatinase-associated lipocalin levels in predicting septic acute kidney injury.

Discussion

Sepsis and septic shock are the biggest causes of mortality in critically ill patients [2,13–15]. Mortality rates range from 20% from sepsis to 60% from septic shock in ICU patients [16]. In a recent meta-analysis restricted to the last decade in high-income countries, the incidence rate was 437 for sepsis and 270 for severe sepsis cases per 100 000 person years, with potentially 5.3 million deaths annually [17].

The overall incidence of AKI in ICU patients ranges from 20 to 50%, with a higher incidence in sepsis patients [18]. Sepsis and septic shock both alone account for 50% or more of AKI in ICUs, and are associated with a very high mortality [19].

Like previous reported results [20] our septic patients who developed AKI were found to stay longer in the ICU compared with septic patients without AKI.

Furthermore, and as found in several studies [21–24], the development of AKI in our sepsis patients has significantly worsened the outcome compared with sepsis alone (44 and 36%, respectively; P=0.022).

These important findings confirm the gravity of sepsis-associated AKI, and highlight the importance of early prediction of AKI in these high-risk patients, aiming for early initiation of supportive therapy to limit the extent of renal injury and to control it by fluid resuscitation, early antibiotic initiation, and restriction of intravenous contrast dye and nephrotoxic antibiotic use.

For detecting AKI, the current clinical definitions still depend on acute and relative rise in serum creatinine levels in RIFLE and Acute Kidney Injury Network criteria [10,25].

Unfortunately, creatinine elevation, the current gold standard for the diagnosis of AKI, has some limitations. Not only being delayed [26], but also serum creatinine is influenced by tubular creatinine secretion and by nonrenal factors such as muscle mass and liver function. Furthermore, serum creatinine does not accurately reflect the glomerular filtration rate in AKI because the patient is not in steady state [27]. Additionally, reduced production of creatinine in sepsis limits its use as a marker of AKI in septic patients [28].

These limitations of serum creatinine may delay the early diagnosis of AKI in septic patients and impede early initiation of management. To overcome this, novel biomarkers are progressively examined for the early prediction of sepsis-associated AKI.

Because several studies reported that AKI occurs early in the course of sepsis, [29,30], we monitored our sepsis patients since their ICU admission and during their first 5 days of ICU stay.

In our work, urine NGAL was markedly higher in sepsis patients than in controls since their ICU admission (14.8±4.2 and 5.5±2.6, respectively; P<0.001). In contrast, urine NGAL on admission did not differ significantly between those who developed AKI and others who did not (13.5±4.6 and 16.8±4.3, respectively; P=0.32).

Daily follow-up of urine NGAL declared no significant change in its value in patients with sepsis who did not develop AKI, whereas in septic patients who developed AKI serum creatinine was associated and more importantly preceded by a significant jump in urine NGAL levels than on admission (on admission 16.8±4.3, 1 day before AKI 40.1±11.7, on AKI onset 58.3+14.3, P<0.001).

That means that AKI insult was associated and even preceded by clear earlier rise in urine NGAL than a defective delayed change in serum creatinine. More precisely, urine NGAL in our work and at its cutoff level of 33.1 ng/ml could efficiently predict AKI development at least 1 day before its onset with sensitivity of 99%, specificity of 85%, and AUC of 0.96.

Explanation for this rise in urine NGAL may be due to increased renal synthesis of NGAL evidenced by upregulation of its genes early in AKI [31], or due to the impaired reabsorption of NGAL in the proximal tubules [32] because of tubular damage induced by sepsis [33].

An additional benefit for urine NGAL was the prediction of the need for renal replacement therapy. Urine NGAL at cutoff level of 48.7 ng/ml predicted the hemodialysis need with a sensitivity of 84% and specificity of 73% and AUC of 0.77. Unfortunately, urine NGAL could not predict intrahospital mortality.

In our examined sepsis patients, urine NGAL did not correlate with serum creatinine on admission or on development of AKI. We did not include the AKI–nonsepsis group of patients in our study to report this relation in the absence of sepsis; however, it was reported before that any correlation of NGAL with serum creatinine in patients without sepsis is lost with onset of sepsis because of increased NGAL synthesis by inflammatory cells [34].

Conclusion

Urine NGAL predicted AKI well in our critically ill septic patients and also predicted their need for dialysis. This diagnostic value can be added to previous similar reports and encourage its widespread use in clinical practice by promoting the daily measurement of urine NGAL at the bedside in sepsis patients with an assay kit without causing anemia as no blood is drawn daily.

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Conflicts of interest

There are no conflicts of interest.

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