Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2017, Vol. 45(3) 1231–1244
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DOI: 10.1177/0300060517709199
journals.sagepub.com/home/imr
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Evaluation of serum neutrophil gelatinase-associated lipocalin in predicting acute kidney injury in critically ill patients

Chen-Chen Hang, Jun yang, Shuo Wang, Chun-Sheng Li and Zi-Ren Tang

Abstract

Objective: This investigation evaluated the real-time point-of-care testing (RT-POCT) of neutrophil gelatinase-associated lipocalin (NGAL) for detecting acute kidney injury (AKI) and prognosis of critically ill patients.

Methods: A total of 249 critically ill patients in the emergency department (ED), who were diagnosed with acute decompensated heart failure, sepsis or diabetic ketoacidosis were enrolled in this study. All enrolled patients were followed up for 28 days or to death and the mortalities were recorded. Serum creatinine (sCr) and NGAL were measured.

Results: 40.6% enrolled patients deteriorated to AKI during the observation period. The NGAL level was significantly higher in the AKI versus non-AKI group. The NGAL levels in the non-survivors group at 7-day and 28-day were significantly higher than in the survivors group. NGAL was detected as an independent risk factor of AKI, and 7-day and 28-day morality. The receiver operating characteristic curve of NGAL was calculated for diagnosing AKI; the area under the curve (AUC) was significantly higher than that of 1-day eGFR.

Conclusions: NGAL is an independent predictor of AKI, and 7-day and 28-day mortality in critically ill ED patients, and can be an early alert for AKI and useful for determining prognosis.

Jun Yang and Chen-Chen Hang contributed equally to this work and should be considered as co-fist author.
Chun-Sheng Li and Zi-Ren Tang contributed equally to this work and should be considered as co-corresponding author.

Corresponding authors:
Chun-Sheng Li and Zi-Ren Tang, Department of Emergency Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, No. 8, Gongrentiyuchangnanlu, Chaoyang District, Beijing 100020, China.
Emails: ysys2001@yeah.net; tangziren@126.com

Department of Emergency Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Beijing, China

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Keywords
Neutrophil gelatinase-associated lipocalin, acute kidney injury, real-time point-of-care test, critically ill patients

Date received: 16 February 2017; accepted: 19 April 2017

Introduction

Acute kidney injury (AKI) is defined as a sudden loss of renal function. AKI is a major clinical issue in critically ill patients, with persistently high rates of hospital re-admission and mortality carrying a substantial economic burden.[1] Delay in diagnosis and treatment of AKI will result in either deterioration of renal function, or permanent renal impairment leading to dialysis.[2] Many critically ill patients with normal kidney function may progress to AKI during the course of treatment in the emergency department (ED). Especially those with sepsis, acute decompensated heart failure (ADHF) and diabetic ketoacidosis (DKA), which may influence the perfusion of the kidney significantly. Therefore, early detection of AKI has become very important in diagnosis and prognosis in critically ill patients.[3]

It has been proven that neutrophil gelatinase-associated lipocalin (NGAL) is a strong biomarker for early detection of AKI in various clinical settings.[4–6] NGAL increases as early as 2 hours after injury to the kidney. It appears to be a novel 'real-time' biomarker of AKI, which can predict AKI several days earlier than serum creatinine (sCr). Real-time point-of-care testing (RT-POCT) is defined as medical testing performed at the site of patient care, and has been used widely in intensive care units and EDs. Since the ED is the first site of contact for most critically ill patients, the use of RT-POCT can not only accelerate triage, but also facilitate evidence-based practices in the ED.[7]

Clinical studies have confirmed the diagnostic and prognostic value of NGAL in various settings,[6,8] but few of them used the RT-POCT NGAL in critically ill patients in the ED for evaluating its efficacy. In this study, we reported our experience of RT-POCT NGAL for detecting AKI in critically ill patients of an urban university tertiary hospital ED.

Methods

Population

Between April 2014 and September 2014, critically ill patients in the ED who were diagnosed with ADHF, sepsis or DKA within 12 hours of admission to the ED, were enrolled in this study. ADHF was defined as the rapid onset or change of symptoms and signs of heart failure.[9] Sepsis was defined according to the Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.[10] DKA was defined as hyperglycemia (blood glucose >11 mmol/L or 200 mg/dl), venous pH < 7.3 or bicarbonate <15 mmol/L, and the presence of ketonemia or ketonuria.[11]

The exclusion criteria were: age <18 years old; pregnancy; previously diagnosed abnormal renal function; autoimmune diseases; terminal cancer; known urinary tract infection; known exposure to nephrotoxic agents during treatment in the ED, which included aminoglycoside, angiotensin-converting enzyme inhibitors, contrast agent et al; treatment time in hospital <3 days (not including died within 3 days); and patients (or their relatives) who declined to participate. The enrolled patients were followed up for 28 days or until death. A flow diagram of patient enrollment is shown in Figure 1.

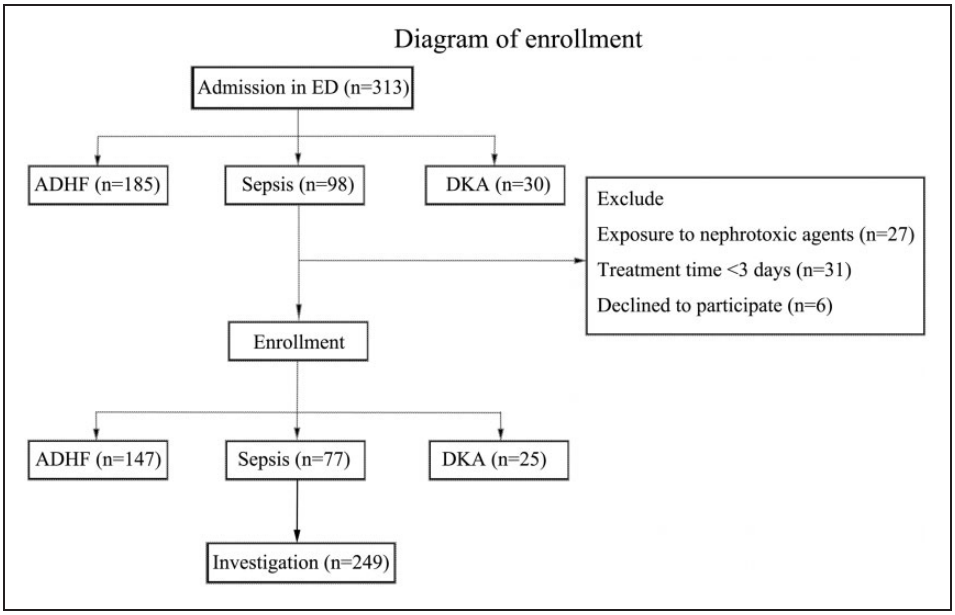

Figure 1. Diagram of enrollment 313 patients were registered when they were admitted to the ED, and 64 were excluded according to the exclusion criteria. Thus, 249 patients were enrolled in this investigation. ADHF, acute decompensated heart failure; DKA, diabetic ketoacidosis.

Study design

The protocols were approved by the ethics committee of Beijing Chao-Yang Hospital, Capital Medical University. The study was conducted in the ED of Beijing Chao-Yang Hospital, Capital Medical University, which is an urban university tertiary hospital with approximately 250,000 ED admissions every year. Subject data, name, age, sex, past medical history, vital signs, and Acute Physiology and Chronic Health Evaluation (APACHE) II score[12] were recorded immediately after enrollment. Within 60 min of arrival in the ED, and as soon as possible, a blood sample was collected from patients for routine laboratory examinations including sCr and RT-POCT NGAL. Treatment for all enrolled patients was based on the routine standard of care and was entirely independent of the study. All patients were followed up for 28 days and then the prognosis was recorded. If a patient was discharged within 3 days, all data about them were excluded from the research, because no definite prognosis was required. The estimated glomerular filtration rate (eGFR) was calculated by the Cockcroft-Gault equation and adjusted for body surface area per 1.73 m^2.[13] AKI is defined as any of the following (not graded): ① increase in sCr by $\times$0.3 mg/dl ($\times$26.5 μmol/L) within 48 hours; ② increase in sCr to $\times$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; ③ urine volume <0.5 ml/kg/h for 6 hours. The classification of AKI was according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines.[14]

Laboratory tests

sCr was tested by the ADVIA® 2400 chemistry system (Siemens, Germany) using an enzymatic method in the hospital lab straight after blood samples were drawn.

RT-POCT NGAL results were obtained using the Alere™ Triage® Meterpro Device (Alere San Diego, Inc., San Diego, CA, USA) with an immunofluorescence kit within 15–20 min. The kit contains an NGAL-specific monoclonal antibody conjugated to a fluorescent nanoparticle and integrated control features including positive and negative control immunoassays, which ensure that the test performs correctly. 200 μl whole blood was dropped on the sample port where cells were separated from plasma through an integrated filter. The antibody-conjugated fluorescent detection nanoparticles flow down to the diagnostic lane via capillary action. Both monomeric and dimeric forms of NGAL in the samples will prevent binding of the fluorescent detection particles to the solid phase. The serum NGAL concentration is inversely proportional to the fluorescence detected. A control zone is located in the same kit. Calibration information is relayed to the device via a code chip module. To decrease bias, the tests were performed by two designated experimenters.

Statistical analysis

All data were analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Categorical data were presented as frequencies and percentages. All continuous variables were skewed distributions and are presented as the inter-quartile range (IQR) (25^{th} percentile to 75^{th} percentile). Chi-square, Mann-Whitney U or Kruskal-Wallis H tests were conducted to detect the differences among the different groups. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated to detect the differences among the indexes for predicting AKI and the 28-day mortality. Based on the optimal thresholds, which were detected by the ROC curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), were then calculated. A Z-test was used for comparing AUCs between the different curves. Binary logistic regressions were applied for determining the risk factors of 28-day mortality and AKI. Multinomial logistic regression was used to determine the predictive effects of NGAL on KDIGO. Curve estimate was performed for establishing the regression equation between the eGFR and NGAL. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

The general characteristics of patients in the different diagnosis groups

A total of 313 patients were registered when they were admitted to the ED, and 64 were excluded according to the exclusion criteria. Therefore, a total of 249 patients were enrolled in this investigation. General characteristics of patients in the different diagnosis groups are summarized in Table 1. No significant difference in sex was found between the different groups (ADHF, sepsis, DKA) at admission, whereas a significant difference in age between the ADHF and DKA groups was found ($P = 0.032$). Both 1-day sCr and 1-day eGFR were normal, and while significant differences were found between them among the different groups, these differences disappeared after the 3^{rd} day of admission. The median value of NGAL and APACHE II score at admission was 119 [IQR 79–264] ng/ml and 14 [IQR 11–18] respectively. 40.6% of the enrolled patients deteriorated to AKI during the observation period. The 7-day and 28-day mortality rate was 9.6% and 29.7% respectively. Significant differences in NGAL were found among the three groups ($P < 0.01$), due to the higher level of NGAL in the sepsis and DKA groups.

Table 1. The general characteristics of patients in the different diagnosis groups.

	Total	ADHF	Sepsis	DKA	X^2	P
Number, n	249	147	77	25		
Age, years	67 (56–78)	72 (58–78)$^{\triangle}$	65 (54–77)	61 (51–68)*	6.888	0.032
Male, n (%)	170 (68.3%)	102 (69.4%)	52 (67.5%)	16 (64%)	0.315	0.854
NGAL, ng/ml	119 (79–265)	102 (74–198)#	152 (88–440)*	154 (84–342)*	11.088	0.004
1-day sCr, mg/dl	0.88 (0.74–1.04)	0.89 (0.76–1.06)$^{\triangle}$	0.89 (0.74–1.05)$^{\triangle}$	0.78 (0.67–0.93)*#	8.877	0.012
3-day sCr, mg/dl	1.06 (0.86–1.48)	1.10 (0.88–1.40)	1.02 (0.81–1.55)	1.00 (0.78–1.85)	0.418	0.812
1-day eGFR, ml/min/1.73 cm^2	74.1 (62.6–96.2)	71.5 (61.4–89.6)$^{\triangle}$	74.6 (62.5–99.6)$^{\triangle}$	99.9 (81.4–113.9)*#	16.094	$<$0.001
3-day eGFR, ml/min/1.73 cm^2	58.3 (40.9–83.6)	57.5 (41.4–79.9)	64.2 (36.6–93.7)	74.9 (40.7–89.6)	1.024	0.599
APACHE II Score	14.0 (11.0–18.0)	14.0 (11.0–17.0)#	15 (12.0–20.5)*	14.0 (12.5–18.5)	6.027	0.049
AKI, n (%)	101 (40.6%)	51 (34.7%)	39 (50.6%)	11 (44.0%)	5.472	0.065
KDIGO 1, n (%)	50 (20.1%)	27 (18.4%)$^{\triangle}$	22 (28.6%)	1 (4.0%)*	15.955	0.014
KDIGO 2, n (%)	23 (9.2%)	13 (8.8%)	6 (7.8%)	4 (16.0%)		
KDIGO 3, n (%)	28 (11.2%)	11 (7.5%)	11 (14.3%)	6 (24.0%)		
7-day Mortality, n (%)	24 (9.6%)	8 (5.4%)	10 (13.0%)	6 (24.0%)	9.884	0.008
28-day Mortality, n (%)	74 (29.7%)	36 (24.5%)$^{\triangle}$	26 (33.8%)	12 (48%)*	6.528	0.039

The values are expressed as the median (IQR, observations available) or number (percentage).

ADHF: acute decompensated heart failure; DKA: diabetic ketoacidosis; NGAL: neutrophil gelatinase-associated lipocalin; sCr: serum creatine; eGFR: estimated glomerular filtration rate; APACHE II Score: acute physiology and chronic health evaluation II score; AKI: acute kidney injury; KDIGO: classification of Kidney Disease: Improving Global Outcomes Clinical Practice Guideline.

*Significant difference was found vs. the HF group; # significant difference was found vs. the sepsis group; $^{\triangle}$significant difference was found vs. the DKA group

The general characteristics of patients in different KDIGO classifications

The general characteristics of patients in different KDIGO classifications are summarized in Table 2. There were no significant differences in age in the different KDIGO classifications, while significant differences in sex, the NGAL level, APACHE II score and mortality among the different KDIGO classifications were found. The percentage of males and the NGAL level were significantly higher in the patients with AKI than without AKI ($P < 0.05$). Moreover, the more severe the KDIGO classification, the higher the NGAL level was. This was not surprising that very significant differences in sCr and eGFR were found among the different KIDGO classifications, because they are determined by sCr level. The 7-day and 28-day mortality increased with the severity of KDIGO classification, to a maximum of 42.9% and 64.3% respectively in KDIGO 3.

NGAL levels in the different groups of patients

When the patients were admitted to the ED, the NGAL levels were higher in the AKI group than in the non-AKI group ($Z = -11.343$, $P < 0.001$, Figure 2(a)). It was also significantly higher in the sepsis group when compared with the ADHF group ($Z = -3.267$, $P = 0.001$). In the sepsis group, the NGAL levels of non -AKI and AKI patients were 113 [IQR 77–235] ng/ml and 406 [IQR 147–1250] ng/ml respectively, and a significant difference was found between the two groups ($Z = -4.206$, $P < 0.001$). The NGAL levels in the non-survivors group at 7-days ($Z = -6.173$, $P < 0.001$, Figure 2(b)) and at 28-days ($Z = -5.562$, $P < 0.001$, Figure 2(c)) was significantly higher than it was in the survivors group.

Risk factors for mortality and AKI

Age, sex, NGAL level, 1-day eGFR and APACHE II were analyzed by binary logistic regression, and only sex and NGAL were confirmed as risk factors for AKI (Table 3). Multinomial logistic regression analysis was performed for KDIGO classification with the same variables as binary logistic regression. The result indicated that high NGAL levels were correlated with high KDIGO classification (Table 4). The increase in serum NGAL was also detected as an independent risk factor for high mortality at 7-day and 28-day by binary logistic regression (Table 5).

Regression analysis of NGAL levels and eGFR

An inverse equation was established between NGAL and 3-day eGFR by curve regression ($R^2 = 0.775$, $F = 93.655$, $P < 0.001$) (Figure 3). The equation was:

$$3 - \text{day eGFR} = 43.461 + 2171.012/\text{NGAL}$$

The diagnostic power of NGAL, eGFR and APACHE II score for AKI and mortality

The ROC curve of NGAL was calculated for diagnosing AKI, the AUC of which was 0.923. This was higher than that of 1-day eGFR ($AUC = 0.534$, $Z = 9.435$, $P < 0.01$). Similar results were found in predicting 7-day and 28-day mortality by NGAL, the AUC of which were 0.883 and 0.723 respectively. Notably, NGAL was the highest of all indexes. The AUC of NGAL combined with the APACHE II score was 0.718 for predicting 28-day mortality; thus, no extra benefit was found compared with NGAL alone ($AUC = 0.723$, $Z = 0.102$, $P > 0.05$). However, an improved result was gained for predicting 7-day mortality when combined

Table 2. The general characteristics of patients in different classifications of KDIGO.

	No AKI	KDIGO 1	KDIGO 2	KDIGO 3	X^2	P
Number, n	148	50	23	28		
Age, years	66.0 (56.0–77.0)	71.0 (57.5–78.5)	70.0 (64.0–84.0)	63.5 (53.3–75.8)	5.838	0.120
male, n (%)	90 (60.8%)	38 (76.0%)	20 (87.0%)	22 (78.6%)	10.260	0.016
NGAL, ng/ml	87 (61–119)$^{\#\triangle\star}$	238 (127–355)$^{*\triangle\star}$	310 (171–404)$^{*\#\star}$	853 (389–1293)$^{*\#\triangle}$	139.319	<0.001
1-day Cr, mg/dl	0.92 (0.82–1.06)$^{\#\triangle\star}$	0.91 (0.74–1.03)*	0.76 (0.68–0.92)*	0.74 (0.66–0.90)*	21.094	<0.001
3-day Cr, mg/dl	0.92 (0.77–1.07)$^{\#\triangle\star}$	1.37 (1.17–1.54)$^{*\triangle\star}$	1.94 (1.57–2.34)$^{*\#\star}$	3.38 (2.87–4.43)$^{*\#\triangle}$	163.144	<0.001
1-day eGFR, ml/min/1.73 cm^2	73.9 (61.9–91.4)*	69.7 (60.0–90.2)*	77.0 (68.1–98.2)	96.2 (72.0–116.1)$^{*\#}$	12.551	0.004
3-day eGFR, ml/min/1.73 cm^2	75.5 (57.6–92.9)$^{\#\triangle\star}$	49.0 (37.9–72.7)$^{*\triangle\star}$	33.2 (27.3–40.8)$^{*\#\star}$	18.6 (13.5–27.7)$^{*\#\triangle}$	128.823	<0.001
APACHE II Score	13 (10–18)$^{\#\triangle\star}$	15 (12–20)**	16 (14–18)**	21 (17–24)$^{*\#\triangle}$	41.992	<0.001
7-day Mortality, n (%)	4 (2.7%)	3 (6.0%)	5 (21.7%)	12 (42.9%)	49.341	<0.001
28-day Mortality, n (%)	31 (20.9%)	17 (34.0%)	8 (34.8%)	18 (64.3%)	22.193	<0.001

The values are expressed as median (IQR, observations available) or number (percentage).

AKI: acute kidney injury; KDIGO: classification of Kidney Disease: Improving Global Outcomes Clinical Practice Guideline; NGAL: neutrophil gelatinase-associated lipocalin; sCr: serum creatine; eGFR: estimated glomerular filtration rate; APACHE II Score: acute physiology and chronic health evaluation II score.

*Significant difference was found vs. the no AKI group; $^{\#}$significant difference was found vs. the KDIGO 1 group; $^{\triangle}$significant difference was found vs. the KDIGO 2 group; *significant difference was found vs. the KDIGO 3 group.

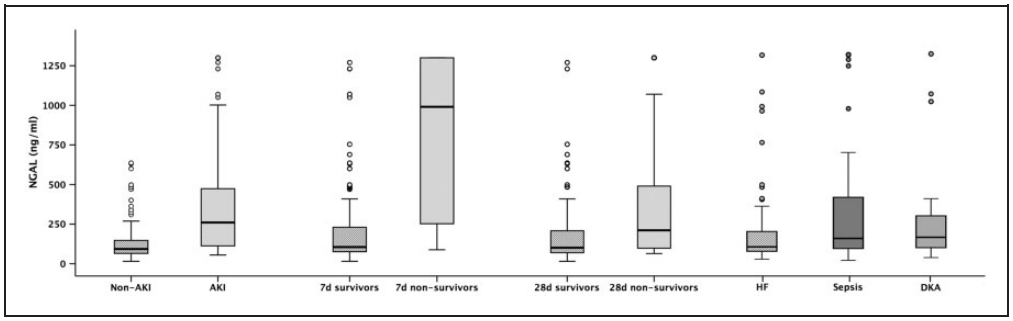

Figure 2. NGAL level in patients with AKI vs. non-AKI and in survivors vs. non-survivors Lines denote median values, boxes represent 25th to 75th percentiles and whiskers indicate the range. Number of samples are indicated in parentheses. (a) NGAL level in patients with AKI and non-AKI; (b) NGAL level in survivors and non-survivors at 7-days; (c) NGAL level in survivors and non-survivors at 28-days. AKI: acute kidney injury; NGAL: neutrophil gelatinase-associated lipocalin.

Table 3. Risk factors for AKI.

					95% C.I.	
	B	OR	S.E.	P	lower	upper
SEX (male)	−0.845	0.430	0.444	0.057	0.180	1.026
NGAL	0.019	1.019	0.003	<0.001	1.014	1.025

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

Table 4. Multinomial logistic regression analysis of NGAL for KDIGO classification.

					95% C.I.	
	B	S.E.	OR	P	lower	upper
KDIGO = 0	−0.002	0.003	0.978	<0.001	0.973	0.983
KDIGO = 1	−0.004	0.001	0.996	<0.001	0.994	0.998
KDIGO = 2	−0.002	0.001	0.998	0.004	0.996	0.999

KDIGO: classification of Kidney Disease: Improving Global Outcomes Clinical Practice Guideline; NGAL: neutrophil gelatinase-associated lipocalin.

Table 5. Binary logistic regression analysis of NGAL for 7-day and 28-day mortality.

					95% C.I.	
	B	S.E.	OR	P	lower	upper
7-day mortality	0.005	0.001	1.005	<0.001	1.003	1.006
28-day mortality	0.003	0.001	1.003	<0.001	1.002	1.004

NGAL: neutrophil gelatinase-associated lipocalin.

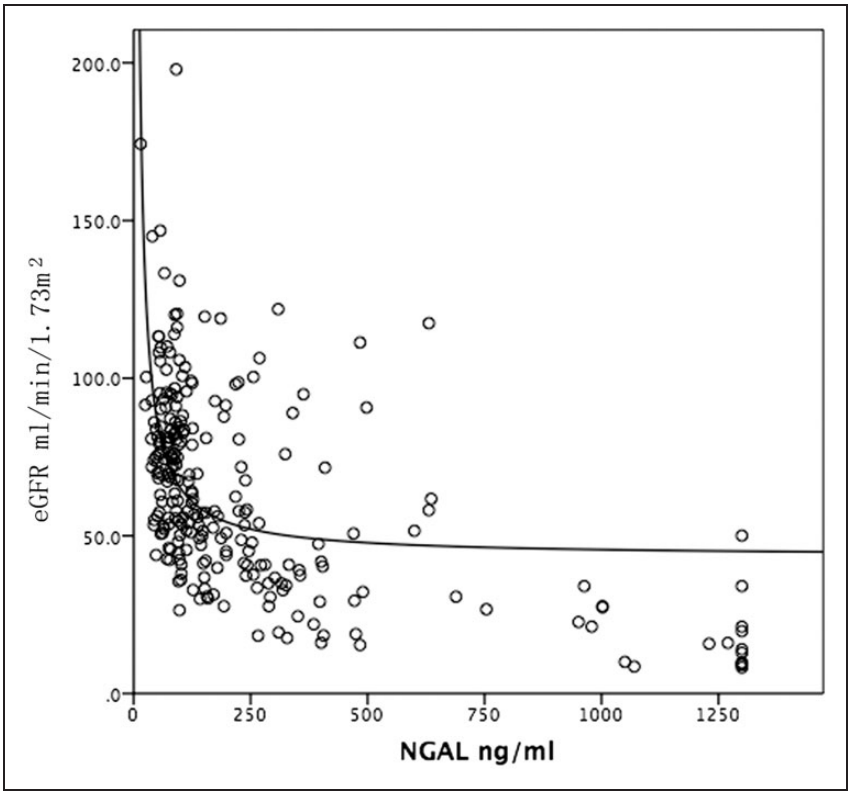

Figure 3. Curve estimate of NGAL and eGFR An inverse equation of 3-day eGFR = 43.461 + 2171.012/NGAL was established between NGAL and 3-day eGFR by curve regression analysis.

eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin.

with APACHE II (AUC = 0.914), which was better than NGAL alone (AUC = 0.883, Z = 13.620, P < 0.01) (Table 6 and Figure 4). The cutoff values of NGAL for predicting AKI, and 7-day, and 28-day mortality in critical ill patients were 125.5 ng/ml, 615.5 ng/ml and 145.0 ng/ml respectively.

Discussion

It is well known that hypoperfusion, especially of the non-crucial organs (including kidneys), is one of the key factors for AKI progressing, which is common in critically ill patients. It was reported by the latest meta-analysis that 1 in 5 adults (21.6%) and 1 in 3 children (33.7%) experienced AKI worldwide using the KDIGO definition.[15] AKI is increasingly observed in critical care settings; meanwhile, critically ill patients with normal renal function can progress quickly to severe AKI. It is crucial to identify those high-risk patients from others for targeted interventions. So far, the golden criteria of diagnosis and classification of AKI is Cr and urine output. However, the defects and the unreliability of Cr and urine output for monitoring renal function in the critically ill and in the acute setting are well known.[16] Cr also lacks the sensitivity to detect minor changes in renal function.

Table 6. The AUC of NGAL, eGFR and APACHE II.

					95% C.I.	
	Variable	AUC	S.E.	P	lower	upper
AKI	NGAL	0.923	0.016	<0.001	0.891	0.956
	1-day eGFR	0.534	0.038	0.362	0.460	0.608
7-day mortality	NGAL	0.883	0.040	<0.001	0.805	0.962
	1-day eGFR	0.525	0.068	0.688	0.392	0.658
	APACHE II	0.765	0.051	<0.001	0.665	0.866
	NGAL + APACHE II	0.914	0.026	<0.001	0.862	0.965
28-day mortality	NGAL	0.723	0.034	<0.001	0.656	0.790
	1-day eGFR	0.492	0.040	0.847	0.413	0.571
	APACHE II	0.633	0.039	0.001	0.556	0.710
	NGAL+ APACHE II	0.718	0.035	<0.001	0.649	0.788

AUC: area under the receiver operating characteristic curve; AKI: acute kidney injury; NGAL: neutrophil gelatinase-associated lipocalin; sCr: serum creatine; eGFR: estimated glomerular filtration rate; APACHE II Score: acute physiology and chronic health evaluation II score.

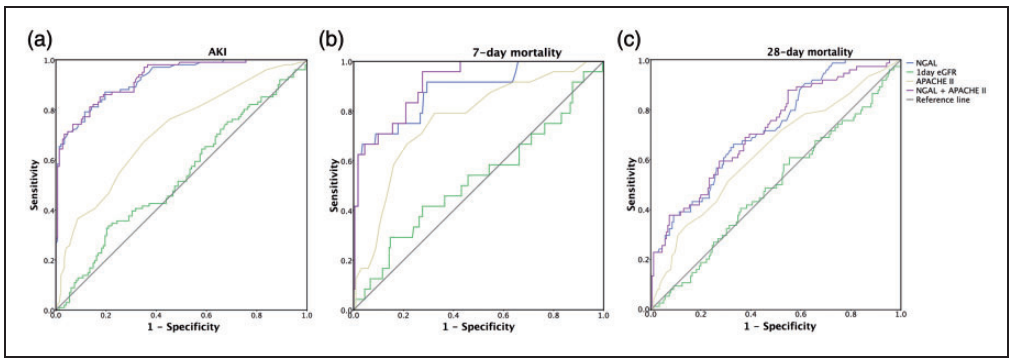

Figure 4. ROC curves ROC curves of NGAL, APACHE II score, eGFR, sCr and NGAL + APACHE II score for predicting AKI and mortality. (a) ROC curves for predicting AKI; (b) ROC curves for predicting 7-day mortality; (c) ROC curves for predicting 28-day mortality.

APACHE II: acute physiology and chronic health evaluation II; eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin; ROC: receiver operating characteristic.

In our study, eGFR was derived from sCr by the Cockcroft-Gault equation. There are more accurate methods for estimating eGFR, such as the Modification of Diet in Renal Disease (MDRD) equation, but that was built from the chronic kidney disease (CKD) population.[17] It is well known that the relationship between eGFR and Cr is not the same in CKD and healthy subjects.[18] Indeed, the MDRD formula may underestimate the true eGFR in healthy subjects, especially when its value is $\geq$60 ml/min/1.73 m^2.[19,20] Since most of our patients, especially in the DKA group, had normal kidney function when they were enrolled, we used the Cockcroft-Gault equation, which correlated with the MDRD equation and is more accurate in normal kidneys.

NGAL is a ubiquitous protein of 178 amino acids with a molecular mass of approximately 25 kDa and is composed of 8 beta sheets that form a shaped structure.[21] In an induced kidney injury experiment, Paragas et al.[22] found that the timing and the intensity of NGAL mRNA and protein were correlated and dependent on the degree of kidney damage. POCT NGAL measurement aided the assessment of renal function during acute burn resuscitation in an ICU, but in this investigation, only 15 patients were involved.[23] A similar result was found in our previous experiments in a porcine model of cardiac arrest for predicting renal function[24]; there was a positive correlation between the grade of renal injury and serum NGAL level.[25] Thus, detection of early renal injury is possible by NGAL levels even when sCr levels are normal.

ADHF, sepsis and DKA are the most common critical diseases in the ED, which can decrease renal perfusion significantly. Therefore, it was not a surprise that AKI was found in these patients after a period of normal renal function. That was why we used them to investigate AKI in non-preexisting renal disease patients. Our previous investigation already confirmed that NGAL was higher in the septic patients with AKI than those without AKI.[5] In this investigation, we shifted the testing time of NGAL as early as we could, and used the fastest RT-POCT technology. We tried to confirm the predictive value of NGAL in critically ill patients with normal sCr. In our study, elevated NGAL levels with the deterioration of renal function during hospital stay were observed. The incidence of AKI was 40.6% in all enrolled patients, and was 34.7%, 50.6% and 44.0% of ADHF, sepsis and DKA patients respectively. This suggests that the presence of underlying acute tubular injury, detected by elevated NGAL level, may be directly associated with development of AKI. Logistic regression also confirmed that the increase of NGAL level was an independent risk factor for the KDIGO classification, and 7-day and 28-day mortality.

Diabetes mellitus (DM) is always accompanied by the potential decline of kidney function with time, although the Cr could be normal. The relatively low reserved renal function may be an issue when patients with DM undergo physiological stress. Moreover, when patients with DM developed DKA, there was always more severe tissue hypoperfusion than in HF and sepsis because of the dehydration. Therefore, it is not surprising that the percentage of KDIGO 3 patients was the highest in the DKA group compared with the other two groups. Furthermore, we have evaluated the power of NGAL in prognosis. The results show that the NGAL combined with the APACHE II score was not any more beneficial than NGAL alone for predicting 28-day mortality. However, this was different when combining them for predicting 7-day mortality, which was better than using NGAL only. That may be because the APACHE II score emphasized the acute physiological condition of a patient with relative normal renal function, so it could not evaluate the future prognosis. However, NGAL can do what the APACHE II score cannot do, which may demonstrate that it is a sensitive marker for evaluating the severity of early AKI and further prognosis. In our investigation, when sCr or eGFR were still normal, NGAL was already abnormal. Notably, eGFR would not decrease until 3 days later. Furthermore, an inverse regression was found between the NGAL and 3-day eGFR, which also supported that there might be a relationship between NGAL and renal function, although this relationship may not be a simple linear one.

Historically, emergency physicians have been caught between the proverbial rock and a hard place when evaluating critically ill patients. Our choices were limited to using rapid but analytically imprecise assays or

more accurate but significantly slower laboratory platforms. Although it is currently agreed that the time delay of the slower tests is "just an hour or so difference",[7] the risk of patient morbidity and mortality increases with more time spent in the ED.[26] Similarly, the earlier the recognition of AKI, the better the kidney function may recover. It is important to recognize that the timing of biomarker measurement has a significant impact on the ability of NGAL to predict the development of AKI, since NGAL was also time dependent. Currently, NGAL can be measured in whole blood, serum, plasma, and urine by several commercially available analytical immunoassays. However, most of the measurements take a relatively long time (at least 2 hours), which may increase the emergency physicians' therapeutic turnaround time and ultimately extend the time of stay in the ED. In this study, we used the RT-POCT NGAL, which was conducted beside the patient in less than half an hour. So far, there are few studies investigating the RT-POCT NGAL in clinical use, especially in the ED. Currently, critically ill patients arrive at the ED, a quick evaluation is done and NGAL is tested as soon as the blood sample is taken. On average, the time it takes for the NGAL test results to return from the time of the patients' arrival was thirty minutes. This was much faster than the central laboratory. Thus, ownership of the RT-POCT NGAL can facilitate ED physicians' ability to confirm a diagnosis of AKI and reduce their therapeutic turnaround time.

Limitations

This was a single-center study and the number of enrolled patients was only 249. In this study, we did not compare other severity score systems and biomarkers. The NGAL level was measured only once and its dynamic changes over time were not observed. In contrast, infection can influence the NGAL level in serum,[27] which may bias our results. However, a significant difference of serum NGAL could be found between patients with or without AKI in the sepsis group, so it may not influence the conclusions of our investigation.

Conclusions

NGAL is an independent predictor of AKI, and 7-day and 28-day mortality in critically ill patients in the ED. POCT NGAL can alert to AKI early and provide a prognosis in critically ill patients.

Acknowledgments

The authors thank the staff of both the ED and local medical research centers for their excellent and skillful guidance.

Authors' contributions

CCH conceived the study, designed the trial, Jun Yang drafted the manuscript. ZRT undertook recruitment of participating centers and patients and managed the data, including quality control. SW provided statistical advice on study design and analyzed the data. CSL took responsibility for the overall content as the guarantor and helped to revise the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

This was a single-center observational study approved by the Beijing Chao-Yang Hospital, Capital Medical University Ethics Committee, and all subjects provided written informed consent.

Funding

This research was supported by a grant from the Natural Science Foundation of China (No. 81372025).

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