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Original Research Article

Delta index of the estimated glomerular filtration rate to amend the overestimated Neutrophil Gelatinase-Associated Lipocalin (NGAL) level in systemic inflammatory response syndrome

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ABSTRACT

This study aimed to investigate a delta index of the estimated glomerular filtration rate (δeGFR-index) to amend an overestimated neutrophil gelatinase-associated lipocalin (NGAL) level in systemic inflammatory response syndrome (SIRS). A δeGFR-index was computed, and the NGAL/δeGFR-index was determined. Patients with SIRS exhibited significantly higher levels in NGAL, the δeGFR-index, and high sensitivity C-reactive protein (hsCRP) than non-SIRS inflammatory patients (216 ng/ml, 1.32, and 5.64 mg/dl vs. 153 ng/ml, 1.18, and 2.92 mg/dl, respectively, $p < 0.05$). After adjusting for potential confounders, the NGAL/δeGFR-index was closely associated with serum hsCRP concentrations (standard $\beta = 0.552$, $p < 0.001$). In a receiver operating characteristic curve, the diagnostic ability of the NGAL/δeGFR-index to identify SIRS in inflammatory diseases was superior to that of the NGAL [0.712 (95% CI, 0.638–0.786) vs. 0.646 (95% CI, 0.567–0.726), $p < 0.001$]. The area under the curve of the NGAL/δeGFR-index was significantly larger than that of NGAL for detecting hsCRP >3.80 mg/dl in SIRS [0.761 (95% CI, 0.660–0.862) vs. 0.728 (95% CI, 0.625–0.831), $p = 0.019$]. In short, the NGAL/δeGFR-index more correctly represents the disease activity in SIRS than the level of plasma NGAL. A measure of the NGAL/δeGFR-index may be of additional help when monitoring patients with SIRS, particularly in conjunction with concurrent renal dysfunction.

Introduction

Systemic inflammatory response syndrome (SIRS) is a complex pathophysiologic response to an insult such as infection, trauma, burns, pancreatitis, or a variety of other injuries (Balk, 2014). SIRS is characterized by a massive inflammatory reaction resulting from the release of systemic mediators and is associated with high mortality often due to multiple organ dysfunction (Bone, 1996; Russell et al., 2000). When SIRS is the result of a confirmed infectious process, it is termed sepsis (Bone et al., 1992). At least 30% of patients with SIRS have or have developed sepsis (Brun-Buisson, 2000; Rangel-Frausto et al., 1995).

Neutrophil gelatinase-associated lipocalin (NGAL), also named siderocalin, uterocalin, or lipocalin-2, is a 25-kDa glycoprotein that was originally identified in human neutrophils and mouse kidney cells (Kjeldsen et al., 1993). NGAL has many diverse functions including as a modulator of inflammation, a scavenger of bacterial products, an agent in iron trafficking, and apoptosis (Cowland and Borregaard, 1997). NGAL is an acute phase reactant, which is comparable to the peripheral inflammatory markers, such as high sensitivity C-reactive protein (hsCRP), interleukin-6, and tumor necrosis factor-α (Naude et al., 2013).

During ischemic and toxic kidney damage, production of NGAL is upregulated in the proximal tubules of the distal nephron, resulting in a marked increase in urinary NGAL levels (Devarajan, 2010). However, the contribution of renal injury to serum concentrations of NGAL has been debated and the main source of plasma NGAL is suggested to originate from activated neutrophils (Rau et al., 2013).

Clinical use of NGAL as a novel marker for early detection of acute kidney injury has been extensively studied because NGAL increases preceding serum creatinine elevation by approximately

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48–72 h (Haase et al., 2011; Mishra et al., 2003). However, there have been few studies, which have closely examined whether the plasma NGAL concentration accurately reflects the inflammatory status in SIRS, particularly under impaired renal function.

Because SIRS is commonly accompanied by multiple organ failure including renal dysfunction, plasma NGAL levels in SIRS are apt to be overestimated owing to the inflammation and coincident impaired renal function. In the present study, we proposed a new parameter, a delta index of the estimated glomerular filtration rate (δeGFR-index), which was designed to minimize the impact of renal dysfunction on plasma NGAL level in SIRS. We also tested the diagnostic accuracy of the NGAL/δeGFR-index to identify SIRS and to detect an increased hsCRP, especially compared with that of NGAL.

Materials and methods

Study populations

A total of 182 patients with SIRS ($n = 95$) and non-SIRS inflammatory diseases ($n = 87$) were investigated. NGAL, cardiac biomarkers, eGFR, and hsCRP levels were measured. Subjects ranged in age from 28 to 84 years (median age, 66 years) and 97 patients were males (53.3%). Age- and sex-matched healthy individuals ($n = 54$), who had no history of recent infection, chronic inflammation, and renal dysfunction, were enrolled as a control group. This study was approved by the Institutional Review Board of our University Hospital.

The patients were admitted to the hospital via emergency room or outpatient departments, and suffered from the following diseases: pneumonia ($n = 47$), upper respiratory tract infection ($n = 32$), acute hepatitis ($n = 25$), urinary tract infection ($n = 23$), acute pyelonephritis ($n = 19$), acute cholecystitis ($n = 13$), acute pancreatitis ($n = 12$), cellulitis ($n = 6$), and cystitis ($n = 5$). Blood sample was obtained from patients at admission, immediately centrifuged, and stored at $-70\,^{\circ}C$ until analysis.

The diagnostic criteria of SIRS were based on the recommendations of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee, as described previously (Bone et al., 1992). Non-SIRS inflammatory patients were defined as the individuals who had clinical and laboratory evidence of inflammation but did not meet the criteria for SIRS. Patients with diabetic nephropathy ($n = 4$), cardiovascular diseases ($n = 3$), and stroke ($n = 1$) were excluded from this study because these conditions may affect plasma NGAL levels. Subjects who had missing values ($n = 6$), a recent operation ($n = 1$), or administration of anti-inflammatory drugs ($n = 2$) were also excluded from this study.

Measurement of laboratory parameters

Plasma concentrations of NGAL were measured by fluorescence immunoassays using the Triage NGAL assay (Alere Inc., San Diego, CA, USA), which can analyze NGAL in a measurable range from 15 ng/ml to 1300 ng/ml. The intra-assay CVs ($n = 20$) for three samples (mean NGAL, 62–509 ng/ml) were 4.2–6.5%; the inter-assay CVs calculated from duplicate results in 10 subsequent assays were 4.3–7.1%. A medical decision point for the plasma NGAL level was defined as 150 ng/ml, as described previously (Haase et al., 2009).

Serum hsCRP level was determined by the particle-enhanced immunonephelometry assay (Dade Behring, Inc, Deerfield, IL, USA), and was set at >0.3 mg/dl for laboratory evidence of inflammation, which was based on the cutoff value of the 95% confidence interval for hsCRP of healthy individuals.

Blood urea nitrogen, serum creatinine, and hsCRP were analyzed with a chemical analyzer (Hitachi 7600; Hitachi, Tokyo, Japan). Assays for cardiac biomarkers, including creatine kinase-MB (CK-MB), and troponin-I were performed on a Cobas 411 immunoassay analyzer (Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacturer's instruction. The cardiac biomarkers were measured by an electrochemiluminescence immunoassay, using the Elecsys anti-CK-MB and anti-cardiac troponin-I (Roche Diagnostics GmbH).

Calculation of the δeGFR-index

The delta eGFR (δeGFR) was calculated, based on a normal eGFR of 90 ml/min/1.73 m^2, from the following equation: δeGFR = (90 – eGFR)/90. For subjects with eGFR >90 ml/min/1.73 m^2, the eGFR value was set to 90 ml/min/1.73 m^2 to avoid a negative value of δeGFR. The δeGFR-index was determined as 1 + δeGFR. The NGAL/δeGFR-index was computed using the following formula: NGAL/δeGFR-index = plasma NGAL concentration (ng/ml)/δeGFR-index. The provisional cutoff limit of the NGAL/δeGFR-index was set to 116 ng/ml and was based on the value of the 95th percentile for healthy controls included in this study. Higher values of this index were considered as elevated.

The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula: $eGFR = 186 \times [sCr\ (mg/dl)]^{-1.154} \times [age\ (years)]^{-0.203}$. A correction factor of 0.742 was used for women. Patients with eGFR <60 ml/min/1.73 m^2 and ≥90 ml/min/1.73 m^2 were regarded as having the impaired- and normal-renal function, respectively (Tsuchikura et al., 2010).

Patients were classified into two groups: SIRS ($n = 95$) and non-SIRS ($n = 87$). Patients were further stratified into each two subgroups, after excluding the subjects with markedly decreased renal function (eGFR <43.5 ml/min/1.73 m^2) and with high-grade inflammation (hsCRP >10.0 mg/dl). These figures were based on the cutoff value of the lower- and upper- 25th percentiles of eGFR and hsCRP levels in our patient populations, respectively: patients with an eGFR ≥43.5 ml/min/1.73 m^2 [SIRS ($n = 67$) and non-SIRS ($n = 72$)]; patients with hsCRP ≤10.0 mg/dl [SIRS ($n = 63$) and non-SIRS ($n = 74$)].

Statistical analysis

Data were expressed as mean ± standard deviation (SD) or median (interquartile range). The normality of the data distribution was confirmed by the Shapiro-Wilk test. Categorical variables were listed as frequencies and proportions. A Mann-Whitney *U* test and a Student *t*-test were used to analyze the data between the two groups. A multivariate regression analysis between hsCRP concentrations and the levels of NGAL and the NGAL/δeGFR-index was conducted. Adjustment for potential confounders, such as age, gender, body mass index (BMI), systolic blood pressure, hemoglobin, and troponin-I, was performed. A receiver operating characteristics (ROC) curve was analyzed to assess the diagnostic competence of NGAL and NGAL/δeGFR-index to identify SIRS in patients with inflammation and to detect the hsCRP >3.80 mg/dl, which was the median hsCRP level in the patients group. A data analysis was done using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). All p values <0.05 were considered statistically significant.

Results

Plasma NGAL level

The baseline characteristics of the study population are summarized in Table 1. There were no significant differences in

Table 1
Baseline characteristics of patient populations included in this study.

	Patient group ($n = 182$)	Healthy controls ($n = 54$)	P value
Anthropometric parameters			
Age (year)	66 (28–84)	63 (2–83)	0.305
Gender (male)	97 (53.3)	27 (52.9)	0.697
BMI (kg/m^2)	22.6 ± 3.8	23.0 ± 2.4	0.570
SBP (mmHg)	127.4 ± 30.4	123.6 ± 19.2	0.291
NGAL levels			
NGAL (ng/ml)	185 (89–417)	63 (52–78)	<0.001
NGAL/δeGFR-index (ng/ml)	145.1 (80.1–299.6)	60.2 (50.7–74.0)	<0.001
Percent difference (95% CI)	20.8 (0.0–46.4)	5.1 (0.0–21.1)	<0.001
NGAL >150 ng/ml (n, %)	101 (55.5)	2 (3.2)	<0.001
NGAL/δeGFR-index >116 ng/ml (n, %)	109 (59.9)	3 (4.8)	<0.001
Renal parameters			
eGFR (ml/min/1.73 m^2)	66.3 (43.5–85.3)	85.1 (76.7–96.6)	<0.001
δeGFR-index	1.26 (1.05–1.51)	1.05 (1.00–1.14)	<0.001
Creatinine (mg/dl)	1.12 (0.83–1.54)	0.87 (0.77–0.95)	<0.001
Inflammation indices			
hsCRP (mg/dl)	3.80 (0.94–10.00)	0.07 (0.05–0.15)	<0.001
Neutrophil (×10^9/l)	6.49 (4.13–10.76)	4.43 (3.44–6.47)	<0.001
Cardiac biomarkers			
CK-MB (ng/ml)	2.75 (1.30–6.50)	2.70 (1.35–5.45)	0.428
Troponin-I (ng/ml)	0.15 (0.10–0.30)	0.10 (0.10–0.30)	0.137

Data are expressed as mean ± standard deviation, median (interquartile range), or frequency (%).
Abbreviations: BMI: body mass index; SBP: systolic blood pressure; NGAL: neutrophil gelatinase-associated lipocalin; eGFR: estimated glomerular filtration rates; δeGFR-index: delta index of eGFR; hsCRP: high-sensitivity C-reactive protein; CK-MB: creatine kinase-MB.

the anthropometric parameters and cardiac biomarkers between the patients and healthy controls. However, plasma NGAL levels and the NGAL/δeGFR-index were significantly increased in the patient group versus the healthy controls (185 ng/ml and 145.1 ng/ml vs. 63 ng/ml and 60.2 ng/ml, respectively, $p < 0.001$). The percent difference between NGAL and NGAL/δeGFR-index in patient group was 20.8% (95% CI, 0.0–46.4%), which was significantly higher than that between the corresponding parameters in the healthy controls [5.1% (95% CI, 0.0–21.1%), $p < 0.001$] (Table 1).

Table 2
Plasma NGAL level and the NGAL/δeGFR-index in SIRS- and non-SIRS patients.

	Patient group		
	SIRS ($n = 95$)	Non-SIRS ($n = 87$)	P value
Anthropometric parameters			
Age (year)	65 (52–75)	67 (53–76)	0.912
Gender (male)	50 (52.6)	47 (54.0)	0.618
BMI (kg/m^2)	22.6 ± 3.8	22.7 ± 3.5	0.981
SBP (mmHg)	122.4 ± 29.2	128.2 ± 22.1	0.304
NGAL levels			
NGAL (ng/ml)	216 (102–583)	153 (84–268)	0.012
NGAL/δeGFR-index (ng/ml)	178.3 (88.4–412.7)	119.2 (79.0–215.6)	0.014
Percent difference (95% CI)	24.5 (0.0–46.2)	16.1 (0.0–46.7)	0.027
NGAL >150 ng/ml (n, %)	57 (60.0)	44 (50.6)	0.204
NGAL/δeGFR-index >116 ng/ml (n, %)	64 (67.4)	45 (51.7)	0.039
Renal parameters			
eGFR (ml/min/1.73 m^2)	60.8 (40.1–81.3)	72.6 (53.2–94.1)	0.039
eGFR <60 (ml/min/1.73 m^2)	46 (48.4)	26 (29.9)	<0.001
δeGFR-index	1.32 (1.09–1.55)	1.18 (1.00–1.40)	0.023
Creatinine (mg/dl)	1.20 (0.96–1.66)	0.97 (0.78–1.30)	0.016
Inflammation indices			
hsCRP (mg/dl)	5.64 (0.84–13.32)	2.92 (0.94–6.72)	0.035
hsCRP >10.0 (mg/dl)	32 (33.7)	13 (14.9)	<0.001
Neutrophil (×10^9/l)	9.74 (5.03–13.32)	5.69 (3.85–7.69)	0.001
Cardiac biomarkers			
CK-MB (ng/ml)	3.25 (1.55–7.35)	2.30 (1.10–5.45)	0.188
Troponin-I (ng/ml)	0.15 (0.10–0.30)	0.12 (0.10–0.25)	0.301

Data are expressed as mean ± standard deviation, median (interquartile range), or frequency (%).
Abbreviations: SIRS: systemic inflammatory response syndrome; BMI: body mass index; SBP: systolic blood pressure; NGAL: neutrophil gelatinase-associated lipocalin; eGFR: estimated glomerular filtration rates; δeGFR-index: delta index of eGFR; hsCRP: high-sensitivity C-reactive protein; CK-MB: creatine kinase-MB.

SIRS versus non-SIRS

Of the 95 SIRS patients, 46 (48.4%) had a decreased eGFR <60 ml/min/1.73 m^2, which was significantly higher than that of the non-SIRS patients [29.9% (26/87), $p < 0.001$]. There were no significant differences in the prevalence of plasma NGAL level >150 ng/ml between the SIRS and the non-SIRS groups. However, the incidence of the NGAL/δeGFR-index >116 ng/ml was significantly higher in the SIRS than in the non-SIRS groups (67.4% vs. 51.7%, $p = 0.039$). The hsCRP level and neutrophil count in the SIRS group were 5.64 mg/dl and 9.74×10^9/l, which were significantly above the values in the non-SIRS group (2.92 mg/dL and 5.69×10^9/l, respectively, $p < 0.05$) (Table 2).

NGAL level in relation to kidney function and severity of inflammation

The impact of decreased kidney function (eGFR <43.5 ml/min/1.73 m^2) and the severity of inflammation (hsCRP >10.0 mg/dl) on the plasma NGAL level were both tested. After excluding the patients with eGFR <43.5 ml/min/1.73 m^2 from the subject populations, the plasma NGAL level was still high in the SIRS group compared to the non-SIRS group (162 ng/ml vs. 120 ng/ml, $p = 0.023$). However, after excluding the patients with hsCRP >10.0 mg/dl, no significant difference was observed in plasma NGAL levels between the two groups (140 ng/ml vs. 137 ng/ml, $p = 0.785$) (Table 3).

Table 3
Plasma NGAL levels in SIRS- and non-SIRS patients after excluding subjects with markedly decreased kidney function and high-grade inflammation.

	After excluding subjects with eGFR <43.5 ml/min/1.73 m^2			After excluding subjects with hsCRP >10.0 mg/dl		
	SIRS ($n = 67$)	Non-SIRS ($n = 72$)	P value	SIRS ($n = 63$)	Non-SIRS ($n = 74$)	*P* value
Anthropometric parameters						
Age (year)	64 (49–73)	64 (47–76)	0.623	63 (49–75)	65 (52–76)	0.511
Gender (male)	26 (52.0)	32 (53.3)	0.213	34 (53.9)	29 (52.7)	0.476
BMI (kg/m^2)	22.5 ± 4.0	22.6 ± 3.8	0.941	22.5 ± 3.7	22.4 ± 3.5	0.858
SBP (mmHg)	125.8 ± 28.2	129.5 ± 19.6	0.476	128.5 ± 31.1	133.6 ± 20.3	0.305
Lipocalin levels						
NGAL (ng/ml)	162 (87–430)	120 (76–206)	0.023	140 (84–275)	137 (80–254)	0.785
NGAL/δeGFR-index (ng/ml)	144.0 (72.7–374.2)	93.7 (70.7–187.2)	0.031	115.4 (69.1–203.2)	111.0 (73.0–196.0)	0.936
Percent difference (95% CI)	17.2 (3.3–25.2)	9.6 (0.0–21.8)	0.038	21.1 (7.7–32.3)	12.2 (0.0–27.8)	0.167
Renal parameters						
eGFR (ml/min/1.73 m^2)	71.3 (59.6–86.8)	80.4 (64.7–96.4)	0.069	65.8 (46.1–82.2)	75.4 (54.9–94.5)	0.220
δeGFR-index	1.21 (1.03–1.33)	1.10 (1.00–1.28)	0.035	1.26 (1.08–1.47)	1.14 (1.00–1.38)	0.167
Creatinine (mg/dl)	1.08 (0.78–1.25)	0.88 (0.76–1.10)	0.016	1.14 (0.89–1.51)	0.95 (0.76–1.26)	0.094
Inflammation indices						
hsCRP (mg/dl)	5.21 (0.84–11.67)	2.82 (0.89–6.27)	0.078	2.75 (0.21–5.84)	2.25 (0.88–4.66)	0.758
Neutrophil ($\times 10^9$/l)	9.90 (5.03–13.32)	5.69 (3.73–7.43)	0.002	9.69 (4.98–12.47)	5.42 (3.73–7.69)	0.001
Cardiac biomarkers						
CK-MB (ng/ml)	2.4 (1.1–6.9)	1.7 (1.0–3.4)	0.375	3.8 (1.9–8.5)	2.3 (1.2–5.7)	0.122
Troponin-I (ng/ml)	0.13 (0.10–0.30)	0.12 (0.10–0.30)	0.086	0.15 (0.10–0.30)	0.13 (0.10–0.16)	0.242

Data are expressed as mean ± standard deviation or median (interquartile range).
Abbreviations: SIRS: systemic inflammatory response syndrome; BMI: body mass index; SBP: systolic blood pressure; NGAL: neutrophil gelatinase-associated lipocalin; eGFR: estimated glomerular filtration rates; δeGFR-index: delta index of eGFR; hsCRP: high-sensitivity C-reactive protein; CK-MB: creatine kinase-MB.

Table 4
Multivariate regression analysis between the NGAL/δeGFR-index and hsCRP level in patients with SIRS.

	NGAL/δeGFR-index			NGAL		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
hsCRP (mg/dl)	0.611 (<0.001)	0.578 (<0.001)	0.552 (<0.001)	0.571 (<0.001)	0.519 (<0.001)	0.483 (<0.001)
Age (year)		0.182 (0.104)	0.153 (0.125)		0.206 (0.045)	0.195 (0.069)
Gender (male)		−0.103 (0.264)	−0.003 (0.975)		−0.140 (0.137)	−0.090 (0.397)
BMI (kg/m^2)		0.141 (0.135)	0.063 (0.534)		0.061 (0.531)	0.045 (0.685)
Systolic BP (mmHg)			0.129 (0.190)			0.042 (0.678)
Hemoglobin (mg/dl)			−0.151 (0.150)			−0.155 (0.120)
Troponin-I (ng/ml)			−0.033 (0.734)			−0.080 (0.426)

Correlations of the NGAL/δeGFR-index and NGAL versus the various independent variables are expressed as standard β (*p* values). Model 1: unadjusted; model 2: adjusted for age, gender, and BMI; model 3: adjusted for age, gender, BMI, systolic BP, hemoglobin, and troponin-I.
Abbreviations: NGAL: neutrophil gelatinase-associated lipocalin; eGFR: estimated glomerular filtration rates; hsCRP: high-sensitivity C-reactive protein; BMI: body mass index.

NGAL versus NGAL/δeGFR-index

After adjusting for potential confounders, serum hsCPR concentrations were closely linked with the NGAL/δeGFR-index (standard $\beta = 0.552$, $p < 0.001$) and NGAL levels (standard $\beta = 0.483$, $p < 0.001$) (Table 4). An example for the scatter plots of NGAL and the NGAL/δeGFR-index versus hsCRP is displayed in Fig. 1.

ROC curve analysis

The diagnostic accuracy of NGAL and the NGAL/δeGFR-index to identify SIRS in inflammatory patients was investigated. In an ROC curve analysis, the area under the curve (AUC) of the NGAL/δeGFR-index was significantly larger than that of the plasma NGAL concentration [0.712 (95% CI, 0.638-0.786) vs. 0.646 (95% CI, 0.567-0.726), $p < 0.001$]. In addition, the diagnostic value of NGAL/δeGFR-index outperformed that of NGAL for detecting an increase in hsCRP >3.80 mg/dl in SIRS [0.761 (95% CI, 0.660-0.862) vs. 0.728 (95% CI, 0.625-0.831), $p = 0.019$] (Fig. 2).

Discussion

In this study, a new parameter, the δeGFR-index, was used to adjust the overestimated plasma NGAL levels in patients with SIRS. The NGAL/δeGFR-index was closely associated with the intensity of inflammation in SIRS. Furthermore, the NGAL/δeGFR-index resulted in better diagnostic performance than NGAL in identifying SIRS. The results suggest that the NGAL/δeGFR-index more accurately represents the disease activity in SIRS patients with renal dysfunction.

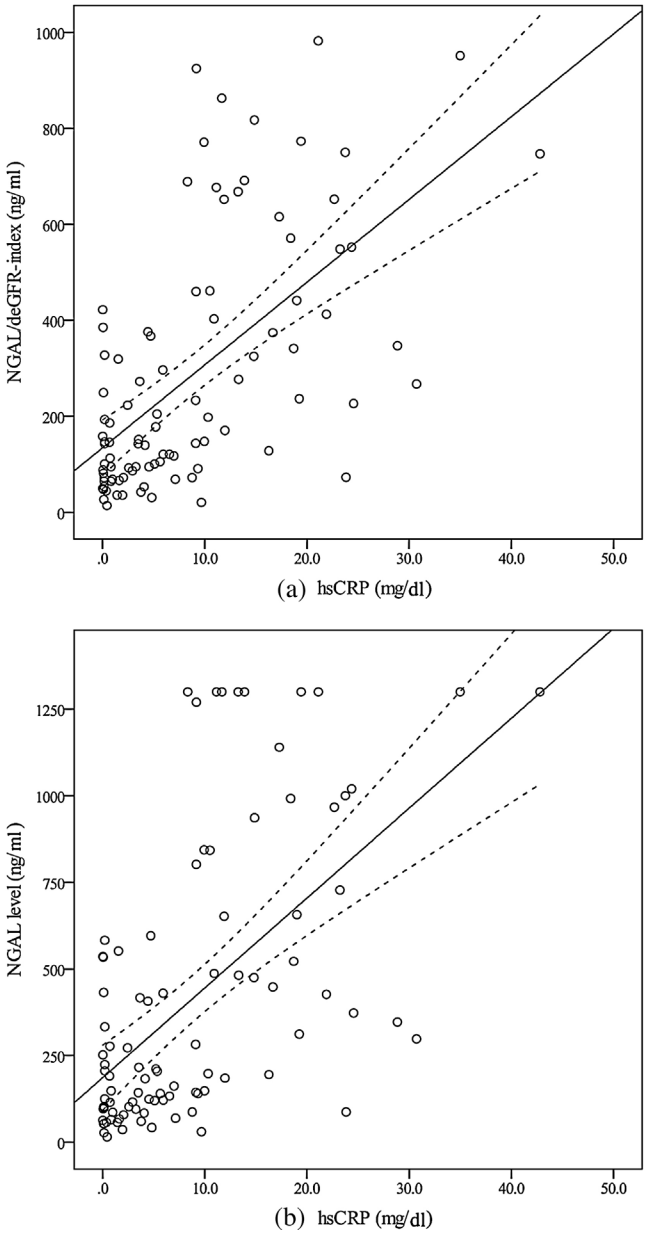

Fig. 1. An example of regression analysis of the NGAL/δeGFR-index (a) and NGAL (b) versus hsCRP levels in SIRS patients [the NGAL/δeGFR-index ($y = 17.24\times + 134.53$, $r^2 = 0.373$; $p < 0.001$); NGAL ($y = 25.94x + 185.97$, $r^2 = 0.326$; $p < 0.001$)].

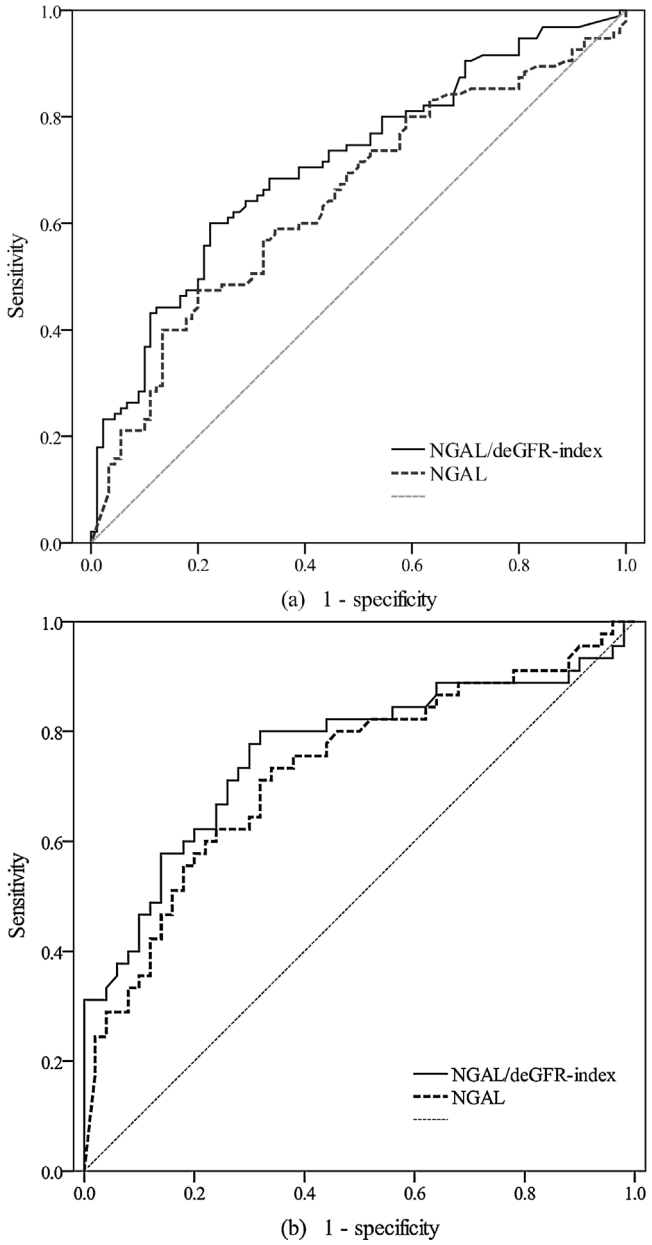

Fig. 2. An ROC curve analysis for the NGAL and the NGAL/δeGFR-index to identify SIRS in inflammatory patients (a) and to detect an increased hsCRP >3.80 mg/dl in SIRS patients (b). The AUCs of the NGAL/δeGFR-index are larger than those of NGAL, respectively: (a) [0.712 (95% CI, 0.638-0.786) vs. 0.646 (95% CI, 0.567-0.726), $p < 0.001$] and (b) [0.761 (95% CI, 0.660-0.862) vs. 0.728 (95% CI, 0.625-0.831), $p = 0.019$].

In our study, the median plasma NGAL concentrations in SIRS patients were significantly above the values in non-SIRS inflammatory patients. Our data are in general agreement with the results of previous studies, which demonstrated that plasma NGAL concentration is increased in patients with SIRS (Martensson et al., 2010), and that NGAL has diagnostic and prognostic potentials as one of the most robust markers for SIRS (Reichsoellner et al., 2014).

Multiorgan dysfunction syndrome, also known as multiple organ failure, represents a broad spectrum of cumulative organ dysfunction from a slightly altered function to irreversible organ failure (Vincent et al., 1996). Infection is the main cause of multiorgan dysfunction, and sepsis contributes to approximately 41% of organ failures (Ferreira and Sakr, 2011). Non-infectious inflammatory diseases may also precipitate organ failure. In a recent multicenter study, Dulhunty et al. (2008) reported that the prevalence of organ failure was 47.6% in patients with SIRS. In our study, 48.5% of patients suffering from SIRS exhibited a renal impairment with eGFR <60 ml/min/1.73 m^2, which significantly exceeded the value (29.9%) of non-SIRS inflammatory patients.

SIRS is frequently associated with the development of acute kidney injury (Uchino et al., 2005). This indicates that plasma NGAL levels can be influenced by impaired renal function as well as by inflammatory response in SIRS. In the current study, we tried to correct plasma NGAL concentration using the δeGFR-index to reduce the impact of kidney function on plasma NGAL level in SIRS. After adjusting for the δeGFR-index, the NGAL/δeGFR-index was more closely associated with hsCRP concentrations. These observations imply that corrected NGAL levels exactly reflect the intensity of inflammation in SIRS.

In this study, the diagnostic value of the NGAL and the NGAL/δeGFR-index were evaluated. The AUC of the NGAL/δeGFR-index, which discriminates SIRS from inflammatory diseases and examines a raised hsCRP level, was significantly larger than that of NGAL. As a cutoff limit, the application of the NGAL/δeGFR-index (116 ng/ml) yielded a better achievement in a prevalence survey than the use of plasma NGAL (150 ng/ml). These findings may be due to the effect of adjustment for augmented NGAL levels.

In our study, the median percent difference between NGAL and the NGAL/δeGFR-index was 20.8%, suggesting that renal dysfunction is accountable for approximately 20.8% of enhanced NGAL production in SIRS. This result emphasizes that the NGAL level in patients with SIRS needs to be amended using the δeGFR-index, especially when patients had a concurrent renal impairment.

NGAL is produced by injured kidney cells and the activated neutrophils in response to bacterial infections. NGAL is freely filtered by the intact glomeruli, and plasma levels are expected to increase when eGFR is decreased (Martensson et al., 2013). However, the origin of elevated NGAL in the plasma during renal dysfunction is still unclear. Back-leak into the circulation of NGAL produced by tubular cells has been suggested but is not supported through experimental animal studies (Schmidt-Ott et al., 2007). A group of researchers reported that in the general population, the neutrophil count is the main determinant of the plasma NGAL level and that the contribution of kidney function to NGAL levels is relatively small (Lindberg et al., 2014).

In our study, we sought to examine which parameter between eGFR and hsCRP more significantly contributes to plasma NGAL level in SIRS. After excluding SIRS patients with hsCRP >10.0 mg/dl from the subject populations, elevated NGAL concentration returned to the level not significantly different from non-SIRS inflammatory patients. However, no significant difference was noted after excluding those with eGFR <43.5 ml/min/1.73 m^2. These results suggest that inflammation plays a more pivotal role in plasma NGAL levels than does the impaired renal function in SIRS. These observations are in partial agreement with the results of Helmersson-Karlqvist et al. (2013), who disclosed that the plasma NGAL concentration mainly reflects inflammation but not chronic kidney disease.

There are several limitations in this study. The urinary NGAL level was not measured and subjects were not stratified into infective- and non-infective SIRS because of the small sample size. The time frame for collecting blood may differ among the subject populations because a fixed-time sampling approach was not applicable. Since the clinical utility of biomarkers is dependent on the time at which they are sampled following renal injury (Pickering and Endre, 2014), a potential impact of collecting time on plasma NGAL level should be considered. Additionally, we stress that the NGAL/δeGFR-index might be influenced by a sudden decrease in eGFR in SIRS patients (e.g., acute kidney injury) and by possibly missing information on renal or other organ injuries. Despite these limitations, our study demonstrates its significance. To our knowledge, this is the first study to investigate the δeGFR-index as an indicator of renal function and as a parameter to correct the overestimated NGAL levels in SIRS. Our data may have important implications for the evaluation of SIRS, particularly in patients with concomitant renal dysfunction. However, further validation is needed in larger randomized prospective trials, although the NGAL/δeGFR-index has a strong association with hsCRP in our patient populations.

In conclusion, this study demonstrates that the NGAL/δeGFR-index correctly represents the inflammatory status in SIRS. The NGAL/δeGFR-index is superior to plasma NGAL in diagnostic efficacy to identify SIRS in patients with inflammation. The measurement of the NGAL/δeGFR-index may be of help for reducing the influence of renal dysfunction on plasma NGAL level in patients with SIRS.

Conflict of interest

The authors declare that they have no conflict of interests regarding the publication of this paper.

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