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Neutrophil gelatinase-associated lipocalin as an early predictor of contrast-induced nephropathy following endovascular therapy for arteriosclerosis obliterans

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Abstract

Serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) are standard biomarkers of contrast-induced nephropathy (CIN). However, recent studies suggest that serum neutrophil gelatinase-associated lipocalin (sNGAL) and urine neutrophil gelatinase-associated lipocalin (uNGAL) may be better predictors, particularly within 24 hours of contrast medium exposure.

We conducted a prospective, observational cohort study of 107 consecutive patients diagnosed with arteriosclerosis obliterans between February 2016 and October 2018. We divided the patients into 2 groups: CIN (n = 22) and non-CIN (n = 85). We assessed the correlation between sNGAL and uNGAL concentrations and standard renal markers at baseline, 6, 24, and 48 hours post-procedure. We constructed conventional receiver operating characteristic (ROC) curves and calculated the area under the curve to assess the performance of SCr, eGFR, sNGAL, and uNGAL. We derived biomarker cutoff levels from ROC analysis to maximize sensitivity and specificity.

The incidence of CIN within our cohort was 20.6%. sNGAL levels correlated significantly with SCr and eGFR at baseline, 6, 24, and 48 hours post-contrast medium exposure. Similarly, uNGAL levels correlated with SCr and eGFR at baseline, 24, and 48 hours post-exposure. sNGAL and uNGAL were significantly elevated as early as 6 hours post-catheterization in the CIN group, whereas only minor changes were observed in the non-CIN group. SCr was also significantly elevated in the CIN group, but not until 24 hours post-catheterization.

Both sNGAL and uNGAL may be superior to SCr and eGFR as early biomarkers of CIN in patients with peripheral vascular disease undergoing endovascular therapy.

Abbreviations: AKI = acute kidney injury, BMI = body mass index, CIN = contrast-induced nephropathy, CT = computed tomography, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, PCI = percutaneous coronary intervention, ROC = conventional receiver operating characteristic, SCr = serum creatinine, sNGAL = serum neutrophil gelatinase-associated lipocalin, uNGAL = urine neutrophil gelatinase-associated lipocalin.

Keywords: arteriosclerosis obliterans, contrast-induced nephropathy, endovascular therapy, neutrophil gelatinase-associated lipocalin, percutaneous angioplasty

1. Introduction

Recent improvements in radiologic imaging and interventional therapy have resulted in rapidly increasing use of contrast media in routine medical practice. During the past 2 decades, use of computed tomography (CT) scanning has increased by 800%, and an increase of 390% in cardiac catheterization has been reported in the United States.[1] Some patients undergoing these diagnostic and therapeutic procedures are at risk for developing contrast-induced nephropathy (CIN).[2] Indeed, CIN is the third-leading cause of hospital-acquired acute kidney injury (AKI),[3] which is associated

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with prolonged in-hospital stay, increased costs, and unfavorable outcomes.[4,5] Poor outcomes are partly caused by the lack of timely and accurate biomarkers to predict CIN occurrence.

Currently, diagnosis of AKI relies on serum creatinine (SCr) and urinary output – 2 markers of kidney function rather than kidney injury. It is widely acknowledged that the use of SCr in diagnosing AKI has several limitations, including its delayed response and its responsiveness to purely hemodynamic adaptations of the glomerular filtration rate, often referred to as "prerenal state."[6–8] Due to the delayed response of SCr and the lack of specific symptoms, AKI is usually diagnosed late, when early specific therapies for intrinsic AKI are unavailable. Moreover, SCr changes often reflect chronic kidney disease rather than AKI. Due to these shortcomings, more reliable biomarkers are needed for the diagnosis of AKI.[9]

Conventionally, CIN is defined as an increase of ≥25% or ≥0.5 mg/dL SCr from baseline readings between 48 and 72 hours after the administration of contrast medium, when alternative explanations for renal impairment have been excluded. However, SCr requires days to accumulate, may not change until 50% or more of the kidney function has already been lost, and may be affected by many nonrenal factors, such as age, gender, intravascular volume, and nutrition, thus limiting its sensitivity and specificity in the early detection of CIN.[10]

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most promising biomarkers of renal epithelial injury.[11] Genomic, transcriptomic, and proteomic techniques have identified NGAL, which is rapidly induced and released from the injured distal nephron, as an early marker of AKI.[12,13] In contrast to serum creatinine, NGAL is specifically produced by the impaired nephron and then released into blood. This study assesses the suitability of NGAL as an early marker of CIN after elective endovascular therapy, compared to traditional markers [SCr and estimated glomerular filtration rate (eGFR)].

2. Methods

This was a prospective observational study of patients admitted to our department of vascular surgery between February 2016 and October 2018. Written informed consent was obtained from all participants.

2.1. Participants and study design

Consecutive patients (ages ≥18 years; n = 165) with arteriosclerosis obliterans undergoing endovascular therapy in our departments were recruited. Exclusion criteria included preexisting renal insufficiency and use of nephrotoxic drugs before or during the study period. We excluded 11 patients who were receiving hemodialysis, 23 patients who were chosen to receive bypass rather than endovascular therapy, and 24 patients without subsequent creatinine measurements, from further analysis (Fig. 1). Urine and blood samples were collected at baseline (prior to percutaneous angioplasty) and at 6, 24, and 48 hours after contrast administration. CIN was defined as an increase in the baseline SCr ≥25% within 48 hours of exposure to contrast medium, in the absence of an alternative etiology. We defined normal kidney function as a baseline eGFR greater than 60 mL/min per 1.73 m^2, with no transient or sustained increases in SCr or decreases in eGFR during the patient's hospital stay.

2.2. Diagnosis of kidney disease

Serum and urine creatinine levels were measured via a modified Jaffe method using an ARCHITECT ci16200 analyzer (LEADMAN, Beijing). Estimated GFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula [$eGFR\_MDRD = 175 \times SCr^{-1.154} \times age^{-0.203}$ ($\times 0.742$ if female)].[14] Urine neutrophil gelatinase-associated lipocalin (uNGAL) was measured on the same analyzer using a 2-step sandwich immunoassay with chemiluminescent signal detection. This assay utilizes high-affinity mouse antibodies generated toward distinct, non-overlapping NGAL epitopes. The functional sensitivity of the assay is 2 ng/mL, with a range extending up to 1500 ng/mL. The coefficient of variation for analytical imprecision (CV_A) for this assay in our laboratory is 4.5%. Serum neutrophil gelatinase-associated lipocalin (sNGAL) was measured by enzyme-linked immunosorbent assay (LEADMAN Beijing, China).

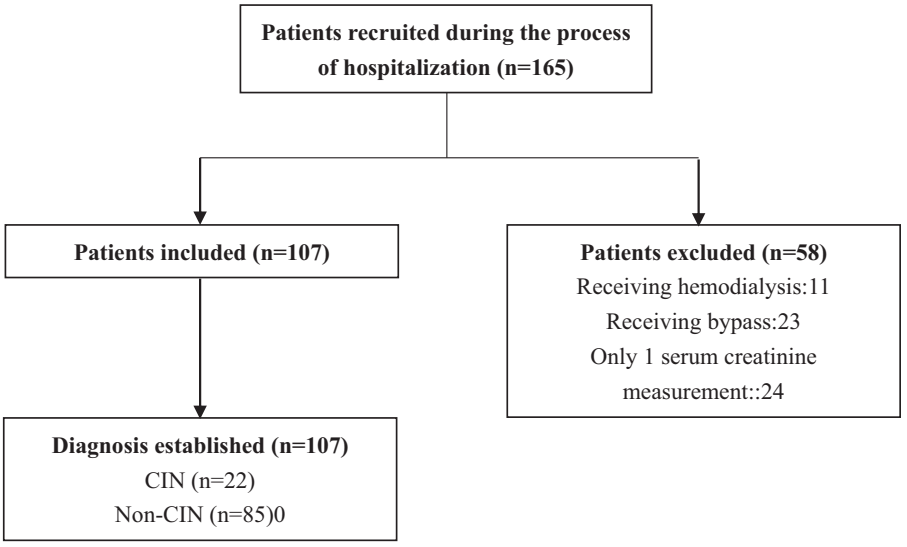

Figure 1. Diagram of study design. CIN = contrast-induced nephropathy.

2.3. Statistical analysis

Graphpad 7.0 and SPSS 22.0 were used for data analysis. Continuous variables between groups were compared using analysis of variance (ANCOVA), rejecting the null hypothesis at $P < .05$. Continuous variables are presented as mean ± standard deviation (SD). As sNGAL and uNGAL levels are not normally distributed, nonparametric tests were used to compare sNGAL and uNGAL concentrations. Spearman correlation coefficients were used to assess the correlation of sNGAL and uNGAL concentrations with standard renal markers. To determine the diagnostic test characteristics and assess performance, conventional receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated for sNGAL, uNGAL, and SCr. The sensitivity, specificity, and positive and negative predictive values of these markers were calculated for predicting CIN. Biomarker cutoff levels were derived from ROC analysis to maximize sensitivity and specificity. We also determined likelihood ratios and 95% confidence intervals (CIs) for each biomarker.

2.4. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Dezhou Municipal Medical Ethics Committee.

3. Results

3.1. Baseline characteristics and demographic data

We received urine and blood samples for biomarker measurements from 165 patients with arteriosclerosis obliterans admitted to our department of vascular surgery for endovascular therapy. Of these, we excluded 58 patients (Fig. 1). We tracked kidney function in the remaining 107 patients (80.4% males) by subsequent measurements of SCr during their hospital stay. Patients were divided into 2 groups based on presence (CIN) or absence (non-CIN) of CIN-AKI. There were no statistically significant differences in body mass index (BMI) or baseline sNGAL or uNGAL between the groups. With the exception of diabetes mellitus and administered contrast volume (significantly higher in the CIN group), the 2 groups were comparable at baseline ($P > .05$) with regard to the prevalence of peripheral vascular disease risk factors, including age, sex, hypertension, dyslipidemia, smoking, prior history of kidney disease or percutaneous angioplasty, and ankle-branchial index. These characteristics are summarized in Table 1.

3.2. Incidence of CIN

Twenty-two out of one hundred seven patients (20.6%) met our criteria for CIN acute kidney disease. Six of these twenty-two patients had non-progressive chronic kidney disease (27.2%). In the non-CIN group, 22 patients had history of kidney disease.

3.3. Serum creatinine, eGFR, sNGAL, and uNGAL

Prior to contrast administration (baseline), there were no differences in SCr ($P = .69$), eGFR ($P = .42$), sNGAL ($P = .69$), or uNGAL ($P = .44$) between patients who developed CIN and those who did not. Serial measurements of SCr, eGFR, sNGAL, and uNGAL during the 48-hour follow-up period are presented in supplemental Table 1, http://links.lww.com/MD/E798 and Figure 2. sNGAL and uNGAL levels showed significant statistical and clinical elevations as early as 6 hours post-catheterization in the CIN group, compared to minor changes in the non-CIN group. In contrast, statistically significant changes in SCr did not appear until 24 hours post-catheterization (supplemental Table 1, http://links.lww.com/MD/E798). In general, patients with stable SCr levels at 48 hours post-contrast medium exposure were discharged later in the day. No patients developed CIN after discharge or required renal replacement therapy.

Table 1

Baseline characteristics and demographic data of patients.

Characteristics	CIN (n = 22)	Non-CIN (n = 85)	P
Age, yr	74 ± 9	73 ± 8	.568
Sex, (M/F)	17/5	69/16	.764
Body mass index, kg/m^2	26.4 ± 3.9	27.5 ± 4.1	.265
Hypertension, % (patients)	72.3 (17/22)	76.5 (65/85)	.245
Diabetes mellitus, % (patients)	31.8 (7/22)	21.2 (18/85)	**.034**
Dyslipidemia, % (patients)	40.9 (9/22)	45.9 (39/85)	.195
Current smoker, % (patients)	31.8 (7/22)	25.9 (22/85)	.165
Previous smoker, % (patients)	63.6 (14/22)	52.9 (45/85)	.095
Non-progressive chronic kidney disease, % (patients)	27.3 (6/22)	18.2 (4/22)	.084
Prior history of PTA, % (patients)	9.1 (2/22)	10.6 (9/85)	.265
Ankle-branchial index	0.45 ± 0.23	0.43 ± 0.38	.578
Contrast volume, mL	356 ± 125	221 ± 85	**<.001**
Serum creatinine, μmol/L	80.5 ± 21.9	82.9 ± 27.4	.689
eGFR, mL/min/1.73 m^2	80.1 ± 18.9	82.4 ± 18.9	.415
Serum NGAL, ng/mL	132.8 ± 38.1	139.4 ± 69.2	.668
Urine NGAL, ng/mL	27.3 ± 5.7	25.5 ± 10.37	.437

Values are indicated as mean ± SD. CIN = contrast-induced nephropathy; PTA = percutaneous angioplasty; eGFR = estimated glomerular filtration rate; NGAL = neutrophil gelatinase-associated lipocalin; SD = standard deviation.

3.4. Correlations between sNGAL and uNGAL and standard renal markers

sNGAL levels correlated significantly with SCr and eGFR at all assessed timepoints, including baseline readings. uNGAL levels were significantly correlated with SCr and eGFR in baseline readings, and at 24 and 48 hours post-catheterization (Table 2).

3.5. Characteristics of serum and urine NGAL for the early diagnosis of CIN

To further characterize the suitability of sNGAL and uNGAL as biomarkers for CIN, we performed ROC analysis (Table 3). The AUC for changes in SCr between baseline and 6 hours post-exposure was 0.56 (95% CI: 0.44–0.68). The AUCs for changes in sNGAL and uNGAL during the same time frame were notably higher, at 0.71 (95% CI: 0.61–0.81, $P < .01$) and 0.89 (95% CI: 70.9–88.7, $P < .01$), respectively (Table 3). The sNGAL and uNGAL ROC curves improve further at 24 hours post-exposure, with AUCs of 0.78 (95% CI: 0.68–0.88, $P < .01$) and 0.89 (95% CI: 0.82–0.97, $P < .01$), respectively (Table 3 and Fig. 3). Using the ROC curves, we established optimum cutoff values for changes in sNGAL, uNGAL, and SCr to maximize sensitivity and specificity. The optimum cutoff value for sNGAL at 6 hours after contrast medium exposure (changes of >143 μmol/L) provided a sensitivity of 90.9% and a specificity of 50.0% for early detection

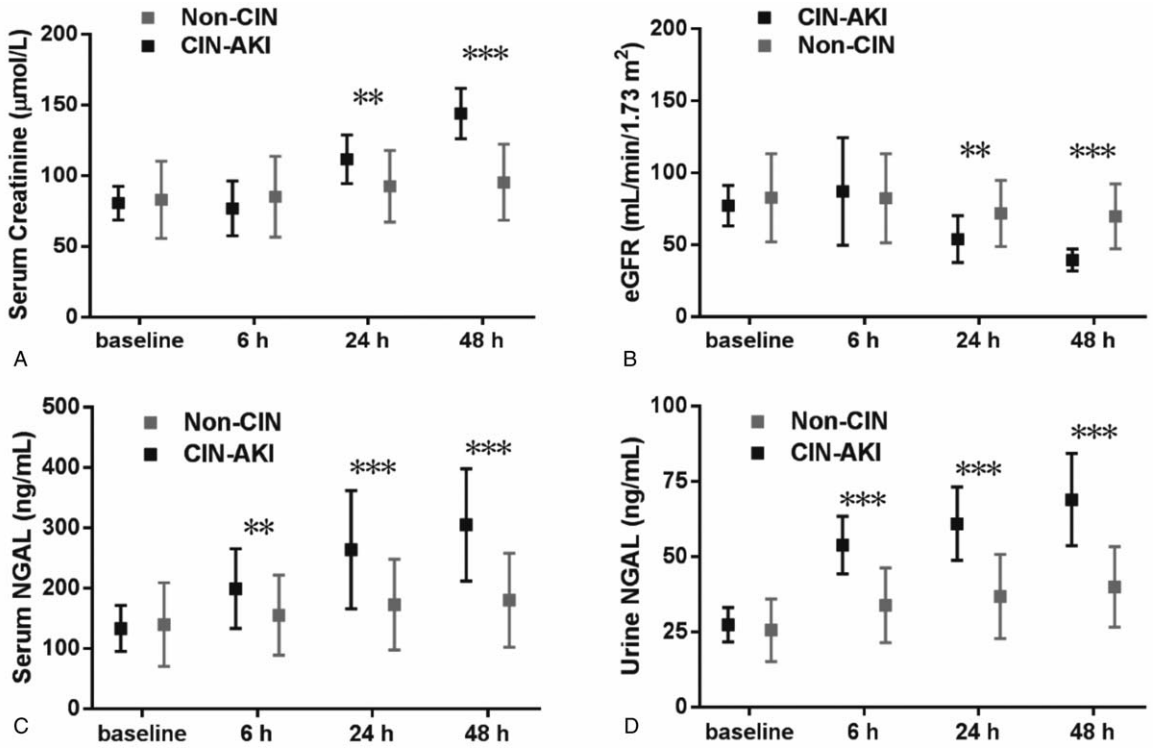

Figure 2. Serial measurements of SCr, eGFR, serum NGAL, and urine NGAL at 6, 24, and 48 h post-catheterization. Baseline indicates readings taken prior to endovascular angioplasty. AKI = acute kidney injury; CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate; NGAL = neutrophil gelatinase-associated lipocalin; SCr = serum creatinine. **, $P < .05$; ***, $P < .01$.

of CIN. In comparison, the optimum cutoff value for SCr (changes of >97.5 μmol/L) had similar sensitivity (90.9%) but lower specificity (31.0%) at the same time point (Table 3 and Fig. 3).

4. Discussion and conclusions

Currently, CIN is defined as a ≥0.5 mg/dL or ≥25% rise in SCr at 48 to 72 hours after contrast exposure.[15] However, there are several limitations to SCr-based CIN diagnosis. First, SCr is highly affected by age, sex, muscle mass, diet, medications, and hydration status. Furthermore, SCr is a biomarker of glomerular filtration rate (GFR), not a direct biomarker of tubular damage that occurs in CIN. This means that substantial increases in SCr can be observed in cases of renal hypoperfusion even with structurally intact kidneys.[15–18] Therefore, SCr-based diagnosis is faulty on 2 fronts: nontubular injuries may be misclassified as CIN; and the absence of changes in SCr does not exclude tubular damage.[19]

NGAL, unlike SCr, is a biomarker responsive to tissue stress and nephron injury, but less so to adaptive hemodynamic responses.[13] Multiple studies have demonstrated that NGAL is a powerful predictor of poor clinical outcomes, which can be used for risk-stratification of patients, in conjunction with SCr.[20,21]

Table 2

Correlation between serum and urine NGAL and SCr and eGFR.

	SCr			eGFR		
Time	***r***	**95% CI**	***P***	***r***	**95% CI**	***P***
sNGAL						
Baseline	0.579	0.437–0.693	<.001	−0.384	−0.536 to −0.209	<.001
6 h	0.468	0.305–0.605	<.001	−0.292	−0.458 to −0.108	.002
12 h	0.395	0.227–0.5390	<.0001	−0.280	−0.441 to −0.101	.0026
24 h	0.093	−0.093 to 0.272	.326	−0.096	−0.275 to −0.089	.301
uNGAL						
Baseline	0.579	0.437–0.693	<.001	−0.384	−0.536 to −0.209	<.001
6 h	0.468	0.305–0.605	<.001	−0.292	−0.458 to −0.108	.002
12 h	0.395	0.227–0.5390	<.0001	−0.280	−0.441 to −0.101	.0026
24 h	0.093	−0.093 to 0.272	.326	−0.096	−0.275 to −0.089	.301

CI = confidence interval; eGFR = estimated glomerular filtration rate; h = hours post-catheterization; *r* = correlation coefficient; sNGAL = serum neutrophil gelatinase-associated lipocalin; uNGAL = urine neutrophil gelatinase-associated lipocalin.

Table 3

Comparison of biomarkers for early detection of CIN after endovascular therapy.

	AUC (95% CI)	*P*	Cutoff value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
SCr, μM					
6 h after PTA	0.56 (0.44–0.68)	.063	97.5	90.9 (70.8–98.9)	31.0 (21.3–42.0)
24 h after PTA	0.76 (0.65–0.86)	<.001	100.5	81.9 (59.7–94.8)	70.2 (59.3–79.7)
48 h after PTA	0.93 (0.88–0.98)	<.001	107	100 (84.56–100)	73.8 (63.1–82.8)
sNGAL, μM					
6 h after PTA	0.71 (0.61–0.81)	.002	143	90.9 (70.8–98.9)	50.0 (38.9–61.1)
24 h after PTA	0.78 (0.68–0.88)	<.001	167	90.9 (70.8–98.9)	52.4 (41.2–63.4)
48 h after PTA	0.86 (0.77–0.94)	<.001	213	86.4 (65.1–97.1)	73.8 (63.1–82.8)
uNGAL, μM					
6 h after PTA	0.89 (0.82–0.97)	<.001	44	81.0 (70.9–88.7)	86.4 (65.1–97.1)
24 h after PTA	0.89 (0.82–0.97)	<.001	48.5	86.4 (65.1–97.1)	83.3 (73.6–90.6)
48 h after PTA	0.90 (0.82–0.98)	<.001	50.5	86.4 (65.1–97.1)	84.5 (75.0–91.5)

AUC = area under the receiver operating characteristic (ROC) curve; CI = confidence interval; CIN = contrast-induced nephropathy; PTA = percutaneous angioplasty; SCr = serum creatinine; sNGAL = serum neutrophil gelatinase-associated-lipocalin; uNGAL = urine neutrophil gelatinase-associated-lipocalin.

Additionally, NGAL is a better early marker for CIN than SCr in certain clinical settings.[12,22] NGAL levels have been shown to rise much more quickly than SCr in response to AKI (within hours rather than days).[23] Bachorzewska and colleagues demonstrated that sNGAL levels increased significantly at 2, 4, and 8 hours after percutaneous coronary intervention (PCI). The rise in uNGAL levels occurred later, at 4, 8, and 24 hours post-procedure; however, SCr levels remained unchanged throughout.[24]

We found that sNGAL was significantly elevated at 6 hours post-procedure in patients with CIN compared with patients without CIN. sNGAL levels increased by more than 25% only 6 hours after contrast exposure in most patients with CIN (19/22 patients, 86.4%); however, similar increases in SCr were seen in only 5 CIN patients (5/22, 22.7%). In agreement with previous reports, both SCr and eGFR were highly correlated with sNGAL and uNGAL at baseline and 24 hours after coronary intervention.[24] Analysis of the ROC curves for changes in sNGAL and

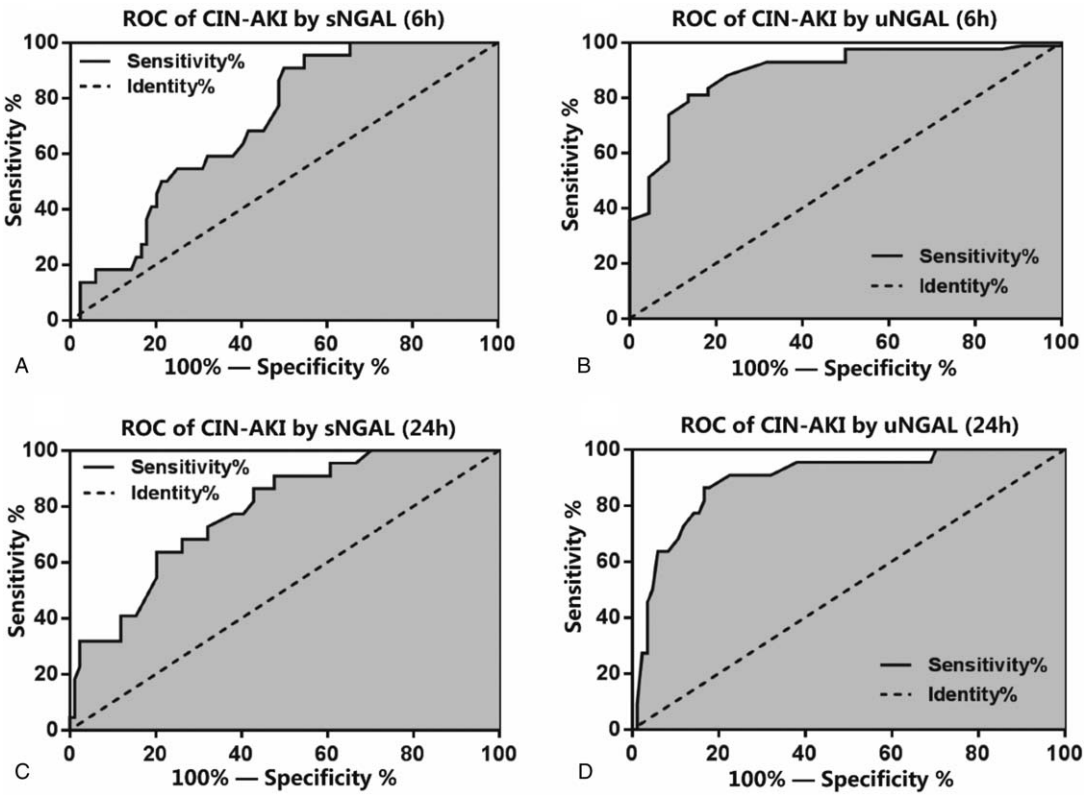

Figure 3. Receiver-operating characteristic (ROC) curves showing the performance characteristics of changes in sNGAL and uNGAL between baseline and 6 (A and B) or 24 (C and D) h after contrast administration for early diagnosis of contrast-induced nephropathy (CIN). The best cutoff Δ values at 6 h, 24 h, and 48 h from baseline for predicting CIN are listed in Table 3.

uNGAL at 6 and 24 hours post-procedure demonstrated that either can be used for the early diagnosis of CIN. Additionally, both serum and urine NGAL had higher sensitivity and specificity than SCr. These findings indicate that CIN can be screened in at-risk patients using urine or serum NGAL levels as early as 6 hours after contrast medium exposure – at least 24 hours earlier than SCr-based screening. By monitoring sNGAL and uNGAL, patients with evidence of CIN can be promptly treated, while the rest are safely discharged. This prospect is particularly important given the high-risk status of patients with peripheral vascular disease.

Another important issue related to predictive biomarkers is the cutoff value. In this study, we used a cutoff of 143 to 213 μmol/L for sNGAL and 44 to 50.5 μmol/L for uNGAL, or a relative rise in plasma/serum NGAL ≥ 25% from the baseline, to define NGAL-based CIN. Further investigation, including large, international prospective studies, is needed to identify the precise cutoff values for urine and serum NGAL levels. Each center using NGAL levels for early CIN diagnosis must also define specific reference ranges and cutoff values for patients with normal or chronically impaired renal function. Additionally, the time point for sampling urine or plasma/serum NGAL levels, which varies widely among existing studies, must be optimized for clinical practice.

Although clearly valuable as an early CIN biomarker, some caution must be taken in interpreting NGAL levels. NGAL is stable and produced in low levels by neutrophils, cardiomyocytes, prostatic cells, and epithelia of the respiratory and gastrointestinal tracts. It may also exist in a urinary dimeric form secreted by activated leukocytes during urinary tract infections.[25] Finally, NGAL's responsiveness to systemic inflammation, which is partially uncoupled from its response to kidney injury, must be considered.

Our study has the typical limitations of small, prospective studies, including a reduced ability to observe differences from baseline to peak in the overall group and subgroups. We only recruited Asian patients, and therefore, cannot estimate NGAL's performance as a biomarker for different racial groups. And NGAL could not be available in every hospital and the cost was higher than SCr. But if NGAL showed a significant value in predicting CIN or AKI, the cost would be similar as SCr and NGAL level test would be widely conducted in many hospitals. Studies by others suggest that NGAL and SCr are complementary in the diagnosis of CIN, and are clinical predictors for the patient's need for renal replacement therapy, length of hospital stay, and mortality. We recognize that NGAL is not specific to CIN-AKI and has been described in a variety of AKI etiologies, including sepsis, critical illness, and extreme exertion.[26,27] Finally, we did not measure other markers of AKI, such as kidney injury molecule-1 or cystatin C, and therefore, do not have an assessment of internal validity with respect to the degree of chronic and acute kidney disease.[28]

Despite these limitations, this study demonstrated that NGAL is superior to SCr as an early biomarker of CIN in patients with arteriosclerosis obliterans after angiography or endovascular therapy. Peripheral arterial angiography, with or without endovascular therapy, is increasingly performed with a 2- to 3-day in-hospital observation period. Monitoring serum and urine NGAL during this time is expected to be useful for identifying patients needing extended hospitalization for better renal and fluid follow-up. Future larger-scale studies are necessary to confirm our results and extend them to patients with peripheral vascular disease.

Author contributions

Conceptualization: Aijun Shang, Zexin Chen, Hongjun Qi.
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Writing – original draft: Zhenjie Liu, Aijun Shang.
Writing – review & editing: Zhenjie Liu, Zexin Chen, Li Yin, Hongjun Qi.

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