Neutrophil Gelatinase-Associated Lipocalin as an Early Predictor of Contrast-Induced Nephropathy Following Endovascular Aortic Repair for Abdominal Aortic Aneurysm

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Abstract
To investigate serum neutrophil gelatinase-associated lipocalin (sNGAL) and urine neutrophil gelatinase-associated lipocalin (uNGAL) as early predictors of contrast-associated acute kidney injury (contrast-induced nephropathy) following endovascular aortic repair for abdominal aortic aneurysm. Prospective cohort study. Subjects included 202 consecutive patients with abdominal aortic aneurysm diagnosed between February 2016 and October 2018. We divided the patients into 2 groups: contrast-induced nephropathy (CIN) (n = 26) and non-CIN (n = 176). We assessed correlations 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 SCr, eGFR, sNGAL, and uNGAL performance. We derived biomarker cutoff levels from ROC analysis results to maximize sensitivity and specificity values. The CIN incidence within our cohort was 12.9%. sNGAL levels correlated significantly with SCr and eGFR at baseline, 6, and 24 hours post-contrast medium exposure. Similarly, uNGAL levels correlated with SCr and estimated glomerular filtration rate (eGFR) at baseline, 6, and 24 hours post-contrast medium exposure. sNGAL and uNGAL were significantly elevated as early as 6 hours post-endotherapy in the CIN group; there were only minor changes in the non-CIN group. SCr was also significantly elevated in the CIN group, but not until 48 hours post-catheterization. Both sNGAL and uNGAL may be more accurate than SCr and eGFR as early biomarkers of CIN in patients with abdominal aortic aneurysm undergoing endovascular therapy.

Keywords
neutrophil gelatinase-associated lipocalin, contrast-induced nephropathy, percutaneous angioplasty, abdominal aortic aneurysm, endovascular therapy

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Introduction
Endovascular aortic repair (EVAR) for abdominal aortic aneurysm has been accepted as a minimally invasive surgery for aortic aneurysm in recent decades; the frequency of EVAR use has been steadily increasing.1,2 The contrast medium used during EVAR is an inevitable cause of contrast-induced nephropathy (CIN), an acute kidney injury (AKI).3,4 CIN is a major cause of AKI in the hospital and a common associated complication of EVAR.5 CIN is associated with prolonged in-hospital stays, increased costs, and unfavorable outcomes.6,7 Poor

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outcomes are partly caused by the lack of timely and accurate biomarkers to predict CIN occurrence.

Diagnosis of AKI relies on measurement of 2 markers of kidney function, serum creatinine (SCr) and urine output, and not on direct measurement of kidney injury. Use of SCr for AKI diagnosis has limitations, including its delayed response and its responsiveness to purely hemodynamic adaptations of the glomerular filtration rate.8-10 Due to the delayed response of SCr and the lack of specific clinical signs, AKI diagnosis usually occurs after the period when the early specific therapies for intrinsic AKI are effective. SCr changes also often indicate the presence of chronic kidney disease rather than AKI. Due to these shortcomings, more reliable biomarkers are needed for the diagnosis of AKI.11

The conventional definition of CIN is an increase of ≥25% or ≥0.5 mg/dL SCr from baseline readings between 48 and 72 hours after the administration of contrast medium, and after 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 been lost, and may be affected by many nonrenal factors (e.g., age, gender, intravascular volume, and nutrition). These factors limit the sensitivity and specificity of SCr for the early detection of CIN.12

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most promising biomarkers of renal epithelial injury.13 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.14,15 Unlike SCr, NGAL is specifically produced by the impaired nephron and then released into the systemic circulation. This study assessed the suitability of NGAL as an early marker of CIN after elective endovascular therapy. We compared NGAL to the standard markers, SCr and estimated glomerular filtration rate (eGFR).

Methods

This prospective observational study consisted of data from patients admitted to our departments from February 2015 to October 2018. Written informed consent was obtained from each participant. The study was performed in accordance with Declaration of Helsinki guidelines. The study protocol was approved by the ethics committee of our hospitals.

Participants and Study Design

Consecutive patients (≥18 years of age; n = 256) with abdominal aortic aneurysm and undergoing EVAR were recruited for the study. Exclusion criteria included preexisting renal insufficiency and use of nephrotoxic drugs before or during the study period. We excluded the data from 9 patients who were receiving hemodialysis, 28 patients who had open surgery instead of EVAR, and 17 patients without subsequent creatinine measurements, from the analysis. Urine and blood samples were collected at baseline (before 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 the contrast medium, with no alternative etiology. We defined normal kidney function as a baseline eGFR >60 mL/min per 1.73 m², with no transient or sustained increases in SCr or decreases in eGFR during the patient’s hospital stay.

Diagnosis of Kidney Disease

A modified Jaffe method was used to measure serum and urine creatinine concentrations (ARCHITECT ci16200 analyzer, LEADMAN, Beijing). The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [eGFR_MDRD = 175 × SCr−1.154 × age−0.203 (× 0.742 if female)].16 Urine NGAL (uNGAL) was measured on the same analyzer using a 2-step sandwich immunoassay with chemiluminescent signal detection. The coefficient of variation for analytical imprecision was 4.5%. Serum NGAL (sNGAL) was measured using enzyme-linked immunoabsorbent assay (LEADMAN Beijing, China).

Statistical Analysis

Continuous variables were compared between groups using analysis of variance (ANOVA). Categorical variables were compared using chi-square tests. The null hypothesis was rejected at a P-value < 0.05. The results for continuous variables were presented as mean ± standard deviation values. The results for categorical variables were presented as numbers and percentage values. Because sNGAL and uNGAL levels do not meet the assumptions of a normal distribution, nonparametric tests were used to compare sNGAL and uNGAL concentrations. Spearman correlation coefficients were used to assess the correlations of sNGAL and uNGAL concentrations with standard renal markers. To determine diagnostic test characteristics and assess performance, conventional receiver operating characteristic (ROC) curves were constructed and area under the curve (AUC) values were calculated for sNGAL, uNGAL, and SCr. The values for diagnostic sensitivity and specificity, and for positive predictive value and negative predictive value were calculated for each of these markers to determine accuracy and validity for the prediction of CIN. Biomarker cutoff levels were derived from ROC analysis to maximize sensitivity and specificity. We also determined 95% confidence intervals (CIs) for each biomarker. Graphpad 7.0 statistical software was used for the data analysis.

Results

Baseline Characteristics and Demographic Data

We received urine and blood samples for biomarker measurement from 256 patients with abdominal aortic aneurysm admitted to our department of vascular surgery for endovascular therapy; data from 54 patients were subsequently excluded from the analysis. We used measurement of SCr to monitor kidney function during the hospital stays of the remaining 202 patients. The patients were divided into 2 groups based on presence (CIN) or absence (non-CIN) of CIN-AKI. There were no statistically significant between-group differences in body mass index or baseline sNGAL or uNGAL values. Two groups were comparable at
In the non-CIN group had histories of kidney disease.

Progressive chronic kidney disease (30.8% acute kidney disease. Eight of these 26 patients had non-

- Na, mmol/L 136.9
- K, mmol/L 5.1
- HGB, g/dL 13.2
- Urine NGAL, ng/mL 28.3
- Serum NGAL, ng/mL 137.8
- eGFR, mL/min/1.73 m² 82.1
- Serum creatinine, mg/dL 83.7
- Contrast volume, mL 256
- Current smoker, % (patients) 57.7 (15/26) 47.4 (84/176) 0.403
- Dyslipidemia, % (patients) 57.7 (15/26) 50.6 (89/176) 0.535
- Diabetes mellitus, % (patients) 7.7 (2/26) 8.0 (14/176) 0.999
- Hypertension, % (patients) 84.6 (22/26) 88.0 (155/176) 0.752

Between serum NGAL and GFR, were statistically significant.

The correlations between serum NGAL levels and SCr, and eGFR for the baseline readings and at 24 and 48 hours post-catheterization (Table 2).

Baseline characteristics and demographic data of patients are presented in Table 1.

Incidence of Contrast-Induced Nephropathy

Twenty-six of 202 patients (12.9%) met the criteria for CIN acute kidney disease. Eight of these 26 patients had non-progressive chronic kidney disease (30.8%). Eighteen patients in the non-CIN group had histories of kidney disease.

Serum Creatinine, eGFR, sNGAL, and uNGAL

Before contrast administration (baseline), there were no statistically significant differences in SCr \((P = 0.652)\), eGFR \((P = 0.445)\), sNGAL \((P = 0.526)\), or uNGAL \((P = 0.498)\) values between patients who developed CIN and those who did not. The results for the serial measurements of SCr, eGFR, sNGAL, and uNGAL during the 48-hour follow-up period are presented in Table 1 and Figure 1. sNGAL and uNGAL levels showed significant statistical and clinical elevations as early as 6 hours post-catheterization in the CIN group, compared with minor changes in the non-CIN group. Statistically significant changes in SCr did not appear until 48 hours post-catheterization. In general, patients with stable SCr levels at 5 days post-contrast medium exposure were discharged later in the day. No patients developed CIN after discharge or required renal replacement therapy.

Correlations Between sNGAL and uNGAL and Standard Renal Markers

The correlations between serum NGAL levels and SCr, and between serum NGAL and GFR, were statistically significant at all assessed timepoints, including the baseline readings. uNGAL levels were significantly correlated with SCr and eGFR for the baseline readings and at 24 and 48 hours post-catheterization (Table 2).

Characteristics of Serum and Urine NGAL for the Early Diagnosis of Contrast-Induced Nephropathy

We performed ROC curve analysis to further characterize the validity of using sNGAL and uNGAL as biomarkers for CIN (Table 3). The AUC value for changes in sNGAL and uNGAL between baseline and 6 hours post-exposure was 0.74 (95% CI: 0.66-0.82, \(P = 0.042\)) and 0.86 (95% CI: 0.79-0.94, \(P < 0.001\)), respectively (Table 3). The sNGAL and uNGAL ROC curves improved further at 24 hours post-exposure; the AUC values were 0.80 (95% CI: 0.72-0.88, \(P < 0.001\)) and 0.87 (95% CI: 0.80-0.95, \(P \leq 0.001\)), respectively (Table 3 and Figure 2). Using the ROC curves, we established optimum cutoff values for changes in sNGAL, uNGAL, and SCr that maximized the sensitivity and specificity of each biomarker. The optimum cutoff value for sNGAL at 6 hours after contrast medium exposure (changes of >143 μmol/L) provided a sensitivity of 92.3% and a specificity of 50.6% for early detection of CIN.

Discussion

CIN is defined as a ≥0.5 mg/dL or ≥25% rise in SCr at 48 to 72 hours after contrast exposure.17 However, there are several limitations to SCr-based CIN diagnosis. First, SCr values are substantially affected by age, sex, muscle mass, diet, medications, and hydration status. SCr is a biomarker of GFR, not a direct biomarker of the tubular damage that occurs in CIN.
Substantial increases in SCr can occur during renal hypoperfusion, even with structurally intact kidneys. Therefore, use of SCr for the diagnosis has low validity because nontubular injuries may be misclassified as CIN and the absence of changes in SCr does not exclude tubular damage. Unlike SCr, NGAL is a biomarker responsive to tissue stress and nephron injury, but it is less adaptive to hemodynamic responses. NGAL is a powerful predictor of poor clinical outcomes and, in conjunction with SCr, can be used for risk-stratification of patients. In certain clinical settings, NGAL is also a better early marker for CIN. Compared with SCr, NGAL levels increase much more rapidly in response to AKI (within hours rather than days). Bachorzewska and colleagues found that sNGAL levels increased significantly at 2, 4, and 8 hours after percutaneous coronary intervention. The increase in uNGAL levels occurred later, at 4, 8, and 24 hours post-procedure; SCr levels remained unchanged throughout the entire period.

In the literature, reported rates of AKI after elective EVAR is 18%. In an Asian population, reported rates of AKI post EVAR is 14%. In our study, 26 of 202 patients (12.9%) met the criteria for CIN acute kidney disease. 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 >25% only 6 hours after contrast exposure in most patients with CIN (21/26 patients, 86.4%); similar increases in SCr were found in only 5 CIN patients (6/26, 23.1%). Consistent with the results of previous studies, both SCr and eGFR were highly correlated with sNGAL and uNGAL at baseline and 24 hours.

| Table 2. Correlation Between Serum and Urine NGAL and SCr and eGFR. |
|-----------------|-----------------|-----------------|
| Time            | SCr             | eGFR            |
|                 | r               | 95% CI          | P    | r               | 95% CI          | P    |
| sNGAL Baseline  | 0.639           | 0.549 to 0.714  | <0.001 | -0.455          | -0.558 to -0.338| <0.001 |
| 6 h             | 0.451           | 0.334 to 0.554  | <0.001 | -0.332          | -0.450 to -0.203| <0.001 |
| 24 h            | 0.337           | 0.208 to 0.454  | <0.001 | -0.247          | -0.373 to -0.113| <0.001 |
| uNGAL 48 h      | 0.604           | 0.467 to 0.713  | <0.001 | -0.455          | -0.594 to -0.290| <0.001 |
| Baseline        | 0.531           | 0.424 to 0.623  | <0.001 | -0.357          | -0.472 to -0.230| <0.001 |
| 6 h             | 0.468           | 0.305 to 0.605  | <0.001 | -0.292          | -0.458 to -0.108| 0.002  |
| 24 h            | 0.432           | 0.312 to 0.538  | <0.001 | -0.395          | -0.505 to -0.272| <0.001 |
| 48 h            | 0.588           | 0.448 to 0.700  | <0.001 | -0.453          | -0.453 to -0.288| <0.001 |

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

| Table 3. Comparison of Biomarkers for Early Detection of CIN After Endovascular Therapy. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | AUC (95% CI)    | P-value         | Cutoff value    | Sensitivity, % (95% CI) | Specificity, % (95% CI) |
| sNGAL, μM       |                 |                 |                 |                 |                 |
| 6 hours after PTA | 0.74 (0.66-0.82) | 0.042           | 143             | 92.3 (74.9-99.1) | 50.6 (42.9-58.2) |
| 24 hours after PTA | 0.80 (0.72-0.88) | <0.001          | 166.5           | 92.3 (74.9-99.1) | 54.6 (46.9-62.1) |
| 48 hours after PTA | 0.85 (0.77-0.92) | <0.001          | 209             | 84.6 (65.1-95.6) | 73.8 (66.7-80.2) |
| uNGAL, μM       |                 |                 |                 |                 |                 |
| 6 hours after PTA | 0.86 (0.79-0.94) | <0.001          | 44              | 80.8 (60.7-93.5) | 81.8 (75.3-87.2) |
| 24 hours after PTA | 0.87 (0.80-0.95) | 0.037           | 48.5            | 80.8 (60.7-93.5) | 84.1 (77.8-89.2) |
| 48 hours after PTA | 0.88 (0.80-0.97) | 0.043           | 50.5            | 80.8 (60.7-93.5) | 85.2 (79.1-90.1) |

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

Figure 2. Receiver operating characteristic (ROC) curves of the performance characteristics of changes in sNGAL and uNGAL between baseline and 6 hours (A and B) or 24 hours (C and D) after contrast administration for early diagnosis of contrast-induced nephropathy (CIN). The results for the best cutoff values at 6 hours, 24 hours, and 48 hours from baseline for predicting CIN are presented in Table 3.
after coronary intervention. Analysis of the ROC curves for changes in sNGAL and uNGAL at 6- and 24-hours post-procedure revealed that either can be used for the early diagnosis of CIN. Additionally, compared with SCr, both serum and urine NGAL had higher values for sensitivity and specificity. These findings indicated that NGAL 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. Use of this approach is particularly important given the high-risk status of patients with peripheral vascular disease.

Determination of cutoff values is an important part of predictive biomarker assessment and development. To define NGAL-based CIN, we used a cutoff of 143-209 μmol/L for sNGAL and 44-50.5 μmol/L for uNGAL, or a relative rise in plasma/serum NGAL ≥25% from the baseline value. Further investigation, including large, international prospective studies, is needed to identify the precise cutoff values for urine and serum NGAL levels. Each medical 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. The time points used for sampling urine and plasma/serum NGAL levels vary widely among existing studies; sampling times must be optimized for clinical practice.

NGAL levels clearly have value as early CIN biomarkers. However, some caution must be used during interpretation of the results. NGAL is stable and is produced in low levels by neutrophils, cardiomyocytes, prostatic cells, and epithelia of the respiratory and gastrointestinal tracts. It may also be present as a urinary dimeric form, which is secreted by activated leukocytes during urinary tract infections. Finally, NGAL’s responsiveness to systemic inflammation, which is partially uncoupled from its response to kidney injury, must also be considered.

Our study had the typical limitations of small, prospective studies, including a reduced ability to observe differences from baseline to peak value in the overall group and subgroups. Because we recruited Asian patients, we could not estimate NGAL’s performance as a biomarker for different racial groups. The results of other studies suggest that NGAL and SCr should be considered as complementary for the diagnosis of CIN. They are both clinical predictors for the patient’s need for renal replacement therapy, length of hospital stay, and mortality risk. We recognize that use of NGAL is not specific to CIN-AKI diagnosis; it has been described for AKI etiologies including sepsis, critical illness, and extreme exertion. Finally, we did not measure other markers of AKI, such as kidney injury molecule-1 or cystatin C. We therefore did not assess internal validity with respect to the degree of chronic and acute kidney disease.

Despite these limitations, this study found that NGAL was more accurate than SCr as an early biomarker of CIN in patients with abdominal aortic aneurysm after angiography or endovascular therapy. Peripheral arterial angiography, with or without endovascular therapy, is more frequently being combined with a 2-to 3-day in-hospital observation period. Serum and urine NGAL monitoring during this period is likely to be useful for identification of patients who require extended hospitalization for better renal and fluid follow-up. Larger-scale studies are necessary to confirm our results and extend them to patients with peripheral vascular disease.

Authors’ Note
L.L. and J.S. contributed equally to this work. S.L. and L.L. contributed for conceptualization; H.C., F.S. and G.L. contributed for data collection. L.L., W.N., and J.S. contributed to formal analysis; L.L. wrote the manuscript; S.L. performed the critical revision of the manuscript. Ethical approval to report this case was obtained from Yantai Yuhuangding Hospital ([2015] 125). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Declaration of Conflicting Interests
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