Serum neutrophil gelatinase-associated lipocalin as a predictor of acute kidney injury in patients with coronary artery disease

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Background
Acute kidney injury (AKI) after a percutaneous coronary intervention (PCI) is a major complexity. Early AKI diagnosis can help in treating this complication. Neutrophil gelatinase-associated lipocalin (NGAL) is a recent marker for the diagnosis of contrast-induced acute kidney injury (CI-AKI). This research targeted to evaluate the early diagnosis of CI-AKI and predictive value of NGAL and study the correlation between renal role tests and serum NGAL in cases with coronary artery disorder.
This research was conducted on 45 cases with coronary artery disorder. Serum NGAL, urea, and creatinine (SCr) were evaluated. The estimated glomerular-filtration rate (eGFR) was measured 2 and 48 h after PCI.

Results
In total, 11 (24.4%) patients had AKI, while 34 (75.6%) patients had no AKI. Serum urea NGAL was significantly greater in AKI cases either 2 or 48 h after PCI, while SCr was significantly greater in AKI cases 48 h after PCI. eGFR 48 h after PCI was significantly decreased in AKI patients. Albumin/creatinine (A/C) ratio was significantly greater in AKI cases. Serum NGAL 2 h after PCI positively correlated with A/C ratio and SCr 48 h after PCI, but is negatively correlated with eGFR 48 h after PCI. After 2 h, serum levels of NGAL had 90% sensitivity and 55% specificity; after 48 h, they had 81% sensitivity and 61% specificity. SCr after 2 h had 63% sensitivity and 82% specificity, and after 48 h, had 90% sensitivity and 88% specificity.

Conclusion
Serum NGAL can represent a sensitive early predictor biomarker for kidney damage after PCI.

Keywords:
acute kidney injury, coronary artery disease, neutrophil gelatinase-associated lipocalin

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Background

One of the common complications of percutaneous coronary intervention (PCI) is acute kidney injury (AKI), which can lead to dialysis and death [1]. Contrast-induced acute kidney injury (CI-AKI) is estimated to occur between 0.6 and 2% of the general population. Nevertheless, the frequency is significantly greater in cases receiving the PCI and coronary angiography, particularly those with renal impairment, diabetes, or congestive heart failure. The percentage rises to be more than 20–30% [2].

CI-AKI detection depends on the variety in serum creatinine (SCr) concentrations after and before contrast-media exposure. SCr increases at the first 24–48 h, peaks at 3–5 days, and comes back close to baseline from 1 to 3 weeks after contrast-induced toxicity attack [3]. Unfortunately, Cr is not a dependable marker through acute changes in the renal role because it may not require alteration, until a significant quantity of renal role has already been lost. Also, it can differ greatly with muscle mass, sex, age, muscle medications, hydration status, and metabolism [4]. This challenge has led the researchers to work and discover new markers of early kidney dysfunction [5].

Several reports have identified the function of new kidney biomarkers in the diagnosis of early kidney dysfunction, such as neutrophil gelatinase-associated lipocalin (NGAL) [5]. NGAL, also characterized as lipocalin-2 or human neutrophil lipocalin, is an estimated bioindicator. This glycoprotein has a unique form that allows multiple compounds to be binding and transported [6]. The objectives of this research were to assess the predictive utility of serum NGAL for the early diagnosis of contrast-induced acute kidney damage.

Patients and methods

This research was performed on 45 cases with coronary artery disorder selected from 110 cases that were

recently exposed to PCI from May 2018 to May 2019. There was a written consent from research individuals. The research was accepted by the ethical committee of the University Faculty of Medicine No. 17100323, with ClinicalTrials.gov ID: NCT03266367.

Patients group: the first group consists of 45 cases with coronary artery disorder after 2 h of exposure to PCI. The second group includes the same patients 48 h after PCI.

Exclusion criteria: diabetes mellitus, chronic kidney diseases, renal-replacement therapy (dialysis), and previous kidney transplant.

Laboratory investigations

Blood sample

In all, 5 ml of venous blood was collected under complete aseptic condition and divided into 2 ml of venous blood that was collected into EDTA, including a tube for a complete blood count. About 3 ml of venous blood was collected into a gel tube; then it was centrifuged at a 2000–3000-rpm speed for 15 min, serum was used for liver function, urea, creatinine, glucose, CK, CK-MB, and troponin I. The remaining serum was collected and kept at − 80°C till the assay time of NGAL. The urine sample was obtained for albumin/creatinine ratio (A/C).

Cell_Dyn Ruby assayed complete blood picture. Liver function, urea, Cr, CK, CK-MB, and troponin I were assayed using Dimension Xpand. A/C ratio was assayed by Cobas Integra 400 plus. The following formula is used to measure the evaluated glomerular-filtration rate (eGFR) based on the alteration of food in kidney disorder: eGFR (ml/min/1.73 m^2) =186×[SCr (mg/dl)]−1.154×[age]−0.203×[0.742 if female]×[1.21 if black]. Serum level of NGAL was estimated via enzyme-linked immunosorbent assay kits: using human NGAL enzyme-linked immunosorbent assay kit, Catalog N0: SG-10403, purchased from SinoGeneClon Biotech Co. Ltd (YuHang District 311112, HangZhou, China).

Statistical analysis

The obtained information was measured by SPSS (Statistical Package for the Social Science, version 20; IBM, Armonk, New York, USA). An independent *t* test was utilized to compare the mean of the two groups. The Pearson's correlation coefficient (*r*) was utilized to assess the relation of NGAL with various factors in the current study. Diagnostic precision of NGAL to diagnose the AKI after PCI was assessed with receiver-operating characteristic curve. *P* value was significant if less than 0.05.

Results

Through the work time, 110 cases were recruited and diagnosed to have CAD and underwent PCI. Out of those patients, 65 patients were excluded secondary to the existence of diabetes mellitus and chronic kidney disorder. Based on the AKI-N classification, out of the studied patients, 34/45 (75.6%) patients did not develop AKI, while only 11/45 (24.4%) patients developed AKI.

Patients without AKI age ranged from 25 to 68 years with a mean value of 51.47 ± 12.11 years, while in the AKI group, age between 30 and 68 years with the mean value of 48.72 ± 11.56 years. In the group without AKI, male patients represented 82.4%, and female patients represented 17.6%, while in the AKI group, male patients represented 81.8%, and female patients represented 18.2%. There was a nonsignificant difference between the two groups regarding baseline data.

There were nonsignificant differences between the two groups regarding all laboratory data (CBC, liver function, CK, CK-MB, and troponin I), except that there is a significant decrease in serum albumin in the AKI group compared with the group without AKI ($P = 0.04$).

Table 1 revealed that there was a statistically significant elevation in serum urea and NGAL in the AKI group after 2 h and after 48 h of PCI compared with the group without AKI ($P = 0.02$, 0.004 and 0.000, 0.03), respectively. There was an insignificant difference between the two groups after 2 h in creatinine and eGFR. At the same time, after 48 h, there was a significant increase in SCr ($P = 0.000$) and a significant decrease in eGFR ($P = 0.01$) in the AKI group compared with the group without AKI. There was a significantly higher A/C ratio in the AKI group than that without AKI group ($P = 0.000$).

Table 2 and Figures 1–3 reveal that the A/C ratio and SCr after 48 h of PCI had a significant positive relation with serum NGAL after 2 h of PCI. eGFR after 48 h had a significant negative relation with serum NGAL after 2 h of PCI.

Table 3 and Figures 4,5 reveal that serum levels of NGAL after 2 h at the cut-off point more than 3.0 μg/l had 55% specificity and 90% sensitivity for diagnosing AKI in patients after PCI, while after 48 h at the cut-off point more than 1.4 μg/l had 61% specificity and 81% sensitivity.

SCr after 2 h at the cut-off point more than 68.5 μmol/l had 82% specificity and 63% sensitivity for diagnosing

Table 1 Kidney-function tests and serum neutrophil gelatinase-associated lipocalin level of the studied groups

Group parameters	Without AKI (*N*=34)	With AKI (*N*=11)	*P*
Serum urea after 2 h (mmol/l)	4.74±1.23	7.16±5.98	0.02
Serum urea after 48 h (mmol/l)	5.67±2.29	13.77±4.5	0.004
Serum creatinine after 2 h (μmol/l)	84.61±18.5	88.72±29.93	0.67
Serum creatinine after 48 h (μmol/l)	89.41±17.65	186.02±96.43	0.008
eGFR after 2 h (ml/min)	89.67±12.64	86.63±36.60	0.79
eGFR after 48 h (ml/min)	85.52±14.45	52.36±36.97	0.000
A/C ratio (mg/g)	21.41±6.63	73.87±56.54	0.000
Serum NGAL after 2 h (μg/l)	3.43±0.67	28.09±24.75	0.000
Serum NGAL after 48 h (μg/l)	1.92±1.14	2.85±1.48	0.03

A/C, albumin/creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular-filtration rate; NGAL, neutrophil gelatinase-associated lipocalin.

Table 2 Correlations of serum levels of neutrophil gelatinase-associated lipocalin with other parameters

	NGAL after 2 h	
	r	*P*
eGFR (ml/min) after 48 h	−0.38	0.008
SCr (μmol/l) after 48 h	0.44	0.002
A/C ratio	0.67	<0.001

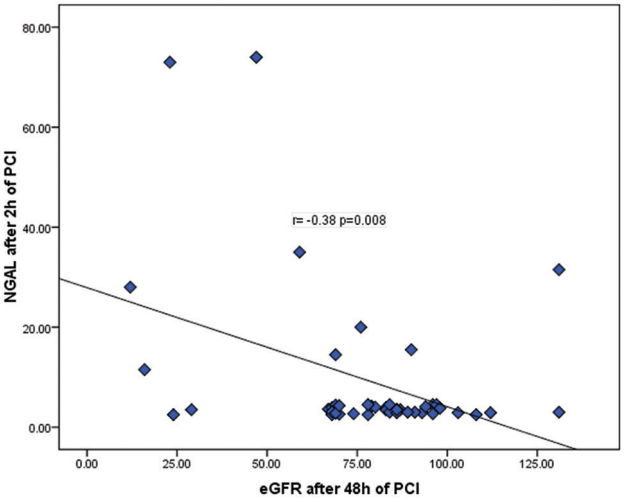
A/C, albumin/creatinine ratio; AST, aspartate transaminase; eGFR, estimated glomerular-filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; SCr, serum creatinine.

Table 3 Diagnostic accuracy of serum levels of neutrophil gelatinase-associated lipocalin and creatinine in acute kidney injury after percutaneous coronary intervention

Indices	Serum NGAL (%)		Serum creatinine (%)	
	After 2 h	After 48 h	After 2 h	After 48 h
Sensitivity	90	81	63	90
Specificity	55	61	82	88
Accuracy	89	51	69	79.7
Cut-off point	>3.0 μg/l	>1.4 μg/l	>68.5 μmol/l	>71.5 μmol/l
Area under the curve	0.90	0.73	0.58	0.90
P value	< 0.001	0.02	0.04	<0.001

NGAL, neutrophil gelatinase-associated lipocalin.

Figure 1



Relations between serum NGAL after 2 h of PCI and eGFR after 48 h of PCI. eGFR, estimated glomerular-filtration rate; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

AKI in patients after PCI, while after 48 h at the cut-off point more than 71.5 μmol/l had 90% sensitivity and 88% specificity.

Discussion

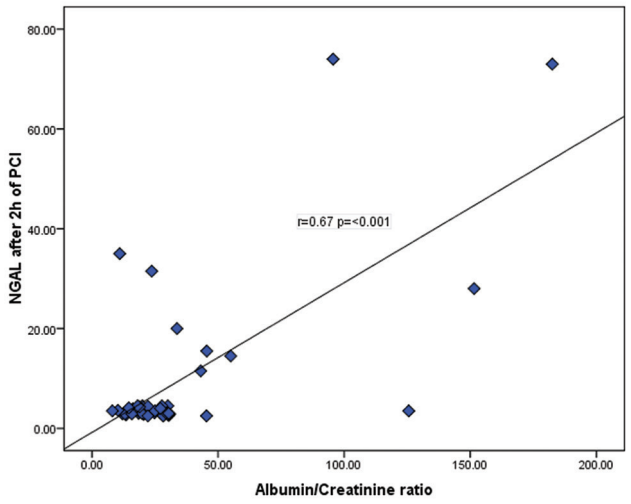
The incidence of CI-AKI ranges from 2% in general individuals to more than 50% in high-risk groups [7]. Cr is not a sensitive indicator in AKI detection, so efforts to identify new biomarkers to diagnose it include interleukin-18, kidney injury molecule-1, fatty acid-binding proteins, cystatin C, NGAL, clusterin, and osteopontin [8].

In this research, we divided the patients according to the AKI-N classification into AKI, and they are presented 24.4% of them, and the other 75.6% did not improve AKI. The definition of stage 1 AKI is a rise in SCr 0.3 mg/dl (26.4 mmol/l) within 48 h and to decrease the required for a baseline Cr but do at least two Cr values at 48 h [9]. So, we took the samples twice, one after 2 h of PCI and the other after 2 days.

In this work, 24.3% of all male patients and 25% of all female patients developed AKI. So, sex had no significant differences in the occurrence of AKI after PCI (P = 0.64). According to Barbieri *et al.* [10], women are linked to a greater incidence of CI-AKI following coronary angiography/PCI. Nevertheless, after adjusting for baseline variables and the higher risk profile, this result was not verified.

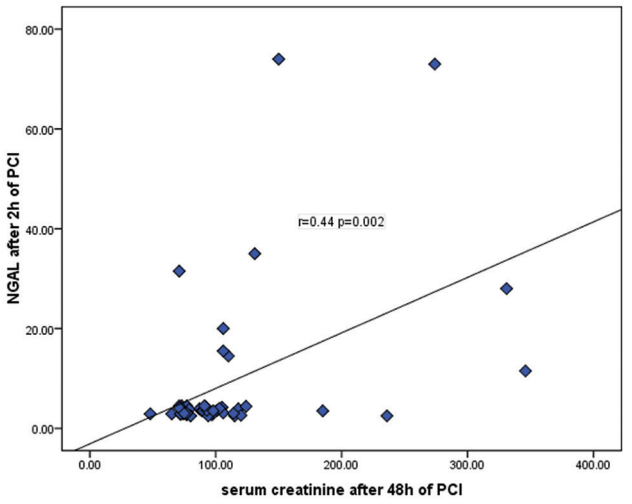
In this study, serum albumin in AKI patients was 3.60 ± 0.28, which is significantly lower than that of patients without AKI (3.81 ± 0.25) (P = 0.04). Wang *et al.*[11] stated that serum albumin is a predicting parameter of CI-AKI, and previous reports have reported a relation between kidney complications and serum albumin. One possible explanation for this relation is that albumin could enhance endothelial cell integrity. The endothelial surface is generated via natural plasma proteins and endothelial glycogen that

Figure 2



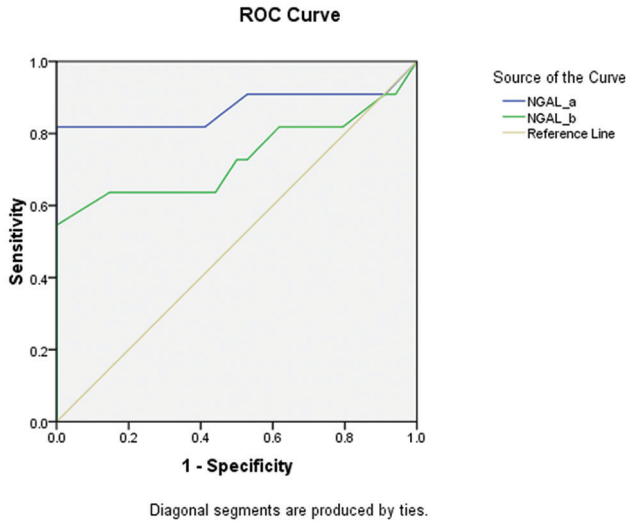
Correlations between serum NGAL and A/C ratio after two hs of PCI. NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

Figure 3



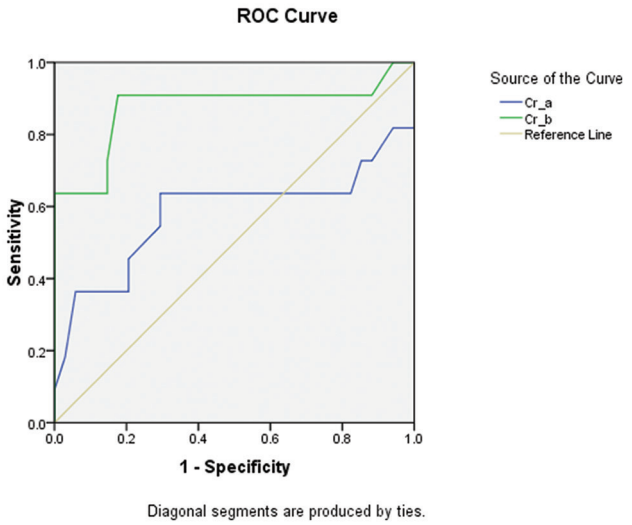
Correlations between serum NGAL after 2 h of PCI and serum creatinine after 48 h of PCI. NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

Figure 4



Diagnostic accuracy of serum NGAL in AKI after PCI. AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin; PCI, percutaneous coronary intervention.

Figure 5



Diagnostic accuracy of serum creatinine in AKI after PCI. AKI, acute kidney injury; PCI, percutaneous coronary intervention.

prevent unrestricted fluid and colloid flow into the interstitial space [12,13].

In this work, urea after 2 and 48 h of PCI was significantly greater in the AKI cases' group. Kirtane *et al.*[14] established that cases with the acute coronary disorder had raised serum urea concentrations, were older in age, had a greater risk of comorbid conditions, and had a greater fatality rate. Additionally, a higher urea-to-creatinine level is related to decreased kidney function and an elevated risk of acute heart failure [15,16].

In this work, Cr level was significantly higher after 48 h of PCI in cases with AKI rather than cases in the absence of AKI (186.02 ± 96.43 vs. 89.41 ± 17.65, P = 0.008). Wacker-Gußmann *et al.*[17] stated that 14.2% of patients had a rise in Cr of more than or equal to 25% or more than or equal to 0.5 mg/dl at 48 h, although the baseline Cr was not prognostic for kidney damage after contrast delivery.

The eGFR after 48 h of PCI was significantly lower in patients with AKI (52.36 ± 36.97 vs. 85.52 ± 14.45, P = 0.000). Grams *et al.*[18] found that high albuminuria and low eGFR are risk factors for AKI in a meta-analysis of almost one million individuals from eight countries. Reduced eGFR is related to an elevated risk of hospitalization.

In this work, urinary albumin/creatinine ratio (UACR) is significantly greater in cases with AKI than patients without AKI (73.87 ± 56.54 vs. 21.41 ± 6.63, $P = 0.000$). Wang *et al.*[19] claimed that UACR was significantly greater in CI-AKI cases (odds ratio = 1.002, 95% confidence interval = 1.000–1.003, $P = 0.01$), that was an independent risk factor CI-AKI. Additionally, Ma *et al.*[20] showed that following PCI, the level of UACR was an independent risk factor for CI-AKI, and those with a greater UACR value showed a greater risk of CI-AKI than those with a reduced UACR value.

In our work, NGAL was significantly greater in the AKI cases than cases without AKI after 2 and 48 h of PCI (28.09 ± 24.75 vs. 3.43 ± 0.67, $P \leq 0.000$) (2.85 ± 1.48 vs. 1.92 ± 1.14, $P = 0.03$), respectively. Wang *et al.*[21] reported that a meta-analysis of 14 researchers suggests that NGAL levels following PCI were reliable at predicting the presence of CI-AKI, with the optimal outcomes achieved once the NGAL concentration was evaluated during 4 h of after contrast-medium exposure.

Bachorzewska-Gajewska *et al.*[22] also reported that cases with normal SCr have significant increases in serum NGAL 2 and 4 h after PCI. Moreover, urinary NGAL 4 and 12 h after PCI and SCr correlate significantly with urinary NGAL and serum at any time following PCI.

In this work, the A/C ratio had a significant positive correlation with serum NGAL after 2 h of PCI ($r = 0.67$, $P \leq 0.001$). Rashad *et al.*[23] stated that serum NGAL levels were significantly positively correlated with UACR. Microalbuminuria was detected early, implying that it is a sign of enhanced capillary permeability to proteins [24].

In this study, there was a positive relation between SCr and serum NGAL ($r = 0.44$, $P \leq 0.001$) and a negative relation between eGFR and serum NGAL ($r = -0.38$, $P = 0.01$). Kumpers *et al.*[25] claimed that the relative level of serum NGAL in cases with AKI correlates with the severity of kidney impairment, and great concentrations of serum NGAL are related to a raised mortality risk. Pronschinske *et al.*[26] claimed a significant inverse correlation of eGFR with serum NGAL ($r = -0.2188$, $P = 0.01$) in heart-failure patients. Lindberg *et al.*[27] found that GFR controls whether NGAL is associated with inflammation or renal function; once eGFR is normal, plasma NGAL indicates inflammation; however, when eGFR is decreased, plasma NGAL indicates the renal function, showing the dual perception of plasma NGAL. Ostermann *et al.*[28] observed that elevated NGAL amounts were detected in urine and plasma 2–4 h after renal damage due to altered glomerular filtration and tubular reabsorption, as well as enhanced secretion in tubular epithelial cells.

Two hours after PCI, NGAL specificity and sensitivity was 55 and 90%, respectively, with area under the curve (AUC)=0.90. In contrast, the specificity and sensitivity of SCr was 82 and 63%, respectively, with AUC = 0.58. However, after 48 h, the sensitivity of NGAL was 81%, specificity was 61%, and AUC was 0.73. In contrast, SCr specificity and sensitivity was 88 and 90%, respectively, with AUC = 0.90, and this is in agreement with previous studies, which have found that serum NGAL diagnoses early CI-AKI 24 h earlier than does SCr [29]. Many studies concluded that the pooled specificity and sensitivity of blood NGAL were 0.80 (95% confidence interval: 0.67–0.89) and 0.86 (95% confidence interval: 0.69–0.95), respectively and blood NGAL may perform better than urine NGAL within 6 h after contrast-media exposure; however, after 6 h, urine NGAL might be a better predictor of CI-AKI than blood NGAL [3].

Conclusion

We concluded from our study that serum NGAL might show a sensitive early biomarker of kidney damage after PCI. The 2-h NGAL levels in plasma are a powerful independent predictor of AKI after PCI, but SCr can be used as a follow-up marker of AKI post-PCI.

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Nil.

Conflicts of interest

None.

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