Research Article

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Neutrophil gelatinase associated lipocalin, an early biomarker for diagnosis of acute kidney injury after percutaneous coronary intervention

[Perkütan koroner girişim sonrası akut böbrek hasarının teşhisi için erken biyolojik belirteç olan nöтроfil jelatinaz ile ilişkili lipokalin]

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Abstract

Objectives: This study was designed to find the reliability of serum NGAL as an early and better diagnostic biomarker than that of serum creatinine for acute kidney injury after percutaneous coronary intervention in Pakistani population.

Materials and methods: One hundred and fifty-one patients undergoing elective percutaneous coronary intervention were included and demographic data were recorded. Blood was drawn by venipuncture in clot activator vacutainers and serum was separated and stored at 4°C. Sample was drawn before the percutaneous procedure and subsequently sampling was done serially for 5 days.

Results: The mean ± SD serum NGAL pre-PCI (39.92 ± 10.35 μg/L) and 4 h post-PCI (100.42 ± 26.07 μg/L) showed highly significant difference (p < 0.001). The mean ± SD serum creatinine pre-PCI (70.1 ± 11.8 μmol/L) and post-PCI (71.2 ± 11.6 μmol/L) showed significant difference (p = 0.005) on day 2 onwards but mean microalbumin showed insignificant results (p = 0.533). The serum NGAL predicted CI-AKI with sensitivity of 95.8% and specificity of 97.6% for a cut off value of 118 μg/L.

Conclusion: Our results suggest that NGAL is an excellent early diagnostic biomarker for acute kidney injury in patients undergoing elective percutaneous coronary intervention.

Keywords: Acute kidney injury; Serum neutrophil gelatinase associated lipocalin; Contrast induced nephropathy; Microalbuminuria; Percutaneous coronary intervention.

Özet

Amaç: Bu çalışma, Pakistanlı nüfusta perkütan koroner müdahale sonrasında akut böbrek hasarı için serum KRAL’ın serum kreatinin düzeyiinden daha erken ve daha iyi tanı amaçlı biyobelirteç olarak güvenilirliğini bulmak için tasarlanmıştır.

Yöntem: Elektif perkütan koroner girişim uygulanan yüzelli bir hasta dahil edilmiş ve demografik veriler kaydedilmiştir. Kan pıhtı aktivatör vacutainerlerde venipuncture ile çekilmiş ve serum ayrıldı ve 40°C’de saklanmıştır. Örnek perkütan prosedürden önce çiğildi ve daha sonra seri örneklemeleri, seri halinde 5 gün yapılmıştır.

Bulgular: Ortalama ± SD serum NGAL pre-PCI (39.92 ± 10.35 μg/L) ve post-PCI (100.42 ± 26.07 μg/L) son derece anlamlı fark gösterdi (p < 0.001).
serum creatinin düzeyi (70.1 ± 11.8 μmol/L) ve post-PCI (71.2 ± 11.6 μmol/L) anlamla fark göstermiştir (p = 0.005), ancak ortalama mikroalbümin anlamla bulunmamıştır (p = 0.533). Serum NGAL, CI-AKI’yi% 95.8 duyarlılıkla ve özgüllüğü% 97.6 ile 118 mikrogram/L’de kesme değeri olarak belirlenmiştir.

**Sonuç:** Sonuçlarımız, elektif perkutan koroner girişim uygulanan hastalarda NGAL’in akut böbrek hasarı için mükemmel bir erken tanı biyobelirteç olduğunu göstermektedir.

**Anahtar kelimeler:** Akut Böbrek Hasarı; Serum Nötrofil Jelatinaz İlişkili Lipokalin; Kontrast nedenli nefropati; Mikroalbüminüri; Per-kutanöz koroner girişim

### Introduction

Acute kidney injury (AKI) is a serious complication of diagnostic angiography and percutaneous coronary intervention due to ischemia or administration of iodinated contrast media resulting in high morbidity and mortality despite great advances in supportive care [1, 2]. AKI is a broad term which covers all the categories of symptom of acute renal failure [3]. Classification of AKI includes three grades based on disease severity i.e. risk, injury, and kidney function failure [4, 5]. Percutaneous coronary intervention (PCI) is a procedure used for the treatment of the stenosed blood vessels of the heart. The contrast media used during the PCI procedure causes toxic and hypoxic renal tubular damage and are responsible for about 12% cases of AKI [6, 7]. The contrast is the third most common cause of AKI with incidence of <5% while the incidence is increased to 20%–30% in patients with risk factors especially in diabetics [8–10]. The PCI is less invasive and cost effective than coronary artery bypass grafting (CABG) in refractory cases of myocardial infarction and AKI is a common complication encountered post procedure [11]. AKI that is angina renalis, currently diagnosed on the basis of serial serum creatinine levels (sCr) [12].

With increasing number of angiographies and PCI procedures due to ease and cost effectiveness, growing trend of contrast induced nephropathy (CIN) is being faced [13]. Traditionally sCr is used to diagnose the AKI with acute increase of 26.4 μmol/L or 25% decrease in glomerular filtration rate (GFR) after contrast administration [14]. However, sCr is influenced by a number of other factors such as age, sex, fluctuation in GFR, race, intravascular volume, muscle catabolism, drugs and nutrition [15]. The insensitivity of sCr as a predictive marker is evident that a peak is typically achieved 3 to 5 days after contrast administration and return to baseline when the patients are discharged from the hospital after 1 to 3 weeks [16, 17]. Since sCr is a marker of renal function and not primarily related to the structural damage so it might increase after at least 50% decrease in renal function [17, 18]. Moreover, the serum creatinine in acute situations does not reflect exact kidney functions [19, 20].

Another biomarker for AKI is microalbuminuria. Microalbuminuria is defined as 30–300 μg/mg of creatinine in a spot collection [21]. The albumin to creatinine ratio (ACR) is more practical and convenient method. Microalbuminuria is the increased passage of albumin through the glomerular filtration barrier. This happens because of ultra-structural changes instead of changes in GFR. A protein-rich layer on the endothelial surface, known as endothelial glyocalyx, is lost in diabetes suggests that damage to this layer causes microalbuminuria. In previous studies it was also shown that if cardiologist use ionic dyes it causes microalbuminuria i.e. AKI and if non-ionic dye was used it causes negligible effects [22–25]. The newer biomarkers for AKI includes neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin 18 (IL-18). Previous studies showed that NGAL may be considered as sensitive and non-invasive biomarker for the diagnosis of nephrotoxic and ischemic kidney injury [26].

NGAL was recognized as a small 25-kDa protein, attached covalently to the gelatinase in neutrophils [1, 12]. NGAL belongs to lipocalin family, initially separated from the supernatant of activated neutrophils of humans [27]. NGAL is also expressed by other human tissues like kidneys, epithelium of the respiratory and alimentary tract and prostate. NGAL is freely filtered and excreted in the urine. High levels of NGAL are known to be found in the cortical tubules in human kidneys and subsequently in urine after ischemic and contrast induced damage. NGAL expression is very low in certain tissues but NGAL is highly induced in damaged epithelium of the kidney [28, 29]. NGAL is a very important gene upregulated after ischemia as observed in animal studies [26]. In the past, NGAL was investigated as a biomarker of AKI in different biological materials and in intensive care patients and in patients after cardiac surgery and kidney transplantation [19, 30].

sCr is a delayed biomarker for AKI. Animal studies showed that if we diagnose AKI earlier even prior to first noted increase in sCr the AKI can be prevented or treated [13, 19, 28, 29, 31]. In the absence of specific therapies and treatment the area of early detection of AKI is very much under investigation and very important to limit the progression and outcome of AKI [32]. A number of biomarkers...
have been investigated for the early, sensitive and timely detection of the kidney injury but none of them has yet achieved the consensus. The aim of this study was to evaluate the sNGAL as a rapid predictive biomarker for diagnosis of CI-AKI first time in Pakistani population.

**Materials and methods**

In this cross-sectional analytical study, one hundred and fifty-one (n = 151) subjects undergoing elective PCI were recruited from Punjab Institute of Cardiology, Lahore Pakistan. One hundred and seven were male and 44 were female. The protocol of the study was approved by the institutional review board of Post Graduate Medical Institute, Lahore, Pakistan and written informed consent from all the subjects was taken before recruitment. Demographic information such as age, sex, blood pressure and family history of diabetes mellitus, renal disease, hypertension and drugs was recorded.

Blood was drawn, after a 12 h overnight fast, by venipuncture in vacutainers (BD Vacutainer® SST™, Singapore). The tubes were inverted gently for 5 to 6 times to allow for uniform clotting. The serum was separated by centrifugation at 2275×g and stored at 4°C. First blood sample was drawn before procedure (pre-PCI). A second blood sample was drawn 4 h after procedure (post-PCI) at first day. Then a third, fourth, fifth and sixth sample at Day 2, Day 3, Day 4 and Day 5. Urine sample was taken for estimation of urinary albumin. Five milliliters of urine were collected and stored at –20°C till the estimation. Urinary albumin and urinary creatinine were measured afterwards to calculate ACR for micro-albuminuria.

Fasting serum glucose and serum creatinine were determined spectrophotometrically by Glucose oxidase and Jaffe’s methods, respectively by using ready-made kits and automatic chemistry analyzer (Microlab LX 300). The serum NGAL was measured by ELISA using monoclonal antibody against human NGAL. Bound NGAL was detected with a horseradish peroxidase (HRP)-conjugated monoclonal antibody and the assay was developed by incubation with a color forming substrate. The measuring range of the kit was 10 ng/mL–3000 ng/mL. Urinary albumin and creatinine were measured on automatic chemistry analyzer using standard methods. sNGAL by ELISA using a cutoff value of 100 μg/L and sCr (Jaffe method) using a cutoff value of 88.4 μmol/L [16]. Microalbuminuria was defined by ACR using a cut off value of less than 30 μg/mg (urinary albumin μg/dL and urinary creatinine mg/dL).

**Statistical analysis**

Quantitative data were reported as mean ± SD and qualitative data were reported as percentage. IBM SPSS statistics (v 22.0) was used for the analysis of repeated measures analysis of variance (ANOVA) for comparison of time as applicable. Med Calc (v16.8.4) was used for analysis of area under the curve (AUC) for receiver operating characteristics (ROC) curves for the calculations of cut offs and their sensitivity and specificity in predicting contrast-induced AKI. The results were considered statistically significant when the p-value was <0.05.

**Results**

Age, sex and diastolic blood pressure of the subjects did not show any significant difference in two groups. The values of sCr, ACR, eGFR [33] and sNGAL for pre and post PCI are given in Table 1. The value of sNGAL 4 h post-PCI is highly significant (p < 0.001). The sCr though significant overall became marginal when compared gender-wise (p = 0.047) as shown in Table 2. The values of sCr over a 5-day time period gender-wise are given in Figure 1. The mean sCr values gender-wise started increasing on day-2 as shown in Figure 2.

Using repeated-measure ANOVA with a Greenhouse-Geisser correction, overall (n = 151) the change in sCr (mean ± SD) from baseline (70.1 ± 11.8 μmol/L) to post-PCI 4 h (71.2 ± 11.6 μmol/L), D2 (72.9 ± 13.0 μmol/L) D3 (81.2 ± 25.6 μmol/L) D4 (80.8 ± 24.8 μmol/L) and D5 (78.2 ± 20.3 μmol/L) was statistically significant (p < 0.001). Similarly, for male subjects (n = 107) the change in sCr (mean ± SD) from baseline (72.2 ± 11.2 μmol/L) to post-PCI 4 h (72.7 ± 10.8 μmol/L), D2 (73.9 ± 1.2 μmol/L) D3 (80.2 ± 2.1 μmol/L) D4 (79.2 ± 1.86 μmol/L) D5 (77.3 ± 1.6 μmol/L) was statistically significant (p < 0.001) and for female (n = 44) the change in sCr (mean ± SD) from baseline (65.1 ± 11.9 μmol/L) to post-PCI 4 h (67.3 ± 12.6 μmol/L), D2 as shown in Figure 2.

**Table 1:** Comparison of mean serum creatinine, ACR, NGAL in pre and post PCI patients (n = 151).

| Biomarkers       | Pre-PCI       | Post-PCI      | p-Value  |
|------------------|---------------|---------------|----------|
| Serum creatinine (μmol/L) | 70.1 ± 11.8   | 71.2 ± 11.6   | 0.005*   |
| ACR              | 16.59 ± 4.37  | 16.61 ± 4.32  | 0.533    |
| Serum NGAL (ng/mL) | 39.92 ± 10.35 | 100.42 ± 26.07 | <0.001* |
| eGFR (%)         | 105.2 ± 25.7  | 94.4 ± 30.2   | <0.001*  |

*Statistically significant.
(70.5±15.7 μmol/L) D3 (83.8±33.2 μmol/L) D4 (84.6±33.5 μmol/L) D5 (80.4±27.7 μmol/L) was statistically significant (p < 0.001) as given in Table 3.

The cut-off value of 118 μg/L for sNGAL at 4 h post-PCI was excellent to predict the CI-AKI with 93% sensitivity and 92% specificity having AUC of 0.96 by ROC curve analysis as is given in Figure 3.

Similarly, a more than 17.8% reduction in eGFR was 100% sensitive and 90.5% specific for the diagnosis of CI-AKI with AUC of 0.95 for ROC curve as shown in Figure 3.

**Discussion**

Historically, creatinine determination for the diagnosis of CI-AKI is considered as gold standard and all AKI definitions are based on creatinine retention in the blood [18]. However, there are concerns over the sensitivity of the creatinine measurement with a view that the rate of increase of creatinine is very slow and requires at least 48 h to 72 h to be increased so as to indicate the renal tubular damage [34].

The definition of CI-AKI has been changing over time to improve the diagnosis and treatment by timely intervention [35]. The absence of a uniform CI-AKI definition explains the variability in the incidence rate of CI-AKI

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**Table 2:** Gender wise comparison of mean serum creatinine, ACR and NGAL in pre and post PCI patients.

| Biomarkers          | Male (n = 107) | p-Value | Female (n = 44) | p-Value |
|---------------------|----------------|---------|-----------------|---------|
|                     | Pre-PCI | Post-PCI | Pre-PCI | Post-PCI |
| Serum creatinine (μmol/L) | 72.2±11.2 | 72.7±10.8 | 0.040 | 65.1±11.9 | 67.3±12.6 | 0.047* |
| ACR                 | 16.59±4.37 | 16.61±4.32 | 1.000 | 17.43±4.31 | 17.50±4.18 | 0.183 |
| Serum NGAL (ng/mL) | 38.79±8.94 | 98.09±22.78 | <0.001 | 42.68±12.86 | 106.07±32.32 | <0.001* |
| eGFR (%)            | 110.4±25.3 | 101.4±28.1 | 0.014* | 92.7±22.2 | 77.4±28.6 | 0.006* |

*aStatistically significant.

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**Table 3:** Comparison of serum creatinine for pre-PCI and post-PCI over time.

|                        | Pre-PCI | 4 h post-PCI | D2 post-PCI | D3 post-PCI | D4 post-PCI | D5 post-PCI | p-Value |
|------------------------|---------|--------------|-------------|-------------|-------------|-------------|---------|
| Total (n=151)          | 71.1±1.8 | 71.2±11.6 | 72.9±13.0 | 81.2±25.6 | 80.8±24.4 | 78.2±20.2 | <0.001* |
| Male (n=107)           | 72.2±11.2 | 72.7±1.1 | 73.9±1.2 | 80.2±2.1 | 79.2±1.8 | 77.3±1.6 | <0.001* |
| Female (n=44)          | 65.1±11.9 | 67.3±1.9 | 70.5±2.4 | 83.8±5.0 | 84.6±5.0 | 80.4±4.2 | <0.001* |

*aStatistically significant.

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**Figure 1:** The change in mean serum Creatinine from D1 to D5.

**Figure 2:** The mean serum creatinine showed significant difference on D2 onwards.
which ranged from 3.3% to 20% [14]. The influence of definition is such that the kidney disease improving global outcomes (KDIGO) definition reported the highest incidence rate of 18.3% followed by, 16.6% by acute kidney injury network (AKIN), 16.1% by risk, injury, failure, loss and end-stage (RIFLE) and 70% by creatinine kinetics (CK) [36]. Therefore, incidence of CI-AKI varies with the definition used. This is the reason this aspect of the study research requires to be taken care while comparing and contrasting different studies. In the present study KDIGO definition of at least 26.5 $\mu$mol/L increase in sCr post PCI was used [14]. As this is the latest refined definition and according to this definition 14.5% of the subjects developed CI-AKI in the present study. This occurrence of CI-AKI also matched to 12.5% in Indian population and other studies [2, 37–41].

The biochemical parameters such as BP, blood glucose, and urea were found same before and after contrast injection. There was no effect of these parameters which could have confounded and, indicated that the subjects have no renal impairment pre PCI. The value of sCr changed over time after PCI and reached at peak at 48 h time and returned to normal at D5. The change was statistically significant and the gender has no confounding effect.

Advanced functional genomic studies have identified the NGAL gene (lipocalin 2 gene [LCN2]), as one of the most upregulated transcripts in the kidney immediately after acute injury. The NGAL is one of the most quickly produced proteins in the kidney after a trial induced AKI [26, 42]. Animal studies also revealed the NGAL as an early induced protein in the kidney after ischemic or nephrotoxic AKI [26]. This explains the suitability of the NGAL as the potential predictive biomarker for the early detection of the AKI. In the past NGAL has been tested for a number of etiologies for AKI. The data for predictive role of NGAL for CI-AKI is however limited and inconclusive due to definitions of the CI-AKI used. The predictive advantage of NGAL further depends on the classification criteria and severity of AKI [43]. There are reports which first time combined the new RIFLE classification of AKI with the validation of NGAL as an early marker of kidney injury in critically ill children [44]. NGAL has been evaluated for the early diagnosis of the AKI while different cutoff values of the creatinine have been used as a reference.

The variability of the creatinine cut off makes it complex to judge about the cut off of the sNGAL. The timing of the NGAL increase after administration of the contrast dye and the biological material used for its estimation may have their influence on the cut off value.

In the present study, sNGAL at 4 h post-PCI for a cut-off value of 118 $\mu$g/L was 95.8% sensitive and 97.6% specific with AUC of 0.96 by ROC analysis. Padhy et al. [41] also reported an increase in sNGAL at 4 h post procedure with a cut-off level of 155.2 $\mu$g/L and sensitivity and specificity of 100% and 96.7%, respectively with AUC of ROC 1.00.

A study in Malaysian population reported sNGAL with sensitivity of 72.7% and specificity of 45.0% for cut off value of 91.8 $\mu$g/L with AUC of 0.683 [45]. The low values of sensitivity and specificity are attributed to the time of estimation which was 24 h. However, in our study sNGAL was measured at 4 h which suggested that the sNGAL increased very early during the injury and a valuable predictor to that effect.

In another study in Chinese population in which though the sNGAL was measured at 4 h post procedure yet it showed very low sensitivity of 51.5% and AUC of 0.662 [46]. The difference seems to be occurred due to the use of sCr value of 44.6 $\mu$mol/L as diagnostic criteria of CI-AKI instead of 26.5 $\mu$mol/L used in present study.

Plasma NGAL predicted contrast induced nephropathy in children using a cut-off value of 100 $\mu$g/L with sensitivity, specificity, and AUC of ROC curve of 73%, 100%, and 0.91, respectively [47]. These are good results but sensitivity is somehow low and since this study was conducted in children so is not comparable with the present study.

It is evident that the levels of NGAL depends on the time of measurement after contrast administration, ethnicity and geographic variability.

The present study is the first study, as far the knowledge of the researchers, conducted in the Pakistan to find out the potential of sNGAL as an early biomarker in Pakistani population. It has been reported that the urinary and

![Figure 3: The ROC curves showing AUC for sNGAL and eGFR.](image-url)
serum NGAL at 2 h are sufficient alone to predict AKI [47, 48]. Similar to the present study, a significant rise in serum NGAL at 2 h and 4 h after PCI has been observed [28]. In addition Bachorzewska-Gajewska and his colleagues in 2009 also noted the raised levels of NGAL and L-FABP and predicted renal tubular [49]. Bachorzewska-Gajewska and his co-investigators predicted, in concordance with present study, the development of CIN after PCI on the basis of increased NGAL and cystatin C levels [16, 50].

It is hence concluded that the sNGAL is a superior biomarker for early prediction of CI-AKI among the existing biomarkers.

**Conflict of interest statement:** The authors have no conflict of interest.

**Limitations of the study:** In the present study sNGAL was measured only at 4 h post PCI and did not determine the effect of time over longer period. Further the hydration status of the subjects could not be monitored during study period.

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