

## Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Predictive Biomarker for Contrast Induced Nephropathy, in Moderate Risk Patients after Cardiac Catheterization

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### Abstract

**Background:** Contrast-induced nephropathy (CIN) is an acute kidney insult (AKI) defined as creatinine (SCr) increase 48 to 72 h after intravenous contrast. Because most subjects undergoing invasive cardiac procedures are discharged within 24 h, SCr is unsuitable for CIN detection. This study compares between serum NGAL, and SCr in moderate risk patients after coronary angiography with/without intervention for the occurrence of CIN.

**Methods:** This was a prospective provisional study carried out from January 2015 to July 2016, in the department of Cardiology, El-Minia University Hospital (EGYPT). 42 moderate risk Subjects (Mehran Score 6 to 10 with estimated 14% risk of developing CIN) undergoing elective coronary angiography with/without intervention were enrolled. Serum NGAL was assessed before and 4 h post-procedure. SCr was measured before and 48 h post-procedure. CIN was defined as SCr increase >25% or >0.5 mg/dL from baseline after coronary angiography within 48 h, without explanation or the presence of any cause.

**Results:** 30 males and 12 females with mean age  $54.92 \pm 10.14$  (36-73) years and mean baseline SCr  $1.01 \pm 0.25$  mg/dl (0.6-1.8) were enrolled. A contrast volume with mean  $161.9 \pm 76.35$  mL (100-300) was administered. CIN was found in twelve subjects (28.6%). Included subjects were classified into those with and without CIN, NGAL was significantly elevated in subjects with CIN versus those without 4 h after coronary intervention  $172.69 \pm 70.48$  (50-280 ng/mL) vs.  $104.19 \pm 53.03$  (75-350 ng/mL) ( $P < 0.001$ ). Using a cutoff value of >174 ng/mL, 4-h NGAL was excellent predictor of CIN with 91.67% sensitivity, 93.33% specificity, 84.6% PPV, 96.6% NPV, 92.86% Accuracy and 92.86 area under (ROC) curve. Baseline demographics show no difference between those with and without CIN among study groups. Serum NGAL at 4 h post procedure ( $P < 0.001$ ) used as a predictor of the occurrence of CIN among study groups.

**Conclusions:** Serum NGAL measured 4 h following coronary angiography with/without intervention after intravenous contrast administration can be used as a novel and helpful biomarker for the occurrence of CIN in moderate risk patient. The percentage of CIN incidence (28.6%) in this study in moderate risk patients highlight the useful use of serum NGAL 4 h post procedure measurement to predict, intervene and may prevent CIN.

**Keywords:** Acute kidney insult; Coronary angiography; Contrast-induced nephropathy; Neutrophil gelatinase-associated lipocalin

### Introduction

CIN is now the one of the causes of acute kidney insult which occurs after intravenous contrast infusion in-hospital and is responsible for approximately 10% of all cases of iatrogenic renal disease [1]. Contrast-induced nephropathy (CIN) is an important cause of hospital-acquired acute renal failure and has a poor prognosis [2]. CIN is defined as the impairment of renal function-measured as either increase in serum creatinine (SCr) about 25% from baseline or a 0.5 mg/dL (44  $\mu$ mol/L) increase in absolute SCr value-within 48-72 h after intravenous contrast administration [3] incidence of CIN after intravenous contrast administration is widely variable in the literature, depending on the baseline risk factors and the definition used of this clinical event [4]. It affects between 1% and 2% of the general population and up to 50% of high-risk subgroups following coronary angiography (CA) or percutaneous coronary intervention (PCI) [5].

The current definition of the CIN is based on the absolute or relative increase in the serum creatinine [6], SCr elevation is relatively slow and is influenced by extra-renal factors [1], Levels peak 2-3 days after contrast medium exposure [7], therefore the use of SCr for the detection of AKI delays therapeutic intervention by about 48 h following the insult to the kidney. Hence, considerable efforts had been put into the search for new biomarkers as early indicators of AKI [8]. One of the promising candidate biomarkers is neutrophil gelatinase-associated lipocalin (NGAL), a 25 kDa siderophore binding protein [9], NGAL has been identified as a sensitive and specific biomarkers for predicting cardiac surgery-associated acute kidney injury [10]. NGAL is indicative of distal nephron damage, as it is massively upregulated in the ascending limb of the loop of Henle, distal tubule and collecting duct [11]. NGAL has emerged as an early, sensitive, non-invasive biomarker for predicting CI-AKI in different cardiovascular conditions [12]. With the continued use of serum creatinine as a marker of kidney function, Treatment regimens for AKI have been unsuccessful over the years, also due to the incomplete understanding of the pathogenesis and biomarkers for early detection,

in addition to poor clinical trial design [13]. Our study therefore aimed to evaluate the role of serum NGAL as a new marker for early detection of CIN after elective coronary angiography with/without intervention, compared with the traditional marker SCr, and to determine the frequency of CIN in these patients.

## Patients and Methods

### Study design

This was a prospective study carried out from January 2015 to July 2016. In the department of cardiology, El-Minia University hospital (Egypt), 42 moderate risk Subjects (Mehran score 6 to 10 with estimated 14% risk of developing CIN) in the cath-lab undergoing elective coronary angiography with/without intervention were enrolled. All patients received intravenous (IV) normal saline at a rate of 1 mL/kg for 12 h pre-procedure for in-patients, 3 ml/kg for 3 h pre-procedure for our patients, serum NGAL was measured before and 4 h post-procedure. SCr was measured before and 48 h post-procedure. CIN was defined as SCr increase >25% or <0.5 mg/dL from baseline after coronary angiography with or without intervention within 48 h, without explanation or the presence of any cause.

### Measurement of NGAL and other variables

The serum for NGAL was first diluted 20-fold using calibrator diluents and then assayed using an enzyme-linked immune-sorbent assay (ELISA) kit from R&D Systems (Minneapolis, Minnesota). The SCr levels were determined by using kinetic Jaffe method (Thermo Scientific Kone lab Prime 60i Clinical Chemistry Analyzer) [14].

### Statistical analysis

Data was statistical analyzed by using SPSS\_20 software package. Categorical data was presented in the form of frequency and percentage. Quantitative data were expressed in the form of mean; SD. One way ANOVA test was used to test the significance between groups for quantitative variables however Chi-square ( $\chi^2$ ) was used for qualitative data. Duncan multi-comparison test was used. Person correlation coefficient was used to get the correlation between variables. Probability (p value) was considered as significant if <0.05. Univariate and multivariate stepwise multiple logistic regression analysis was undertaken to assess predictors of CIN. A receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) was used to calculate the sensitivity and specificity for plasma NGAL measurements to predict the occurrence of CIN at varying cut-off values, and to quantify the accuracy of plasma NGAL as a biomarker (Medcalc, version 12.2.1). An AUC of 0.5 is no better than expected by chance, whereas a value of 1.0 signifies a perfect biomarker.

## Results

Forty-two moderate risk patients (Mehran Score 6 to 10 with estimated 14% risk of developing CIN) in the Cath-Lab undergoing elective coronary angiography with/without intervention, male/female 30/12, mean age  $54.92 \pm 10.14$  (36-73) years, with mean baseline SCr  $1.01 \pm 0.25$  mg/dL (0.6-1.8) were enrolled. Volume of the contrast used was  $161.9 \pm 76.35$  mL (range 100-300 mL) was administered. CIN was found in twelve subjects 12/42 (28.6%), but detection by SCr was only possible 48 h post-procedure.

According to our results subjects were classified into those with and without CIN. Baseline patient demographic data shows no significant differences were noted between CIN and non-CIN groups (Table 1).

	Nephropathy		P value
	No	Yes	
	(n=30)	(n=12)	
<b>Age</b>			
<b>Range</b>	(36-67)	(37-73)	0.314
<b>Mean <math>\pm</math> SD</b>	$53.66 \pm 8.94$	$58.08 \pm 12.54$	
<b>Sex</b>			
<b>Male</b>	21 (70%)	9 (75%)	1
<b>Female</b>	9 (30%)	3 (25%)	

**Table 1:** Statistical comparison between subjects with and without CIN as regard to age and sex.

There was a statistically significant increase in SCr from baseline and at 48 h post-procedure in all 42 patients:  $1.01 \pm 0.25$  mg/dl (0.6-1.8) and  $1.2 \pm 0.29$  mg/dl (0.8-2.4),  $p \leq 0.001$ , with a statistically significant increase in SNGAL from baseline then at 4 h post-procedure:  $104.19 \pm 53.03$  ng/ml (50-280) and  $172.69 \pm 70.48$  ng/ml (75-350),  $p \leq 0.001$  (Table 2).

	Pre catheterization	After catheterization	P value
<b>Creatinine</b>			
<b>Range</b>	(0.6-1.8)	(0.8-2.4)	<0.001*
<b>Mean <math>\pm</math> SD</b>	$1.01 \pm 0.25$	$1.2 \pm 0.29$	
<b>NGAL</b>			
<b>Range</b>	(50-280)	(75-350)	<0.001*
<b>Mean <math>\pm</math> SD</b>	$104.19 \pm 53.03$	$172.69 \pm 70.48$	

**Table 2:** The data shows plasma creatinine at baseline and at 48 h after catheterization and plasma NGAL at baseline and at 4 h after catheterization

A statistically significant differences were noted between non-CIN and CIN groups in SNGAL at baseline and at 4 h post-procedure: at baseline  $88.86 \pm 31.21$  ng/ml (55-170) and  $142.5 \pm 75.33$  ng/ml (50-280),  $p=0.005$ , at 4 h post  $139.1 \pm 38.92$  ng/ml (75-240) and  $256.66 \pm 61.24$  ng/ml (130-350),  $p \leq 0.001$  (Table 3).

	Nephropathy		P value
	No	Yes	
	(n=30)	(n=12)	
<b>NGAL pre-catheterization</b>			
<b>Range</b>	(55-170)	(50-280)	0.005*
<b>Mean <math>\pm</math> SD</b>	$88.86 \pm 31.21$	$142.5 \pm 75.33$	
<b>NGAL after catheterization</b>			

<b>Range</b>	(75-240)	(130-350)	<0.001*
<b>Mean ± SD</b>	139.1 ± 38.92	256.66 ± 61.24	
<b>P 2</b>	<0.001*	0.002*	

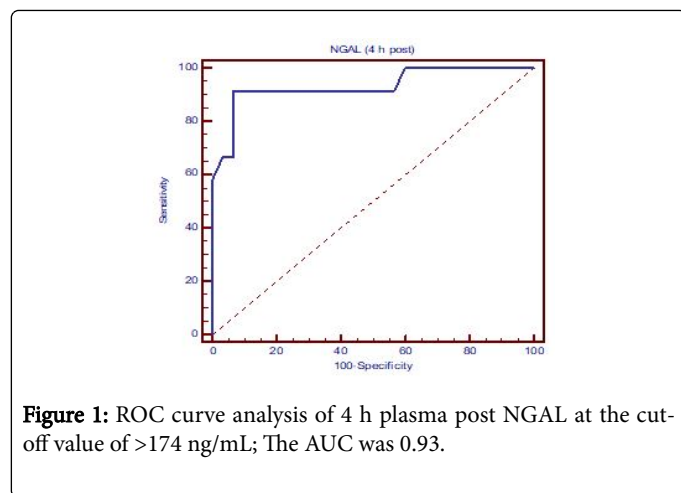
**Table 3:** The statistical comparison between subjects with and without CIN as regards NGAL levels, pre and 4 h after catheterization.

There were statistically significant differences regarding EF, NGAL pre, 4 h post catheterization, CHF, diabetes, contrast volume and total Mehran score among study subjects with and without CIN by using simple logistic regression analysis (Table 4).

	<b>OR</b>	<b>95% CI</b>	<b>P value</b>
<b>EF&gt;50%</b>	0.79	0.69-0.91	0.001*
<b>NGAL pre</b>	1.02	1.004-1.04	0.014*
<b>NGAL post</b>	1.04	1.02-1.07	0.001*
<b>CHF</b>	5.18	1.15-23.29	0.032*
<b>Anemia</b>	NA	NA	NA
<b>Diabetes</b>	6	1.32-27.19	0.020*

<b>Variable</b>	<b>Optimal cutoff</b>	<b>AUC</b>	<b>P value</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>	<b>Accuracy</b>
<b>NGAL 4 h post</b>	>174	0.933	<0.001*	91.67%	93.33%	84.60%	96.60%	92.86%

**Table 6:** ROC curve analyses for prediction of CIN for 4 h post NGAL and contrast volume.



**Figure 1:** ROC curve analysis of 4 h plasma post NGAL at the cut-off value of >174 ng/mL; The AUC was 0.93.

## Discussion

Our study demonstrates that measuring plasma NGAL *via* enzyme-linked immune-sorbent assay (ELISA) 4 h after intravenous contrast administration to be a clinically useful, novel, early and helpful biomarker for the early prediction of CIN in moderate risk patient undergoing elective catheterization biomarker in the early prediction of CIN. Therefore, plasma NGAL appears to be a powerful early biomarker of CIN that precedes the increase in Scr by several hours. Furthermore, the high incidence of the occurrence of CIN observed and detected in this study (28.6%) makes attention to the importance

<b>Contrast volume</b>	1.01	1.004-1.02	0.007*
<b>Total Mehran score</b>	2.02	1.23-3.31	0.005*

**Table 4:** Shows simple logistic regression analysis of study variables in CIN and non-CIN groups

Multiple stepwise logistic regression analysis revealed that 4 h NGAL post as the most predicted significant variable (Table 5).

	<b>OR</b>	<b>95% CI</b>	<b>P value</b>
<b>NGAL 4 h post</b>	1.05	(1.01-108)	0.007*
<b>Contrast volume</b>	1.02	(0.99-1.05)	0.067

**Table 5:** Multiple stepwise logistic regression analysis

The ROC curve analysis for prediction of CIN for 4 h post NGAL shows that the SNGAL at a concentration of >174 ng/ml showed the best cutoff value where the sensitivity was 91.67% and the specificity was 93.33% and the PPV was 84.6% and the NPV was 96.6% with accuracy 92.86% (Table 6 and Figure 1).

of early prediction of CIN by a rapid new biomarker as plasma NGAL 4 h post procedure measurement.

Prior studies demonstrate the usefulness of measurement of NGAL as an early biomarker of CI-AKI in different scenarios, especially after coronary angiography with or without intervention after contrast administration; however the optimal timing for its determination following coronary angiography has not yet been well elucidated. Our results demonstrate that excellent performance of plasma NGAL with overall AUC-ROC of 0.933 for CIN, when measured 4 h post procedure, with a sensitivity of 91.6% and specificity of 93.3% these findings was in agreement was that found in a meta-analysis studies that found an overall AUC-ROC of 0.894 for CIN prediction, when plasma or urine NGAL was measured within 6 h after contrast administration for coronary procedures with or without interventions [15].

In contrast to our results the increase in urinary NGAL measured by a research-based assay at 24 h post-procedure was significantly high in CIN group when compared to the non CIN group in a Chinese Study where CIN was detected in 8.7% of adult with normal renal function undergoing coronary angiography [16].

Recently and In marked contrast to our findings urinary NGAL failed as an early predictor of CIN in a study from Austria conducted on 617 patients with chronic kidney disease (CKD) undergoing intra-arterial angiography, only 10 of them exhibited a significant rise of uNGAL exceeding the threshold for randomization and only one single patient out of these developed CI-AKI [17] this may be explained by observation reported by Mori and Nakao “the forest fire theory” which assume that increased NGAL in CKD is the

consequence of its sustained production by inflamed but viable tubular cells [18].

Recently also, in agreement with this study, 8% of patients developed CIN in Indian study conducted on 240 patients with baseline creatinine <1.4 mg/dl, Urinary NGAL at 4 hours post coronary angiogram was an excellent predictor for contrast induced acute kidney injury with sensitivity and specificity of 94.7% and 99.1% respectively, and with positive and negative predictive values of 90% and 99.5% respectively [19].

With CIN, using the same definition as a 25% increase in SCr from baseline another study also from Egypt, significant increase was present in serum NGAL 4 and 24 h after coronary interventions among adults with normal SCr was detected in 6.7% of the participants. Devarajan used serum NGAL 4 h post-procedure in agreement with our study with another definition and longer follow up of NGAL after 24 h [20].

The relatively high incidence of CIN reported in this study 28% should be taken into account for the result interpretation and analysis and this is may be due to variations in study designs and methodology used for NGAL measurements either plasma or urine for CIN definition.

The baseline renal function and also the normal pre-procedure renal function both considered an important predictive performance of NGAL results.

Our study population consisted of subjects at moderate risk for CIN involved only elective catheterization excluding emergent ones that are usually performed in subjects with major co-morbidities and potentially at higher risk of CIN.

An additional strength of our study is that all subjects started with low levels of plasma NGAL. In the current study, there was no significant difference in the baseline SCr between the two groups (CIN/non-CIN), and also all included subjects started the study with low levels of plasma NGAL. Our study design allowed a direct comparison between any alterations in the level of NGAL concentration when compared to changes in SCr, which is considered the current reference standard test for the definition of CIN. So the magnitude of any rise for NGAL from baseline found in our study supports that present in other literature data that NGAL highly discriminatory biomarker with a good cut-off values that allow for risk assessment and stratification with a wide dynamic range.

In the current study plasma NGAL was measured instead of urine NGAL which is more accurate and precise for early detection of CIN it is revolutionized in clinical medicine as the use of troponins for the early diagnosis of acute myocardial infarction and the value of B-type natriuretic peptide for prognostication in acute coronary syndromes.

## Limitations

Although this is a single center trial and the number is relatively small, yet statistical analysis was valid for the conclusions taken. However, a large number might be needed for firmer conclusions.

Subjects at higher risk of CIN such as patients with advanced CKD, emergency patients, and thermodynamically unstable must be included in further studies.

## Conclusion

Serum NGAL measured by ELISA 4 hours following coronary angiography with/without intervention after intravenous contrast administration can be used as a novel and helpful biomarker for the occurrence and prediction of CIN in moderate risk patient undergoing elective catheterization.

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