The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1523-1528

Predictive value of Neutrophil-Gelatinase-Associated Lipocalin on the Severity of coronary artery diseases and development of Contrast-Induced Nephropathy after Percutaneous Coronary Interventions

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ABSTRACT

Background: Contrast-induced acute kidney injury (CI-AKI) is a common complication among patients undergoing percutaneous coronary intervention (PCI). Neutrophil gelatinase associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils released by renal tubular cells following acute tubular damage.

Objective: This study aimed to assess the role of neutrophil gelatinase associated lipocalin (NGAL) as a novel noninvasive biomarker in prediction of contrast-induced nephropathy (CIN) and the severity of coronary artery disease (CAD). **Patients and Methods:** This study was conducted as an observational Cross-sectional study included 50 patients who were admitted to the catheterization laboratory at Zagazig University Cardiovascular Department for PCI from the period of 2014-2020. Patients were divided into two groups: Group A (nephropathy group) included patients who developed impairment of kidney function and group B (non-nephropathy) group. All patients were subjected to demographic data taking, full general (BP, Pulse, etc.) and local examination. ECG analysis, laboratory investigation, echocardiographic examination (According to ASE 2015) and coronary angiography.

Results: The difference between the two groups regarding post-PCI serum creatinine, pre-PCI NGAL and post-PCI NGAL was statistically significant. ROC curve was constructed for estimating the validity of post-PCI NGAL as a predictor for contrast-induced nephropathy and it was found that at cut-off value of 131 µg/l was 92% for sensitivity and 76% for specificity with AUC of 0.92 by ROC analysis

Conclusions: We concluded that among ischemic heart disease patients who underwent PCI, baseline NGAL levels identified patients at high risk for the development of CI-AKI. Also we found that pre-coronary angio NGAL can predict the severity of CAD.

Keywords: Contrast-induced acute kidney injury, Neutrophil gelatinase-associated lipocalin, Contrast-induced nephropathy.

INTRODUCTION

Despite the revolution in therapeutic approaches, coronary heart disease (CHD) remain one of the prime causes of death. According to the global burden of disease analysis, the highest mortality rate was attached to CHD. However, 80% of the global cases of CHD are diagnosed in low-income countries. Among CHDs, acute coronary syndrome (ACS), including ST-segment elevation myocardial infarction (STEMI), non– ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), make up a significant proportion of clinical manifestations of CHD [(1)].

Interventional procedures requiring contrast media administration are increasingly prevalent in contemporary practice. Yet, a common complication arising from these procedures is rapid, though often temporary, declines in kidney function in the ensuing days. The pathophysiology underlying this clinical manifestation is complex and multifactorial, but a clear role has been related to the nephrotoxic and hemodynamic effects of iodinated contrast media, which result in increased oxidative stress and cell injury [(2)]. Among patients undergoing percutaneous coronary interventions (PCI), the incidence of contrast-associated acute kidney injury (CA-AKI) have been reported between 3.3% and 14.5%, according to the definition used [(3)].

Deterioration of renal function resulting in acute kidney injury (AKI) is a significant complication associated with adverse outcomes in patients with ACS undergoing primary percutaneous coronary intervention (PCI). Many risk factors have been suggested to play an important role in the development of CI-AKI. The change of serum creatinine level was well-documented as a risk factor for CI-AKI. However, serum creatinine level does not elevate until glomerular filtration rate (GFR) has decreased by at least 50%. Thus, assessment of renal dysfunction according to serum creatinine is not reliable [(4)].

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils and is found to be released by renal tubular cells following acute tubular damage [(5)]. In the present study, we aimed to assess the role of neutrophil gelatinase associated lipocalin (NGAL) as a novel non-invasive biomarker in prediction of contrast-induced nephropathy (CIN) and the severity of coronary artery disease (CAD).

PATIENTS AND METHODS

This observational cross-sectional study included 50 patients who were admitted to the catheterization laboratory at Zagazig University Cardiovascular Department for PCI through the period from 2014 to 2020.

Received: 25/10/2021
Accepted: 23/12/2021

Inclusion criteria: Age 20- 80 years old, both sexes were included. Patients admitted for coronary angiography through one year in the cardiac catheterization laboratory of the Zagazig University Hospital, Cardiology Department and Damietta Cardiology Center.

Exclusion criteria: Patients with impaired renal functions (serum creatinine more than 1.3 mg/dl). Refusal of participation in the study.

Patients were divided into two groups: Group A (nephropathy group) included patients with impairment of kidney function measured as either a 25% increase in serum creatinine (SCr) from baseline or a 0.5 mg/dl (44 µmol/l) increase in absolute SCr value within 48-72 hours after intravenous contrast administration [(3)]. Group (B), non-nephropathy group.

All patients were subjected to:

Demographic data taking, full general (BP, Pulse, etc.) and local examination. ECG analysis and laboratory investigation (serum creatinin before and 48 hours after the coronary angiography and the percutanous coronary intervention). serum neutrophil gelatinase-associated lipocalin (NGAL) was estimated before and 2 hours after the coronary angiography and the percutanous coronary intervention (PCI)**.** All patients were examined by transthoracic echocardiography and coronary angiography.

Coronary angiography was performed and multiple views were obtained in all patients. More than 50% of lesions were in left main coronary artery, left anterior descending artery or its first diagonal branch, circumflex artery or its first obtuse marginal branch, and right coronary artery were evaluated as significant and the number of affected coronary arteries were determined and the severity of coronary artery disease (CAD) was assessed by calculating the coronary stenosis index (CSI) as the sum of the following scores of stenosis for each lesion**.**

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans

Statistic analysis

All data were collected, tabulated and statistically analyzed using the BM SPSS (Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Chi-Square test was used for comparison of 2 or more groups. Student t-test was used to compare 2 independent groups. Mann-Whitney U test was used to compare 2 independent groups. Significance of the obtained results was judged at the (0.05) level.

RESULTS

Table (1) showed that there was statistically non-significant increase as regards age and gender in group (A) as compared to group (B). The p-value comparing gender and age was 0.96 and 0.33 respectively. There was statistically non-significant difference as regards hypertension, DM, smoking, and past history of CVD in group (A) as compared to group (B), (p-value =0.42, 0.58, 0.7, and 0.87).

Table (1): Demographic data of the study population

	Nephropathy group(A) (n = 4)		**Non-nephropathy group(B) (n = 46)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Gender						
Male	3	75	34	74	χ^2= 0.002	0.96
Female	1	25	12	26		
Age (years)						
Min. – Max.	50– 76		33– 77		t=1.11	0.33
(Mean ± SD.)	64.25±10.9		57.91±10.57			
Hypertension	2	50	32	69.5	0.65	0.42
DM	3	75	28	60.8	0.31	0.58
Smoking	3	75	30	65.2	0.157	0.7
PH of CVD	2	50	21	65.2	0.028	0.87

χ^2: Chi square test, t: Student t-test: p-value >0.05: Non significant (NS); p-value <0.05: Significant(S); p-value< 0.01: highly significant (HS)

Table (2) showed that there was statistically significance increase in EF in group (A) as compared to group (B), the median (IQR) was 73.3 (58.5-75.5) versus 61.5 (53-67) for nephropathy group and non-nephropathy group, respectively (p-value= 0.049).

Table (2): Echocardiographic data among the study groups

ECHO parameter	Nephropathy group(A) (n = 4)	Non-nephropathy group(B) (n = 46)	Test of Sig. U	P
LVEDD (mm) Median (IQR)	5.6 (5.17-6.02)	5.15 (4.7-5.8)	58	0.22
LVESD (kg) Median (IQR)	3.4 (2.97-3.75)	3.2 (3-4.12)	86	0.83
EF (%) Median (IQR)	73.3 (58.5-75.5)	61.5 (53-67)	37	0.049**

U: Mann Whitney test, p: p-value >0.05: Non-significant (NS); p-value <0.05: Significant(S); p-value< 0.01: highly significant (HS)

Table (3) showed that there was statistically significant increase in the amount of contrast (mg) in patients who underwent coronary angiography (CA) only and those who underwent coronary angiography and PCI (CA & PCI) in group A as compared to group B (p-value= 0.039, 0.037, and 0.001 respectively).

Table (3): Comparison of PCI data between the two groups

	Nephropathy group(A) (n = 4)		Non-nephropathy group(B) (n = 46)		Test of Sig. χ^2	P
	No.	%	No.	%		
C.A	0	0	25	54.3	4.34	0.039**
C.A & PCI	3	75	30	65.2	4.35	0.037**
CSI PCI					4.7	0.32
0	0	0	16	34.8		
1	0	0	1	2.2		
2	0	0	5	10.8		
3	0	0	4	8.7		
4	4	100	20	43.5		
Amount of contrast (mg) Min. – Max. Median (IQR)	100-120 100(100-115)		30-90 50 (40-60)		U=0	0.0001**

χ^2: Chi square test,p: p-value >0.05: non-significant (NS); p-value <0.05: significant(S); p-value< 0.01: highly significant (HS), **: statistically significant CSI: coronary stenosis index .

Table (4) showed that there was statistically non-significant increase in pre-PCI serum creatinine in group (B) as compared to group (A) (p-value=0.39). There was statistically significant increase in post-PCI serum creatinine in group (A) as compared to group (B) (p-value=0.0.001). There was statistically significant increase in pre-PCI NGAL and post-PCI NGAL in group (A) as compared to group (B) (p-value=0.0.001).

Table (4): Laboratory parameters between the two groups

Lab parameter	Nephropathy group(A) (n = 4) Mean ± SD	Non-nephropathy group(B) (n = 46) Mean ± SD	Test of Sig.	p
Pre-PCI SCr (mg/dl)	0.75±0 .13	0.8± 0.16	U=68.5	0.39
Post-PCI SCr(mg/dl)	2.5± 0.52	0.82±0.15	U=0	0.001**
Pre-PCI NGAL (ng/ml)	244.25±16.48	166.34±31.18	T=-3.9	0.001**
Post-PCI NGAL (ng/ml)	409.5±55.91	167.36±24.25	T=10.31	0.001**

U: Mann Whitney test, t: student t test,p: p-value >0.05: Non-significant (NS); p-value <0.05: Significant(S); p-value< 0.01: highly significant (HS), **: statistically significant.

When we compared both serum creatinine and NGAL before and after PCI in nephropathy group (group B), There was significant increase in both serum creatinine and NGAL in post-PCI as compared to pre-PCI (p-value=0.045 and 0.005, respectively) as shown in table (5).

Table (5): Comparison regarding serum creatinine and serum NGAL before and after contrast among nephropathy group

Lab parameter	Pre PCI Mean ± SD	Post PCI Mean ± SD	Test of Sig.	p
SCr (mg/dl)	0.75 ± 0.13	0.8 ± 0.16	Z=-2.17	0.045**
NGAL (ng/ml)	244.25 ± 16.48	409.5 ± 51.91	T= -7.28	0.005**

Z: Wilcoxon rank test, t: paired t test,p: p-value >0.05: Non-significant (NS); p-value <0.05: Significant(S); p-value< 0.01: highly significant (HS), **: statistically significant.

Table (6) showed that there was a positive correlation between age and pre-PCI NGAL (rs=-0.415) and was statistically significant (p-value < 0.05). We also found a positive correlation between CSI and pre-PCI NGAL (rs=-0.429) and was statistically significant (p-value < 0.05). There was a positive correlation between pre- and post-PCI NGAL (rs=-0.488) and was statistically very highly significant (p-value < 0.005). There was no correlation between pre-PCI NGAL and other parameters (LVEDD, LVESD, EF, pre-PCI S. creatinine and post-PCI S. creatinine) and was statistically non-significant (p-value > 0.05).

Table (6): Correlation between pre-PCI NGAL and different parameters among all the studied cases

	Pre-PCI NGAL(ng/ml) All patients (N=50)	
	r_s	P
Age (years)	0.415**	0.032**
LVEDD (mm)	0.194	0.177
LVESD (mm)	0.144	0.226
EF (%)	-0.049	0.736
CSI	0.429**	0.018**
Pre-PCI sCr (mg/dl)	0.066	0.65
Post-PCI sCr (mg/dl)	-0.064	0.658
Post-PCI NGAL (ng/ml)	0.488	0.001**

rs: Spearman coefficient, *: weak correlation, **: moderate correlation, ***: strong correlation, p: p-value >0.05: non-significant (NS); p-value <0.05: significant(S); p-value< 0.01: highly significant (HS), **: Statistically significant at p ≤ 0.05.

For prediction of contrast-induced nephropathy: Receiver Operator Characteristics (ROC) curves were constructed for estimating the validity of post-PCI NGAL as a predictor for contrast induced nephropathy (Figure 1).

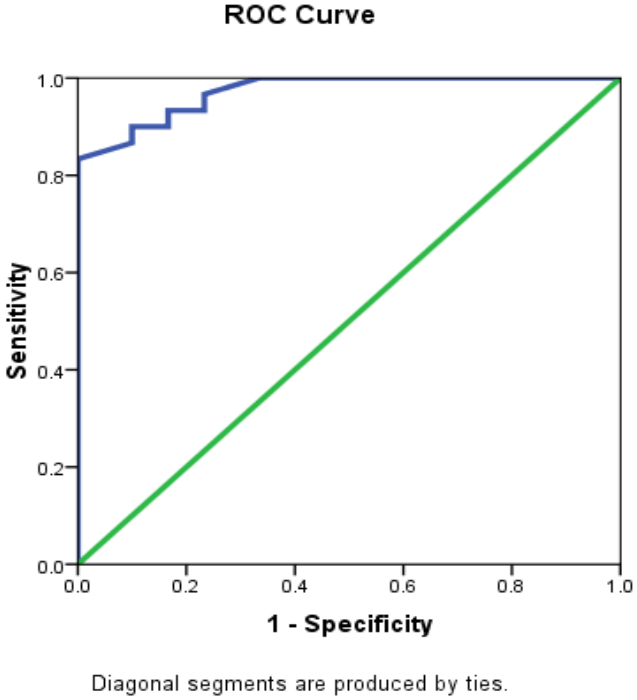

Figure (1): ROC curve of post-PCI NGAL in differentiating contrast induced nephropathy cases

DISCUSSION

In the present study, there was no significant difference between the 2 studied group regarding age and sex as males represented 75% in both of the studied groups. Another Lebanese study on the socioeconomic disparities in heart disease also found male sex was non-modifiable-independent risk factors for CAD [(6)]. The increased incidence of CAD among males can be explained as the sexual hormones drive differences in gene expression and the function of cardiovascular system [(7)]. In male sex, cardiovascular risk increases over time, as well as atherosclerosis process continues. In contrast women are protected from atherosclerosis during the fertile age by estrogens that exert favorable effect on cardiovascular system. The effect disappears after menopause. Women and men manifest a similar cardiovascular profile with a difference of 10 years of age [(8)].

In the present study we found that age among the nephropathy group was 64.25±10.9 years and among the non-nephropathy group was 57.91±10.57 years. The cardiovascular system is strongly affected by the ageing process leading to progressive deterioration in structure and function of the heart and vasculature that contribute to the development of CVD [(9)].

As for the risk factors, the difference was statistically non-significant between the two groups, (p-value =0.42, 0.58, 0.7, and 0.87 respectively) regarding hypertension, DM, smoking, and past history of CVD. In the present study, we found that 75% of the nephropathy group and 60.8% of the non-nephropathy group were diabetic. It was reported that increased factor like oxidative stress, coagulability, endothelial dysfunction and autonomic neuropathy are associated with DM and lead to the development of CVD [(10)]. In the present study we found that 75% of the nephropathy group and 65.2% of the non-nephropathy group were smokers. This can be explained as cigarette smoking increases inflammation and thrombosis leading to oxidative stress manifestation, prothrombotic activity, platelet aggregation, leukocyte activation, lipids peroxidation and smooth muscle proliferation [(11)]. Nicotine affects the cardiovascular system by increasing systolic and diastolic blood pressure, heart rate and cardiac output [(12)]. In the present study, we found that 50% of the nephropathy group and 69.5% of the non-nephropathy group had hypertension (HT). HT is not only an increase in blood pressure, but is also a complex cardiovascular disease, where inflammation, endothelial dysfunction and platelet activation also play a role in pathophysiology [(13)]. Increased inflammatory activity has been demonstrated in HT patients [(14)].

There was statistically non significance increase in LVEDD in group (A) as compared to group (B), the median (IQR) was 5.6 cm (5.17-6.02) versus 5.15 cm (47-5.8) for nephropathy group and non-nephropathy group (p-value= 0.22).

In the present study, we found significant positive correlation between NGAL and coronary stenosis index. Our findings are in accordance with a previous study detected a correlation between increased NGAL level in ACS patients and the number of diseased vessels as detected by angiography and the Gensini score [(15)]. In another study, higher NGAL levels were demonstrated in patients with acute coronary syndrome compared to patients with stable coronary artery disease [(16)]. The positive correlation of NGAL with coronary stenosis index can be explained as the local inflammatory response in the plaque site is higher in complex lesions compared to simple lesions [(15)].

In the present study, we found positive correlation between NGAL and age. The correlation of NGAL with renal dysfunction is a well-investigated subject [(17)]. Therefore, factors, such as age, blood pressure, and creatinine, which are used for calculating the Grace risk score, are also stimulants for NGAL expression. In addition, NGAL may have different roles in the atherosclerotic process that we are not yet aware where NGAL is an inflammatory marker released by neutrophils and is also an adipokine secreted by the liver and adipocytes [(18)].

In the present study, ROC curve was constructed for estimating the validity of post-PCI NGAL as a predictor for contrast-induced nephropathy and it was found that at cut-off value of 131 µg/l was 92% sensitivity and 76% specificity with AUC of 0.92 by ROC analysis. A previous study showed that, sNGAL at 4 h post-PCI for a cut-off value of 118 µg/l was 95.8% sensitivity and 97.6% specificity with AUC of 0.96 by ROC analysis [(19)]. **Padhy and his colleagues** also reported an increase in sNGAL at 4 h post-procedure with a cut-off level of 155.2 µg/l and sensitivity and specificity of 100% and 96.7%, respectively with AUC of ROC 1.00 [(20)]. 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 2 h, which suggested that 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 [(21)]. The difference seems to be occurred due to the assessment timing of NGAL.

CONCLUSION

We concluded that among ischemic heart disease patients who underwent PCI, baseline NGAL levels identify patients at high risk for the development of CI-AKI. Also we found that pre-coronary angio NGAL can predict the severity of CAD. Further studies on larger populations are required to validate our reports and evaluate the potential utility of NGAL measurements in monitoring specific CKD-associated conditions. Further research into the use of NGAL along with other currently well-known biomarkers to detect CI-AKI prior to therapeutic strategies in clinical studies.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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