

Urinary NGAL (Neutrophil Gelatinase Associated Lipocalin) as an Early Predictor of Acute Kidney Injury after Cardiac Surgeries

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Abstract

Background: Acute Kidney injury is one of the most common and serious complications that can develop after cardiac surgeries. Currently serum creatinine is the gold standard for detecting AKI. But various other studies have shown that there is a delay in rise in serum creatinine following renal injury thereby causing delay in early diagnosis and appropriate treatment. **Aim:** This study evaluates role of Urine NGAL (Neutrophil Gelatinase Associated Lipocalin) in diagnosing AKI early after cardiac surgeries. **Materials & Methods:** We prospectively enrolled 57 adult patients admitted for various cardiac surgeries over a period of 2 years from 2018 to 2020. Preoperative (0 hour) and postoperative (4 hour) urine NGAL was measured using an Enzyme linked immune sorbent assay. Mean of 0 hour and 4 hour uNGAL levels in AKI group was compared with that of non AKI group. **Results:** Among 57 patients, 6 (10.5%) patients developed AKI which was defined as rise in serum creatinine by 0.3 mg/dL within 7 days after the procedure. There was a significant rise in uNGAL levels in patients who developed AKI when compared to those who did not developed AKI. P value was <0.001 and the observations were statistically significant. ROC was generated and the AUC was 0.99. NGAL cutoff value was calculated as 0.2335 ng/ml for the prediction of AKI. All the 6 patients who developed AKI had 4 hour NGAL levels more than this cutoff. **Conclusion:** The results of this study suggest that urinary NGAL predicts AKI early after cardiac surgeries when compared to serum creatinine.

Keywords: Acute kidney injury; Cardiac surgeries; Urinary NGAL

Introduction

Acute kidney injury is a sudden episode of kidney damage or kidney failure that happens within a few hours or a few days. It can occur in various clinical settings, which can lead to worsening of underlying condition and even death when it is severe. Cardiac surgeries, being one of the most common surgical procedures done worldwide, are at high risk of developing AKI. [1] Based on various studies, the incidence of AKI after cardiac surgeries ranges up to 31% depending on the criteria used to define AKI. [2,3] Among this, patients requiring dialysis ranges from 1%-5% and are associated with increased morbidity, mortality and ICU care. [2] Acute kidney injury can manifest as either rise in creatinine levels or reduction in urine output. AKI has been often associated with prolonged hospital stay, worsening of the primary condition, poor prognostic outcome including death. It has been widely observed that even smaller reductions in renal function has paramount importance and are associated with increased morbidity and mortality. [3-5] Currently serum creatinine is the single most laboratory parameter to assess renal function and is the gold standard for detecting AKI. But studies have shown that there is often a delay in rise in serum creatinine following renal injury of any cause and thereby causing delay in early diagnosis and appropriate treatment. Serum creatinine level in the blood is affected by multiple factors like age, gender,

muscle mass, drugs and hydration status of the patient. Also serum creatinine is not a direct marker of renal tubular injury. It mostly reflects the changes in the GFR. Serum creatinine can be seen elevated in pre renal diseases even when kidneys are structurally normal. Serum creatinine is considered to be an imperfect gold standard in diagnosing AKI as it can be elevated in renal diseases in which kidneys are structurally normal, as in prerenal diseases. [6] Hence there arises the need for a new biomarker which can detect AKI much earlier than the rise in serum creatinine. Multiple biomarkers are being studied for this purpose. [7-9] Among these newer biomarkers urinary NGAL (Neutrophil Gelatinase Associated Lipocalin) seems to be promising in the early detection of AKI. NGAL is a 25 kDa protein which is present at very low concentrations in plasma. The expression of NGAL is upregulated immediately following a renal injury. Kidney tubules also express NGAL at markedly high levels following various insults like ischemia, sepsis and post transplantation. Thus it can be attributed as a direct marker

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of tubular injury. The aim of this study is to determine the role of urinary NGAL in predicting acute kidney injury early after cardiac surgeries.

Materials and Methods

This was a prospective cross sectional validity study, conducted in Department of General Medicine and Department of Cardiovascular Thoracic Surgery and was approved by Scientific and Ethical committee of Amrita Institute of Medical Sciences, Kochiand Kerala, where this study was conducted. The duration of the study was 2 years, from 2018-2020.

Selection and description of the participants

A total of 57 patients who were undergoing various cardiac surgeries were enrolled for this study. Cases included in this study were all adult patients undergoing different cardiac surgeries admitted under Department of cardiovascular Thoracic Surgery at Amrita Institute of medical sciences from October 2018 to August 2020. Patients who were excluded from the study were CKD patients, patients who have taken nephrotoxic drugs 1 week prior to the surgery and emergency procedures.

Based on the sensitivity of NGAL to predict acute kidney Injury (sensitivity 82%) observed in an earlier publication (Reference: Michael Bennett et al. published in Clinical journal of the American Society of Nephrology) and with 95% confidence and 10% allowable error, the minimum sample size comes to 57.

Technical information

The primary objective of the study was to assess the role of urinary NGAL as an early predictor of Acute Kidney Injury after cardiac surgeries.

For this study 10 ml of urine samples were collected preoperatively (0 hour) and post operatively (4 hours after the procedure) from all the patients. Urine samples were centrifuged at 3000 rpm for 10 minutes and were stored at 0°C for up to 3 months. Urine NGAL was measured within first 3 months. Serum creatinine was measured preoperatively (0 hour) and post operatively for 7 consecutive days. Patients who had a rise in serum creatinine from the baseline value (0 hour value) that fitted in the criteria for acute kidney injury defined by KDIGO criteria were diagnosed to have AKI. Urine output of the patients was also monitored post-surgery. Preoperative (0 hour) and postoperative (4 hour) urinary NGAL were compared between AKI and non AKI groups. Human Lipocalin-2 ELISA

kit was used for this study. It quantitatively measures Human Lipocalin 2 in urine.

Statistics

Statistical analysis was done using IBM SPSS 20 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are given in Mean \pm SD and for categorical variables as percentage. To obtain the association of categorical variables, chi square test with Fisher's exact test was applied. To compare the mean difference of numerical variables between groups, independent two sample 't' test was applied. To compare the Pre and post-operative NGAL values, paired t test was applied. ROC curve was used to find out the cutoff value of urine NGAL Value to predict AKI. P-value <0.05 was considered as statistically significant.

Results

Out of the 57 patients enrolled for this study, 43(75.4%) were males and 14(24.6%) were females. 5 patients (8.77%) were in the age group of 20 years-40 years of age, 23(40.35%) were between 41 years-60 years of age and 29(50.8%) were in the age group of 61 years-80 years of age [Table 1]. 32(56.1%) patients were having Diabetes Mellitus (DM) and 35(61.4%) patients had systemic hypertension.

Among the 57 patients who were enrolled in this study, 37 patients (64.9%) underwent CABG, 6 patients (10.5 %) underwent aortic valve replacement, 7 patients (12.3 %) underwent mitral valve replacement, 2 patients underwent mitral valve repair. Double valve replacement, Septalmyectomy, Sinus venosus ASD closure, Left ventricular aneurysm repair and ascending aorta repair was done in one patient each [Table 2]. Serum creatinine was measured for next seven days after the procedure. Out of all the 57 patients who participated in this study 6 patients developed acute kidney injury (10.5%) as defined by KDIGO guidelines. Acute kidney injury was diagnosed by observing the rise in serum creatinine that fitted the criteria outlined by

Table 1: Details of study population.

	Category	Frequency	Percentage
Age distribution	20years– 40 years	5	8.77
	41years– 60 years	23	40.35
	61years– 80 years	29	50.8
Gender distribution	Male	43	75.4
	Female	14	24.6
Diagnosis	AKI	6	10.5
	No AKI	51	89.5

Table 2: Distribution of AKI with various Cardiac surgeries done in this study.

Cardiac Surgery	Frequency N=57	Percentage	AKI			
			Yes (n=6)	%	No (n=51)	%
CABG	37	64.9	3	50	34	66.6
AVR	6	10.5	0	0	6	11.7
MVR	7	12.3	1	16.7	6	11.7
DVR	1	1.8	1	16.7	0	0
LV aneurysm repair	1	1.8	1	16.7	0	0
MV repair	2	3.5	0	0	2	3.9
Septal myectomy	1	1.8	0	0	1	1.9
SV ASD closure	1	1.8	0	0	1	1.9
Ascending aorta replacement	1	1.8	0	0	1	1.9

KDIGO (Kidney Disease Improved Global Outcome) [Table 3].

In our study mean of preoperative (0 hour) urine NGAL in non AKI group was 0.055 ng/ml ± 0.017 ng/ml and postoperative (4 hour) urinary NGAL levels among non AKI group was 0.079 ng/ml ± 0.073 ng/ml. P value Was 0.022 indicating there was significant difference between 0 hour and 4 hour urine NGAL levels in patients who did not developed AKI. Mean of 0 hour urine NGAL in AKI group was 0.053 ng/ml ± 0.023 ng/ml and at 4 hour urine NGAL were 0.534 ng/ml ± 0.160 ng/ml. P value was 0.001 indicating significant difference in uNGAL levels among these two groups which suggests that rise in urine NGAL 4 hours after the procedure was significant.

This analysis shows that patients who developed AKI after cardiac surgeries showed significant rise in urinary NGAL levels post-surgery compared to non AKI group. As there was significant increase in urinary NGAL levels 4 hours after cardiac surgery in AKI patients, it can be used as an early predictor of acute kidney injury after cardiac surgeries.

Receiver operator curve was generated and AUC was 0.99. NGAL cutoff value was calculated as 0.2335 ng/ml. All the 6 patients who developed AKI had risen in urine NGAL level more than the cutoff value. It was observed that 1 patient who did not developed AKI also had risen in NGAL levels more than cutoff. P value was <0.001 suggesting rise in NGAL levels were statistically significant. The sensitivity of the urinary NGAL in detecting cardiac surgery associated AKI at 4 hours after the procedure was 100% and specificity of the test was 98.04%. Positive predictive value was 85.71% and negative predictive value was 100%. The accuracy of the study was 98.25%. Only 1 patient had reduced urine output defined by the KDIGO criteria. It was found that there was no correlation between urine NGAL levels and urine output. None of the patients who developed Acute Kidney Injury required dialysis and none of the patients died [Figure 1].

Table 3: Comparison of pre (0 hour) and postoperative (4 hour) urinary NGAL levels in AKI and non AKI groups.

uNGAL	AKI, n=6		Non AKI, n=51	
	Mean	SD	Mean	SD
Preoperative (0 hour)	0.053	0.023	0.055	0.017
Postoperative (4 hour)	0.534	0.159	0.079	0.073
P value	0.001		0.022	

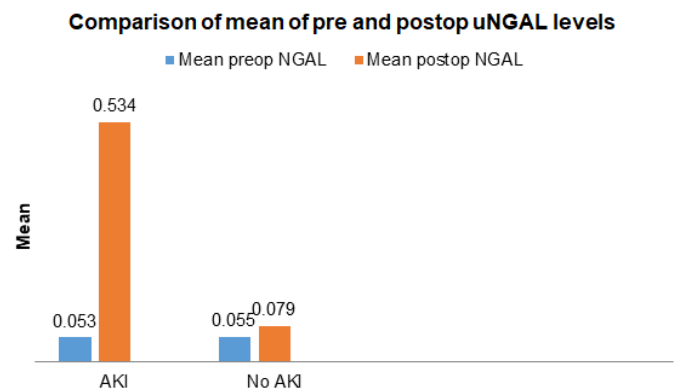


Figure 1: Comparison of mean of pre and postop uNGAL levels.

Discussion

As already mentioned development of AKI is more frequent after cardiac surgeries and is associated with high morbidity and mortality. Various studies have also shown that increased duration and severity of AKI was associated with prolonged hospital stay. Currently serum creatinine is used as the marker for diagnosis of AKI and even slightest increase was associated with increased morbidity and mortality. But serum creatinine is now considered to be an inadequate marker for AKI diagnosis because it was observed that there was a delay of 2 to 3 days for the rise in serum creatinine after the renal insult. By this time there will be significant loss of GFR and it will lead to a delay in starting early treatment for AKI. Hence there arises the need for newer biomarkers for predicting acute kidney injury early, so that effective measures can be undertaken to reduce the severity of AKI [Figure 2].

Multiple studies have demonstrated utility of urinary NGAL as an early predictor of AKI after cardiac surgeries. [10-12] Role of NGAL as an early predictor of acute kidney injury was studied previously. Michael Bennet and colleagues studied role of urinary NGAL as predictor of severity of acute kidney injury after cardiac surgeries in children. 196 children undergoing Cardio Pulmonary Bypass (CPB) was studied and it was found that AKI developed in 99 patients. But there was a delay of 2 days to 3 days in the diagnosis of AKI using serum creatinine. It was observed that mean urinary NGAL concentrations increased 15 fold within 2 hours and 25 fold within 4 hours and 6 hours after CPB. Mishra et al studied effectiveness of Urinary NGAL in early prediction of AKI in children and was found to have an AUC-ROC of 0.99 at 2 hours and 1 at 4 hours. These two studies were done in children without any comorbidities contributing to renal failure. Most of the adult patients undergoing cardiac surgeries may have comorbidities like Type 2 Diabetes Mellitus, systemic hypertension, CKD, peripheral vascular disease. So adult patients with these comorbidities are highly prone to develop AKI following cardiac surgeries. [13]

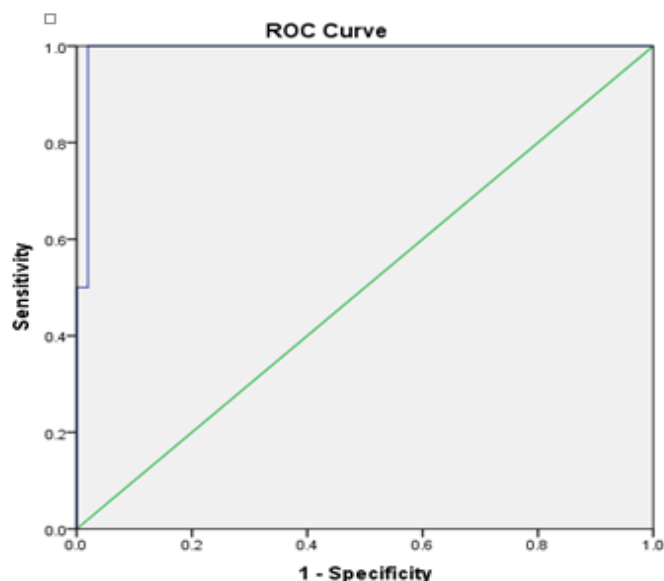


Figure 2: Receiver operator curve.

In this study 57 patients underwent different cardiac surgeries. Among these 6(10.5%) patients developed AKI. Urine NGAL measurement was done preoperatively (0 hour) and post operatively (4 hour). It was observed that 4 hour urine NGAL levels were significantly elevated in 6 patients who developed AKI and also in one patient who did not developed AKI. Mean of urine NGAL at 0 hour and 4 hours were compared among AKI and non AKI groups and it was found that there is significant association between rise in urinary NGAL levels and development of acute kidney injury. Among the 6 patients who developed AKI only one patient had reduced urine output defined by the KDIGO criteria. Hence there was no correlation found between urine NGAL and urine output in this study. None of the patients who developed AKI required dialysis. And none of the patients died.

The limitation of our study is that, we measured urine NGAL only 4 hours after the procedure; hence the time of earliest rise of urine NGAL could not be assessed. As multiples urine NGAL measurements were not done the time of peak rise of urine NGAL after the procedure was not assessed.

Conclusion

In our study we measured urine NGAL, 4 hours after various cardiac surgeries. We have observed that there is a significant increase in urine NGAL levels after cardiac surgery in patients who developed acute kidney injury. The sensitivity of the test was 100% and specificity was 98.04%. Serum creatinine, which is the gold standard assay for detection of AKI, starts rising only by 24 hours to 48 hours. Hence early diagnosis of AKI is important. Based on our study we suggest that urine NGAL can be used for early detection of AKI after cardiac surgeries. We have also found that, there was no correlation between urine NGAL levels and urine output. We also observed that there was no significant association with Diabetes Mellitus and systemic hypertension with development of AKI after cardiac surgeries.

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