

# Prognostic Utility of Ngal in Cardiac ICU

## Original Research Article

### ABSTRACT

**Introduction:** There is paucity of data for using NGAL (Neutrophil Gelatinase associated Lipocalin) as a biomarker in management of acute kidney injury (AKI) in patients admitted in cardiac ICU. Our study aims to evaluate the role of NGAL as an early surrogate marker in predicting AKI and mortality in patients of cardiac diseases.

**Study Design:** Prospective observational study.

**Place and Duration of Study:** Department of cardiology, Swaroop Rani Nehru (SRN) Hospital, Prayagraj, India between August 2020 to March 2021.

**Methodology:** The study included critically ill cardiac patients of various etiologies requiring admission to the cardiac ICU. Patients of chronic kidney disease or other renal diseases were excluded from the study. Samples for blood and urinary NGAL and other laboratory parameters were collected within 8 hours of admission to the ICU.

**Results:** 152 patients were included in the study, out of which 56 patient who developed acute kidney injury were the cases, while 96 were our controls. The cutoffs for serum and urinary neutrophil gelatinase associated lipocalin for predicting acute kidney injury were found to be >42.5 ng/mL and >40.5 ng/mL respectively ( $P < 0.001$ ). A positive correlation between low density lipoprotein and neutrophil gelatinase associated lipocalin was also found ( $P=0.0005$  and  $P=0.0011$  for serum and urinary NGAL respectively). NGAL was found to have a prognostic role and lower values were significantly associated with increased chances of survival ( $P=0.0201$  and  $0.0255$  for serum and urinary NGAL respectively).

**Conclusion:** Our study clearly states that NGAL measurement at the time of admission can be used to predict development of acute kidney injury as well as mortality, hence, improving the outcome of patients with cardiac diseases.

*Keywords: NGAL; cardiac ICU; prognosis; AKI; dyslipidemia.*

## 1. INTRODUCTION

In the recent years, NGAL has been shown to be a potential marker for renal dysfunction and has been compared to be as important as troponin in cardiac diseases. It has been studied to be a potential biomarker in various diseases such as after cardiac surgery [1], nephropathy in sickle cell anemia [2], post Cardiopulmonary Bypass [3], contrast induced nephropathy [4], following ECMO (Extra Corporeal Membrane Oxygenation) [5].

The epidemiology of AKI in cardiac ICU has been reported upto 50% in few studies [6], which was also associated with increased mortality. Hence, patients at risk of AKI should be actively sought for so that appropriate interventions may be done

timely to improve the outcome of patients in cardiac ICU.

The aim of this study is to evaluate the efficiency of serum and urine NGAL to detect AKI, earlier than traditional indicators, thus decreasing morbidity and mortality of cardiac patients.

## 2. PATIENTS AND METHODS

### 2.1 Study Design

The study comprised of patients admitted to cardiac ICU from August, the 1st, 2020 to March, the 15th, 2021 at SRN Hospital, Prayagraj, and was a prospective cohort analysis study. Patients with age >18 years (male or female), patients of cardiac disease irrespective of etiology were included. Exclusion criteria comprised of : CKD and/or on Renal Replacement Therapy or

raised baseline serum creatinine > 1.3 mg/dl prior to admission or eGFR < 90 ml/min, due to any renal cause and those unwilling for study related diagnostic procedures. The patients were monitored during their hospital stay, and the results were recorded.

## 2.2 Laboratory Investigations

Laboratory investigations were done after obtaining clearance from ethical committee and informed consent. The laboratory investigations were sent to Tejas Microlabs. For the study purposes, baseline serum creatinine was defined as the steady level of creatinine 4 weeks before admission. If unavailable, the admission value or the lowest serum creatinine during the hospital stay was used as a surrogate baseline. Samples for blood and urinary NGAL were collected within 8 h of admission to ICU aseptically. NGAL was tested by ELABSCIENCE® kit (USA) using the sandwich ELISA principle. Repeat samples of necessary blood parameters were collected for three consecutive days, or for the duration of hospital stay, whichever was later. Cases were defined as patients who developed AKI during the course of hospital stay, while the patients who did not develop AKI were defined as controls. AKIN criteria was used for staging of AKI. The primary result (the onset of AKI) as well as the secondary outcomes (mortality and the requirement for Renal replacement therapy (RRT)) were recorded.

## 2.3 Statistical Analysis

The quantitative data were expressed as mean  $\pm$  SD, while the categorical variables were expressed in numbers and percentages. Spearman's rho correlation coefficient was used for correlation of various parameters. Receiver operating characteristic (ROC) curves were

drawn to determine the area under the curve (AUC) and assess the sensitivity, specificity and diagnostic accuracy of NGAL for prediction of outcomes of the patients. SPSS version 23 was used for all statistical analyses.

## 3. RESULTS

### 3.1 Baseline Characteristics

The study enrolled a total of 165 patients admitted to the cardiac ICU, with 13 individuals being excluded due to exclusion criteria (6 patients were newly diagnosed to have CKD while 7 had raised baseline serum creatinine values). Table 1 shows the demographic profile of the patients. The population was matched in terms of age and sex. Older age was found to have an increased incidence of AKI. However, the difference was not statistically significant. Among the various etiologies, most patients who developed AKI belonged to the subgroup having acute coronary syndromes.

A small number of patients developed AKI (n=56; 36.84%) during the hospital stay. There was a dominance of stage I (n=36; 23.68%) over stage II (n=8; 5.26%) and stage III (n= 12; 7.89%) in AKI patients.

Table 2 depicts the laboratory parameters and their association with AKI.

Receiver operator curves were drawn to find out the cut-off value, sensitivity and specificity of NGAL for prediction of AKI, as shown in Fig. 1. AUC for Serum and urinary NGAL was 0.869, 0.899 respectively. Serum NGAL at values >42.5 was found to have a sensitivity of 78.57%, and specificity of 100.0% while urinary NGAL >40.5 has a sensitivity of 78.57% and specificity of 100.0% (P value <0.001).

**Table 1. Baseline demographic characteristics (n=152)**

SN	Characteristic	AKI (n=56)	Non AKI (n=96)
1.	Age -Mean $\pm$ SD* (in years)	65.143 $\pm$ 18.2709	54.750 $\pm$ 17.1648
2.	Sex- Male	40 (71.43%)	76 (79.16%)
	Female	16 (28.57%)	20 (20.83%)
3.	Hypertension	28 (50%)	44 (45.83%)
4.	Type 2 DM	32 (57.14%)	44 (45.83%)
5.	Etiology		
A	Heart Failure	16(28.57%)	24(25%)
B	Acute coronary syndrome	24(42.85%)	32(33.33%)
C	Valvular heart disease	12(21.42%)	28(29.16%)
D	Others	4(7.14%)	12(12.5%)

*Data were expressed in % and mean  $\pm$  SD\* (Standard Deviation)*

**Table 2. Association of various laboratory parameters with AKI (n=152)**

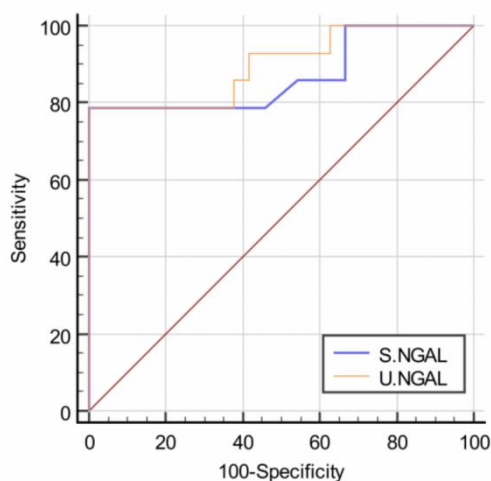
SN	Variable	AKI (n=56)		NO AKI (n=96)		P value
		Mean	SD	Mean	SD	
1.	Hemoglobin (g/dL)	11.662	2.4516	12.259	2.9833	0.53
2.	TLC (/mm <sup>3</sup> )	13987.857	6108.9269	11791.667	4830.9290	0.22
3.	Neutrophil (%)	79.857	10.6918	72.277	13.5785	0.08
4.	Lymphocyte (%)	12.671	8.2030	16.097	7.1666	0.18
5.	Platelet count (lac/mm <sup>3</sup> )	1.840	0.9650	2.060	1.0112	0.54
6.	S. Bilirubin (mg/dL)	1.201	0.8305	1.229	0.8652	0.94
7.	SGPT (U/L)	68.104	70.0467	48.711	46.5949	0.62
8.	S. Cholesterol (mg/dL)	134.65	46.95	128.71	41.12	0.41
9.	S. TGL (mg/dL)	239.949	105.6018	139.496	60.6752	< 0.001*
10.	HDL (mg/dL)	39.423	14.2516	45.524	11.4471	0.15
11.	LDL (mg/dL)	201.643	54.1133	98.458	41.3721	< 0.001*
12.	Day1 S.Urea (mg/dL)	47.042	33.8220	45.146	27.4650	0.85
13.	Day 1 S.Creatinine (mg/dL)	1.863	1.0386	1.505	0.6720	0.19
14.	Day3 S.Urea (mg/dL)	90.326	48.2734	59.857	61.6815	0.12
15.	Day 3 S.Creatinine (mg/dL)	2.841	1.1735	1.535	0.8959	< 0.001
16.	S.NGAL (ng/mL)	149.921	99.7421	25.421	6.3597	< 0.001*
17.	U.NGAL (ng/mL)	149.100	97.0200	26.537	7.3467	< 0.001*

\*There is significant difference when the two groups (AKI and non- AKI) are compared in terms of serum triglyceride, LDL, serum NGAL and urine NGAL levels, using paired t-test. TLC- Total leukocyte count, TGL- Triglyceride, NGAL- Neutrophil gelatinase associated lipocalin

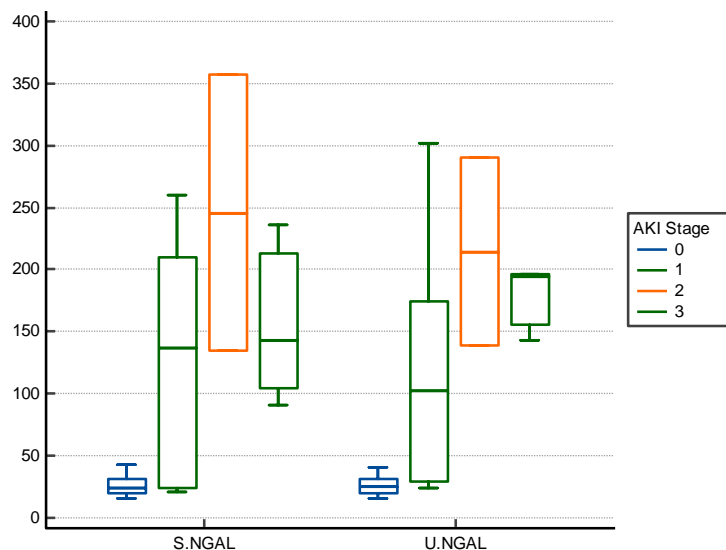
**Table 3. Treatment outcomes with AKI and their correlation (n=152)**

SN	Characteristic	AKI (n=56)		No AKI (n=96)		Statistical significance
1	Need of RRT (Renal replacement therapy)	12 (25%)		0		$\chi^2=5.429$ ; $P=0.01^*$
2	Hospital stay (days)	11.929	4.8590	11.125	5.8407	$P=0.667$
3	Mortality	24 (42.85%)		8 (8.33%)		$\chi^2=6.714$ ; $P=0.01^*$

\*There is significant difference between need of RRT and mortality between group with and without AKI using chi-square,  $P=0.01$



**Fig. 1. ROC Analysis for projection of cut-off values of serum and urinary NGAL for prediction of AKI. The graph demonstrates the prediction of AKI using serum and urinary NGAL with a 95% confidence interval of 0.720 to 0.956 ( $P$  value<0.001) for serum NGAL and 0.757 to 0.973 ( $P$  value<0.001) for urinary NGAL respectively**



**Fig. 2. Box and whisker plot curves showing the association of NGAL with various stages of AKI**

The higher value of NGAL correlated with the higher stage of AKI, which has been depicted in Fig. 2 using box and whisker plot curves.

Lipid profile has always been of paramount importance in patients of heart diseases. Both Serum triglyceride and LDL levels correlated with the development of AKI and raised serum and urinary NGAL as shown in Table 4.

Kaplan Meier survival curves were drawn which demonstrated that the patients with lower NGAL (less than median) had better prognosis and event free survival than the patients with higher NGAL. This difference was statistically significant ( $P=0.02$  for serum and  $0.02$  for urinary NGAL).

#### 4. DISCUSSION

To our knowledge, this is the first prospective study to investigate the association between NGAL and patients admitted in cardiac ICU.

AKI is a common complication in cardiac patients, thus, this study is an attempt to diagnose AKI early in such patients, and make timely efforts to reduce morbidity and mortality.

In our study, a total of 56 patients (36.84%) developed AKI. A total of 24 out of 56 patients of

ACS (acute coronary syndrome) developed AKI, which was the highest incidence (42.8%) while 16 out of 40 patients of heart failure developed AKI (40%). Both subgroups had the highest incidence of developing AKI. Ghonemy et al. [7] found a similar incidence of AKI in his study with 47% of patients with CHF and 45% of patients with acute MI developing AKI.

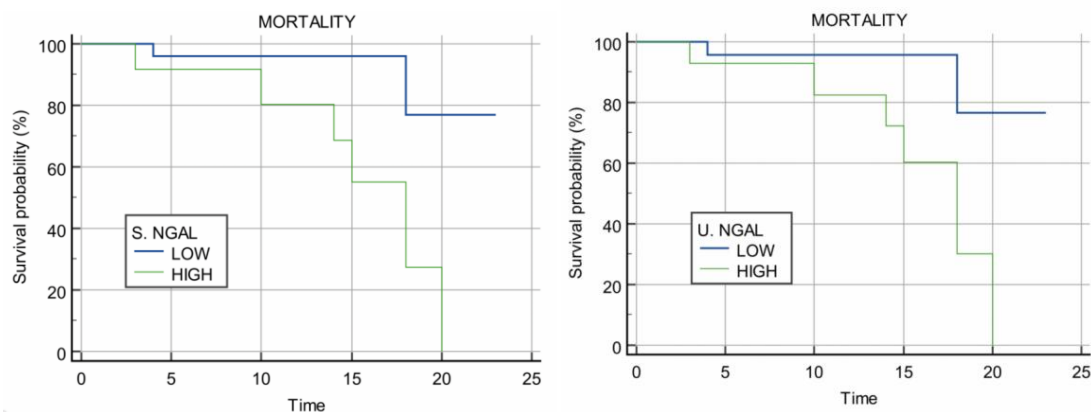
We found that NGAL values were significantly higher in patients who developed AKI when compared with patients who did not develop AKI. The area under ROC curve was 0.869 for serum NGAL with sensitivity and specificity of 78.57% and 100% respectively. This is a pioneer study demonstrating role of NGAL in cardiac ICU. Mosa [8] did a similar study in patients of open heart surgery and found that Baseline serum NGAL was  $103.5 \pm 41.69$   $\mu\text{g/L}$  in the AKI group compared to  $79.12 \pm 48.02$   $\mu\text{g/L}$  in the non-AKI group ( $p < 0.01$ ) Another study done by Haase-Fielitz et al. [9] on patients with cardiac surgery found similar performance of NGAL with AUC-ROC of 0.95, sensitivity-80%, and specificity-97%.

Serum NGAL was found to have a positive correlation with both S. Triglyceride and LDL Cholesterol levels, while urinary NGAL had a positive correlation only with LDL cholesterol

levels. Na et al. [10] found similar results in non-diabetic healthy women.

**Table 4. Correlation of NGAL with Lipid profile**

	S. NGAL		U. NGAL	
	Correlation coefficient r	P value	Correlation coefficient r	P value
TGL	0.3612	P=0.02	0.3512	P=0.05
LDL	0.5362	P=<0.001	0.5103	P=0.001



**Fig. 3. Kaplan Meier Survival analysis curves showing raised mortality with higher NGAL (a) Serum (b) Urine**

In our study raised NGAL was significantly associated with a poorer prognosis and increased mortality. Van Deursen et al. [11] studied the prognostic value of NGAL in patients with heart failure and found that raised NGAL was associated with increased mortality (P=0.02).

This study is a pilot study for patients of cardiac ICU. The study was limited by small sample size and further studies with larger sample sizes should be undertaken.

## 5. CONCLUSION

It is a well-established fact that NGAL correlates with development of AKI and we have reinstated the fact in our study. Our study clearly demonstrates the strong association between dyslipidemia and AKI. Furthermore, the development of AKI and a rise in NGAL were observed to be linked to mortality. Thus, judicious use of NGAL is recommended for a multifaceted treatment approach for cardiac patients.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

Ethical approval was sought and obtained from the Ethics Committee of MLN Medical College, Prayagraj.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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