Original Research Article

PROGNOSTIC UTILITY OF NGAL IN CARDIAC ICU

ABSTRACT

Introduction: There is paucity of data for using NGAL (Neutrophil Gelatinase associated Lipocalin) as a biomarker for acute kidney injury in patients admitted in cardiac ICU. Our study aims to evaluate the role of NGAL as an early surrogate marker in predicting acute kidney injury 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 only patients of cardiac diseases of various etiologies requiring ICU admission. Patients of known renal diseases were excluded from the study. Blood as well as urinary samples for NGAL and other laboratory parameters were collected within 8 hours of admission.

Results: The study was done on 152 patients, 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 uptil 50% in few studies[2], which was also associated with increased mortality. Hence, patients at risk of AKI should be actively sought for so that timely intervention can be done to decrease morbidity and mortality in patients admitted in cardiac ICU.

The aim of this study is to evaluate the efficiency of serum and urine NGAL to detect AKI in cardiac ICUs, earlier than traditional indicators.

2. PATIENTS AND METHODS

2.1 Study Design

This study was designed as a prospective cohort analysis in patients admitted to cardiac ICU from August, the 1st, 2020 to March, the 15th, 2021 at SRN Hospital, Prayagraj. The patients were followed during the hospital stay and their outcomes were noted. Inclusion criteria comprised age >18 years (male or female), patients of cardiac disease irrespective of etiology, while patients with raised baseline serum creatinine > 1.3 mg/dl prior to admission or eGFR < 90 ml/min, patients of CKD and on Renal Replacement Therapy and those unwilling for study related diagnostic procedures were excluded.

2.2 Laboratory Investigations

After obtaining ethical committee clearance and informed consent, clinical data and laboratory investigations were collected. The laboratory investigations were sent to Tejas Microlabs. Baseline serum creatinine was defined as the steady state level of creatinine 4 weeks before admission. If not available, the admission value or the lowest serum creatinine

during the hospital stay was used as a surrogate baseline. Blood samples for NGAL were collected within 8 h of admission to ICU aseptically via venipuncture. The first urine of the day (mid-stream), was collected aseptically into a sterile container and tested for urinary NGAL. NGAL was tested by ELABSCIENCE® kit (USA) using the sandwich ELISA principle. Other laboratory parameters were measured for three consecutive days, or for the duration of hospital stay, whichever was later. Patients developing AKI during hospital stay were noted and defined as our cases, while the patients who did not develop AKI were our controls. Staging of AKI was done using AKIN criteria. The primary outcome (development of AKI) and the secondary outcomes (mortality, need of Renal replacement therapy (RRT)) were noted.

2.3 Statistical Analysis

The quantitative data were expressed as mean ± SD. Categorical variables were expressed in number and percentages. Correlation of various parameters was calculated using Spearman's rho correlation coefficient. Receiver operating characteristic (ROC) curves were drawn, and the area under the curve (AUC) was calculated to find the cut-off points and calculate the threshold specificity, sensitivity and diagnostic accuracy for predicting AKI and mortality outcomes. All statistical analyses were conducted using SPSS version 23.

3. RESULTS

3.1 Baseline Characteristics

A total of 165 patients admitted in cardiac ICU were enrolled in the study, out of which 13 patients were excluded owing to the 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.

Table 1: Baseline demographic characteristics (n=152)

SN	Characteristic	AKI (n=56)	Non AKI (n=96)
1.	Age -Mean ± SD* (in years)	65.143±18.2709	54.750±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 ± SD* (Standard Deviation)

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.

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

SN		AKI (n=56)		NO AKI (n=96)		
	Variable	Mean	SD	Mean	SD	*P* value
1.	Hemoglobin (g/dL)	11.662	2.4516	12.259	2.9833	0.53
2.	TLC (/mm3)	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/mm3)	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		χ^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%)		χ^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

Receiver operator curves were drawn to find out the cut-off value, sensitivity and specificity of NGAL for prediction of AKI, as shown in figure 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).

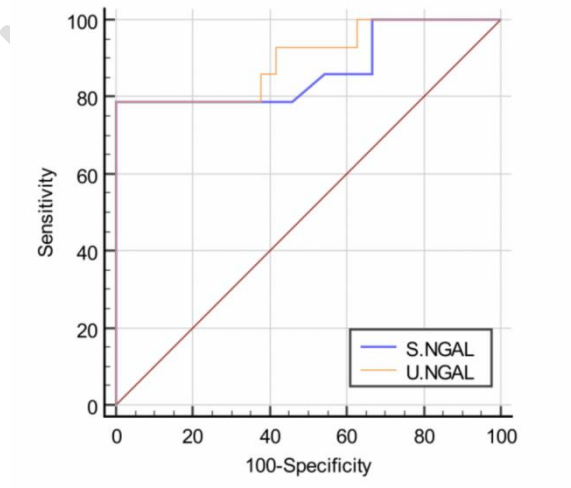

Figure 1: ROC Analysis for projection of cut-off values of serum and urinary NGAL for prediction of AKI. The graph demonstrates the prediction of AKI using serum and urinary NGAL with a 95% confidence interval of 0.720 to 0.956 (*P* value<0.001) for serum NGAL and 0.757 to 0.973 (*P* value<0.001) for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

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

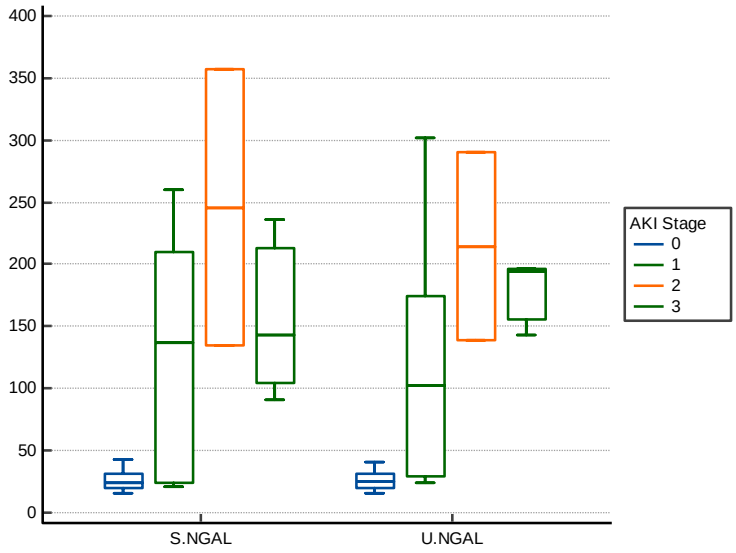

Figure 2: Box and whisker plot curves showing the association of NGAL with various stages of AKI

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.

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

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).

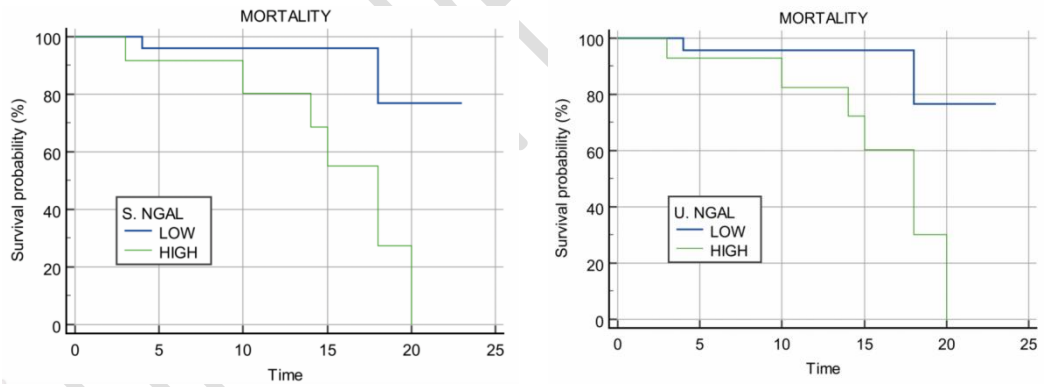

Figure 3: Kaplan Meier Survival analysis curves showing raised mortality with higher NGAL (a) Serum (b) Urine

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 ± 41.69 µg/L in the AKI group compared to 79.12 ± 48.02 µg/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.

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. Further studies with larger sample sizes are recommended.

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, mortality was found to be associated with development of AKI and raised NGAL. Thus, judicious use of NGAL is recommended to decrease morbidity and mortality in patients admitted in cardiac ICU.

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 DISCLAIMER:

Authors declare that no competing interests exist. 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.

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