Prognostic Role of Ngai In Critically Ill Patients

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Abstract

Background: Acute kidney injury (AKI) is a frequently encountered outcome in critically ill patients, accounting for increased mortality. Neutrophil gelatinase associated lipocalin (NGAL) has been of paramount importance as a novel biomarker of AKI. This study is an attempt to assess the use of NGAL in critically ill patients so that timely interventions can be done to reduce morbidity and mortality in such patients.

Methods: A prospective observational study was conducted at SRN Hospital from August 1st 2020 to March 15th 2021, which included only critically ill patients with SOFA score >1 and 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. Patients who developed renal dysfunction were noted as our cases and the others were noted as controls.

Results: The study was done on 125 patients, out of which 67 developed AKI while 58 did not develop AKI. Higher mortality was seen in patients with higher stage of AKI (P- 0.011). The cutoff of serum and urinary NGAL for predicting AKI were >42.3 ng/mL, >40.5 ng/mL respectively (P value <0.001). Hazard Ratio for all cause mortality of raised serum and urinary NGAL was 2.0062 (p value- 0.0001, 95% CI- 1.0031 to 1.0092) and 2.0046 (p value-0.0035, 95% CI-1.0015 to 1.0078) respectively. Serum and urinary neutrophil gelatinase associated lipocalin at values >91 and >131 respectively were found to predict requirement of hemodialysis (p value <0.001).

Conclusion: A single measurement of NGAL at the time of admission had good predictive ability for AKI. Higher values of NGAL were associated with staging of AKI and thus, correlated with need of hemodialysis. Furthermore, mortality was found to be associated with development of AKI and raised NGAL. Thus, NGAL maybe used to assess the prognosis of ICU patients so that patients at high risk may be managed aggressively, thus reducing mortality.

Background

Acute kidney injury (AKI) is a heterogeneous syndrome that not only affects acute morbidity and mortality, but is also an important risk factor for developing chronic kidney disease (CKD) thus affecting the long-term prognosis of the patient.¹

The most common causes of AKI include sepsis, major surgery such as coronary artery bypass, heart failure and hypovolemia, which are commonly seen in patients admitted in ICUs.² AKI is seen in nearly 30%-50% patients admitted in ICU, and may increase in-hospital mortality upto 50%.³ Thus, there should be a focus on prediction and early detection of AKI, so that timely intervention can be done to decrease morbidity and mortality in patients admitted in ICU patients.

In the past years, NGAL has emerged to be an excellent biomarker for predicting acute kidney injury⁴. However, it is an expensive biomarker and is not used routinely yet. The aim of this study is to evaluate the

efficiency of serum and urine NGAL to detect AKI and for early prediction of mortality in critically ill patients.

Materials And Methods

This study was designed as a prospective cohort analysis in patients admitted to various ICUs from 1st August 2020 to 15th March, 2021 at SRN Hospital, Prayagraj. The study was done in accordance with the guidelines after obtaining ethical clearance from the ethical committee of MLN Medical College, Prayagraj. The patients were followed during the hospital stay and their outcomes were noted. Inclusion criteria comprised of age >18 years (male or female), admitted in ICU with SOFA score >1 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. Written informed consent was obtained from all the participants and/or their legal guardians. Thereafter, clinical data and laboratory investigations were collected and noted.

Baseline serum creatinine is 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 ELISA kit- ELABSCIENCE® using the sandwich ELISA principle. Serum urea and serum creatinine and 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 Hemodialysis (HD)) were noted.

Statistical Analyses

The quantitative data was expressed as mean $\pm$ SD. Categorical variables were expressed in number and percentages. Correlation of various parameters are 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.

Results

A total of 140 patients admitted in various ICUs were enrolled in the study, out of which 15 patients were excluded owing to the exclusion criteria (9 patients were newly diagnosed to have CKD while 6 had raised baseline serum creatinine values). Out of 125 patients, 67 (53.6%) developed AKI while 58 (46.4%) did not develop AKI.

Table 1 & 2 show the demographic profile and clinical characteristics of the patients respectively.

Table 1		
Baseline demographic characteristics (n=125)		
Parameters	Mortality	
	Yes	No
	(n = 32)	(n = 93)
Age (Years)	61.25 ± 19.92	52.87 ± 16.33
Gender		
Male	23 (71.9%)	49 (52.7%)
Female	9 (28.1%)	44 (47.3%)
HTN (Yes)	15 (50.0%)	35 (39.3%)
DM (Yes)	12 (37.5%)	40 (43.0%)
AKI		
HTN- Hypertension, DM- Diabetes mellitus		

Table 2
Association between Mortality and Laboratory Parameters, Outcomes

Parameters	Mortality		p value
	Yes (n = 32)	No (n = 93)	
Hemoglobin (g/dL)	11.62 ± 2.27	11.62 ± 3.00	0.786
TLC			0.046
≤11000 /mm ³	10 (31.2%)	48 (51.6%)	
>11000 /mm ³	22 (68.8%)	45 (48.4%)	
Neutrophils (%)	76.20 ± 13.44	71.49 ± 14.90	0.097
Lymphocytes (%)	13.04 ± 8.30	17.98 ± 12.19	0.038
NLR	8.74 ± 5.86	6.69 ± 5.70	0.029
Platelet Count (Lacs/mm ³)	1.99 ± 0.88	2.03 ± 1.05	0.935
S. Urea (mg/dL) (Day 1)	53.18 ± 37.71	51.97 ± 36.24	0.881
S. Urea (mg/dL) (Day 3)	78.16 ± 51.36	60.61 ± 46.06	0.066
S. Creatinine (mg/dL) (Day 1)	1.54 ± 0.80	1.45 ± 0.73	0.526
S. Creatinine (mg/dL) (Day 3)	2.60 ± 1.59	1.98 ± 1.31	0.020
Total Bilirubin (mg/dL)	1.33 ± 2.07	1.33 ± 1.37	0.407
SGPT (IU/L)	66.76 ± 81.58	64.17 ± 68.14	0.937
HbA1c (%)	6.54 ± 2.14	6.87 ± 2.28	0.493
Serum Triglycerides (mg/dL)	161.70 ± 85.10	167.55 ± 91.14	0.724
Hospital Stay (Days)	9.72 ± 5.19	10.01 ± 5.79	0.874
Need Of Dialysis (Yes)	8 (25.0%)	2 (2.2%)	<0.001
S. nGAL (ng/mL)	121.04 ± 88.57	45.76 ± 58.84	<0.001
Urine nGAL (ng/mL)	108.60 ± 89.63	45.55 ± 53.54	<0.001
AKI Stage			0.011
Absent	8 (25.0%)	50 (53.8%)	
Stage 1	10 (31.2%)	24 (25.8%)	
Stage 2	2 (6.2%)	6 (6.5%)	
Stage 3	12 (37.5%)	13 (14.0%)	

The following variables were significantly associated ($p < 0.05$) with mortality: Age, TLC, Lymphocytes (%), NLR, S. Creatinine (mg/dL) (Day 3), Need Of Dialysis, Serum NGAL, Urine NGAL, AKI Stage. Higher mortality was seen in patients with AKI, which increased with higher stage of AKI.

Figure 1 depicts the association of both serum and urine NGAL and raised levels in various stages of AKI, using box and whisker plots.

Receiver operator curves were drawn to find out the cut-off value and the sensitivity, specificity of values of NGAL for prediction of development of AKI in critically ill patients. AUC for Serum and urinary NGAL was 0.884, 0.875 respectively as shown in figure 2. Serum NGAL at values >42.3 ng/mL was found to have a sensitivity of 76.00%, and specificity of 97.33% while urinary NGAL >40.5 ng/mL has a sensitivity of 76.00% and specificity of 96%. (p value < 0.001). The graph demonstrates the prediction of AKI using serum and urinary NGAL with a 95% confidence interval of 0.814 to 0.934 (p value < 0.001) for serum NGAL and 0.804 to 0.927 (p value < 0.001) for urinary NGAL respectively.

Kaplan Meir survival curves were drawn to determine the prognosis using NGAL as a biomarker for all cause mortality as depicted in figure 3. Hazard Ratio for all cause mortality of raised Serum NGAL was 2.0062 (p value- 0.0001, 95% CI-1.0031 to 1.0092) and of raised urinary NGAL was 2.0046 (p value- 0.0035, 95% CI-1.0015 to 1.0078).

Receiver operator curves were also drawn to find out the cut-off value and the sensitivity, specificity of values of NGAL for prediction of need of hemodialysis in critically ill patients. AUC for Serum and urinary NGAL was 0.894, 0.931 respectively as shown in figure 4. Serum NGAL at values >91 ng/mL was found to have a sensitivity of 100%, and specificity of 77.39% while urinary NGAL >131 ng/mL has a sensitivity of 90% and specificity of 88.7%. (p value < 0.001)

Discussion

Renal injury in ICU patients is a common phenomenon and is the consequence of complex interactions between the actual insult and subsequent activation of inflammation and coagulation. Even small changes in serum creatinine concentrations are associated with a substantial increase in the risk of death.

The incidence of AKI in our study group was found to be 53.6%. The AKI patients were distributed in three stages. Nayak *et al.*⁵ studied 102 patients, who were admitted in ICU and AKI was diagnosed based on AKI network criteria and the incidence of AKI was found in 42 patients (41.16%) while the rest, 60 patients did not develop AKI. This is due to patient selection criteria, different criteria applied for diagnosis, epidemiological factors, and associated comorbidities.

At a cutoff of ≥ 91.3 ng/mL, serum NGAL predicts AKI with a sensitivity of 46% and a specificity of 97%, while the cutoff for urine NGAL for predicting AKI was ≥ 38.9 ng/mL with sensitivity and specificity of 52% and 90% respectively. Khatami *et al.*⁶ concluded in his study that the sensitivity and specificity of

NGAL with cut-off of 22.5 ng/ml were 71.4% and 57.9% in 12 hour urine sample with NPV and PPV of 97.1% and 9.4% respectively for contrast induced nephropathy. The variation in the cutoff value is due to use of various commercial kits available.

NGAL was also found to have a prognostic role in critically ill patients. Hazard Ratio for all cause mortality of raised Serum NGAL was 2.0062 (p value- 0.0001, 95% CI-1.0031 to 1.0092) and of raised urinary NGAL was (p value-0.0035, 95% CI-1.0015 to 1.0078). Similar results were seen in the study by Nayak et al.⁵

The AUC for serum NGAL and urine NGAL predicting need of hemodialysis was 0.902 (95% CI: 0.84 - 0.964) and 0.933 (95% CI: 0.884 - 0.983) respectively, which was statistically significant (p = <0.001). Similar results were seen in the study done by Hjortrup et al.⁷ who studied 222 patients with severe sepsis. Areas under receiver-operating characteristics curve (AUC) for predicting use of hemodialysis in ICU were 0.70 (95% confidence interval 0.61–0.78) and 0.62 (0.51–0.73) for plasma and urine NGAL, respectively.

The earlier an injurious process to the kidneys can be identified, the timelier preventive and supportive measures (removal of the precipitating factor for injury and renal replacement therapy [RRT]) can be initiated.

The study was undertaken as an attempt to reduce ICU mortality. However, the study had few limitations. The number of participants was limited due to the COVID pandemic. Also, it was a single centre study. Further studies with larger sample sizes are recommended.

Conclusion

A single measurement of NGAL at the time of admission had good predictive ability for AKI. Higher values of NGAL were associated with staging of AKI and thus, correlated with need of hemodialysis. Furthermore, mortality was found to be associated with development of AKI and raised NGAL. Thus, NGAL maybe used to assess the prognosis of ICU patients so that patients at high risk may be managed aggressively, thus reducing mortality.

List Of Abbreviations

NGAL- Neutrophil gelatinase associated lipocalin

AKI- Acute kidney injury

RRT- Renal replacement therapy

AUC- Area under the curve

ROC- Receiver operating characteristic

ICU- Intensive care unit

CKD- Chronic kidney disease

SOFA- Sequential Organ Failure Assessment score

HD- Hemodialysis

AKIN- Acute Kidney Injury Network

Declarations

Ethics approval and consent to participate

The study was conducted after approval from ethical committee, MLN Medical College, Prayagraj. No harm was perceived from the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

Authors' contributions

A.G. and U.N. designed the study. A.B. and U.N. wrote the main manuscript text. All authors reviewed the manuscript.

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Figures

Figure 1

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

Figure 2

ROC Analysis for projection of cut-off values of serum and urinary NGAL for prediction of AKI.

Figure 3

Kaplan Meir Survival Curves for Raised NGAL with all cause mortality

Figure 4

ROC Curves for Hemodialysis. The graph demonstrates the prediction of requirement of hemodialysis using serum and urinary NGAL with a 95% confidence interval of 0.826 to 0.942 (p value<0.001) for serum NGAL and 0.871 to 0.969 (p value<0.001) for urinary NGAL respectively.