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NGAL: Role in Determining Need of Hemodialysis in Critically Ill Patients

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Abstract

Introduction: Acute kidney injury is a frequently encountered outcome in critically ill patients, accounting for increased mortality. A large proportion of these patients require hemodialysis. This study is an attempt to assess the use of neutrophil gelatinase associated lipocalin to timely predict the requirement of hemodialysis so that such patients can be managed aggressively.

Methods: A prospective observational study was conducted at various tertiary care Hospital from August 1st 2020 to March 15th 2021, which included only critically ill patients with sequential organ failure assessment score >1 and requiring intensive care unit admission. Patients of known renal diseases were excluded from the study. Blood as well as urinary samples for neutrophil gelatinase associated lipocalin 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 375 patients, out of which 201 developed acute kidney injury while 174 did not develop acute kidney injury. The Area under curve for serum and urinary neutrophil gelatinase associated lipocalin was 0.902 (95% CI- 0.846-0.964) and 0.933 (95% CI- 0.884-0.983) respectively (p value <0.001).

Conclusion: Neutrophil gelatinase associated lipocalin has distinguished itself to be a marker of acute kidney injury and our study reinforces the same, while also demonstrating its role in early prediction of hemodialysis so that various metabolic derangements can be corrected at the earliest, thus, decreasing mortality.

Keywords: NGAL• Hemodialysis • Critically ill • Biomarker • AKI

Introduction

Acute Kidney Injury (AKI) has been recognized a heterogeneous syndrome that not only affects acute morbidity and mortality, but also long-term prognosis of the patient and may even be a risk factor for Chronic Kidney Disease (CKD) [1].

In critically ill patients, the etiology of AKI is multifactorial [2]. ICU patients have usually have multiple comorbidities and are on various life-supportive modalities. These patients are also prone to multiorgan dysfunction, fluid overload, electrolyte and acid-base disturbances. Therefore, Renal Replacement Therapy (RRT) should be initiated in these patients before the development of extreme metabolic derangements [3].

AKI requiring RRT affects approximately 6% of critically ill patients and results in a hospital mortality of 45 to 60% [4,5]. Increases in serum creatinine substantially lag behind reductions in Glomerular Filtration Rate (GFR) and thus do not provide a useful real-time assessment of GFR. Neutrophil gelatinase associated lipocalin was found to be an excellent biomarker for the early detection of AKI in the emergency department [6], after exposure to radiocontrast media [7], and post Cardiopulmonary Bypass [8]. Hence, this study was planned to assess the role of NGAL and other biomarkers in predicting the need of hemodialysis, so that such critically ill patients are managed intensively.

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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, Balaji Hospital, Prayagraj, Phoenix Hospital, 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. After obtaining ethical committee clearance and informed consent, 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 ELABSCIENCE® (USA) kit 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 ± SD. Categorical variables

were expressed in number and percentages. Correlation of various parameters is 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 400 patients admitted in various ICUs were enrolled in the study, out of which 25 patients were excluded owing to the exclusion criteria (12 patients were newly diagnosed to have CKD while 13 had raised baseline serum creatinine values). Table 1 outlines the baseline demographic profile of the patients. Table 2 portrays the laboratory parameters and outcomes of the patients requiring hemodialysis. The following biochemical parameters were significantly associated ($p<0.05$) with the requirement of Hemodialysis: Neutrophils (%), Lymphocytes (%), NLR, serum NGAL, Urine NGAL, S. PCT. Figure 1 demonstrates the association of NGAL with staging of AKI, which was done using AKIN staging. Higher values are seen in stage 3 AKI, which includes all patients requiring hemodialysis. Receiver operator curves were drawn to find out the cut-off value and the sensitivity, specificity of values of various biomarkers for prediction of development of need of Hemodialysis in critically ill patients, as shown in in Figure 2 and Table 3.

Discussion

Severe Acute Kidney Injury (AKI) receiving Hemodialysis (HD) carries significant negative effects on quality of life and health-care costs, prolonged hospitalization, increased risk for chronic comorbidities, and mortality [9]. Hence, there is a need to identify these patients at the earliest so that appropriate intervention can be undertaken timely. Our study is an attempt to fill this gap in critically ill patients.

The AUC for serum and urinary NGAL predicting need of hemodialysis was 0.902 (95% CI: 0.84-0.964) and 0.933 (95% CI: 0.884-0.983), which was statistically significant (p=<0.001), thus demonstrating their excellent diagnostic performance. Similar results were seen in the study done by Hjortrup PB, et al. [10], 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 Klein SB, et al. [11], also confirmed similar results in their study.

In our study, neutrophil lymphocyte ratio (NLR) and procalcitonin were also found to be associated with increased risk of development of AKI and requirement of Hemodialysis. This can be explained by the fact that sepsis is a major risk factor for development of AKI. Similar results were depicted in the study by Zhu J, et al. [12], who concluded that NLR predicted the AKI progression to hemodialysis requirement (OR, 1.65; 95% CI, 1.01–2.71). Another study done by Nierhaus A, et al. [13], on 1089 patients, concluded that higher levels of serum procalcitonin measured within first 24 hours of ICU admission was useful in predicting the requirement of hemodialysis in ICU patients with sepsis (AUROC- 0.67, P value <0.001). Thus, the routine biomarkers used for evaluation of sepsis in critically ill patients can be used conveniently to assess the requirement of hemodialysis as well.

NGAL has distinguished itself to be a marker of acute kidney injury and

Table 1. Baseline demographic characteristics (n=375).

Parameters	AKI	
	Present (n = 201)	Absent (n = 174)
Age (Years)	56.46 ± 18.16	53.34 ± 16.98
Gender		
Male	111 (55.2%)	105 (60.3%)
Female	90 (44.8%)	69 (39.7%)
HTN (Yes)	84 (41.8%)	66 (37.9%)
DM (Yes)	84 (41.8%)	72 (41.4%)

AKI: Acute Kidney Injury; HTN: Hypertension; DM: Diabetes Mellitus

Table 2. Association between various laboratory parameters, clinical outcomes and requirement of hemodialysis (n=375).

Parameters	Need of Dialysis		p value
	Yes (n = 30)	No (n = 345)	
Hemoglobin (g/dL)	12.40 ± 2.44	11.55 ± 2.85	0.406
TLC (/mm³)	14252.00 ± 5250.42	12412.26 ± 6175.00	0.184
Neutrophils (%)	82.00 ± 13.53	71.88 ± 14.50	0.011
Lymphocytes (%)	7.55 ± 3.63	17.52 ± 11.61	0.001
NLR	13.41 ± 6.38	6.68 ± 5.43	0.001
Platelet Count (Lacs/mm³)	2.02 ± 1.09	2.02 ± 1.00	0.938
S. Urea (mg/dL) (Day 1)	61.05 ± 52.95	51.52 ± 34.90	0.866
S. Urea (mg/dL) (Day 3)	103.39 ± 54.81	61.77 ± 46.01	0.011
S. Creatinine (mg/dL) (Day 1)	1.76 ± 1.16	1.45 ± 0.70	0.788
S. Creatinine (mg/dL) (Day 3)	4.05 ± 1.91	1.97 ± 1.23	<0.001
Total Bilirubin (mg/dL)	0.70 ± 0.38	1.39 ± 1.63	0.051
SGPT (IU/L)	58.81 ± 47.12	65.36 ± 73.35	0.978
S. NGAL (ng/mL)	179.40 ± 77.75	55.09 ± 66.23	<0.001
Urine NGAL (ng/mL)	182.85 ± 56.41	51.15 ± 60.64	<0.001
S. PCT	13.11 ± 11.99	3.73 ± 5.20	<0.001
Mortality (Yes)	8 (80.0%)	24 (20.9%)	<0.001
Hospital Stay (Days)	9.00 ± 3.50	10.02 ± 5.77	0.795

TLC: Total Leukocyte Count; NLR: Neutrophil Lymphocyte Ratio; S: Serum; NGAL: Neutrophil Gelatinase Associated Lipocalin; PCT: Procalcitonin.

Table 3. Area under the ROC curve (AUC) of various biochemical parameters predicting need of Hemodialysis.

Parameter	Serum NGAL	Urine NGAL
Area under the ROC curve(AUC)	0.902	0.933
95% Confidence interval	0.846-0.964	0.884-0.983
P value	<0.001	<0.001
Cutoff value (ng/mL)	≥ 91.3	≥ 132
Sensitivity	100%	90%
Specificity	80%	90%

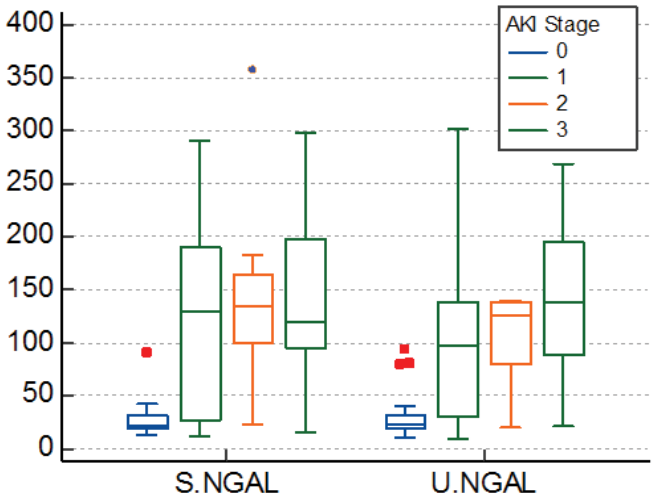

Figure 1. Box and whisker plot curves showing the association of NGAL with various stages of AKI.

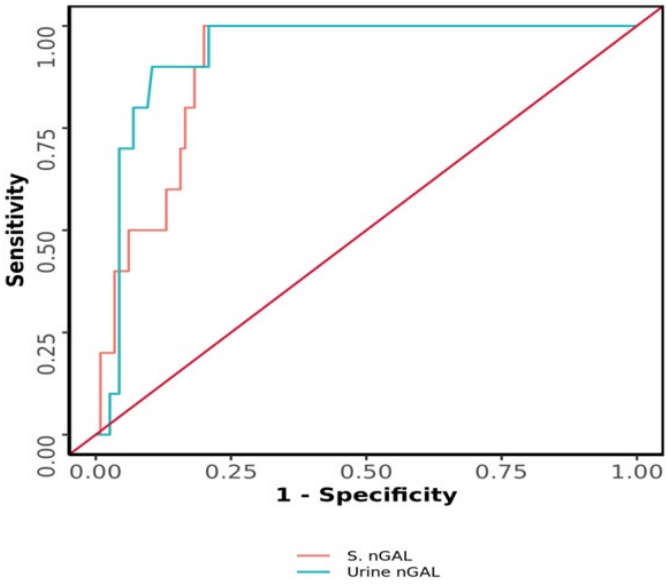

Figure 2. Area under the ROC curve (AUC) of various biochemical parameters predicting need of Hemodialysis.

our study reinforces the same, while also demonstrating its role in prediction of hemodialysis. Further studies with larger sample size should be undertaken.

Conclusion

In critically ill patients without pre-existing kidney disease, both serum and urinary NGAL measured at admission can predict AKI occurrence. NGAL has also proven to be a useful biomarker in early prediction of requirement of hemodialysis so that various metabolic derangements can be corrected at the earliest, thus, decreasing mortality.

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