

Urinary Neutrophil Gelatinase-associated Lipocalin as a Diagnostic and Prognostic Marker for Acute Kidney Injury in Hospitalized Cirrhotic Patients: A Study from North Indian Population

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ABSTRACT

Background: A serious problem in cirrhosis is acute renal injury. The study aimed to examine the urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a diagnostic and prognostic marker of acute kidney injury (AKI) in cirrhotic patients.

Methods: A prospective study was carried out over a period of 1 year. A total of 490 patients suffering from cirrhosis who visited an indoor hospital were screened, and after the exclusion, a total of 90 subjects admitted to the medicine intensive care unit (MICU) fulfilling inclusion criteria were enrolled. Those having a history of renal diseases, on nephrotoxic drugs, in septic shock, peritonitis, UTI, and no urine output were excluded. On admission, for the estimation of uNGAL, urinary levels of sodium, creatinine, fresh urine samples were obtained, and blood samples were taken for serum creatinine estimation.

Results: Out of 90 patients, 33.3% did not develop AKI, and 66.7% developed AKI. Urinary neutrophil gelatinase-associated lipocalin levels were six times higher in patients with acute tubular necrosis (259.08 ± 118.41 ng/mL) and three times higher in Hepatorenal syndrome (HRS)-AKI (124.97 ± 16.38) as compared with patients with normal kidney function (39.76 ± 5.7). Those who died had a higher uNGAL (171.6 ng/mL) in comparison to those who survived (133.7 ng/mL). At a cutoff value of ≥ 114.9 (ng/mL), urinary NGAL represents a sensitivity of 86.92% and specificity of 100% to diagnose AKI and AUC 0.966 (95% CI: 0.919–0.990) in cirrhotic patients.

Conclusion: Urinary NGAL is good for diagnosing AKI and is a marker to distinguish the types of AKI in liver cirrhosis.

Keywords: Acute kidney injury, Biomarker, Liver cirrhosis, Model for end-stage liver disease, Outcome, Urinary neutrophil gelatinase-associated lipocalin.

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HIGHLIGHTS

- Decompensated cirrhotic patients are much more prone to the development of acute kidney injury and a high value of urinary neutrophil gelatinase-associated lipocalin (uNGAL) at admission was suggestive of severe renal dysfunction.
- It proves to be a good predictor of acute kidney injury (AKI) in cirrhotic patients.

INTRODUCTION

Acute renal injury is a known and detrimental consequence of cirrhotic liver. Twenty percent of hospitalized patients with cirrhosis are at risk for the development of acute kidney injury (AKI), which increases their mortality risk by four times.^{1,2} Different types of acute renal injury in patients with cirrhosis are prerenal azotemia, hepatorenal syndrome (HRS), and acute tubular necrosis (ATN), but they have different risk associations with mortality. Unfortunately, clinical differentiation between these forms of AKI is very difficult, because S. creatinine has a poor discriminative capacity between all three types of AKI in patients with cirrhosis.^{3,4} Although serum creatinine is not a very specific marker of AKI, elevation in S. creatinine has a strong association with mortality in cirrhosis.^{2,5,6}

Several novel biomarkers for kidney damage are identified to diagnose early and to differentiate between different types of AKI after studying ischemic tubular kidney damage response.⁷ There is

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a need for an ideal biomarker that not only predicts the severity of AKI and mortality in such patients but is specific, easy to test, and unaffected by any factor that could alter serum creatinine levels in cirrhotic patients. These urinary biomarkers could bring drastic changes to the way AKI is studied.^{8,9}

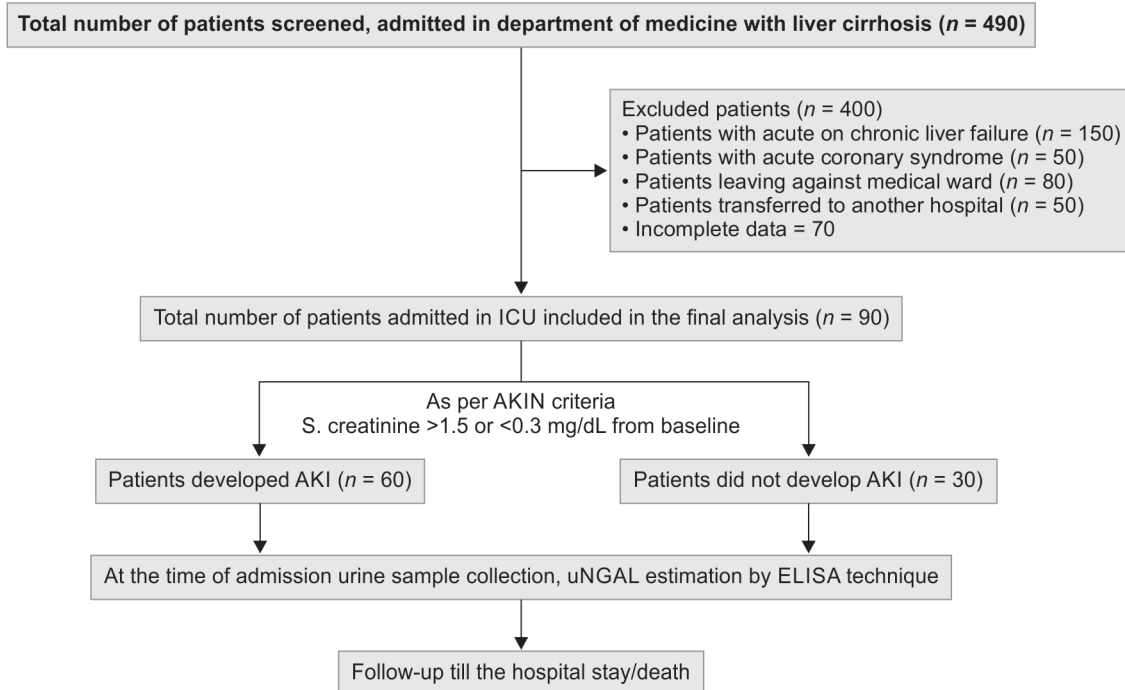


Fig. 1: Study flow diagram showing the number of patients identified during the study period

Injury to the kidney tubular epithelium leads to the release of a protein called NGAL. Urinary NGAL value exponentially increases before S. creatinine value rises in early stages of AKI¹⁰ and they can predict AKI in patients with liver transplants.^{11,12} Volume status, use of diuretics, or prerenal azotemia have little impact on uNGAL levels.¹³ Additionally, uNGAL expression is induced by progressive chronic kidney disease (CKD).^{13,14} Increased urinary NGAL value alone may predict clinical outcomes, such as short-term mortality according to mounting data.^{7,13,15} The study aimed to examine the uNGAL (urinary neutrophil gelatinase-associated lipocalin) as a diagnostic and prognostic marker of AKI in cirrhotic patients.

METHODS

A prospective study was carried out in medicine intensive care unit (MICU) at the tertiary academic center of North India, King Georges Medical University, Lucknow, India between August 2020 and July 2021. After informed and written consent, a total of 490 patients admitted to indoor medical wards in the Department of Medicine were screened. After exclusion, a total of 90 patients were analyzed. For pursuing this work, permission was obtained from the ethics committee of this university (*Reference Code: 103rd ECM II B-Thesis/P44*). Strobe guideline was followed during this study (Fig. 1).

All subjects, 15–60 years of age with evidence of cirrhotic liver and stable kidney function, were included. Cases with long-term hemodialysis, no urine for the first 24 hours (urine not available for NGAL measurement), UTI (WBC count >10/high power field/positive urine culture sensitivity), proteinuria more than 500 mg/day, RBC, >50/HPF or casts in the urine, obstructive uropathy or recipients of liver or kidney transplant were excluded. Clinical, biochemical, and ultrasonographic data were used for the diagnosis of cirrhosis. Acute kidney injury was defined as per AKIN criteria 2007.¹⁶

Procedure

Just after admission, 5 mL blood samples were withdrawn after an overnight fast with full aseptic precaution from antecubital vein and complete blood count, liver function tests (LFT), and kidney function tests (KFT) were performed, and patients were followed. As per ICU protocol, all the above investigations were carried out till the patients stabilized. Clinical and biochemical data were extracted from records as well as from the history provided by the patients and their attendants. Modification of diet in renal diseases (MDRD) formula to calculate the estimated glomerular filtration rate (GFR) was done. For the estimation of uNGAL, urinary levels of sodium, creatinine, 5 mL fresh urine samples were obtained on day 1 at admission, centrifuged at 1500 rpm, and the supernatant was stored at -80°C and uNGAL levels were estimated by using an ELISA kit (Elabscience, Houston, Texas, USA) in relation to urinary creatinine by ELISA technique as per the manufacturer's protocol. Urine routine microscopy test and ultrasonography of the whole abdomen were done in all participants. Follow-up of all patients was carried out till discharge from the hospital or death.

Normal kidney function is defined as stable S. creatinine less than 1.5 mg/dL and <0.3 mg/dL from baseline. No history of renal toxic drugs intake; absence of parenchymal renal disease and/or abnormal renal ultrasonography.

Stable CKD is defined by an estimated eGFR of less than 60 mL/min/1.73 m² over 3 months prior to admission.

Pre-renal azotemia is a transient rise in serum creatinine of more than 1.5 mg/dL or 0.3 mg/dL from baseline, followed by a decrease in serum creatinine less than 1.5 mg/dL or to mean baseline creatinine after the treatment with diuretics withdrawal and IV hydration within 48 hour.^{17,18}

To define, ATN clinical history suggestive of ischemic or nephrotoxic kidney injury is a must with an acute rise in S. creatinine to >1.5 mg/dL or 0.3 mg/dL from baseline and no response to

Table 1: Patient characteristics at enrollment upon hospital admission (entire cohort) (n = 90)

SN	Characteristic	Normal (n = 30)		Prerenal (n = 15)		ATN (n = 25)		HRS-AKI (n = 20)		Statistical significance	
1.	Age, median (IQR)	49.5 (36.75–56.75)		41 (31–58)		40 (27–53.5)		46 (22–74)			
	Mean age ± SD (Range)	43.93 ± 14.30 (22–60)		43.93 ± 14.30 (22–60)		40.80 ± 13.24 (18–60)		47.4 ± 13.80 (24–60)		F = 0.870; p = 0.423 (ANOVA)	
2.	Male gender	22 (73.3)		8 (53.3)		17 (68.0)		18 (90.0)		c ² = 1.826; p = 0.401	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p
3.	SBP (mmHg)	112.1	11.77	117.1	10.42	112.3	15.89	113.66	14.64	0.802	0.453
4.	DBP (mmHg)	71.47	7.84	70.27	6.58	69.92	9.41	72.17	9.26	0.264	0.769
5.	MAP (mmHg)	85.02	8.38	85.81	7.07	84.04	9.68	70.50	7.54	0.210	0.811
6.	Weight (kg)	60.37	8.19	62.10	11.49	63.88	9.86	65.5	5.67	0.922	0.403
7.	Height (m)	1.61	0.06	1.62	0.06	1.64	0.06	1.58	0.05	1.282	0.284
8.	BMI (kg/m ²)	23.10	2.46	23.69	3.89	23.77	3.32	22.5	2.56	0.359	0.699
9.	Diabetes	3	10.0	5	33.3	7	28.0	4	20	4.231	0.121

ATN, acute tubular necrosis; HRS-AKI, hepatorenal syndrome–acute kidney injury

Table 2: Complications and etiology of the study population (n = 90)

Complications	Normal (n = 30)		Prerenal (n = 15)		ATN (n = 25)		HRS-AKI (n = 20)		Statistical significance	
	No.	%	No.	%	No.	%	No.	%	c ²	p
Pallor	12	40.0	6	40.0	10	40.0	10	50.0	0	1
Icterus	12	40.0	5	33.3	10	40.0	5	25.0	0.221	0.895
Ascites	23	76.7	11	73.3	22	88.0	18	90.0	1.625	0.444
Bleeding manifestation	10	33.3	4	26.7	5	20.0	12	60.0	1.228	0.541
Etiology	Normal (n = 30)		Prerenal (n = 15)		ATN (n = 25)		HRS-AKI (n = 20)		Statistical significance	
Alcohol	13	43.3	5	33.3	5	20.0	12	60.0		
Autoimmune	0	0.0	1	6.7	2	8.0	1	5.0		
Cryptogenic	8	26.7	2	13.3	8	32.0	1	5.0		
Hep B	5	16.7	3	20.0	7	28.0	4	20.0		
Hep C	3	10.0	4	26.7	3	12.0	2	10.0		
Wilson	1	3.3	0	0.0	0	0.0	0	0.0	10.094	0.432

treatment within 48 hour of volume replacement, and not fulfilling the criteria of HRS.

HRS is defined as per the criteria of International Club of Ascites.¹⁷ If cirrhosis and ascites present with a rise in s. creatinine, more than 1.5 mg/dL without any improvement after 48 hours of cessation of diuretics and intravenous hydration, presence of albumin, without shock, renal toxic drugs, or parenchymal renal disease with evidence of proteinuria, more than 500 mg/day, microhematuria (>50 red blood cells/high power field), and/or abnormal renal imaging.^{17,18}

Sample Size Calculation

$$n = Z^2 P(1 - P)/d^2$$

where (n) sample size, Z-statistic for a level of confidence; for the level of confidence of 95%, which is conventional, Z = 1.96, p – expected prevalence, d = precision (in proportion to one; if 5%, d = 0.05)

$$n = 1.96 \times 1.96 \times 0.076 \times 0.93/0.05^2$$

Type I error α = 5%, corresponding to a 95% confidence level, and Type II error β = 10% for detecting results with 90% power of the study. So the required sample size n = 89.

Statistical Analysis

Data were analyzed by MedCalc® Statistical Software version 19.8 (MedCalc Software Ltd., Ostend, Belgium). The continuous

variables were presented as Mean ± SD and the categorical variables were represented as percentage values. Student's t-test and Chi-square test was used to compare the means. ANOVA followed by a Bonferroni *post hoc* test for comparison of three or more groups. Bivariate analysis was used to evaluate factors associated with 30-day mortality, factors found significant were analyzed in multivariate analysis. The receiver operating curve (ROC) curve was used to evaluate uNGAL as a diagnostic marker for AKI. p-value < 0.05 is statistically significant.

RESULTS

Overall, 33.3% cases had stable kidney function and 66.7% had different types of acute kidney injury. Out of these 60 patients having AKI, 16.7% of patients had prerenal azotemia, 22.2% HRS, and 27.8% had ATN. The mean age was 43.93 ± 14.30 years in the healthy population, 43.93 ± 14.30 years in the prerenal group, 40.80 ± 13.24 years in the ATN group, and 47.4 ± 13.80 years in the HRS AKI group. About 73.3% were male (Table 1). In our study, alcohol abuse (38.89%) was one of the main causes of cirrhotic liver. Complications of this disease were ascites in 82.2%, esophageal varices in 34.5%, and anemia in 42.2% (Tables 1 and 2).

Serum creatinine values were elevated in patients with kidney dysfunction, but unable to differentiate different types of AKI. As found in our study, this was higher in HRS-AKI (2.85 ± 0.56) compared with prerenal azotemia (1.55 ± 0.26) but similar to patients with ATN (2.16 ± 0.86) (Fig. 2 and Table 3).

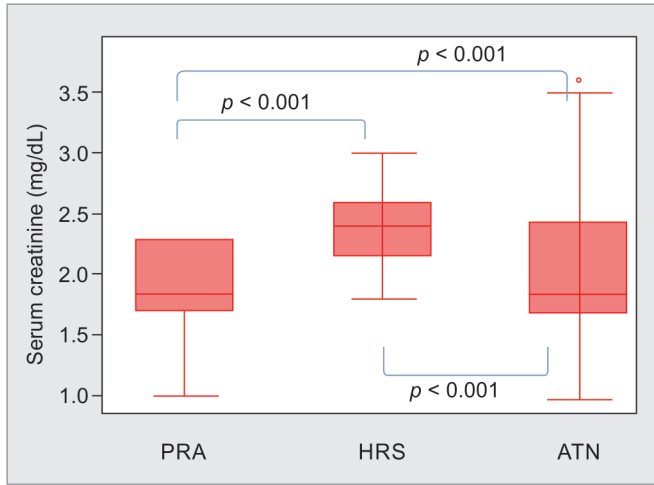


Fig. 2: Box-plot for serum creatinine in different types of AKI

In addition, FENa was higher in ATN (3.41 ± 0.26) as compared with HRS-AKI (0.95 ± 0.36) and prerenal azotemia (0.34 ± 0.12). However, the mean FENa was $<1\%$ in HRS-AKI due to prerenal causes. This was associated with volume deficit, not because of tubular injury. Diagnosis of ATN by FENa alone was not specific. FENa did not differentiate between HRS-AKI and prerenal azotemia (Table 3).

The uNGAL values were highest in patients with ATN (259.08 ± 118.41 ng/mg creatinine), followed by HRS-AKI (124.97 ± 16.38) and lowest in prerenal causes (51.31 ± 7.37). Urinary neutrophil gelatinase-associated lipocalin values were significantly different in patients with stable kidney function (39.76 ± 5.7) as compared with patients with prerenal acute kidney injury, HRS-AKI, and ATN. uNGAL showed a significant variation in values among different groups (Table 3, Fig. 3).

At cut-off value of ≥ 114.9 (ng/mL) urinary NGAL showed sensitivity and specificity to diagnose AKI were 86.92% and 100% and area under the curve (AUC) was 0.966 (95% CI: 0.919–0.990) in cirrhotic patients (Fig. 4).

About 28.8% of patients died during the hospital course of admission. Those patients who survived and were discharged from the hospital had a uNGAL of 133.66 ± 18.10 ng/mg creatinine. Patients who died had a higher baseline uNGAL of 171.6 (40.8–276.5) ng/mg creatinine than patients who survived. The odds ratio of 1.26 (95% CI: 1.03–1.55) for length of ICU stay (in days) and 1.0 (95% CI: 0.99–1.01) for uNGAL was observed in multivariate logistic regression analysis for predicting the 30-day mortality (Tables 4 and 5).

DISCUSSION

Acute kidney injury is a well-known problem found in patients suffering from cirrhosis. Acute kidney injury (AKI) can develop in up to 20% of hospitalized cirrhotic patients.^{1,2} Each of these has a different mortality risk and clinical presentation. Due to malnutrition and reduced muscle mass, which are frequently seen in individuals with severe liver disease, the elucidation of the serum creatinine value in cirrhosis might be perplexing. A normal serum creatinine value in a healthy human being might not be considered normal in patients with cirrhosis. Serum creatinine of 1 mg/dL, which is considered normal for a healthy individual, on this value in cirrhotic patients, mortality increases by up to three times.¹⁷ In cirrhotic

Table 3: Laboratory characteristics of studied patients

Variable	Normal N = 30	ATN N = 25	HRS-AKI N = 20	PRA N = 15	p-value
Hemoglobin (gm/dl)	8.53 ± 2.10 (3.9–12.1)	8.83 ± 2.96 (3.3–12.6)	8.02 ± 2.13 (4–12.9)	9.44 ± 2.90 (3.4–15.8)	p = 0.14
TLC (X10 ³ /mm ³)	9365.32 ± 734.53 (1900–35200)	7562.86 ± 3498.75 (1300–14,600)	9491.43 ± 5792.04 (1200–24,100)	12189.08 ± 6579.39 (2100–25,100)	p < 0.05
Platelet count (Lacs/mm ³)	0.97 ± 0.43 (0.25–1.7)	1.21 ± 0.73 (0.2–2.9)	1.12 ± 0.35 (0.6–1.8)	1.55 ± 0.85 (0.33–3.0)	p < 0.001
SGOT (U/L)	68.20 ± 33.62 (7.3–145)	165.51 ± 348.11 (15–1533)	77.53 ± 70.59 (19–289)	62.92 ± 44.88 (15–172)	p = 0.07
SGPT (U/L)	41.92 ± 23.46 (10–102)	70.0 ± 88.71 (11–385)	47.59 ± 32.57 (15–122)	33.0 ± 20.75 (11–65)	p < 0.05
Alkaline Phosphate (U/L)	282.04 ± 160.29 (139–900)	309.66 ± 113.79 (133–609)	286 ± 190.94 (120–922)	209.59 ± 172.75 (18–620)	p < 0.05
Blood Urea (mg/dL)	32.45 ± 10.13 (14.8–44.8)	61.33 ± 29.49 (22.7–106)	69.8 ± 13.14 (42–90.4)	45.12 ± 17.94 (17.8–83)	p < 0.001
Serum. Creatinine (mg/dL)	0.88 ± 0.21 (0.54–1.2)	2.16 ± 0.86 (0.62–3.2)	2.85 ± 0.56 (1.6–3.2)	1.55 ± 0.26 (0.76–1.6)	p < 0.001
Urinary creatinine (mg/dL)	58.27 ± 41.02 (40–87)	217 ± 34.23 (30–250)	80.5 ± 26 (35–125)	90.02 ± 36.2 (28–165)	p < 0.001
Urinary sodium (mmol/L)	40.24 ± 4.75 (10–50)	120.4 ± 36.4 (70–184)	36.15 ± 12.45 (18–60)	18.5 ± 7.24 (12–52)	p < 0.001
Serum.Na ⁺⁺ (mEq/L)	133.86 ± 5.82 (123–144)	132.34 ± 5.18 (120–143)	126.48 ± 5.32 (120–140)	132.41 ± 6.97 (123–143)	p = 0.66
Serum.K ⁺ (mEq/L)	3.76 ± 0.81 (2.3–5.3)	3.71 ± 1.06 (2.4–7.0)	4.03 ± 0.63 (2.4–4.7)	3.39 ± 0.85 (2.4–5)	p < 0.05
FENa (%)	0.8 ± 0.21 (0.3–1.7)	3.41 ± 0.26 (1.7–5.9)	0.95 ± 0.36 (0.4–1.7)	0.34 ± 0.12 (0.15–0.7)	p < 0.001
uNGAL (ng/mL creatinine)	39.76 ± 5.7 (8.0–40.2)	259.08 ± 118.41 (89.5–393.1)	124.97 ± 16.38 (50.5–287.9)	51.31 ± 7.37 (10.8–70.8)	p < 0.001
eGFR (mL/min)	90.77 ± 29.26 (38–137)	34.37 ± 5.47 (14.5–34.2)	25.5 ± 5.40 (13.5–37.4)	42.11 ± 7.82 (24–53)	p = 0.13
DOH (days)	11.16 ± 4.43 (4–20)	11.45 ± 4.34 (2–20)	21.94 ± 5.61 (8–29)	15.54 ± 4.16 (5–20)	p < 0.001
Length of ICU stay (days)	4.76 ± 2.83 (1–10)	8.76 ± 4.01 (2–16)	18.03 ± 5.64 (7–28)	10.84 ± 4.68 (2–18)	p < 0.001

A significant difference in the mean values of DOH (p < 0.001), Length of ICU stay (p < 0.001), Sodium (p < 0.001), FeNa (p < 0.001), Creat (p < 0.001), uNGAL (p < 0.001) and Score-Meld (p < 0.001) was observed in the AKI groups as compared with the normal group (Table 3).



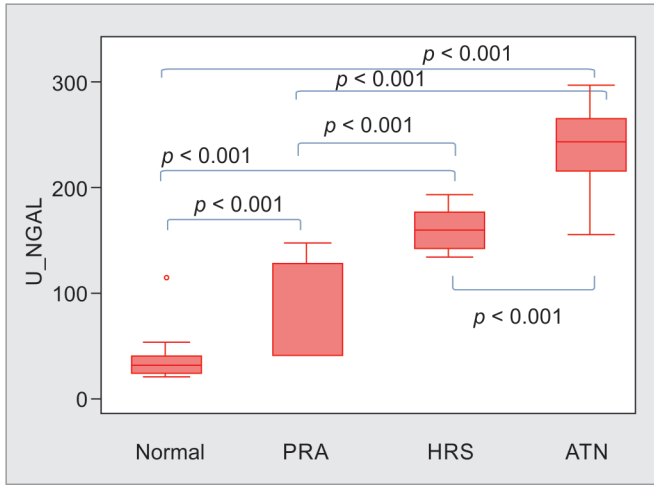
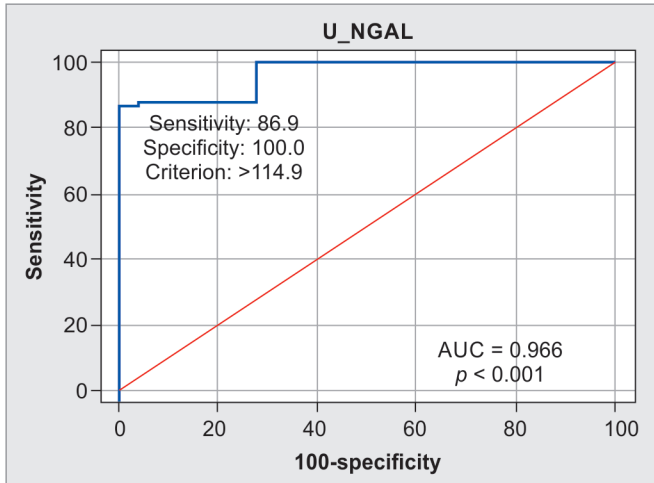


Fig. 3: Box-plot for urinary NGAL (uNGAL) in different types of AKI. A significant difference was observed in the mean values of Urinary NGAL in various groups (Normal, PRA, HRS, and ATN) and similarly, significant differences were observed in the mean values of serum creatinine in various groups (PRA, HRS, and ATN) (Figs 1 and 2).



Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.966
Standard error ^a	0.0143
95% confidence interval ^b	0.919–0.990
Z statistic	32.464
Significance level <i>p</i> (Area = 0.5)	<0.0001
• DeLong et al., 1988	
• Binomial exact	

Fig. 4: Receiver operating characteristic (ROC) curve of urinary NGAL (ng/mg) as predictive markers of AKI in cirrhotic patients

The sensitivity and specificity for urinary NGAL to predict AKI at a cut-off value of ≥ 114.9 (ng/mL) were 86.92% and 100% respectively. The area under the receiver operating curve (ROC) for the Urinary NGAL for predicting AKI in patients was 0.966 (95% CI: 0.919–0.990) in predicting AKI in cirrhotic patients

patients with renal dysfunction, input/output monitoring is also not a reliable marker. There is an urgent need to search for a more reliable biomarker that could diagnose kidney dysfunction in the early stage of cirrhosis.

Table 4: Urinary uNGAL (ng/mg) values in patients who survived and in those who died

Variable	Survivors (n = 64)	Non-survivors (n = 26)	<i>p</i> -value
Urinary NGAL			
Mean \pm SD	133.66 \pm 18.10	171.65 \pm 68.75	
Median (Range)	(21.7–296.4)	(40.8–276.5)	<i>p</i> < 0.05

Significantly higher values of urinary NGAL (*p* < 0.05) were observed in non-survivors as compared with survivors

Table 5: Logistic regression with the Mortality at day 30 with the dependent variable

Variable	Odds ratio	Std. Error	z	<i>p</i> -value	95% CI
Serum albumin	0.73	0.30	−0.77	0.44	0.32–1.63
uNGAL	1.00	0.01	0.27	0.78	0.99–1.01
Serum creatinine	0.98	0.51	−0.04	0.97	0.35–2.71
Length of hospital stay (days)	0.82	0.09	−1.84	0.06	0.66–1.01
Length of ICU stay	1.26	0.14	2.20	<i>p</i> < 0.05	1.03–1.55

The odds ratio of 1.26 (95% CI: 1.03–1.55) for the length of ICU stay (in days), and 1.0 (95% CI: 0.99–1.01) for uNGAL was observed in multivariate logistic regression analysis for predicting the 30-day mortality

Higher values of creatinine are observed in patients with acute renal injury, but they do not effectively distinguish between the different kinds of AKI. In this study, higher levels of serum creatinine were observed in patients having HRS-AKI as compared with those with prerenal azotemia although similar values were obtained in patients with ATN. Thereby, delaying the early identification of the cause behind AKI, which explains the need for another biomarker that could be of use to identify the type of AKI developing in cirrhotic patients much before its progression.

Urinary neutrophil gelatinase-associated lipocalin is a 25-kD protein released by damaged renal tubular epithelium. Both urine and plasma levels of uNGAL are increased after renal damage, but urine levels are easier to detect since urine concentrations are at least five times higher than plasma levels.⁸

For the prognosis of AKI and deaths, serum and urinary NGAL have been demonstrated as helpful markers for the diagnosis of renal injury. However, there is a dearth of information on the function of uNGAL in cirrhotic and HRS.^{11,12,19} Prior to the rise in blood creatinine levels, values of uNGAL increased dramatically before the development of acute renal injury. Each group of AKI in the current study had significantly different uNGAL levels: ATN had the highest levels, HRS had intermediate values, and prerenal disease had the lowest levels.

In the present study, uNGAL values were six times increased in patients with ATN (259.08 \pm 118.41 ng/mL) and three times higher in HRS-AKI (124.97 \pm 16.38) as compared with patients with normal kidney function (39.76 \pm 5.7).

Western literature first reported that urinary NGAL differentiates, prerenal AKI, HRS-AKI, and ATN. As per the literature median uNGAL, 20 ng/mL, 105 ng/mL, and 325 ng/mL in patients of prerenal azotemia, HRS-AKI, and ATN, respectively.¹⁸ One study revealed mean uNGAL values of 21.70 \pm 7.31 ng/mg in prerenal azotemia, 115.53 \pm

68.19 ng/mg creatinine in HRS-AKI, and 240.83 ± 116.94 ng/mg creatinine in ATN.⁸ In another study, it was observed that NGAL values were 115 ng/mL in HRS-AKI and it was less in ATN (565 ng/mL).²⁰ Other groups observed that uNGAL can differentiate different types of kidney failure, but they found high mean uNGAL values in their studies, 161 ng/mL in prerenal azotemia, HRS-AKI 380 ng/mL, and in ATN 580 ng/mL.²¹

In one study, NGAL was able to distinguish between ATN (344 µg/g creatinine) and prerenal AKI (45 µg/g creatinine) and HRS AKI (110 µg/g $p < 0.001$) at an acceptable cut-off value of 244 µg/g creatinine.²² In another study, three subgroups had significantly different median event uNGAL levels (PRA (37), HRS (134), and ATN (2625) ng/mL). In particular, the HRS group's median uNGAL level was significantly higher than that of the PRA ($p < 0.001$) and ATN ($p < 0.001$) groups.²³

It is common that patients with prerenal AKI do not have intrinsic tubular damage, whereas patients with ATN do. When the tubular epithelial cells are damaged in AKI, the renal tubular cells, particularly the distal nephrons, synthesize and produce NGAL. Because splanchnic vasodilatation and compensatory renal vasoconstriction cause functional kidney failure, cases with HRS have levels that fall between those of prerenal and ATN.

In the present study, uNGAL diagnostic accuracy for AKI, at a cut-off value of 114.9 (ng/mg) with 95% CI, AUC 0.966, had a sensitivity of 86.92% and a specificity of 100%. Another author found that the ability to predict AKI in cirrhotic patients using uNGAL at a value of 143 ng/mg creatinine had a sensitivity of 75%, a specificity of 80%, positive predictive value (PPV) of 84.3%, and negative predictive value (NPV) of 69.1%.⁸ In another study, day 3 uNGAL at a value of 220 µg/g creatinine was found to have the highest accuracy for differentiating ATN and other kidney injuries.²⁴ Another Indian study observed that uNGAL with a baseline value of 124 ng/mL creatinine was able to differentiate a severe form of kidney involvement from stable kidney function with a sensitivity of 86%, specificity of 84%, PPV of 76.1%, NPV of 84.9%, and the diagnostic acuity was 0.8.²⁵

Patients with prerenal damage and HRS had an overlap in value ranges for urine creatinine and FENa in the current study, and the mean value of FENa was less than 1% in both groups, as previously described by another author.⁸

The findings of the current study highlighted the inability of serum creatinine to distinguish different types of acute kidney injuries in patients with cirrhotic liver (ATN from HRS-AKI), while uNGAL has a good ability to distinguish different types of AKI. That is why this is a good prognostic marker.

In our study, in the non-survivor group, urinary NGAL was >171.6 (40.8–276.5) ng/mg creatinine, which was high as compared to the survivor group. Another study reported that uNGAL levels >32 ng/mg creatinine also have a capacity to predict mortality, with an AUC 0.698, sensitivity of 79.17%, and a specificity of 65.22%.⁸ One author reported that an uNGAL of >110 ng/mg creatinine could predict mortality in cirrhotic patients developing AKI.

As per observation, uNGAL had good diagnostic ability to predict acute renal injury in cases of cirrhotic liver at a value of 114.9 ng/mg creatinine, good sensitivity (86.92%), and 100% specificity.

The limitation of the present study was that it was carried out in the academic center only and the sample size was small. Hence, results could be lacking in wide use; thus, we recommend larger studies to draw a better conclusion.

CONCLUSIONS

A single baseline uNGAL measurement in hospitalized patients with cirrhosis has good prognostic ability because it distinguishes between prerenal AKI, HRS-AKI, and ATN. This may help to discriminate between different types of AKI during decision-making for early management. Urinary NGAL ≥ 171.6 (40.8–276.5) ng/mg creatinine was associated with high mortality in cirrhotic AKI; uNGAL might predict mortality in cirrhotic patients developing AKI. uNGAL showed good diagnostic accuracy with a cut-off value of 114.9 ng/mg creatinine with a specificity of 100% for AKI prediction.

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