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Urinary Neutrophil Gelatinase Associated lipocalin (NGAL) as A Biomarker of Acute Kidney Injury in Patients with Liver Cirrhosis

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ABSTRACT

Background: The severity of acute kidney injury (AKI) syndrome varies. The blood urea nitrogen (BUN) and creatinine (Cr) retention, as well as a rapid drop in the glomerular filtration rate (GFR), are its defining features. The discovery of a superior gold standard to serum Cr concentration or urine output, as well as proof that a marker-directed therapy strategy may enhance clinical outcomes, would be significant step forward for AKI biomarker research.

Objective: To determine if urine neutrophil gelatinase associated lipocalin (uNGAL) is a reliable indicator of AKI in patients with liver cirrhosis.

Patients and methods: This study included 80 cirrhotic patients. Patients were allocated into two groups as follows: group I: 30 cirrhotic cases with normal kidney functions (without AKI) and group II: 50 cirrhotic cases with AKI who were divided into 3 subgroups according to type of AKI: group IIa included 20 cases with prerenal AKI, group IIb included 20 cases with hepatorenal syndrome (HRS-AKI) and group IIc included 10 cases with acute tubular necrosis (ATN).

Results: In terms of uNGAL, there were statistically significant variations across the groups that were examined (P value <0.001) with mean uNGAL value is highest in group IIc (ATN) (259.80±44.364 ng/ml) followed by group IIb (HRS-AKI) (192.85±40.782 ng/ml) than group IIa (Pre-renal AKI) (61.00±8.706 ng/ml) and group I (29.00±5.420 ng/ml). uNGAL at a cut-off value ≥239 ng/ml could differentiate ATN from HRS with sensitivity of 80%, 90% specificity, 80% PPV, 90% NPV, with an area under curve (AUC) = 0.880, and P value of < 0.001. uNGAL at cut-off value >190 ng/ml had 100% sensitivity, 88.24% specificity, 60% PPV, and 100% NPV for predicting inhospital mortality in cirrhotic patients with AKI (AUC = 0.96; P < 0.001).

Conclusion: To diagnose and differentiate between various causes of AKI in cases with liver cirrhosis, uNGAL may be employed as an accurate biomarker. Additionally, it has prognostic value in such patients.

Keywords: uNGAL, AKI, Liver Cirrhosis.

INTRODUCTION

Together with liver cancer, cirrhosis ranks third among the causes of mortality for adults between the ages of 45 and 64 and is responsible for 3-5% of fatalities globally [(1)].

Chronic liver inflammation results in cirrhosis, which is followed by widespread hepatic fibrosis, in which regenerating hepatic nodules replace the normal hepatic architecture and finally cause liver failure [(2)]. It may result from a variety of factors, which include obesity, non-alcoholic fatty liver disease, excess alcohol use, infection with hepatitis B or C, autoimmune disorders, cholestatic diseases, and an excess of iron or copper [(3)].

Decompensated cirrhosis frequently leads to the extremely deadly condition known as AKI. Relative variations in serum creatinine are used to categorise and characterise AKI in cirrhosis. A higher AKI stage, or a more serious damage, is linked to a higher 90-day death rate [(4)]. It is connected to a worse prognosis [(5)].

In cirrhotic patients, the prevalence of kidney impairment ranges between 14% and 50%. According to estimates, 50% of those with cirrhosis and ascites and 20% admitted to the hospital with severe cirrhosis [(6)]. Prerenal azotemia, HRS, ATN, and postrenal causes are all possible causes of renal failure. While ATN entails structural injury to the kidney, prerenal azotemia reflects the functional renal component [(7)].

Actual alterations in renal function are frequently detected after the diagnosis of AKI based on plasma creatinine [(8)].

Cirrhosis dramatically alters the kinetics of creatinine. Because of decreased muscle and liver generation of Cr, reduced the conversion of creatine to Cr in the liver, high volume of distribution, enhanced tubular secretion of Cr, and altered creatinine excretion owing to medications, the levels stay low. It takes between 24 to 48 hours for blood creatinine to increase after a renal tubule injury. Serum creatinine does not accurately represent the functioning condition of the kidney in circumstances with abrupt declines in GFR until a steady state equilibrium is attained. Jaffe's technique for estimating Cr can be interfered with by high serum bilirubin. Additionally, serum creatinine does not distinguish between various AKI etiology [(9)].

A 25-kD member of the lipocalin family of proteins, NGAL serves as a growth and differentiation factor in a variety of cell types and participates in iron transport in the renal epithelium [(10)]. NGAL levels increase three hours after cellular damage, and depending on the degree of the injury, its concentration peak can be seen between 6 and 12 hours later. This

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elevation may last up to 5 days if the damage is severe [11]. Urine and plasma concentrations thereafter rise quickly and in direct proportion to the degree of the injury [12].

Our study aimed at determination of the use of uNGAL as a biomarker of AKI in cirrhotic patients.

PATIENTS AND METHODS

This comparative cross-sectional study enrolled 80 patients with cirrhosis who were admitted at Internal Medicine Department, Benha University Hospitals.

Inclusion criteria: Patients with established cirrhosis, as determined by clinical, biochemical, and ultrasonographic characteristics, who were older than 18 years. AKI is diagnosed based on high serum Cr level ≥0.3 mg/dL within 48 hrs or ≥1.5-fold baseline that has happened within the previous seven days, as known or presumptively occurred [13].

Exclusion criteria: Patients with pre-existing renal parenchymal disease or on renal replacement therapy (RRT), patients on nephrotoxic medications, patients with spontaneous bacterial peritonitis (SBP), septic shock, proteinuria > 500 mg/day, hematuria > 50 RBC/HPF or RBC cast in urine, urinary tract infection, obstructive uropathy and those who underwent liver or kidney transplantation.

Patients were allocated into 2 groups; group I: 30 cirrhotic cases with normal kidney functions and group II: 50 cirrhotic cases with AKI who were divided into 3 subgroups based on type of AKI:

- Group IIa included 20 cases with prerenal AKI: diagnosed by antecedent history of volume loss: hemorrhage, excessive diuretic use, gastrointestinal fluid loss with resolution of AKI within 48 hrs with diuretics cessation and volume expansion with saline/ albumin.
- Group IIb included 20 cases with hepatorenal syndrome (HRS-AKI) diagnosed based on the international club of ascites (ICA) 2015 criteria of HRS-AKI) [14].
- Group IIc included 10 cases with acute tubular necrosis (ATN): defined as acute increase in serum Cr ≥0.3 mg/dL or ≥1.5 folds from baseline, which not responding with 48 hrs of volume resuscitation and not meeting HRS criteria or presence of renal tubular epithelial cells or casts, muddy brown or mixed casts in the urine [15].

Each patient was subjected to detailed history taking, complete clinical examination with emphasis on stigmata of chronic liver disease, laboratory investigation at time of admission including complete blood picture (hemoglobin level, platelet count and white blood cells), liver function tests (AST, ALT, albumin, bilirubin, prothrombin time (PT) and INR), kidney function tests (blood urea and serum Cr), estimated glomerular filtration rate (eGFR) using modification of diet in renal disease formula (MDRD) [16], serum Na, urine analysis, and urinary NGAL which was evaluated by ELISA method using Sun Red® Human (NGAL) ELISA Kits. Diagnostic paracentesis with ascitic fluid analysis for absolute polymorph nuclear leucocytic count (PMN) to rule out SBP (PMN ≥ 250 cell/mm^3) [17].

An assessment of cirrhosis severity using MELD score [18], MELD Na [19] and Modified Child Pugh classification [20], pelviabdominal ultrasound to detect the radiological signs of liver cirrhosis, presence of ascites, kidney size and exclusion of any evidence of obstructive uropathy.

Ethical consideration:

After permission from the Banha University Faculty of Medicine's Institutional Review Board, all patients provided informed consents. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Using the IBM SPSS software package version 20.0 (IBM Corp., Armonk, New York), data were analysed. Numbers and percentages were utilized to represent qualitative data. The normality of the distribution was confirmed by the Kolmogorov-Smirnov test. Ranges, means, and standard deviations were utilized to represent quantitative data. The Chi-square test was utilized to compare quantitative data. Independent t-test was used to compare normally distributed data between 2 groups. For more than 2 groups, ANOVA test was utilized to compare normally distributed quantitative data. In order to diagnose AKI and predict death, the best uNGAL cut-off values with the highest sensitivity and specificity were identified using ROC curve analysis. P value < 0.05 was rendered as significant.

RESULTS

Regarding age, gender, and comorbidities, no significant difference existed among the 2 primary investigated groups, however the cause of cirrhosis was significantly different **(Table1)**.

Table (1): Comparison between groups as regards demographics, comorbidity and cause of cirrhosis

		Group (I) (n=30)	Group (II) (n=50)	P Value
Age (years)		56.45±3.146	56.84±2.460	0.146
Sex	**Male**	18(60%)	32(64%)	0.273
	Female	12(40%)	18 (36%)	
Comorbidity	**DM**	8 (26.6%)	16 (32%)	0.468
	HTN	6 (20%)	8 (16%)	0.083
Cause of cirrhosis	**HCV**	30 (100%)	46(92%)	<0.001*
	HBV	0 (0%)	4(8%)	
	Others	0 (0%)	0 (0%)	

*: Statistically significant

Laboratory parameters including complete blood count and liver function tests were higher in group (II) in comparison to group (I) with significant differences, however serum albumin was lower in group (II) than group (I) with significant difference **(Table 2)**.

Table (2): Laboratory investigations of the studied groups

	Group (I) (n=30)	Group (II) (n=50)	P Value
Hb (g/dL)	9.95±0.569	9.87±0.735	0.089
TLC × 10^3	6.55±1.377	6.85±1.050	0.717
PLT × 10^3	165.50±27.412	150.15±32.245	0.043*
AST (U/L)	63.90±8.869	82.95±14.446	<0.001*
ALT (U/L)	35.35±4.742	37.5±6.315	<0.001*
T. Bilirubin (µmol/L)	2.086±0.351	3.048±0.713	<0.001*
Alb (g/dL)	3.2±0.250	2.74±0.259	<0.001*
PT	14.9±1.447	16.08±1.683	<0.001*
INR	1.41±0.128	1.54±0.203	<0.001*
Creatinine (mg/dl)	0.81±0.106	2.524±0.612	<0.001*
Urea (mg/dL)	27.80±3.212	106.5±11.57	<0.001*
eGFR (ml/min)	93.18±20.912	28.69±6.10	<0.001*
Na (mmol/L)	135.30±1.604	134.12±2.56	0.063

*: Statistically significant

Regarding kidney function tests of the studied groups: eGFR was significantly lower in group IIc (ATN) and group IIb (HRS), however, serum Cr and blood urea were significantly higher in group IIc (ATN) and group IIb (HRS), but they did not have the ability to differentiate between them **(Table 3)**.

Table (3): Kidney function tests of the study groups

	Group (I) (n=30)		Group (II)						P Value	P1	P2	P3
			Group (IIa) (n=20)		Group (IIb) (n=20)		Group (IIc) (n=10)					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Creatinine (mg/dl)	0.81±0.106		1.75±0.173		3.00±0.324		3.12±0.230		<0.001*	<0.001*	<0.001*	0.111
Urea (mg/dl)	27.80±3.212		96.20±9.501		112.50±7.017		115.20±6.663		<0.001*	<0.001*	<0.001*	0.220
eGFR (ml/min)	93.18±20.912		39.117±6.239		22.19±2.619		20.83±1.799		<0.001*	<0.001*	<0.001*	0.678
Na (mmol/L)	135.30±1.604		135.70±1.455		131.9±1.656		135.40±1.075		<0.001*	<0.001*	0.346	0.002*

P: Comparison between the study groups P1: Comparing between Group (IIa) and Group (IIb) P2: Comparing between Group (IIa) and Group (IIc) P3: Comparing between Group (IIb) and Group (IIc)

*: Statistically significant

MELD and MELD Na were significantly higher in group IIb (HRS) and group IIc (ATN). uNGAL showed significant difference between the studied groups with mean value was highest in group IIc (ATN) followed by group IIb (HRS) then group IIa compared to group I **(Table 4)**.

Table (4): Comparison between study groups regarding uNGAL, MELD, MELD Na

	Group (I) (n=30)	Group (II)			P Value	P1	P2	P3
		Group (IIa) (n=20)	Group (IIb) (n=20)	Group (IIc) (n=10)				
uNGAL ng/ml								
Mean± S.D	29.00±5.420	61.00±8.706	192.85±40.782	259.80±44.364	<0.001*	<0.001*	<0.001*	0.001*
MELD								
Mean± S.D	12.73±1.143	17.50±1.357	24.05±1.731	24.00±0.667	<0.001*	<0.001*	<0.001*	0.784
MELD Na								
Mean± S.D	14.20±1.424	18.65±1.424	24.75±1.482	25.00±0.667	<0.001*	<0.001*	<0.001*	0.314

P: comparison between the study groups P1: comparing between Group (IIa) and Group (IIb) P2: comparing between Group (IIa) and Group (IIc) P3: comparing between Group (IIb) and Group (IIc)
*: Statistically significant

uNGAL at a cut-off value ≥239 ng/ml could differentiate between ATN and HRS **(Table 5)**.

Table (5): Diagnostic ability of uNGAL to differentiate between ATN and HRS-AKI in cirrhotic patients with AKI

	Cut-off value	Sensitivity	Specificity	PPV	NPV	AUC	P value
uNGAL	≥239	80.0	90.0	80.0	90.0	0.880	<0.001*

*: Statistically significant

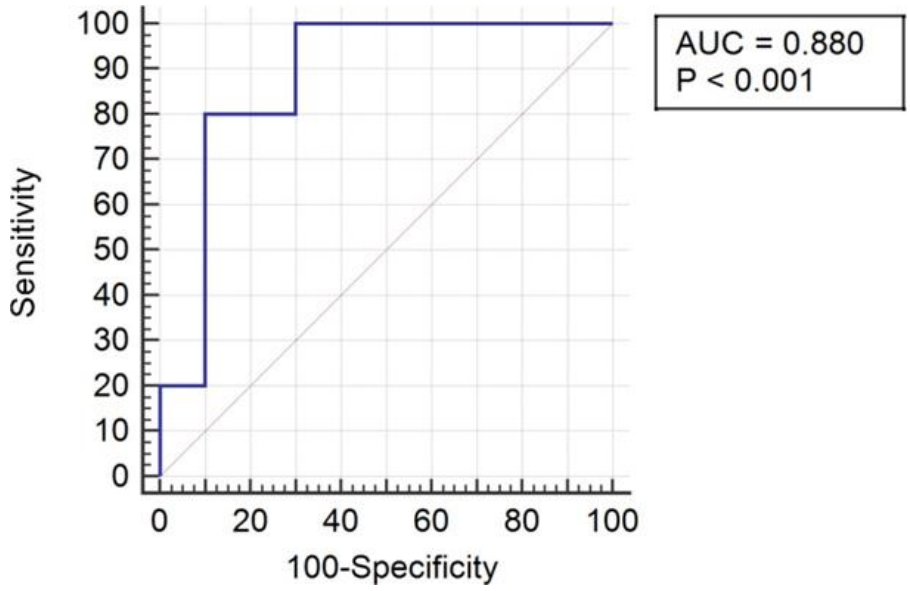

Figure (1): ROC curve of uNGAL as diagnostic biomarker to differentiate ATN from HRS-AKI in cirrhotic cases with AKI

All patients in group I and group IIa improved and were discharged, however 40% of patients in groups IIb and IIc died. Patients who died showed higher mean uNGAL values and MELD scores compared with survivors with a significant difference **(Table 6 and 7)**.

Table (6): Inhospital mortality in different studied groups

In hospital mortality	Group (I) (n=30)		Group (II)						P Value	P1	P2	P3
			Group (IIa) (n=20)		Group (IIb) (n=20)		Group (IIc) (n=10)					
	No.	%	No.	%	No.	%	No.	%				
No	30	100	20	100	12	60.0	6	60.0				
Yes	0	0	0	0	8	40.0	4	40.0	<0.001*	0.017*	0.017*	1.00
Total	30	100	20	100	20	100	10	100				

P: Comparison between study groups P1: comparing between Group (IIa) and Group (IIb) P2: comparing between Group (IIa) and Group (IIc) P3: comparing between Group (IIb) and Group (IIc)
*: Statistically significant

Table (7): uNGAL and MELD score values in cases that survived versus cases that died

	Survived (n=68)	Died (n=12)	P value
MELD			
Min.-Max. Mean± S.D Median	10-25 17.09±4.724 16.00	22-28 24.25±1.960 23.50	<0.001*
MELD Na			
Min.-Max. Mean± S.D Median	11-26 18.31±4.526 18.00	23-28 24.92±1.730 24.00	<0.001*
NGAL ng/ml			
Min.-Max. Mean± S.D Median	20-254 81.07±70.307 50.50	192-337 252.67±48.434 250.50	<0.001*

*Statistically significant

Lastly, our study revealed that uNGAL at cut-off value >190 was able to predict inhospital mortality among cirrhotic cases with AKI **(Table 8 and Figure 2**)

Table (8): uNGAL as a predictor of inhospital mortality among cirrhotic cases with AKI

	Cut of value	Sensitivity	Specificity	PPV	NPV	AUC	P value
NGAL ng/ml	>190	100	88.24	60.0	100	0.961	<0.001*

*: Statistically significant

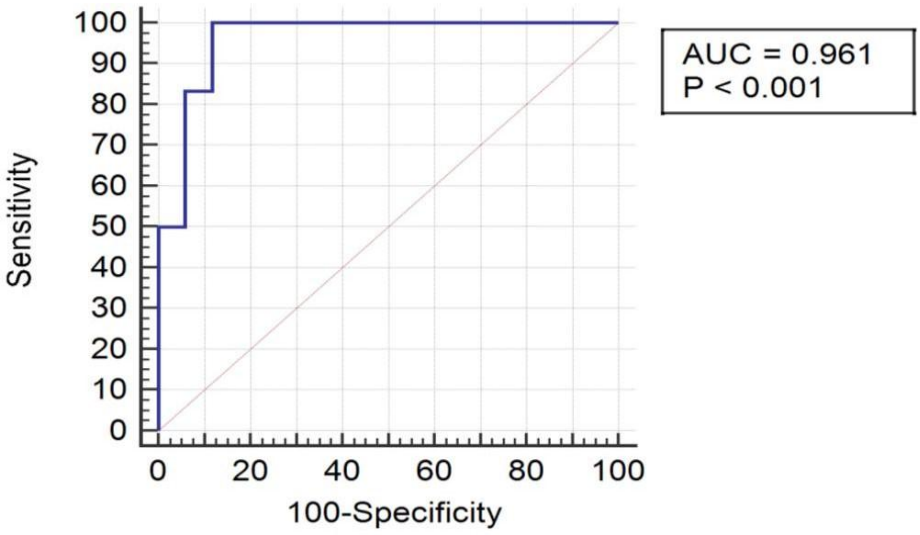

Figure (2): ROC curve of uNGAL as a predictor of inhospital mortality in cirrhotic cases with AKI.

DISCUSSION

In patients with cirrhosis, AKI is very prevalent. AKI can happen to up to 20% of hospitalized cirrhotic patients. AKI has been linked to a fourfold increase in mortality risk [(21)]. AKI forms associated with cirrhosis include prerenal azotemia, HRS, and ATN [(22)].

Applying particular therapy for each reason requires a differential evaluation of the causes of AKI in cirrhosis. Plasma volume expansion has to be used to treat pre-renal azotemia even if patients with ATN may have negative side effects or even death from it [(23)]. In addition, HRS may today be effectively treated pharmaceutically [(24)]. Thus, the necessity for reliable methodologies in the differential diagnosis of kidney dysfunction in cirrhotic individuals is crucial.

Although serum creatinine is the most often used test for identifying all kinds of renal failure, its level may not accurately represent the severity of renal damage since it rises only after kidney injury becomes apparent. Additionally, additional variables such body weight, race, age, sex, total body volume, medications, metabolism of the muscles, and protein consumption might have an impact on serum creatinine [(25)].

The distal nephron produces NGAL, a 25-kDa ion-transporting protein, usually in low concentrations. In response to renal damage, its production is increased [(26)]. As a measure of kidney damage rather than function, NGAL may be more helpful than serum creatinine. NGAL is a reliable indicator of the development of renal disease. NGAL is a potent tool for tracking chronic kidney disease (CKD) because its blood concentrations rise before those of serum creatinine [(27)].

Although NGAL levels are increased in both urine and plasma during renal damage, urine testing is more straightforward since urine concentrations are at least five times higher than plasma levels [(15)].

So, The aim of this study was to evaluate use of uNGAL as a biomarker of acute renal damage in cirrhotic individuals. Between the analysed groups in the current investigation, there was a significant difference with regard to uNGAL (P value < 0.001) with mean uNGAL value was highest in group IIc (ATN) 259.80±44.364 ng/ml followed by group IIb (HRS) 192.85±40.782 ng/ml then group IIa 61.00±8.706 ng/ml compared to group I 29.00±5.420 ng/ml. uNGAL at a cut-off value ≥239 ng/ml could differentiate between ATN and HRS with 80% sensitivity, 90% specificity, 80% PPV, and 90% NPV with AUC=0.880 (P <0.001).

This supports a research by **Fagundes *et al.*** [(28)] that evaluated the use of uNGAL concentrations in the differential diagnosis of kidney dysfunction in 241 cirrhotic individuals. Only 84 individuals (with and without ascites) showed a grade of kidney dysfunction and had higher uNGAL levels than the remainder of the group. In comparison to patients with various etiologies of AKI, CKD, and HRS, patients with ATN had the highest levels of uNGAL (P <0.001).

A study by **Qasem *et al.*** [(29)] assessed the utility of two urinary markers of impaired renal function (NGAL and Interleukin-18). One hundred and sixty hospitalized cirrhotic patients were allocated into 3 groups: non-ascitic group (n = 42), ascitic group without kidney dysfunction (n = 50), and ascitic group with kidney dysfunction (n = 68). Concentrations of uNGAL and urinary IL-18 (uIL-18) were significantly higher in the ascitic group with kidney dysfunction than in the other groups. Besides, both markers could differentiate between causes of AKI, with highest levels in ATN (uNGAL: 580.51±238.75 µg/ g creatinine, uIL-18: 1687±447 µg/ g creatinine), intermediate levels for HRS (uNGAL: 380.6±132.32 µg/ g creatinine, uIL-18: 953±273 µg/ g creatinine), and the lowest levels in prerenal azotemia (uNGAL: 161.15±60.75 µg/ g creatinine, uIL-18: 451.47 ± 121.73 µg/ g creatinine). In those with cirrhosis and CKD, the authors reported medium values of uNGAL

(232.63±41.31 µg/ g creatinine) and uIL-18 (582±98.24 µg/ g creatinine), ranged between those of prerenal azotemia and HRS groups.

This agrees with **Hamdy *et al.*[30],** who discovered that the mean uNGAL concentrations in patients with prerenal azotemia, HRS, and ATN were, respectively, 21.70±7.31, 115.53±68.19, and 240.83±116.94 ng/mg creatinine. Additionally, they discovered that uNGAL had the capacity to distinguish between individuals with intrinsic AKI (iAKI) and AKI from other causes when the cut-off value was ≥143 ng/mg creatinine.

It is common knowledge that people with prerenal increase in kidney function do not have intrinsic tubular injury, but patients with ATN do. However, despite the fact that hemodynamic alterations in HRS with renal vasoconstriction and decreased GFR can be considered pre-renal state, pathological studies have revealed minor kidney tubular and glomerular damages in HRS kidneys, primarily as a result of chronic activation of angiotensin-aldosterone signalling. Because of this, the uNGAL concentrations in HRS patients are in the middle of those in patients with prerenal and those with ATN [30].

In the current study regarding inhospital mortality, all patients in group I and group IIa survived and discharged, however 40% of patients in groups IIb and IIc died. Patients who died had higher uNGAL values (252.67±48.434 ng/ml) and MELD scores (24.25±1.960) than patients who survived (P=<0.001). Our study demonstrated that uNGAL at a cut-off value >190 could accurately predict inhospital mortality in cirrhotic patients with AKI with 100% sensitivity, 88.24% specificity, 60% PPV, and 100% NPV with AUC 0.961 and P <0.001.

This agrees with **Gungor *et al.*** [31] who found that urine NGAL levels were connected with death rates in patients with HRS (dead cases: 449.6±444.2 µg/L, survivors: 137.2±249.5 µg/L; P = 0.009).

The findings of **Verna *et al.*** [15], which showed that mortality was considerably greater in cases with HRS (60%, P>0.001) and iAKI (27%, P = 0.02) than in the remainder, further corroborated this. They also demonstrated that uNGAL has improved sensitivity in predicting inhospital mortality at cut-off ≥110 ng/ml.

This is in accordance with **Udgirkar and colleagues[32],** who discovered 30-day mortality in the HRS group was 39.30% (13 patients) and in the iAKI group was 36.36% (3 instances), with 0 and 2 patients, respectively, in the CKD and pre-renal groups.

Limitation of the study: The study is single centered, and variations may occur among other settings.
Small sample size of the study.

CONCLUSION

To diagnose and differentiate between various causes of AKI in cirrhotic individuals, uNGAL may be employed as an accurate biomarker. In hospital mortality in cirrhotic patients with AKI can also be predicted by it.

- **Conflicts of interest:** None.
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