The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 5121-5127

Urinary Neutrophil Gelatinase-Associated Lipocalin for Assessment of Acute Kidney Injury in Patients with Liver Cirrhosis

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ABSTRACT

Background: Urine neutrophil gelatinase-associated lipocalin (uNGAL) has been recognized as a promising diagnostic indicator for acute kidney injury (AKI). It is a 25-kDa polypeptide that is significantly elevated and excreted during the onset of AKI.

Objective: To determine the utility of uNGAL as a preliminary marker for the detection of AKI in patients with cirrhosis.

Patients and Methods: This cross-sectional observational study was performed on 60 patients with liver cirrhosis, who were allocated into three equal groups: group 1 included patients without ascites, group 2 included ascitic patients without kidney impairment, and group 3 composed of ascitic participants with recently developed kidney impairment.

Results: The Child-Pugh score was significantly elevated in group 2 and group 3 when related with group 1 ($p = 0.005$ and $p < 0.001$, respectively). The End-Stage Liver Disease (MELD) score was also markedly elevated in group 3 relative to both group 1 and group 2 ($p < 0.001$ and $p = 0.003$, respectively). uNGAL demonstrated strong diagnostic performance for identifying AKI, with a statistically significant result ($p < 0.001$) and AUC of 0.960. At a cutoff value of >350.4 ng/mL, uNGAL showed 90.0% sensitivity, 92.5% specificity, PPV of 85.7%, and NPV of 94.9%. uNGAL was significantly elevated in Group 2 and Group 3 than Group 1 (P value=0.005 and <0.001 respectively) and elevated in Group 3 than Group 2 (P value<0.001).

Conclusion: In participants with cirrhosis, uNGAL can significantly be used as an indicator for diagnosis of AKI.

Keywords: uNGAL, AKI, Liver Cirrhosis, Hepatorenal Syndrome, Acute Tubular Necrosis.

INTRODUCTION

Liver disease affects populations globally, regardless of age, gender, race, or geographic locations. As reported by the World Health Organization, chronic liver diseases are responsible for nearly 46% of liver-related deaths worldwide and contribute to 59% of worldwide mortality. It is estimated that chronic liver disease is responsible for approximately 35 million deaths annually [1].

Liver cirrhosis constitutes the late stage of multiple chronic liver diseases and typically develops following sustained hepatic injury. It is defined by progressive fibrosis and the disruption of healthy architecture, leading to the formation of architecturally distorted regenerative nodules [2].

AKI is a prevalent adverse outcome in individuals with liver cirrhosis, observed in up to 20% of hospitalized individuals with the condition [3]. The onset of AKI in individuals with cirrhosis is accompanied with a fourfold increase in mortality risk[4].

AKI is a rapid decline in glomerular filtration rate (GFR) below the normal threshold. Over the past decades, its diagnostic criteria and classification systems have undergone significant refinement and standardization [5,6].

In individuals with cirrhosis, AKI can be categorized into prerenal azotemia, hepatorenal syndrome (HRS), and acute tubular necrosis (ATN), with reported frequency estimates of approximately 68%, 25%, and 33%, respectively. However, these AKI subtypes differ significantly in their associated mortality risks [3].

In clinical settings, serum creatinine and urine volume continue to serve as the principal markers of kidney disorder, in spite of their well-documented restrictions—mainly in patients with progressive stages of cirrhosis [7,8]. Moreover, serum creatinine levels in cirrhotic patients can be modulated by a range of variables, as age, gender, nutritional status, and reduced muscle mass [9].

Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has gained attention as a promising diagnostic indicator for AKI. It is a 25-kDa polypeptide that is significantly elevated and excreted in the urine in the onset of kidney injury [10].

NGAL has emerged as a sensitive and biomarker of tubular injury, with validated cut-offs that help distinguish structural damage from functional kidney impairment. Its utility in the cirrhotic population may improve diagnostic accuracy and guide timely therapeutic interventions [11].

Causes of AKI in liver cirrhosis were pre-renal: hypovolemia (bleeding, vomiting, diarrhea), diuretics, large paracentesis, systemic vasodilation. Intrinsic kidney: ATN (sepsis, shock, nephrotoxic drugs), glomerulonephritis (e.g., HCV-related). Post-renal: urinary obstruction. Hepatorenal syndrome (HRS): prerenal AKI secondary to severe kidney vasoconstriction without structural damage [12].

Therefore, this study was designed to determine the diagnostic usage of uNGAL as an indicator for AKI in patients with liver cirrhosis.

Received: 17/05/2025
Accepted: 19/07/2025

PATIENTS AND METHODS

This cross-sectional observational study was conducted on 60 participants with liver cirrhosis, aged 18 to 80 years, of both sexes. The study was performed from February 2023 and July 2023.

Ethical considerations:

This study was authorized from the Institutional Ethics Committee of Tanta University Hospitals, Egypt (Approval No: 36264MS66/2/23), date (18/2/2023). A documented consent was gathered from all participants preceding enrollment in the research. The study adhered to the Helsinki Declaration throughout its execution.

Exclusion criteria included a history of liver or kidney transplantation, the presence of hepatocellular carcinoma or cholangiocarcinoma, and pre-existing chronic kidney disease (CKD).

Participants were classified into three groups based on their clinical condition:

Group I: Participants with liver cirrhosis without ascites. Group II: Participants with liver cirrhosis and ascites but without kidney impairment. Group III: Participants with liver cirrhosis, ascites, and developed kidney impairment.

All participants had a clinical evaluation, as detailed medical history and physical examination. Laboratory tests comprised complete blood count (CBC), liver function tests, kidney function tests including blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), serum creatinine, electrolytes (Na, and K), albumin, total bilirubin, liver enzymes (ALT and AST), and INR as well as complete urine analysis. Additional tests included viral serologies for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (HCV Ab), urinary sodium levels, and uNGAL, which was determined using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA).

Radiological assessments included thyroid ultrasonography, pelvi-abdominal ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI).

Human (NGAL) ELISA technique

Test principle:

Assay procedure:

The NGAL ELISA kit included a stock standard reagent, which was diluted following the manufacturer's instructions. The number of assay plates used depended on the number of samples and standards to be tested. It was proposed that all standards and blank wells be run twice, and samples should also be tested twice when feasible to ensure accuracy.

For the assay, wells were prepared as follows: blank wells received only chromogen solutions A and B and stop solution, without any sample or reagents (NGAL-biotin antibody or streptavidin–HRP); standard wells received 50µL of standard solution and 50µL of streptavidin–HRP (as the standard is already pre-bound to the biotin antibody, the addition of antibody is not required); test wells were filled with 40µL of sample, followed by 10µL of biotin-labeled NGAL antibody and 50µL of streptavidin–HRP. The plate was sealed with a membrane and incubated at 37°C for 60 minutes with gentle shaking.

Following incubation, the wells were rinsed using a 1:30 dilution of the 30× wash buffer concentrate in distilled water. After washing and removing residual liquid, 50µL of chromogen solution A and 50µL of chromogen solution B were filled to each well. Following gentle mixing, the plate was incubated at 37°C for 10 minutes in the dark. The enzymatic reaction was ceased by adding 50µL of stop solution to each well, leading to a colorimetric shift from blue to yellow.

The optical density (OD) was determined at a wavelength of 450 nm via a microplate reader, with the blank well serving as the zero reference. The absorbance values of the standards were used to construct a standard curve through linear regression analysis. Sample concentrations were calculated by applying their OD values to the regression equation. Data analysis and curve fitting could be performed using standard statistical or graphing software.

Calculate sample concentrations:

To determine sample concentrations, a standard calibration curve was performed by plotting the known standard concentrations on the x-axis (horizontal) and their corresponding OD values on the y-axis (vertical) using graph paper or appropriate software. Sample concentrations were then determined either by identifying the corresponding concentration from the standard curve based on the sample OD value or by calculating the linear regression equation derived from the standard curve. The sample OD values were applied to this equation to compute the corresponding concentrations.

Sensitivity, assay range:

Sensitivity: 10.511 ng/ml and assay range:12 ng/ml→3000 ng/ml.

Specificity:

This ELISA assay demonstrates robust sensitivity and high specificity for the determination of NGAL, with no notable cross-reactivity or interference observed among NGAL and related analogues. However, due to current technical limitations, it was not feasible to evaluate cross-reactivity with all possible NGAL analogues; therefore, the possibility of undetected cross-reactions cannot be entirely excluded.

Risks:

This study was not associated with any anticipated risks. In the event that any unforeseen risks arose during the research process, they were promptly

disclosed to both the patients and the institutional ethics committee. The study also provided direct clinical benefit to patients through the measurement of urinary NGAL levels, which contributed to improved diagnostic evaluation and facilitated more effective management.

Statistical analysis

It was carried out using SPSS version 26. One-way ANOVA test was used to evaluate the quantitative data, which were displayed as mean ± SD. Tukey's post hoc test was then used for cross-group comparisons. X^2-test was used to compare categorical variables, which were shown as frequencies and percentages. The significance level was set at a two-tailed p-value <0.05. Each test's diagnostic performance was assessed using ROC curve analysis.

RESULTS

Age and Child-Pugh scores were markedly elevated in group 2 and 3 versus group 1. There were no meaningful variations among the three groups in terms of sex or social status. The MELD score was significantly elevated in group 3 relative to both group 1 and group 2.

Regarding laboratory findings, serum sodium levels were significantly lowered in groups 2 and 3 versus group 1. Serum potassium levels and international normalized ratio (INR) were significantly elevated in groups 2 and 3 versus group 1. No notable differences were noted among the three groups in hemoglobin concentration, platelet count, total leukocyte count, or prothrombin time **(Table 1).**

Table (1): Demographic data, Child-Pugh scoring system, MELD score and laboratory investigations of the studied groups

		Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	P value	Post Hoc
Age (years)		56.8 ± 12.13	67.2 ± 7.55	65.1 ± 8.37	0.003*	P1=0.003* P2=0.022* P3=0.768
Sex	**Male**	11 (55%)	12 (60%)	9 (45%)	0.626	
	Female	9(45%)	8(40%)	11(55%)		
Social status	**Rural**	8 (40%)	11 (55%)	15 (75%)	0.081	
	Urban	12 (60%)	9 (45%)	5 (25%)		
Child-Pugh scoring system and MELD score						
Child-Pugh scoring system		7.5 ± 2.24	9.8 ± 1.4	10.2 ± 1.84	<0.001*	P1=0.005* P2<0.001* P3=0.822
MELD score		13.1 ± 3.82	16.6 ± 4.54	25.6 ± 10.27	<0.001*	P1= 0.237 P2<0.001* P3=0.003*
Laboratory investigations						
Hb (g/dl)		10.5 ± 1.64	10.1 ± 0.69	10.5 ± 1.42	0.636	
PLT (× 10^9/L)		223.8 ± 8.11	169.7 ± 5.31	202.3 ± 9.09	0.055	
TLC (× 10^3/µL)		8 ± 2.53	9.4 ± 2.44	10.1 ± 2.36	0.161	
Na level (mEq/L)		146.3 ± 9.69	137 ± 3.65	135.4 ± 6.78	0.013*	P1=0.050* P2=0.020* P3=0.915
K level (mmol/L)		3.9 ± 0.64	4.7 ± 1	5.3 ± 1.28	0.001*	P1=0.034* P2=0.001* P3=0.134
PT (sec)		14.5 ± 2.04	16.3 ± 3.26	15.9 ± 3.62	0.160	
INR		1.2 ± 0.08	1.5 ± 0.12	1.5 ± 0.21	*0.001	P1<0.001* P2<0.001* P3=0.481

Data are shown by Mean ± SD, *: Significant, P1:P value among GP 1 and GP 2, P2: P value among GP 1 and GP 3, P3: P value among GP 2 and GP 3, PLT: platelets, TLC: Total Leucocyte Count, PT: Prothrombin time, INR: International normalized ratio.

Causes of cirrhosis were hepatitis C in 50 (83.33%) patients, hepatitis B in 3 (5%) patients, cryptogenic cirrhosis in 4 (6.67%) patients, bilharziasis in 2 (3.33%) patients, and autoimmune hepatitis in 1 (1.67%) patient (**Table 2).**

Table (2): Causes of cirrhosis of the studied patients

	(n=60)
Hepatitis C	50 (83.33%)
Hepatitis B	3 (5%)
Cryptogenic cirrhosis	4 (6.67%)
Bilharziasis	2 (3.33%)
Autoimmune hepatitis	1 (1.67%)

Data is presented by numbers and frequency (%).

Regarding liver function tests, serum albumin levels were significantly lower in groups 2 and 3 compared with group 1 and significantly reduced in group 3 than in group 2. Total bilirubin levels were significantly elevated in groups 2 and 3 versus group 1 and notably elevated in group 3 than in group 2. Aspartate transaminase (AST) levels were significantly elevated in group 3 versus group 1. Alanine transaminase (ALT) levels showed no marked variations among the three groups.

Regarding kidney function tests, serum creatinine and urea levels didn't vary significantly among groups 1 and 2; however, both parameters were significantly elevated in group 3 relative to groups 1 and 2. As for uNGAL, levels were notably more in groups 2 and 3 compared with group 1, and significantly higher in group 3 than in group 2 as shown in **Table 3.**

Table (3): Liver function test, kidney function test and uNGAL of the studied groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	P value	Post Hoc
Albumin level (g/dL)	3.5 ± 0.35	2.8 ± 0.51	2.3 ± 0.22	<0.001*	P1<0.001* P2<0.001* P3=0.002*
Total bilirubin (mg/dL)	2.2 ± 0.53	4.4 ± 1.08	6.8 ± 1.68	<0.001*	P1=0.015* P2<0.001* P3=0.003*
ALT (U/L)	23.1 ± 4.21	25.3 ± 5.82	23.4 ± 4.07	0.277	
AST (U/L)	31.7 ± 7.36	42.7 ± 10.48	47 ± 10.99	0.006*	P1=0.06 P2=0.005* P3=0.644
Kidney function test					
Serum creatinine level (mg/dl	1.0 ± 0.18	1.0 ± 0.16	3.4 ± 0.84	<0.001*	P1=0.993 P2<0.001* P3<0.001*
Urea (mg/dl)	32.4 ± 7.54	33.5 ± 8.10	103.1 ± 24.58	<0.001*	P1=0.994 P2<0.001* P3<0.001*
uNGAL					
uNGAL (ng/mL)	211.6 ± 51.79	304.4 ± 51.92	458.9 ± 98.95	<0.001*	P1=0.005* P2<0.001 P3<0.001*

Data are shown by Mean ± SD, *: Significant.

Finally, uNGAL can significantly diagnose AKI (P value <0.001 and AUC =0.960) at cut-off >350.4 ng/mL with 90.00 % sensitivity, 92.50 % specificity, 85.7% PPV and 94.9% NPV (**Figure 1).**

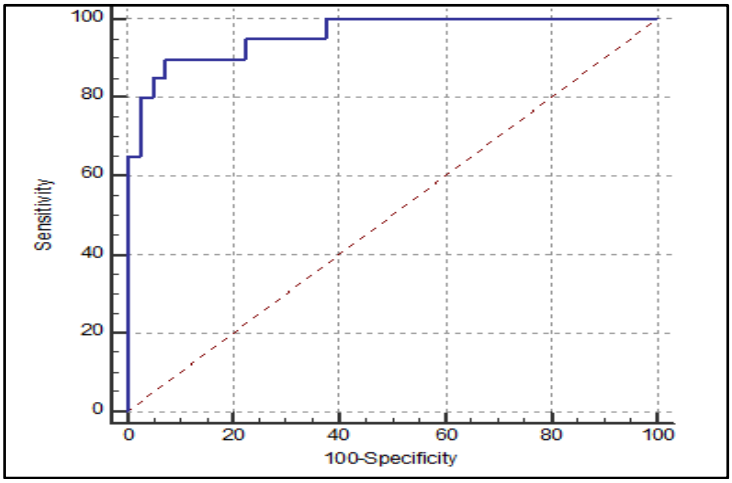

Figure (1): ROC curve of uNGAL in diagnosis of AKI of the studied patients.

The data show no statistically significant correlations between NGAL levels and the assessed laboratory parameters across the 3 groups (Group 1, 2, and 3) **(Table 4).**

Table (4): Correlation between NGAL and different laboratory markers in each group

	NGAL in Group 1		NGAL in Group 2		NGAL in Group 3	
	r	P value	r	P value	r	P value
Hb (g/dl)	-0.175	0.46	-0.130	0.583	-0.104	0.660
PLT (× 10^9/L)	-0.131	0.582	-0.378	0.099	0.406	0.075
TLC (× 10^3/µL)	0.077	0.748	-0.331	0.153	-0.074	0.755
Na level (mEq/L)	0.04	0.868	0.411	0.071	0.073	0.763
K level (mmol/L)	0.021	0.93	-0.173	0.464	0.032	0.895
PT (sec)	-0.364	0.114	0.200	0.397	-0.122	0.606
INR	0.096	0.687	-0.173	0.465	-0.302	0.195
Albumin level (g/dL)	-0.09	0.706	0.230	0.327	0.151	0.5248
Total bilirubin (mg/dL)	-0.093	0.697	-0.133	0.575	-0.227	0.335
ALT (U/L)	0.103	0.667	-0.195	0.409	-0.423	0.062
AST (U/L)	0.058	0.808	-0.136	0.566	-0.190	0.420
Serum creatinine level (mg/dl	0.183	0.441	-0.242	0.303	0.295	0.206
Urea (mg/dl)	0.441	0.993	0.185	0.433	0.192	0.415

r: Correlation coefficients, *: Significant difference when (P value ≤0.05).

In all the patients in the three groups, there were a positive correlation between uNGAL and serum creatinine (r = 0.721), as well as urea levels (r = 0.610), INR (r = 0.337) and no correlations with uNGAL and other parameters including demographic data (age and sex), hemoglobin, platelet count, white blood cell count, electrolytes, liver enzymes (ALT, AST, total bilirubin), albumin, and prothrombin time **(Table 5).**

Table (5): Correlation between NGAL and (demographic data and different laboratory markers) in all the patients in the three groups

	NGAL	
	r	P value
Age (years)	0.195	0.134
Sex	0.142	0.279
Hb (g/dl)	-0.051	0.696
PLT (× 10^9/L)	-0.032	0.805
TLC (× 10^3/µL)	0.128	0.326
Na level (mEq/L)	-0.229	0.08
K level (mmol/L)	-0.049	0.708
PT (sec)	0.083	0.528
INR	0.337	**0.008***
Albumin level (g/dL)	-0.114	0.385
Total bilirubin (mg/dL)	0.089	0.494
ALT (U/L)	-0.112	0.393
AST (U/L)	0.234	0.071
Serum creatinine level (mg/dl)	0.721	**<0.001***
Urea (mg/dl)	0.610	**<0.001***

r: Correlation coefficients, *: Significant.

DISCUSSION

Liver cirrhosis represents a common end phase of prolonged liver diseases, known by progressive fibrosis and the transformation of normal hepatic architecture into aberrant regenerative nodules [2]. Between 1990 and 2017, Egypt consistently recorded the highest global age-standardized mortality rate due to cirrhosis, reaching 103.3 deaths per 100,000 population, despite a 22.4% reduction over this period [13].

In the current study, reasons for cirrhosis were hepatitis C in 83.33% of patients, hepatitis B in 5% individuals, cryptogenic cirrhosis in 6.67% patients, bilharziasis in 3.33% patients and autoimmune hepatitis in 1.67% patients.

In line with our result, **Ahmed *et al.*** [14] documented that the etiology of cirrhosis were hepatitis C in 78% patients, hepatitis B in 15% patients, and other causes in 6.25 % patients. Also, **Verna *et al.*** [15] observed that causes of cirrhosis were hepatitis C in 44.9%, hepatitis B in 3.3% patients, cryptogenic cirrhosis in 10.16% autoimmune hepatitis in 4.23 % patients.

However, **Patel *et al.*** [16] showed that reasons for cirrhosis were hepatitis C in 13.3% of patients and hepatitis B in 21% of patients. Their patients were with stable kidney function, which could explain this difference from our results.

In our result, the Child-Pugh scoring system was notably raised in group 2 and group 3 relative to group 1 while insignificantly different among group 2 and group 3. As group 2 and 3 were more decompensated, this explains the high Child-Pugh scoring. The MELD score was insignificantly variant among group 1 and group 2 and notably elevated in group 3 than group 1 and group 2.

Supporting our result, **Ahmed *et al.*** [14] showed that Child-Pugh scoring system and MELD score were notably different among no ascites, ascites and ascites accompanied by kidney dysfunction groups being elevated in ascites accompanied by kidney dysfunction.

Also, **Verna *et al.*** [15] found that MELD score was higher in HRS than normal, stable CKD, prerenal and AKI Groups.

Different from our result, **Cizmic *et al.*** [17] found that Child-Pugh scoring system was insignificantly different between ascites group and non ascites group. The ascites group had the high value.

In our findings, Na level was significantly reduced in group 2 and group 3 than in group 1 and there was no notable variation among group 2 and group 3. K level and INR were significantly elevated in group 2 and group 3 than group 1 and insignificantly different among group 2 and group 3.

In patients with kidney insufficiency, the kidneys' ability to excrete potassium is compromised, which can lead to hyperkalemia [18].

Supporting our result, **Patel *et al.*** [16] found that Na level was significantly different between groups. K level was meaningfully elevated in HRS-AKI than normal kidney cirrhotic patients.

Supporting our result, **Ahmed *et al.*** [14] observed that K level was significantly different in the three groups being higher in CKD patients.

In the current trial, albumin level was significantly reduced in group 2 and group 3 than in group 1 and was significantly lower in group 3 than Group 2. Total bilirubin was notably elevated in group 2 and group 3 than group 1 and elevated in group 3 than group 2. AST was insignificantly variant among group 2 and groups 1 and 3 while significantly raised in group 3 than group 1. There was no notable variation among the three groups as regards ALT.

Low serum albumin is a frequent feature in cirrhotic individuals, particularly those with advanced liver disease. This is due to multiple contributing factors, including decreased synthesis by the liver, increased redistribution into the interstitial space, and dilution from sodium and water retention [19].

In the same line **Sasso *et al.*** [20] observed that albumin level was significantly reduced in HRS cirrhotic patients than those without HRS. Also, bilirubin was significantly higher HRS cirrhotic patients than those without HRS.

Supporting our result, **Ahmed *et al.*** [14] observed that albumin level was significantly different between no ascites, ascites and ascites accompanied by dysfunction of kidney function groups, with low value in ascites without impairment of kidney function. Bilirubin was significantly different among no ascites, ascites and ascites accompanied by impairment of kidney function groups, the lowest value was in no ascites patients.

In contrast, **Treeprasertsuk *et al.*** [21] showed that albumin level, AST and ALT were insignificantly different between cirrhotic patients with acute kidney failure (ARF) than those without ARF. The different sample sizes could explain this difference from our results.

In the present study, serum creatinine level and urea were insignificantly different among group 1 and group 2, while significantly elevated in group 3 than group 1 and group 2.

In the same line **Sasso *et al.*** [20] showed that creatinine was significantly elevated in HRS cirrhotic patients than those without HRS. Also, **Patel *et al.*** [16] documented that serum creatinine level and urea were notably variable among normal people, prerenal and ATN and HRS-AKI.

In our result, uNGAL was significantly elevated in group 2 and group 3 than group 1 and in group 3 than group 2.

In line with our data, **Patel *et al.*** [16] documented that the uNGAL values were significantly elevated in patients with ATN and HRS than patients with normal kidney function. Also, **Ahmed *et al.*** [14] found that individuals with kidney dysfunction had elevated uNGAL levels relative to those without kidney dysfunction, either with or without ascites.

In our finding, uNGAL can significantly diagnose AKI (P value <0.001 and AUC =0.960) at cut-off >350.4 ng/mL with 90.00 % sensitivity, 92.50 % specificity, 85.7% PPV and 94.9% NPV.

This is also in line with **Gambino *et al.*** [22] who illustrated that uNGAL is an appropriate indicator for a variant identification of AKI in cirrhosis. In agreement with our finding, **Ahmed *et al.*** [14] recorded that uNGAL showed an excellent discriminative for discriminating ATN from HRS with AUC of 0.909, sensitivity 95.5 %, specificity 76.1.

The limitation of this study is its one-center design, relatively dimensioned sample size, and the absence of a healthy control Group.

CONCLUSION

In patients with cirrhosis, uNGAL can significantly be used as clinical indicator of AKI.

Acknowledgement: I would like to express my sincere gratitude to Dr. Ahmed Metawea Elsefy for his invaluable support, guidance, and encouragement throughout this work. His insightful suggestions, unwavering patience, and dedication have played a functional role in the completion of this project.

No funding.
No conflict of interest.

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