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uNGAL IS SUPERIOR THAN SERUM CREATININE AS A DIAGNOSTIC MARKER OF ACUTE KIDNEY INJURY IN CIRRHOTIC PATIENTS

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ABSTRACT

Background: Acute kidney injury (AKI) is known to increase mortality in hospitalized cirrhotic patients; therefore early identification is utmost significance. There are only a few studies evaluating the cut-off level of urine neutrophil gelatinase-associated lipocalin (uNGAL) for diagnosing AKI and its prognostic value in cirrhotic patients. The AKI diagnosis in the early possible period in the hospitalized cirrhotic patients can save many lives. But it is difficult to detect AKI early without conventional biochemical tool, serum creatinine. **Objective**: The aim of this study was to evaluate uNGAL is superior than serum creatinine as a diagnostic marker of acute in cirrhotic patients. **Materials and methods**: This cross sectional study was carried out at Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka. A total 70 Patients of decompensated cirrhosis and decompensated cirrhosis with AKI prone conditions admitted into Department of Hepatology in BSMMU were included for the study. They were evaluated by proper history and clinical examination. Initial investigations were done to meet up inclusion and exclusion criteria including liver function test [serum bilirubin (total), serum albumin, prothrombin time (PT)], renal function tests (serum creatinine), ascitic fluid analysis (cytology, total protein, albumin, SAAG), abdominal ultrasonography, CXR-PA view, ECG, echocardiography. Decompensated cirrhosis were diagnosed with a combination of physical, biochemical, radiological and endoscopic findings. The patients were chosen according to purposive sampling. Serum creatinine (sCr) levels 03 months before the admission was collected wherever available and used as baseline sCr. In patients without a previous sCr value, the sCr on admission was used as baseline. Where the baseline sCr was normal then the patients were included for the study. Patients were then monitored with sCr at 24 hours and 48 hours. The presence of AKI was diagnosed when the patients were fulfilled the criteria proposed by the International club of ascites for cirrhotic patient. Urine sample for NGAL was collected within 24 hours after admission. **Results**: The mean age of the respondents was 43.49±12.46 years and 46.09±14.90 years in Group A and Group B respectively. Twenty-six (74.3%) were male and 9(25.7%) were female in Group A. Twenty-seven (77.1%) were male and 8(22.9%) where female in group B. Male patients were predominant in both groups. Out of 70 cirrhosis patients, HBV was found 45(64.3%) cases, cryptogenic 11(15.7%), NASH 7(10.0%), HCV 5(7.1%) and Wilson's disease 2(2.9%). Out of 35 acute kidney injury (AKI) patients, the contributing conditions of AKI were hepatic encephalopathy (HE) 8(22.9%), acute on chronic liver failure (ACLF) 7(20.0%), variceal haemorrhage 6(17.1%), spontaneous bacterial peritonitis (SBP) 6(17.1%), pneumonia 2(5.7%). Regarding laboratory parameters platelet count, prothrombin time, INR, serum albumin were statistically difference between two groups. Hb%, TC, ESR, AST, ALT, serum bilirubin, serum ALP were not statistically significant between two groups. Mean serum creatinine were 1.02±0.24 in Group A and 2.27±1.01 in Group B. Comparison of mean uNGAL between Patients of decompensated cirrhosis with AKI and without AKI, uNGAL was significantly higher in AKI group. ROC- AUC of 0.984 (95 % confidence interval [CI]: 0.962–1.000, $p < 0.001$). The optimal cutoff value was ≥50 ng/mL providing 91.4% sensitivity, 94.3% specificity, 92.8% accuracy, 94.1% positive predictive value (PPV), 91.7% negative predictive value (NPV), respectively. **Conclusion:** In patients with cirrhosis for early diagnosis and treatment of AKI within possible shortest time the uNGAL is utmost significance Our prospective study indicates that uNGAL is a valid marker for the early detection of AKI in cirrhotic patients with AKI-prone conditions.

KEYWORDS: Microbial Aetiology, phenotypic, genotypic, Acinetobacter.

INTRODUCTION

The AKI diagnosis in the early possible period in the hospitalized cirrhotic patients can save many lives. But it is difficult to detect AKI early without conventional biochemical tool, serum creatinine and other predictors of AKI such as cystatin-c, kidney injury molecule-1 and interleukin-8. Abrupt increase of the level of serum creatinine by at least 0.3 mg/dl may be termed as acute kidney injury (AKI). It may occur in about 20% of hospitalized patients in decompensating liver cirrhosis.[1] Cirrhosis is a progressive vasodilatory state, reduced effective circulatory volume and stimulation of vasoconstrictor hormones in cirrhotic patients may induce AKI. The commonest causes of AKI in cirrhotic patients are pre-renal azotemia, hepatorenal syndrome and acute tubular necrosis. So the actual mechanism of AKI in liver cirrhosis is to stimulate functional vascular renal insufficiency that may results azotemia. Through severe peripheral arterial vasodilation with coexistent hyper stimulation of powerful vasoconstrictor system; here the AKI may be due to prerenal form of hepatorenal syndrome (HRS) or acute tubular necrosis (ATN) (Hartleb et al. 2012).[2] Type 1 hepatorenal syndrome (HRS), which is an acute form of renal failure associated with significant morbidity and mortality.[3] Because of the rigid diagnostic criteria of type 1 HRS, which requires a serum creatinine of >2.5mg/dL (233µmol/L) for its diagnosis.[3] Patients with lesser degrees of renal dysfunction are less likely to be treated. However, there is emerging evidence suggesting that even milder degrees of renal dysfunction in cirrhosis are associated with a poor prognosis.[4] Furthermore, serum creatinine, the most widely accepted measure of renal function, does not accurately reflect renal function in advanced cirrhosis.[5] Therefore, in decompensated cirrhosis, patients with normal serum creatinine may already have significant renal dysfunction.

In clinical practice, serum creatinine and urine output are used as indicators of renal dysfunction. Although SCr has been used to identify patients with AKI, there is a great concern about its limitations especially in advanced cirrhotic group. Besides being a marker of renal function rather than kidney injury, SCr may be under- estimated in cirrhotic patients because of their hypervolemic state, low muscular mass, and decreased hepatic production of creatinine. Furthermore, SCr may take up to 2 days to increase after kidney injury. For these reasons, using SCr to identify high-risk patients among those with cirrhosis may overlook a significant number of patients. Here the zenith indicator of AKI is serum creatinine level, but the rising of serum creatinine lags behind the onset of AKI at least 24 hours, which limit its sensitivity and previous study found that the severity of renal injury associated with increased mortality in hospitalized cirrhotic patients. So, prompt diagnosis and provide early treatment of AKI is utmost significance.

It is eliminated in urine and its concentration may rise 6-48 hours before serum creatinine in patients with AKI. Moreover, some studies have reported that uNGAL alone may remain predictive for AKI in the presence of normal serum creatinine level.[5] Some studies have demonstrated the utility of early uNGAL measurements for predicting the severity and clinical outcomes of AKI.[6] In terms of prognostic value, uNGAL can also predict mortality in these patients that are reported in several studies.[7,8] So, early diagnosis and treatment of AKI within possible shortest time the uNGAL are utmost significance.[9] The above studies were done about the predictor, mortality and prognostic value of uNGAL in AKI with non cirrhotic patients.

OBJECTIVES

General objectives

Evaluation of uNGAL is superior than serum creatinine as a diagnostic marker of acute in cirrhotic patients.

Specific objectives

1. To determine the accuracy of uNGAL as a diagnostic marker of AKI in cirrhotic patients.
2. To find out the cut off value of uNGAL level to diagnose AKI in cirrhotic patients.

METHODOLOGY

Type of study	**Cross sectional study**
Place of study	Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka
Study period	September 2016 to April 2017
Study population	All hospitalized patients with decompensated cirrhosis & decompensated cirrhosis with AKI prone condition and who fulfilling the inclusion and exclusion criteria. They were interviewed with structured questionnaire. The patients were thoroughly examined and findings were noted in structured form.
Sampling Size	Estimated sample 70

Inclusion criteria

1. All hospitalized patients with decompensated cirrhosis & decompensated cirrhosis with AKI prone condition.
2. Age > 18 years.

Exclusion criteria

1. Patient with co-morbid condition (COPD, CKD, CCF etc.)
2. Patients with the history of pre-existing liver or kidney transplantation.
3. Patients with the history of hemodialysis
4. Patients who will had urinary tract obstruction.

Study procedure

Patients with decompensated cirrhosis and decompensated cirrhosis with AKI prone condition (such as, gastrointestinal bleeding, GI fluid loss, over-diuresis, SBP, pneumonia, hepatic encephalopathy, ACLF etc.) admitted into Department of Hepatology in BSMMU were primarily targeted. They were evaluated by proper history and clinical examination. Initial investigations were done to meet up inclusion and exclusion criteria including liver function test [serum bilirubin (total), serum albumin, prothrombin time (PT)], renal function tests (serum creatinine), ascitic fluid analysis (cytology, total protein, albumin, SAAG), abdominal ultrasonography, CXR-PA view, ECG, echocardiography.

Data collection procedure

Data collection was conducted in Department of Hepatology, BSMMU. Subjects were included after primary screening with inclusion criteria. Structured questionnaire were used to collect the necessary information. Informed written consent was taken from each participant before collecting data. The procedure of urine collection was well explained to the patients. They were compliant. After explaining the procedure, patient's first urine of the day was collected in a sterile container.

RESULT

Age distribution

Table-1 showed the age distribution, maximum patients 13(37.1%) and 14(40.0%) belonged to age group 41-50 years in Group A (Patients of decompensated cirrhosis without AKI) and Group B (Patients of decompensated cirrhosis with AKI) respectively. The mean age of the respondents was 43.49±12.46 years and 46.09±14.90 years in Group A and Group B respectively. Difference of mean age was not statistically significant (p>0.05) between two groups.

Table 1: Distribution of the study patients by demographic characteristics between two study groups (N=70).

Age in years	Group A (n=35) Mean ±SD	Group B (n=35) Mean ±SD	P value
20-30	6 (17.1%)	7 (20.0%)	
31-40	7 (20.0%)	3 (8.6%)	
41-50	13(37.1%)	14(40.0%)	
51-60	6 (17.1%)	6(17.1%)	
61-70	3(8.6%)	5(14.3%)	
Mean ±SD Range	43.49±12.46 (20 – 66)	46.09±14.90 (20– 70)	0.431^{ns}

Sex distribution

It was observed that, regarding gender, 26(74.3%) were male and 9(25.7%) were female in Group A. Twenty-seven (77.1%) were male and 8(22.9%) were female in Group B. Male patients were predominant in both groups. The association was not statistically significant (p>0.05) between two groups.

Table 2: Sex distribution of the study patients (n=70).

Sex	Group A (n=35)		Group B (n=35)		P value
	No.	%	No.	%	
Male	26	74.3	27	77.1	0.780^{ns}
Female	9	25.7	8	22.9	
Total	35	100.0	35	100.0	

Causes of cirrhosis

Out of 70 cirrhosis patients, HBV was found 45(64.3%) cases, cryptogenic 11(15.7%), NASH 7(10.0%), HCV 5(7.1%) and Wilson's disease 2(2.9%).

Table 3: Distribution of the patients by causes of cirrhosis (n=70).

Causes of cirrhosis	Frequency	Percentage (%)
HBV	45	64.3
HCV	5	7.1
NASH	7	10.0
Wilson's disease	2	2.9
Cryptogenic	11	15.7
Total	70	100.0

Conditions contribute development of AKI in cirrhotic patients

Out of 35 AKI patients, 8(22.9%) was hepatic encephalopathy (HE), 7(20.0%) acute on chronic liver failure (ACLF), 6(17.1%) variceal haemorrhage, 6(17.1%) spontaneous bacterial peritonitis (SBP), 2(5.7%) pneumonia, 2(5.7%) ACLF with SBP, 2(5.7%) septicaemia, 1(2.9%) SBP with HE and acute watery diarrhea (AWD) was, 1(2.9%).

Table 4: Distribution of Cirrhotic Patients with AKI prone condition (n=35).

AKI prone condition	Frequency	Percentage (%)
HE	8	22.9
ACLF	7	20.0
Variceal haemorrhage	6	17.1
SBP	6	17.1
Pneumonia	2	5.7
ACLF with SBP	2	5.7
Septicaemia	2	5.7
SBP with HE	1	2.9
AWD	1	2.9
Total	35	100.0

Serum creatinine

Table showed mean serum creatinine and uNGAL 1.02±0.24 and 14.75±16.82 in Group A and 2.27±1.01 and 119.32±48.16 in Group B.

Table 5: Comparison of mean serum creatinine between two groups (n=70).

Variables	Group A (n=35) Mean ±SD	Group B (n=35) Mean ±SD	P value
Serum creatinine (mg/dl)	1.02±0.24	2.27±1.01	<0.001[s]
uNGAL (ng/ml)	14.75±16.82	119.32±48.16	<0.001[s]

uNGAL

Table showed the comparison of mean uNGAL between Patients of decompensated cirrhosis with AKI and without AKI, uNGAL was significantly higher in AKI group.

Table 6: Comparison of mean uNGAL between two groups (n=70).

Variables	Group A (n=35)	Group B (n=35)	P value
	Mean±SD	Mean±SD	
uNGAL (ng/ml)	14.75±16.82	119.32±48.16	<0.001[s]

Cut off level of uNGAL of ≥ 50ng/mL

We found that those patients with uNGAL ≥50 ng/mL were significantly higher serum creatinine, prothrombin time, lower serum albumin, more AKI patients, than those with uNGAL <50 ng/mL.

Table 7: Patient characteristics at baseline categorized by the uNGAL cut off level of ≥ 50ng/mL (n=70).

Variables	uNGAL		P value
% or mean ±SD	< 50 ng/ml (n=36)	≥ 50 ng/ml (n=34)	
Age	43.3±12.8	46.4±14.6	0.347
Male No. (%)	26(72.2%)	27(79.4%)	0.483
Hb% (g/dl)	9.9±1.7	9.3±1.7	0.111
TC (--x109 /L)	7.2±3.0	8.7±4.5	0.108
ESR	48.5±30.2	38.1±36.7	0.136
Platelet count (--´109 /L)	138.9±53.4	115.3±50.8	0.063
AST (U/L)	100.1±69.9	109.3±85.1	0.625
ALT (U/L)	62.8±35.1	67.8±50.1	0.635
Prothrombin Time: Pt (sec)	20.9±5.7	24.8±8.2	0.025[s]
INR	1.8±0.62	2.1±0.69	0.056
Serum Albumin (g/dl)	2.4±0.39	2.1±0.35	<0.001[s]

Serum Bilirubin (mg/dl)	5.1±7.0	7.8±8.7	0.160
Serum ALP (U/L)	162.0±106.1	160.5±77.2	0.947
Serum creatinine (mg/dl)	1.04±0.36	2.28±1.02	<0.001[s]

DISCUSSION

In present study maximum patients 13(37.1%) and 14(40.0%) belonged to age group between 41-50 years without AKI and with AKI respectively. The mean age of the AKI patients were 46.09±14.90 years. Fifty-three (75.71%) patients were male and 17(24.29%) patients were female. Male patients were predominant in this study. In accordance Rocha et al. (2015) studied 24 patients with a mean age of 48.4±16.4 years and most were male.[9] Treeprasertsuk et al. (2015) revealed the mean age of the patients were 57.3 ± 14.7 years, and 62 % were male.[10]

In this study among 70 cirrhotic patients, HBV was found in 45(64.3%) cases, cryptogenic 11(15.7%), NASH 7(10.0%), HCV 5(7.1%) and Wilson's disease 2(2.9%). In accordance a study of Treeprasertsuk et al. (2015) underlying etiologies of cirrhosis were chronic hepatitis B/C (52.1 %), alcoholic cirrhosis (26.4 %), cryptogenic cirrhosis (11.6 %), NASH (5.8 %), and autoimmune hepatitis (4.1 %), respectively.

In present study among 35 AKI patients, the contributing conditions of AKI were hepatic encephalopathy (HE) 8(22.9%), acute on chronic liver failure (ACLF) 7(20.0%), variceal haemorrhage 6(17.1%), spontaneous bacterial peritonitis (SBP) 6(17.1%), pneumonia 2(5.7%), ACLF with SBP 2(5.7%), septicaemia 2(5.7%), SBP with HE 1(2.9%) and acute watery diarrhea (AWD) 1(2.9%). Treeprasertsuk et al. (2015) demonstrated contributing conditions of AKI were hepatic encephalopathy (22.8%), variceal haemorrhage (11.4%), SBP (17.1%), septicaemia (20.0%), pneumonia (11.4%), UTI (5.7%), hepatobiliary infection (8.6%), skin and soft tissue infection was (2.9%).[10]

In present study the mean uNGAL significantly higher in patients of decompensated cirrhosis with AKI compared to non- AKI, which was consistent with previous study in cirrhotic patients. Treeprasertsuk et al. (2015) observed the markedly higher uNGAL in AKI patients compared to non-AKI. Slack et al. (2013) also revealed significantly higher uNGAL in AKI patients compared to non-AKI.[10]

Ximenes et al. (2015) observed that the cutoff values of 68 ng/ml uNGAL with an accuracy of 77.8% to predict AKI (sensitivity 80%; specificity 75%; positive predictive value 80%; and negative predictive value 75%). This findings correlates with present study[11]

Patel et al. (2016) conducted a similar study stated that the accuracy for the prediction of septic AKI, as quantified by the area under the receiver-operating characteristic curve AU-ROC for the peak uNGAL: 0.82 (95% CI, 0.75–0.88) vs. AU-ROC for the baseline uNGAL: 0.81(95% CI: 0.73–0.89). The cutoff value of 34.32 ng/mL had a sensitivity and specificity of 86.36 and 80.60 respectively.[12]

Makris et al. (2009) showed uNGAL levels at admission were significantly higher among patients who subsequently developed AKI [155.5 (50.5-205.9) ng/mL vs. 8.0 (5.7-17.7) ng/mL, p=0.0000]. On the basis of receiver-operating characteristic analysis both uNGAL measurements could predict AKI [area under the curve (95% confidence interval) 0.977 (0.823-0.980) and 0.789 (0.556-0.906), respectively], the area under the curve for uNGAL was significantly larger ($p=0.024$)[6]. A cut-off point >25 ng/mL for uNGAL had a sensitivity of 91% and specificity of 95% in predicting AKI, whereas in our study ROC curve showed uNGAL cut off value ≥50 with the AUC of 0.984 (95 % confidence interval [CI]: 0.962–1.000, $p < 0.001$) and providing 91.4% sensitivity, 94.3% specificity, 94.1% positive predictive value (PPV), 91.7% negative predictive value (NPV), respectively. Li et al. (2013) studied the urinary NGAL level of the AKI group was significantly higher than the group without AKI at all time points.[13] Using a cutoff value of 53.9 ng/mL, the area under the receiver-operating characteristic curve for urinary NGAL was AUC 0.876 with a sensitivity of 69% and specificity of 95%.

In our study, in comparison of decompensated cirrhotic patients with cut off value of uNGAL ≥50ng/mL by ROC curve analysis. It was found that those patients with uNGAL ≥50 ng/mL were significantly higher serum creatinine, prothrombin time, lower serum albumin and more AKI patients than those with uNGAL <50 ng/mL. Treeprasertsuk et al. (2015) conducted a study of cirrhotic patients with cut-off uNGAL of ≥56 ng/mL, they found that those patients with uNGAL ≥56 ng/mL were significantly older, had higher serum creatinine, higher proportion of AKI and more number of death rate than those with uNGAL <56 ng/mL, these findings are similar to present study.[10]

CONCLUSIONS

In patients with cirrhosis for early diagnosis and treatment of AKI within possible shortest time the uNGAL is utmost significance. uNGAL can be used as a diagnostic marker of AKI in cirrhotic patients it will help in the better management of cirrhotic patients with risk of AKI.

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