Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Urinary Neutrophil Gelatinase Associated Lipocalin, As a Diagnostic Marker of Acute Kidney Injury in Cirrhotic Patients

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DOI: 10.36347/sjams.2021.v09i12.012 | **Received:** 12.11.2021 | **Accepted:** 16.12.2021 | **Published:** 22.12.2021

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Abstract **Original Research Article**

Background: Acute kidney injury leads the liver cirrhosis patients to the doom of multiorgan failure. The acute kidney injury diagnosis in the early possible period in the hospitalized cirrhotic patients can save many lives. But it is difficult to detect acute kidney injury early without conventional biochemical tool, serum creatinine. Abrupt increase of the level of serum creatinine by at least 0.3 mg/dL may be termed as acute kidney injury. It may occur in about 20% of hospitalized patients in decompensating liver cirrhosis. The commonest causes of acute kidney injury in cirrhotic patients are pre-renal azotemia, hepatorenal syndrome and acute tubular necrosis. ***Objective***: The aim of this study was to assess of an increase urinary Neutrophil Gelatinase Associated Lipocalin level predicts the development of acute kidney injury in cirrhotic patients, to determine the accuracy of urinary Neutrophil Gelatinase Associated Lipocalin as a diagnostic marker of acute kidney injury in cirrhotic patients and to find out the cut off value of urinary Neutrophil Gelatinase Associated Lipocalin level to diagnose acute kidney injury in cirrhotic patients. ***Materials and methods***: This was a cross sectional study at the department of hepatology, BSMMU, Dhaka, during September 2016 to April 2017. Total 70 hospitalized patients with decompensated cirrhosis & decompensated cirrhosis with AKI prone condition and who fulfilling the inclusion and exclusion criteria were included in this study. Patient with co-morbid condition (COPD, CKD, CCF etc.), history of pre-existing liver or kidney transplantation, hemodialysis and urinary tract obstruction were excluded from this study. ***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%) were female in group B. Male patients were predominant in both groups. Out of 70 cirrhosis patients, Hepatitis B virus was found 45(64.3%) cases, cryptogenic 11(15.7%), Non- alcoholic steatohepatitis 7(10.0%), Hepatitis C virus 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:*** uNGAL is a valid marker for the early detection of AKI in cirrhotic patients with AKI-prone conditions.

Keywords: Urinary Neutrophil Gelatinase Associated Lipocalin, acute kidney injury, cirrhotic patient.

INTRODUCTION

Acute Kidney injury (AKI) leads the liver cirrhosis patients to the doom of multi-organ failure.

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) [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. 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.

The International club of ascites recently proposed that acute renal injury (AKI) in cirrhosis should be re-defined as a rise in serum creatinine of ≥0.3mg/dL (26.5 µmol/L) within 48 hours or a percentage increase in serum creatinine ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days, irrespective of the final serum creatinine level. In cirrhosis, the prevalence rate of AKI types include pre renal azotaemia, HRS and ATN are 68%, 25% and 33% respectively and varies in mortality [6].

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- estimat ed 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.

Neutrophil gelatinase associated lipocalin (NGAL) is a novel 22-KDa protein of human neutrophils that is in part covalently complexed with neutrophil gelatinase and encoded by LCN2 gene. NGAL is involved in innate immunity by sequestrating iron that in turn limits bacterial growth. It is expressed in neutrophils and in low levels in the kidney, prostate and epithelia of the respiratory and alimentary tracts. NGAL is used as a biomarker of kidney injury, expressed by activated neutrophils and injured kidney tubular cells.

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 [7]. Some studies have demonstrated the utility of early uNGAL measurements for predicting the severity and clinical outcomes of AKI [8]. In terms of prognostic value, uNGAL can also predict mortality in these patients that are reported in several studies [9]. *So, early diagnosis and treatment of AKI within possible shortest time the uNGAL are utmost significance [1]*. The above studies were done about the predictor, mortality and prognostic value of uNGAL in AKI with non-cirrhotic patients.

Now-a-days, several studies were done on uNGAL for early predictor of AKI in cirrhotic patients, but yet have fallacies to become a better predictor of AKI in cirrhotic patients. So, further studies are needed for diagnostic accuracy of uNGAL for predicting AKI in cirrhotic patients [10]. The main aim of this study is to determine the accuracy of uNGAL as a biomarker for the early identification of AKI in adult hospitalized cirrhotic patients.

METHODS AND MATERIALS

This cross sectional study was carried out at department of hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Total 70 patients of decompensated cirrhosis and decompensated cirrhosis with AKI prone conditions admitted into department of hepatology in Bangabandhu Sheikh Mujib Medical University 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, serum ascitic albumin gradient), abdominal ultrasonography, X-ray chest-PA view, electrocardiography, echocardiography. Decompensated cirrhosis was diagnosed with a combination of physical, biochemical, radiological and endoscopic findings. The patients were chosen according to purposive sampling. Serum creatinine levels 03 months before the admission was collected wherever available and used as baseline serum creatinine. In patients without a previous serum creatinine value, the serum creatinine on admission was used as baseline. Where the baseline serum creatinine was normal then the patients were included for the study. Patients were then monitored with serum creatinine at 24 hours and 48 hours. The presence of acute kidney injury was diagnosed when the patients were fulfilled the criteria proposed by the International club of ascites for cirrhotic patient. Urine sample for Neutrophil Gelatinase Associated Lipocalin was collected within 24 hours after admission.

RESULT AND OBSERVATION

This cross-sectional observational study was carried out with the aim to assess of an increased uNGAL level predicts the development of AKI in cirrhotic patients in the Department of Hepatology, BSMMU, Dhaka. During the study period of total 70 patients (35 decompensated cirrhosis with AKI patients and 35 decompensated cirrhosis without AKI) were enrolled for the study.

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	

Group A: Patients of decompensated cirrhosis without AKI

Group B: Patients of decompensated cirrhosis with AKI

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

Laboratory findings

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.

Table 5: Comparison of laboratory findings between two groups (n=70)

Laboratory findings	Group A (n=35) Mean±SD	Group B (n=35) Mean±SD	P value
Hb% (g/dl)	9.9±1.7	9.3±1.7	0.124
TC (--x10^9 /L)	7.1±2.7	8.7±4.7	0.082
ESR	46.3±31.1	40.7±26.6	0.421
Platelet count (--´10^9 /L)	143.1±56.7	111.7±44.8	0.012^s
AST (U/L)	105.4±75.1	103.7±80.4	0.927
ALT (U/L)	62.6±32.2	67.9±51.6	0.609
Prothrombin Time: Pt (sec)	20.7±5.6	24.9±8.1	0.015^s
INR	1.8±0.6	2.1±0.7	0.038^s
Serum Albumin (g/dl)	2.4±0.4	2.1±0.3	<0.001^s
Serum Bilirubin (mg/dl)	5.8±8.5	7.0±7.5	0.517
Serum ALP (U/L)	166.7±105.5	155.9±78.6	0.630

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 6: 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

4.7 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 7: 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[$]

ROC curve analysis

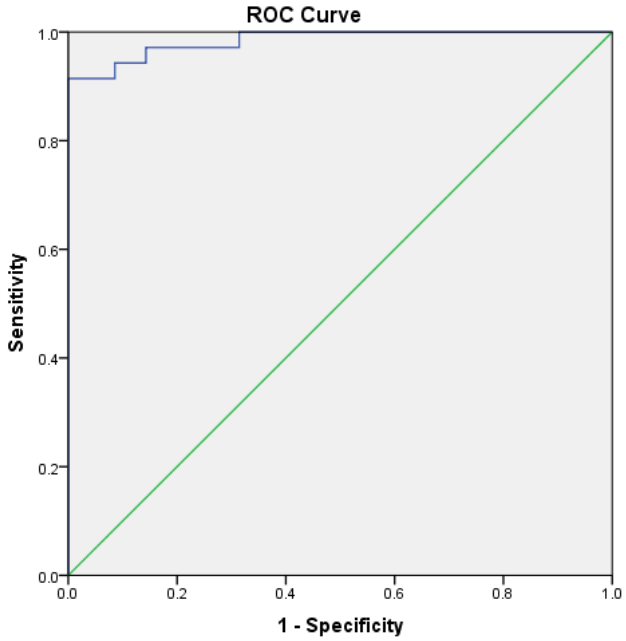

Fig 1: ROC curve

ROC curve showed that uNGAL level could be used to diagnose AKI in hospitalized cirrhotic patients with AKI-prone conditions with the 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.

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 [11]. Treeprasertsuk *et al*., (2015) revealed the mean age of the patients were 57.3 ± 14.7 years, and 62 % were male [12]. 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 [12].

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%) [12].

In this study regarding laboratory parameters platelet count, prothrombin time, INR, serum albumin were statistically significant difference between AKI and non-AKI patients. Treeprasertsuk *et al.,* (2015) found in term of laboratory data, ALP and platelet count were significant difference between AKI and non-AKI group, which correlates with the present study[12]. 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.

In present study ROC curve showed that uNGAL level could be used to diagnose AKI in hospitalized cirrhotic patients with AKI-prone conditions with the 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, 94.1% positive predictive value (PPV), 91.7% negative predictive value (NPV), 92.8% accuracy respectively. In accordance with study performed by Treeprasertsuk *et al*., (2015) showed uNGAL was a good biomarker for early diagnosis of AKI with AUC-ROC (0.83) and cut-off value of ≥56 ng/mL providing 77.1% sensitivity, 73.3% specificity, 54% positive predictive value (PPV), 88.7% negative predictive value (NPV), respectively. The level might be used for the early detection of AKI in hospitalized AKI-prone cirrhotic patients, for example, those with bacterial infection, acute decompensated cirrhosis or GI bleeding, which occurred frequently during admission. Previous studies validated that uNGAL in other settings including hematopoietic stem cell transplantation, critically ill and after coronary angiography, which were the high risks for AKI. Those studies' provided good diagnostic efficacy of uNGAL and were superior to other kidney biomarkers such as urinary kidney injury molecule-1, liver-type fatty acid-binding protein. ROC analysis, AUC for KIM-1, NGAL and L-FABP was 0.713, 0.958 and 0.642, respectively, in the coronary angiography group, and 0.716, 0.916 and 0.743 in the cardiac surgery group. Urinary KIM-1 12 h after intervention is predictive of AKI in adult patients undergoing coronary angiography, but NGAL shows higher sensitivity and specificity (Torregrosa I *et al*., 2014; Taghizadeh-Ghehi *et al*., 2015) [13, 14]. Our study extended these observations to specific group in cirrhotic patients. Former study showed that the severity of renal injury in hospitalized cirrhotic patients related with poor clinical outcome and early treatment could provide better result. Therefore, it is crucial to early detect AKI with effective marker in order to provide early intervention (DuCheyron *et al*., 2005 & D'Amico et al., 2006) [15, 1]. 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 [16].

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) [17]. The cutoff value of 34.32 ng/mL had a sensitivity and specificity of 86.36 and 80.60 respectively. A study done by Constantin *et al*., (2010) in the adult population observed that plasma NGAL at ICU admission was an early biomarker of AKI with sensitivity of 85% and specificity of 97% with an AUC equivalent of 0.956 (0.864–0.992) [18]. 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 [19].

CONCLUSION

The present study revealed on the usefulness of uNGAL is a valid marker for the early detection of AKI in cirrhotic patients with AKI-prone conditions. With a cut-off value of 50ng/ml, it provides an of AUC 0.984, with a sensitivity and specificity of 91.4% and 94.3%, respectively.

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