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Determination of the Relationship Between Urinary Albumin to Creatinine Ratio and the Severity of Liver Disease in Patient with Decompensated Cirrhosis of Liver

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Key words:
Microalbuminuria, UACR, Decompensated Cirrhosis of Liver, CTP Score, MELD Score.

Abstract

Background: *Decompensated cirrhosis of liver may lead to renal hypoperfusion and dysfunction that may be predicted by urinary albumin-to-creatinine ratio (UACR) and this UACR value may be one of the predictors of severity of liver disease.* ***The aim of the*** *study was to determine the relationship of urinary albumin creatinine ratio with severity of liver disease in patients with decompensated cirrhosis of liver.* ***Methods:*** *A cross-sectional observational study was carried out in the Department of Hepatology, Bangladesh Medical University (Former - BSMMU), Dhaka on 100 patients of decompensated cirrhosis of liver of different etiology. Patients were divided into two groups as based on UACR ≤30mg/g (group 1) and UACR ≥30 mg/g (group 2). The groups were compared of cirrhosis related features, complications, CTP, (Child-Turcotte-Pugh) score and Model for end-stage liver disease (MELD) score. A receiver-operator characteristic curve was used for prediction of UACR with CTP class.* ***Results:*** *Male female ratio was 3:2. Sixty six (66%) patients had hepatitis B. Mean CP score 9.34±1.2, mean MELD score 20.6±6.96, mean urinary creatinine 81.5±78.0, urinary microalbumin 31.5±37.33 and mean UACR was 41.86±43.96. The difference was statistically significant (p<0.05) between two groups. ROC curve was constructed by using UACR, which gave a cut off value 32.43mg/g, with 78.3% sensitivity and 81.5% specificity for severity of decompensated liver diseases termed by Child Pugh Class C.* ***Conclusion:*** *This study shows microalbuminuria measured by UACR, at e" 32.43mg/g level is associated with more severity in patients with decompensated cirrhosis of liver and positively correlated with CTP score and MELD score.*

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Introduction:

Cirrhosis is a diffuse process with fibrosis and nodule formation. The fibrosis causes distortion of hepatic parenchyma and vasculature and leads to increase intra-hepatic vascular resistance and develops portal hypertension[1]. It is clinically described as compensated or decompensated. Decompensation is defined by the development of ascites, gastrointestinal bleeding, encephalopathy or jaundice[2]. Hepatotropic viruses, alcohol, Non alcoholic steatohepatitis

(NASH) and metabolic cause are mainly responsible for cirrhosis. Some co-factors like age, sex, obesity, iron intake, diabetes mellitus, insulin resistance, immunosuppression and genetic factors may contribute to development of cirrhosis[3]. Widespread systemic and splanchnic vasodilatation occurred in cirrhosis, which eventually leads to abnormalities in the systemic and several regional vascular beds (like kidney, brain and muscle).

In decompensated liver diseases, functional renal abnormalities occur due to several important components like splanchnic and systemic arterial vasodilatation, renal vasoconstriction, and cardiac dysfunction. Acute kidney injury, chronic kidney disease and acute-on-chronic kidney diseases are the spectrum of renal dysfunction in decompensated cirrhosis of liver. Child-Pugh score depends on ascites, encephalopathy, jaundice, serum albumin label and prothrombin time gives a good short-term prognostic guide. The total score classifies patients into grade A, B or C[4]. MELD is a numerical scale express disease severity index for chronic liver diseases[5]. It determines three months prognosis in patients undergoing TIPS and liver transplantation and is calculated from serum creatinine, prothrombin time (INR), serum bilirubin and sodium concentration.

Urinary Albumin Creatinine ratio (UACR) is calculated as the ratio of albumin to creatinine in a spot urine sample, expressed in milligrams per gram[6]. Microlbuminuria is defined when UACR is greater than 30 mg/g. It is an earlier sign of vascular damage and considered as a predictor of worse outcomes for both kidney and heart patients associated with metabolic syndrome. Micro-albuminuria has a significant correlation between hypertension and insulin resistance[7]. Microalbuminuria also emerged to be animportant risk factor for development of cardio-vasculardisease[8].

HCV infection is associated with microalbuminuria, which can be reduced by pegylated interferon-ribavirin therapy and may be associated with SVR[9]. Microalbuminuria is more prevalent among NAFLD, Non alcoholic fatty liver disease (NAFLD) patients compared with control cases and its prevalence was increasing with the advanced stages of NAFLD[10]. The relationships between microalbuminuria and liver histology with biopsy-proven NAFLD showed a significantly higher mean fibrosis scores[11].

Several biomarkers were established for structural kidney disease like NGAL, IL-8, KIM-1, Cystatin C etc. Creatinine is an inaccurate renal function index. Renal biopsy is usually not performed in cirrhosis, so albuminuria could be an alternative marker of renal dysfunction for decompensated liver diseases.

Methods:

A hospital based Cross-sectional Observational study was carried out at the department of Hepatology, Bangladesh Medical University (former-BSMMU), Dhaka during March 2018 to August 2018. Patients admitted into hospital with decompensated cirrhosis of liver who met inclusion criteria were decompensated cirrhosis of liver-cirrhotic patients with one or more of the following: ascites, jaundice, variceal bleeding and hepatic encephalopathy and exclusion criteria were patients with diabetes mellitus, hypertension or other cardiac dysfunction, intrinsic renal disease, on ACEi/ ARB or other nephrotoxic drugs, with other co-morbid conditions (CKD, COPD, CCF etc), pregnancy with CLD with informed written consent of patients or their guardians. Patients were evaluated by history, clinical examination and relevant investigations. A predesigned structured data collection sheet was used. Patients were chosen by purposive sampling. A memorandum of understanding was made between department of hepatology and department of Biochemistry and Molecular Biology, BMU. Severity of liver disease was measured by CTP class and MELD score. Spot urine sample was collected and UACR was measured in the department of Biochemistry and was estimated by an analyzer; DCATM System: Siemens Medical Solutions Diagnostics, Tokyo,

Japan. Total 100 patients in two groups were enrolled for the study. Group 1 contains 50 patients with UACR <30 mg/g and group 2 contains 50 patients having UACR >30 mg/g. The statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows. The mean values were calculated for continuous variables and Chi-Square test was used to analyze the categorical variables. Student t-test was used for continuous variables. Multivariate logistic regression analysis was performed. P value of <0.05 was taken as significant. Confidentialities of all data were ensured and quality assurance strategy was maintained.

Results:

In Table : 1 we found that 100 patients of decompensated cirrhosis of liver were included in two groups. Here mean age was found 52.28±13.8 with a male female ratio of 3:2. 66% patients had hepatitis B, 8% had Hepatitis C and 26 % had other causes. Most patients were presented with abdominal distension (78%), abdominal pain (62%), scanty micturation (44%), and jaundice (22%). Some patients presented with hepatic encephalopathy (14%) and bleeding manifestation (10%).

In present study we also observed that it was observed that mean Hb% was 9.67±2.14gm/dl in group 1 and 9.37±2.07 gm/dl in group 2. Mean TC was found 6.8±3.24 x109/L in group 1 and 8.1±3.38 x109/L in group 2. Mean serum sodium was 133.36±5.25 mmol/L in group 1 and 131.0±4.8 mmol/L in group 2. Mean AST was 116.72±215.4 U/L in group 1 and 128.84±255.07 mmol/L in group 2. Mean ALT was 82.32±202.4 U/L and 120.5±281.93 U/L in group 1 and group 2 respectively. Mean serum albumin was 2.4±0.6 g/dl in group 1 and 2.2±0.54 g/dl in group 2, which were statistically not significant (p<0.05) between the groups. Similarly Erythrocyte Sedimentation Rate (ESR), random blood sugar (RBS), serum bilirubin, and serum ALP were not statistically significant (p>0.05) between the groups. But diastolic blood pressure (66.8±4.8 mm Hg vs 70.0±5.4 mm Hg, *p*=.031), serum creatinine (1.05±.32mg/dl vs 1.96±1.8mg/dl, *p*=.020), serum potassium (3.63±0.4mmol/l vs 3.96±0.73 mmol/l, *p*=.049), prothrombin time (16.01 ±4.5 sec vs 20.34±7.37 sec, *p*=.016), INR (1.34±0.38 vs 1.7±0.62, *p*=.018) and urinary microalbumin (12.7±20.75g/dl vs 50.32±40.95, *p*=.000) were found statistically significant (p<0.05) between the groups.

Table I: Baseline characteristics of study population

Baseline characteristics	Mean ±SD
Age (Years)	52.28±13.8
Sex	
Male	60
Female	40
Cause of cirrhosis	
Hepatitis B	66
Hepatitis C	8
Hb% (g/dl)	9.5±2.1
Platelet count (x109/L)	176.46±110.7
S. Creatinine (mg/dl)	1.45±1.34
S. Sodium (mmol/L)	132.18±5.1
S. Bilirubin (mg/dl)	4.45±5.3
AST (U/L)	122.78±233
Prothrombin time (Sec)	18.9±6.4
INR	1.5±.55
Serum albumin (g/dl)	2.3±0.6
CP score	9.34±1.2
MELD score	20.6±6.96
U. albumin	31.4±37.33
U. creatinine	81.5 ±78.0
UACR	41.85±43.96

In Table II CTP score of the patients, it was observed that majority patients 38 (38%) were in Child B in group 1 and 38 (38%) in Child C in group 2, the difference was statistically significant (p>0.05) between the groups.

Table-II: Distribution of the study patients by CTP score

CP score	Group I (%)	Group II (%)	*P value*
Child A	4	0	0.000s
Child B	38	12	0.000s
Child C	8	38	0.000s

Mean MELD score was 16.4±5.7 in group 1 and 24.8±5.45 in group 2. The difference was statistically significant (p<0.05) between the groups in figure :1.

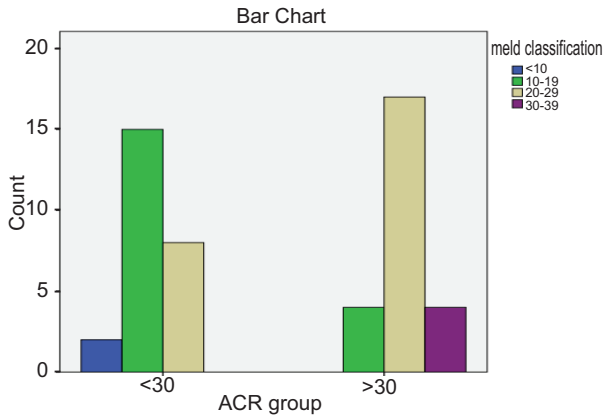

Figure 1: *1Distribution of the study patients by MELD score*

In Table: 3Univariant analysis of different parameters of this study show that diastolic blood pressure (66.8±4.8 mm Hg vs 70.0±5.4 mm Hg, *p* =.031), serum creatinine (1.05±.32mg/dl vs 1.96±1.8mg/dl, *p* =.020), serum potassium (3.63±0.4mmol/l vs 3.96±0.73 mmol/l, *p* =.049), prothrombin time (16.01 ±4.5 sec vs 20.34±7.37 sec, *p* =.016), INR (1.34±0.38 vs 1.7±0.62, *p* =.018) and urinary microalbumin (12.7±20.75g/dl vs 50.32±40.95, *p* =.000) were found statistically significant (p<0.05) between two groups.

Table III : Univariate analysis for predictor of UACR of the study patients by lab parameters

Lab parameters	Group 1 (UACR ≤30 mg/g) (n=50) Mean±SD	Group 2 (UACR >30 mg/g) (n=50) Mean±SD	P value
Hb% (g/dl)	9.67±2.14	9.37±2.07	0.622^{ns}
TC (x10^9/L)	6.78±3.24	8.1±6.75	0.164^{ns}
Platelet count (x10^9/L)	176.9±105.75	176.0±117.6	0.97^{ns}
S. Creatinine (mg/dl)	1.05±0.32	1.92±1.79	0.02^{s}
S. Sodium (mmol/L)	133.36±5.2	131.0±4.76	0.101^{ns}
S. Potassium (mmol/L)	3.63±0.39	3.97±0.73	0.049^{ns}
S. Bilirubin (mg/dl)	3.48±6.03	5.4±4.5	0.205^{ns}
AST (U/L)	116.72±215.4	128.84±255.07	0.857^{ns}
ALT (U/L)	82.32±202.4	120.52±281.933	0.585^{ns}
Prothrombin time (Sec)	16.01±4.48	20.34±7.37	0.016^{s}
INR	1.34±0.38	1.7±0.63	0.018^{s}
Serum albumin (g/dl)	2.4±0.6	2.2±0.55	0.221^{ns}
Serum ALP (U/L)	149.9±86.14	167.52±80.12	0.457ns
U. Albumin (g)	12.66±20.7	50.32±40.95	0.000 s
U. Creatinine (mg/L)	101.99±100.22	61.62±38.44	0.064 ns
UACR (mg/g)	11.36±6.54	68.35±37.68	0.000s

•Results are expressed as mean ± SD, P value reached from unpaired t-test , s= significant, ns=non significant

In Table IV multivariate analysis shows no one is statistically significant except urinary albumin with UACR >30 mg/g.

Table IV: Multivariate logistic regression analysis as predictor of UACR:

Lab parameters	Group I (UACR <30mg/g) Mean±SD	Group II (UACR <30 mg/g) Mean±SD	*P value*
Creatinine (mg/dl)	1.05±0.32	1.92±1.79	0.021s
Prothrombin time	16.01±4.48	20.34±7.37	0.14
INR	1.34 ±0.38	1.7±0.63	0.251
U. Albumin (mg/g)	12.66±20.74	50.31±40.95	0.001
CTP score	8.36±1.5	10.32±1.49	0.099
MELD Score	16.4±5.7	16.4±5.7	0.011
UACR	11.36 ±6.54	68.35±37.68	0.000

Pearson's Correlation test shows that there is a positive correlation between Child-Pugh (r, 0.598 with p, 0.000) and MELD score (r, 0.551 with p, 0.000) with UACR.

A Receiver-operator characteristic (ROC) curve of Child-Pugh C and UACR was constructed and it was shown that UACR e" 30mg/g had area under curve 0.794. It gave a cut off value of 32.43mg/g, with 78.3% sensitivity and 81.5% specificity for severity of decompensated liver diseases termed by Child-Pugh Class C.

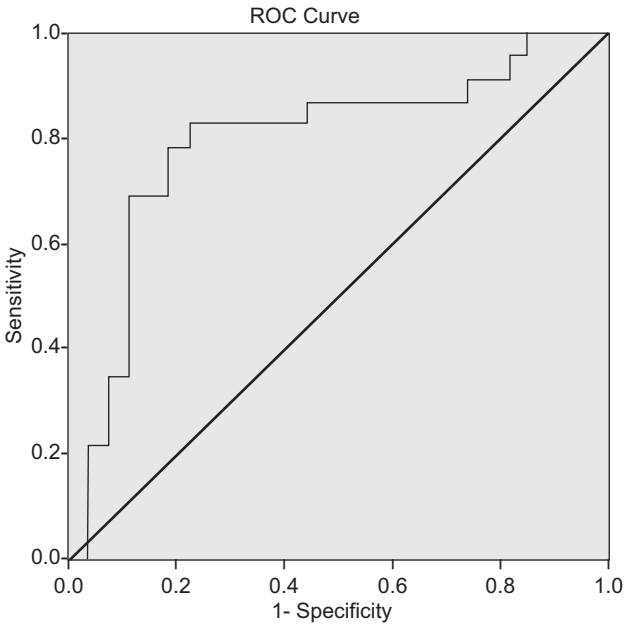

Figure 2: ROC curve between Child-Pugh C and UACR >30 mg/g of study patients

Discussion:

This cross-sectional observational study was carried out with the aim to establish the relationship between the microalbuminuria measured by urinary albumin-to-creatinine ratio for assessment of severity of liver disease measured by Child-Pugh class and MELD score in patients with decompensated cirrhosis of liver. Here patients in two groups were enrolled, Group 1 contains patients with UACR <30 mg/g and group 2 contains patients having UACR >30 mg/g. In this study it was observed that mean age was 52.28±13.79 years of the study population, where 55.04±12.99 years in group1 and 49.52±14.25 years in group 2. We also observed that 24.0% patients were male in group 1 and 36.0% were in group 2. 26.0% patients were female in group 1 and 14.0% in group 2.

The mean age difference and sex difference were not statistically significant (p>0.05) between the groups. In a study by Cholongitas et al.[12] also the similar result found, where out of 220 patients 159 (73%) were male and 61(28.00%) were female and the difference was not statistically significant (p>0.05). Our enrollment showed that 66% patients of hepatitis B, 8% patients of Hepatitis C and 26% patients of NBNC were included in both groups. Here etiological factor of cirrhosis of liver was not statistically significant (p>0.05) between the groups.

In this current study it was observed that mean haemoglobin (gm/dl) conc. was 9.67±2.14 in group 1 and 9.37±2.07 in group 2, and mean total WBC count was found 6.7±3.25 $x10^9$/L in group 1 and 8.1±6.75 $x10^9$/L in group 2. These difference were not statistically significant (p>0.05) between the groups. Mean systolic blood pressure was 109.7± 12.5 mm of Hg and mean diastolic blood pressure was 68.4± 5.3 mm of Hg. Serum sodium was 133.36±5.2 mmol/L in group 1 and 131.0±4.76 mmol/L in group 2 which were found statistically not significant (p<0.05) between the groups. Mean ALT was 82.32.7±202.4 U/L and 120.52±281.93 U/L in group 1 and group 2 respectively. Mean serum albumin was 2.4±0.6 g/dl in group 1 and 1.7±0.63 g/dl in group 2, which were found statistically not significant (p<0.05) between the groups. Similarly Platelet count, RBS, serum ALP, serum AST were not statistically significant (p>0.05) between the groups. In present study mean serum bilirubin in group 1 was 3.48±6.03 mg/dl and in group 2 was 5.4± 4.5 mg/dl and the difference was not statistically significant ($p = 0.205$) that was found significant in study done by Cholongitas et al. which showed that, UACR >30 mg/g had higher bilirubin than UACR <30mg/g group (3.4 vs. 1.4 mg/dl, $p = 0.028$). In present study several factors were significantly associated with high UACR in univariate analysis including serum creatinine, serum Potassium, Prothrombin time, INR, CTP class and MELD score. Age, sex, etiology, Hb%, TC, Platelet count, RBS, S. Sodium, S. Bilirubin, AST, Serum ALP were not significantly associated with raised UACR (p>0.05). In multivariate analysis, only urinary microalbumin was significantly associated with raised UACR (>30mg/g) with a p value >0.001.

Regarding CTP score of the patients, it was observed that majority patients were in Child C in groups 2, which was 38.0% and in group 1 majority

of patients were in Child B, 38.0%. The difference was statistically significant (p = 0.000; p>0.05) between the groups.

MELD score was calculated by using online websites from serum creatinine, serum bilirubin, INR and serum sodium conc. We observed that mean MELD score was 16.4±5.7 in group 1 and 24.4±6.8 in group 2. The difference was statistically significant (p<0.05) between the groups. Cholongitas et al. (2016) showed in their study that, mean MELD score was 13.4±6.0 in UACR<30 mg/g group and 18.2±2.0 in >30 mg/g group.

Here we also have correlate the data with CTP class, MELD score and UACR. Pearson correlation test show that there is a positive correlation Of UACR >30 gm/g with MELD scoring (.551) and CTP class C (.598).

A receiver-operator characteristic (ROC) curve was constructed by using UACR level in relation with CTP class C. UACR >30gm/g had area under curve 0.794 which gave a cut off value 32.43 mg/g ìg/L, with 78.3 % sensitivity and 81.5% specificity for prediction of severity of liver diseases in decompensated patients calculated by CTP score.

Conclusion:

We shown that microalbuminuria measured by UACR (> 32.4 gm/g), may be related with more severe liver disease that is measured by CTP score and MELD score in patients with decompensated cirrhosis and this microalbuminuria level positively correlate with CTP class and MELD scoring system.

Conflict of interest:

No conflicts of interest.

Ethical standard:

The study protocol conforms to the ethical guidelines BMU (former, BSMMU).

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