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Original Article

Spot Urine Sodium to Potassium Ratio as a Tool to Assess Severity and Mortality among Patients with Decompensated Cirrhosis having Ascites

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Abstract:

Background: *Decompensated cirrhosis of liver is considered as a systemic disease affecting the functions of several other organs. Renal function is an independent prognostic factor for patients with decompensated cirrhosis, but assessing renal function through glomerular filtration rate are not convenient, especially for routine use. Previous study found that spot urinary sodium to potassium ratio (UNa/K) was associated with renal dysfunction which influences the severity and outcome in decompensated cirrhosis of liver patients having ascites.*

Aims and objectives: *The present study was aimed to determine the relation of the ratio of sodium to potassium in randomly collected urine samples with severity of disease and mortality in decompensated cirrhosis having ascites.*

Materials and Methods: *This longitudinal study was conducted at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders, BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh, from July, 2019 to August, 202l. A total of 150 patients with a confirmed diagnosis of decompensated cirrhosis with ascites were enrolled in this study. A detailed history and thorough clinical examination were carried out in each patient, along with relevant investigations. Data collection was done through a structured questionnaire. Data were analyzed using the statistical software SPSS 23.*

Results: *Age of the patients was 59.0±12.91 (mean±SD) years, male predominance was observed (52%). The UNa/K ratio was 4.24±3.25 (mean±SD) with a range of 0.42 to 18.46. Diagnostic accuracy of UNa/K ratio in the detection of severity and mortality was estimated by the receiver operating characteristic (ROC) curve. The AUC of UNa/K ratio was 0.608 and 0.640 for severity and mortality respectively. Sensitivity, specificity, PPV and NPV at cut-off 2.55 were 50.0, 66.0, 42.4 and 72.5; at 2.65 were 54.0, 66.0, 44.3, and 74.2; at 2.87 were 58.0, 62.0, 43.3, and 74.7; at 3.21 were 58.0, 58.0, 40.8, and 73.4 respectively for severity score (MELD). Patients with UNa+/K+ less than 2.87 or equal, had a significantly higher MELD score category (p= 0.02). At 3 months follow-up, 24.7% mortality was observed. Sensitivity, specificity, PPV and NPV at cut-off 1.62 were 51.4, 85.8, 54.3 and 84.3; at 1.79 were 54.1, 79.7, 46.5 and 84.1; at 1.83 were 59.5, 77.0, 45.8 and 85.3; at 2.87 were 58.0, 62.0, 43.3, and 74.7 respectively for mortality. The UNa/K ratio was statistically low among the patients who didn't survive (p<.05).*

Conclusion: *This study revealed that decreased ratio of spot urinary sodium to potassium was associated with the severity and mortality among decompensated cirrhosis of liver patients with ascites.*

Key words: *Ascites, Decompensated Cirrhosis, Spot Urine Sodium to Potassium Ratio.*

Introduction:

Cirrhosis of liver is a major health problem and a significant source of morbidity and mortality. It represents the main indication for liver transplantation all over the world. In the United States, cirrhosis is the 12th leading cause of death overall and the fifth leading cause of death for patients aged 45 to 54.[1] The prevalence of cirrhosis was approximately 0.27%, corresponding to 633,323 adults.[2] Globally the common primary etiologies for liver cirrhosis were chronic hepatitis B, chronic hepatitis C, alcoholic liver disease and non-alcoholic fatty liver disease. There is no major difference compared with developing regions. Liver disease causes significant burden to the economy and healthcare delivery system of Bangladesh. It is the 3rd leading cause of death of patients admitted in tertiary care hospitals. Chronic liver disease (CLD) represents the most common form (37-69%) of liver related morbidity.[3] Hepatitis B is the predominant cause of all form of liver disease and cirrhosis[4,5]as Bangladesh falls in the intermediate prevalence zone of hepatitis B virus (HBV) with an estimated prevalence of 5.4% in the general population.[6]

All chronic liver diseases are characterized by their capacity to progress into cirrhosis. The fibrogenic process goes through various phases where excessive collagen deposition results in qualitative and quantitative changes of the extracellular matrix. Cirrhosis is the structural subversion of the liver with the formation of regenerative nodules, and it represents late-stage liver disease. Advanced cirrhosis (decompensated cirrhosis) is a condition with limited treatment options.

Patients with decompensated cirrhosis have a poor prognosis

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in comparison to patients with compensated cirrhosis. Decompensated cirrhosis means cirrhosis complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy or bleeding varices.

Once cirrhosis transitions from the compensated to the decompensated stage, it is associated with short-term survival (3–5 years) and evaluation for liver transplant is recommended in the absence of contraindications.[7]

Decompensated cirrhosis (DC) is considered a systemic disease affecting the function of several extra-hepatic organs as a result of bacterial translocation from the gut and the development of hyperdynamic circulation. Thus, patients with DC have decreased effective arterial blood volume leading to renal hypoperfusion, deterioration of glomerular filtration rate (GFR) and simultaneous compensatory activation of the endogenous sympathetic system and renal vasoconstrictor systems, such as renin-angiotensin-aldosterone system (RAAS). In fact, in patients with DC, greater activation of RAAS correlates with the severity of renal dysfunction. [8,9]

Liver cirrhosis is strongly linked with high mortality rate. Therefore, using the scoring system to define mortality and prognosis is inevitable. Child-Turcotte-Pugh (CTP) score was the first of its kind in stratifying the seriousness of end-stage liver disease & has been used for several years to predict the prognosis of cirrhosis patients. The scoring system consists of five indicators, including albumin, international-normalized ratio (INR), bilirubin, ascites, and hepatic encephalopathy.[10] Many studies have proved the capability of CTP score in predicting prognosis among the diverse cirrhotic population, compensated and decompensated patients, and it does not need computational analysis. Therefore, bedside interpretation can be carried out.[11-13] The Model for End-Stage Liver Disease (MELD) is a scoring system initially developed as a model in predicting poor survival in patients after transjugular intrahepatic portosystemic shunt (TIPS).[14] A modification of this score was developed to predict mortality in patients with cirrhosis of different etiologies and severities of liver disease. It has been shown by a number of studies to correlate with short-term mortality risk and also to evaluate priorities in transplantation candidates.[15,16]

Ascites is the most common complication of decompensated cirrhosis and urinary sodium excretion is a useful tool to evaluate and manage this group of patients.[17]

In normal population, spot urinary sodium/potassium ratio is 2.85±2.15 (mean±SD).[18] Patients with decompensated cirrhosis have reduced 24-hour urinary sodium excretion (24UNa). Refractory ascites with or without HRS are characterized by no weight loss with 24UNa less than 78 mmol/d despite high-dose diuretic treatment.[17] Random urine sodium to potassium ratio (UNa/K) is correlated significantly with a 24UNa.[19]

Random urine sodium to potassium ratio less than 1 has the best sensitivity and specificity for the presence of 24UNa less than 78 mmol/d irrespective of characteristics of diuretic treatment (type, dose, and duration), or the presence of refractory ascites. Random UNa/K can replace 24-hour collection for sodium excretion in daily clinical practice.[19]

However, the association between a random urine Na/K ratio and its prognostic impact on severity and mortality in patients with decompensated cirrhosis have not been investigated.

In this study, we aimed to evaluate prospectively the association between a random urine Na/K ratio and its predictive role on severity and mortality in patients with decompensated cirrhosis having ascites.

MATERIALS AND METHODS

This was an observational study carried out at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh from July, 2019 to August, 2021. Purposive type of non-probability sampling technique were applied to recruit patients who presented with decompensated cirrhosis with ascites. Sample size was calculated at 5% level of significance and confidence interval at 95% level. Inclusion criteria were all patients of decompensated cirrhosis of liver with ascites diagnosed on the basis of clinical, biochemical, radiological and endoscopic procedures with age ≥18 years. Exclusion criteria were primary or secondary malignancies of liver, intrinsic renal disease such as the presence of proteinuria >1 gm/day or active urinary sediment, end stage renal disease (ESRD) and patients on dialysis, received albumin during last 2 weeks, receiving nephrotoxic drugs, patients of shock and haemodynamically unstable.

In this longitudinal study a total of 150 patients were enrolled. Diagnosis of decompensated cirrhosis was made based on clinical, laboratory, and by ultrasonography. History of each patient was taken and recorded. A questionnaire was filled up by the investigator, which contained information regarding past history of CLD, alcohol intake, viral hepatitis, hepatic encephalopathy, ascites, variceal bleeding and jaundice, drug

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history (diuretics) and other co-morbidities. Diuretics should be on stable dosage at least 10 days before admission. A physical examination was done systematically. All patients were tested for complete blood count, liver function tests, renal function tests. Urinary sodium and potassium estimation were done using ARCHITECT Sample Diluent 2P32 reagent by Ion-selective electrode diluted (Indirect) methods, ARCHITECT c 8000, Abbott, USA.

The UNa/K ratio was calculated based on the values of sodium and potassium in ''spot'' urine sample. Patients' mortality were recorded by follow-up (by hospital records or over phone) at 3 Months.

Collected data were recorded in separate case record forms and checked for errors. After collection of information data were checked, verified for consistency & edited for finalized result. After editing & coding, the coded data were entered into the computer by using the SPSS (Statistical Package for Social Sciences) version 23 software. Data cleaning validation & analysis was performed using the SPSS software. Receiver-operating characteristic (ROC) curves were made to determine the cut-off value of random urinary sodium to potassium ratio. Diagnostic accuracy was measured by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy. Statistical association was determined by using an appropriate statistical tool like independent t-test for continuous variables and chi-square test for categorical variables. The result was presented in tables in mean, standard deviation (SD), frequency, and percentages. Statistical significance was set at 0.05 level and confidence interval at 95% level.Ethical clearance was sought from the ethical review committee.

RESULTS

Between December 2019 and August 2021, a total of 166 patients were screened, of whom 10 patients were found to have CKD, 6 patients had a diagnosis of HCC. So 150 patients were evaluated for inclusion as they presented as decompensated cirrhosis of liver with ascites.

Majority of the patients were in 61-70 years of age (34.7%) followed by 51-60 years (27.3%), 41-50 years (17.3%) and >70 years (12.0%). Mean age was 59.0±12.91 years ranging from 23 to 90 years of age. Male predominance (52.0%) was seen and male to female ratio was 1.08:1.

Table I: Baseline characteristics of the study population (N=150)

Characteristics		n (%)
Age (Mean ± SD)	59 ± 12.91	
Age group	18-30 years	6 (4)
	31-40 years	7 (4.7)
	40-50 years	26 (17.3)
	51-60 years	41 (27.3)
	61-70 years	52 (34.7)
	>70 years	18 (12)
Sex	Male	78 (52)
	Female	72 (48)
Aetiology of cirrhosis		
Hepatitis B		60 (40)
Hepatitis C		12 (8)
Non B Non C		78 (52)
Clinical features		
Ascites		150 (100)
Edema		101 (67.3)
Altered mental status		41 (27.3)
GI bleeding		26 (17.3)
Jaundice		17 (11.3)
Medication		
Furosemide		110 (73.3)
Spironolactone		110 (73.3)

Most patients of decompensated cirrhosis had Non B Non C as the main underlying cause 52%. HBV accounted for 40% and HCV 8% of cirrhosis. All the patients had ascites followed by pedal edema 67.3%, altered mental status 27.3%, GI bleeding (hematemesis/ melena) 17.3% and jaundice 11.3%. Majority of the patients took diuretics; total 110(73.3%) had furosemide and spironolactone combination. Mean values of major investigation profile are given below in the following table.

Table II: Laboratory data of decompensated cirrhosis patients in the study (N=150)

Laboratory data	Mean±SD	Range
Serum bilirubin (mg/dL)	2.46±2.23	0.40-13.9
Serum albumin (gm/L)	26.98±5.03	14.90-41.00
Serum creatinine (mg/dL)	1.17±0.58	0.60-3.90
Serum Na^+ (mmol/L)	132.79±5.63	118.0-144.0
Serum K^+ (mmol/L)	4.10±0.67	2.20-6.60
Serum Cl^- (mmol/L)	99.21±14.44	24.0-144.0
Serum HCO_3^- (mmol/L)	20.89±4.23	10.0-34.0
Spot urinary Na^+(mmol/L)	71.11±37.80	19.0-215.0
Spot urinary K^+(mmol/L)	21.67±11.40	6.50-69.10
Urinary Na^+/K^+ ratio	4.24±3.25	0.42-18.46
CTP score	9.97±1.96	7-14
MELD score	14.03±5.34	6-28
MELD-Na score	16.31±7.06	6-34

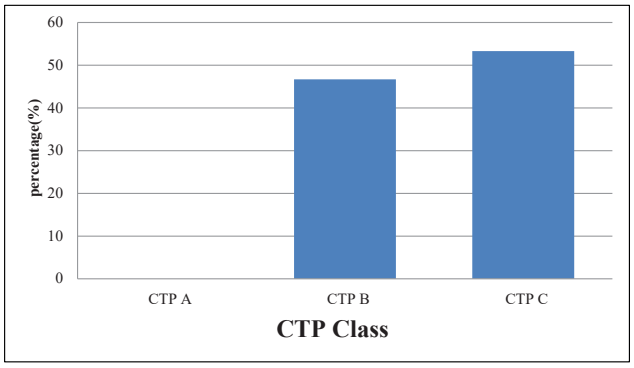

Figure 1: Child-Turcotte-Pugh class of the study population (N=150)

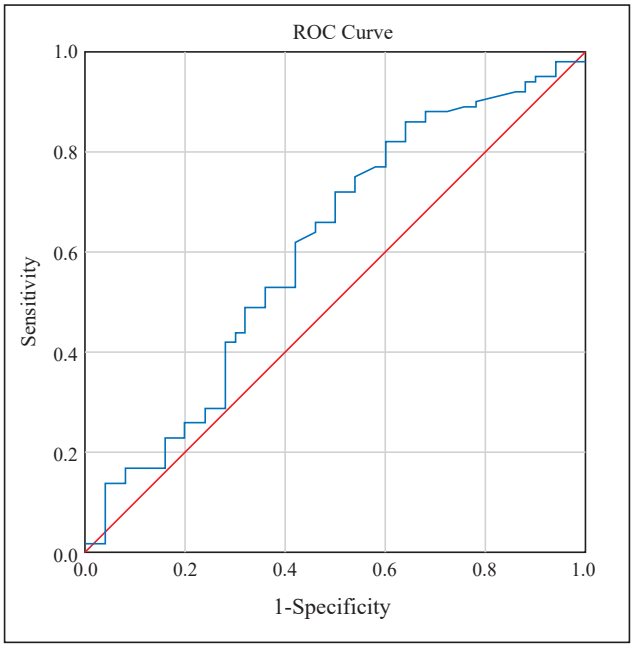

Figure 2: ROC curve of urinary Na^+-K^+ ratio for severity score (MELD)

Table III: Area under the curve of urinary Na^+-K^+ ratio for severity score (MELD)

AUC	Std. Error	*P* value	95% CI	
			Lower Bound	Upper Bound
0.608	0.05	0.031	0.51	0.707

AUC: Area under the curve; CI: Confidence interval

Table IV: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at different cut off values of urinary Na^+-K^+ ratio (N=150)

Diagnostic accuracy	Cut off value 2.55	Cut off value 2.65	Cut off value 2.87	Cut off value 3.21
Sensitivity (%)	50.0	54.0	58.0	58.0
Specificity (%)	66.0	66.0	62.0	58.0
PPV (%)	42.4	44.3	43.3	40.8
NPV (%)	72.5	74.2	74.7	73.4
Accuracy (%)	60.6	62.0	60.7	58.0

According to the Child-Turcotte-Pugh classification, the proportions of patients diagnosed with Child-Pugh B, and C were 70(46.7%), and 80(53.3%) respectively (fig-1). Spot urinary Na^+-K^+ ratio at a cutoff value of 2.87 for MELD category showed sensitivity 58.0%, specificity 62.0%, PPV 43.3% and NPV 74.7% (Table IV). Significant difference was found between urinary Na+/K+ ratio category and MELD score category at a cut off value of 2.87 (p=0.020) (Table V). Total 113 (75.3%) subjects survived while 37 (24.7%) died at 3 months follow up.

Table V: Association between MELD (Model for End Stage Liver Disease) score category and spot urinary Na^+/K^+ ratio (N=150)

	MELD score category		
Urinary Na^+/K^+ ratio	>15	≤15	*P* value*
≤2.87	29 (58.0%)	38 (38.0%)	0.020
>2.87	21 (42.0%)	62 (62.0%)	
Total	50 (33.3%)	100 (66.7%)	

MELD: Model for End Stage Liver Disease

**p* value measured by Chi-square test

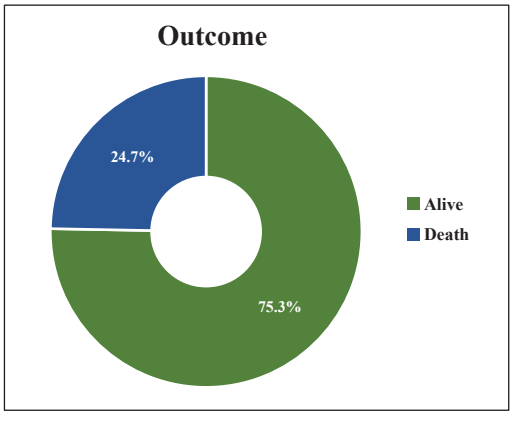

Figure 3: Outcome of the study population after 3 months (N=150).

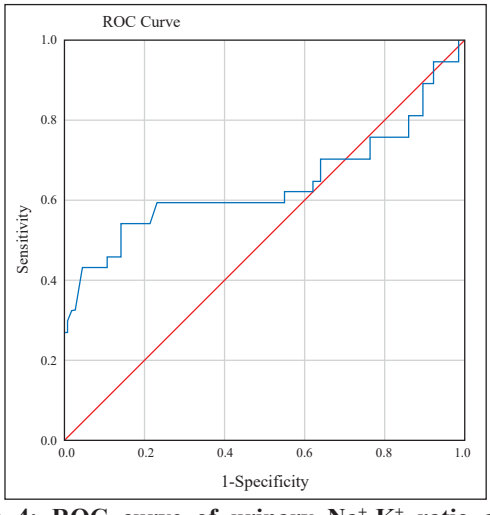

Figure 4: ROC curve of urinary Na^+-K^+ ratio among survivability/mortality

Table VI: Area under the curve of urinary Na^+-K^+ ratio for mortality

AUC	Std. Error	*P* value	95% CI	
			Lower Bound	Upper Bound
0.640	0.065	0.010	0.513	0.768

AUC: Area under the curve; CI: Confidence interval

Table VII: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at different cut off values of urinary Na+-K+ ratio (N=150)

Diagnostic accuracy	Cut off value 1.62	Cut off value 1.79	Cut off value 1.83	Cut off value 2.87
Sensitivity (%)	51.4	54.1	59.5	59.5
Specificity (%)	85.8	79.7	77.0	60.2
PPV (%)	54.3	46.5	45.8	32.8
NPV (%)	84.3	84.1	85.3	81.9
Accuracy (%)	77.3	73.3	72.7	60

Spot urinary Na^+-K^+ ratio at a cutoff value of 1.83 for mortality outcome showed sensitivity 59.5%, specificity 77.0%, PPV 45.8% and NPV 85.3% (table VII). The urinary Na^+/K^+ ratio was significantly different between the patients who were alive (n=113) and the patients who died (n=37) within 3 months ($p<0.001$) (table VIII).

Table VIII: Association of urinary Na^+/K^+ ratio with 3 months outcome in the study population at a cut off value of 1.83 (N=150)

Urinary Na^+/K^+ ratio	Alive (n=113)	Death (n=37)	*P* value
≤1.83	26 (23.0%)	22 (59.5%)	<0.001*
>1.83	87 (77.0%)	15 (40.5%)	

**p* value measured by Chi-square test

DISCUSSION

Cirrhosis, a final pathway for a wide variety of chronic liver diseases, is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules. Ascites is the most common complication of decompensated cirrhosis and urinary sodium excretion is a useful tool to evaluate and manage this group of patients.[20]It is defined as the pathological accumulation of fluid in the peritoneal cavity. There are three theories to explain the development of ascites in individuals with liver cirrhosis: underfill, overflow and vasodilatation.[21]The modern view suggests that the three states are in greater or lesser extent, present in the same patient with cirrhosis. This study was aimed to evaluate the correlation between ratio of sodium to potassium in random urine samples with CTP (Child-Turcotte-Pugh) score, MELD (Model for End Stage Liver Disease) and MELD-Na.

In this study, 150 patients having decompensated liver cirrhosis with ascites were taken. Most of the patients were between the age of 61-70 (34.7%) years followed by 27.3% in 51-60 years and 17.3% in 41-50 years. Overall 91.3% patients with liver cirrhosis aged >40 years. Mean age was 59.0±12.91 years. In a previous finding in Bangladesh, the incidence of decompensated cirrhosis of liver was found 77.3% above 40 years.[22] In India, however 37% were patients of ≤35 years.[23] Male predominance was found in our study (52.0%) with male to female ratio of 1.08:1. Other studies also had male predominance with mean ages of the cirrhotic patients being 57.5, 47 and 58.8 years respectively.[24-26]

All the patients had ascites followed by pedal edema 67.3%, altered mental status 27.3%, GI bleeding (hematemesis/ melena) 17.3% and jaundice 11.3%. Maskey R et al found 100% young and 84.4% adult cirrhotic patients had ascites followed by jaundice (93.3% and 84.4%).[27] AU Kakehasi did a study of clinical symptoms of patients with liver cirrhosis and found that there were various symptoms in decompensated state, but not in compensated state. Most symptoms were due to liver cell dysfunction and portal hypertension. There was no difference in clinical symptoms between aged patients and young patients.[28]

In the study, mean values of serum bilirubin and creatinine was 2.46±2.23 mg/dL and 1.17±0.58 mg/dL. Mean serum Na^+ (132.79±5.63 mmol/L) was lower than normal values indicating hyponatraemia in such patients. Renal dysfunction and edema or water retention in different body space especially in the abdomen is common in liver failure. This may be the cause of such biochemical changes. In order to maintain hemodynamic circulation, neurohormonal vasoconstriction system is activated, which includes renin-angiotensin-aldosterone system, the sympathetic nervous system and non-osmotic hypersecretion of antidiuretic hormone (ADH). Thus, sodium retention occurs leading to ascites and edema, free water retention, and renal vasoconstriction. The reduced renal blood flow causes fall in GFR and ultimately kidney failure.[29]

CTP, MELD and MELD-Na scores are widely used scoring systems in CLD patients, not only to assess disease severity but also to estimate survival. MELD and MELD-Na score are also used to prioritize patients on liver transplant waiting list. Mean CTP score in our study population was 9.97±1.96 while mean MELD score was 14.03±5.34.Mean MELD-Na was also 16.31±7.06. About 53.3% were in child-Pugh B category and 46.7% in C category. Previous study found mean CTP and MELD score was 9±4 and 13±7.[30]

In current study, mean spot urinary Na^+/K^+ ratio was 4.56±3.25. ROC curve analysis of UNa^+/K^+ ratio for MELD score and mortality showed significance. The AUC of UNa/K ratio was 0.608 and 0.640 for severity and mortality respectively. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) in different cut off values of UNa^+/K^+ ratio were measured. At a cutoff value 2.55 were 50.0, 66.0, 42.4 and 72.5; at 2.65 were 54.0, 66.0, 44.3, and 74.2; at 2.87 were 58.0, 62.0, 43.3, and 74.7; at 3.21 were 58.0, 58.0, 40.8, and 73.4 respectively for severity score (MELD). Diagnostic accuracy of UNa^+/K^+ ratio value at 2.87 was observed more. Similarly, to predict mortality, a cutoff

value off value 1.62 were 51.4, 85.8, 54.3 and 84.3; at 1.79 were 54.1, 79.7, 46.5 and 84.1; at 1.83 were 59.5, 77.0, 45.8 and 85.3; at 2.87 were 58.0, 62.0, 43.3, and 74.7 respectively. Diagnostic accuracy ofUNa^+/K^+ ratio value at 1.83 was observed more. Previous study found that, patients with a UNa^+/K^+ ratio of 1 or higher, compared with those with a UNa^+/K^+ less than 1.0, had significantly better survival.[30]

In the study, the patients with UNa^+/K^+ less than 2.87 or equal, compared with those with UNa^+/K^+ greater than 2.87 had a significantly higher MELD score category (p= 0.02). Cholongitas et al. also found, patients with a UNa^+/K^+ ratio of 1 or higher, compared with those with a UNa^+/K^+ less than 1.0, had similar result.[30] Similar to [21 and 31] we also found inverse correlation between UNa^+/K^+ ratio and MELD score.[21,31] Splanchnic arterial vasodilatation and activation of vasoconstrictive systems in advanced cirrhosis, such as significantly worse ascites and lower systolic arterial pressure and serum sodium levels. Thus, random UNa^+/K^+ less than or equal 2.87 seems to reflect the severity of liver dysfunction in patients with decompensated cirrhosis.

Patients with UNa^+/K^+ ratio ≤1.83 had significantly more mortality (59.5%) after 3 months (p<0.001). Previous study also found similarly that, patients with a UNa^+/K^+ ratio of 1 or higher, compared with those with a UNa^+/K^+ less than 1.0, had significantly better survival.[30]

Renal dysfunction is usually assessed by serum creatinine level and it is a key component in MELD score.[32] Optimal management of renal dysfunction in cirrhosis is extremely important as it frequently complicates the clinical course of advanced liver disease and is invariably associated with poor clinical outcomes.[33] Cholongitas et al. reported renal dysfunction and high mortality in decompensated cirrhotic patients with spot UNa^+/K^+ ratio less than 1.[30]

CONCLUSION

In this study, the decreased ratio of urinary sodium to potassium was associated with severe liver disease and mortality among patients with decompensated cirrhosis having ascites. However, further extensive study is recommended involving a larger and generalized study population.

Conflicts of interest: Nothing to declare

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