The serum sodium level and the severity of liver cirrhosis complications: A cross sectional study in BSMMU, Dhaka, Bangladesh

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Abstract

Patients with advanced cirrhosis of liver present with clinical manifestations such as intractable ascites, severe hyponatremia, and reduced arterial blood pressure. The purpose of this study was to observe the relationship between serum sodium levels and the severity of complications associated with liver cirrhosis. From April 2019 to September 2020, this cross-sectional study was done at the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Total 96 patients with cirrhosis of liver from both sexes in the study were enrolled by using sequential sampling. Patients were divided into Child-pugh classes, and the severity of complications were evaluated. The serum sodium level was tested in all of the patients. The relationships between it and various stages and complications of cirrhosis were statistically investigated. Serum sodium level was decreased significantly from child pugh class A to B to C (p value <0.0001). Patients with severe ascites had lower serum sodium level than mild and moderate ascites (p=0.00). In complications of ascites like refractory ascites, spontaneous bacterial peritonitis and hepatorenal syndrome, mean sodium level was low (<130 mmol/L) but there was no significant difference among them(p=.091). Level of serum sodium lowered significantly in hepatic encephalopathy of grade III & IV than grade I & II and those with no hepatic encephalopathy (p=0.00). But there was no significant difference of serum sodium level among different grades of esophageal varices (P=0.336). Low serum sodium levels were shown to be linked with greater liver dysfunction and the severity of liver cirrhosis-related complications.

Introduction

Cirrhosis is a systemic disease that causes hepatic fibrosis and abnormal nodule development in liver. The natural course of cirrhosis, which is defined by an asymptomatic compensated period followed by a decompensated phase highlighted by overt clinical manifestations like ascites, gastrointestinal bleeding, encephalopathy and jaundice. Renin and aldosterone levels are elevated in cirrhosis due to increased blood pressure in the biliary ducts vessels and impaired blood vessel responsiveness to vasoactive medications, resulting in intractable ascites, severe hyponatremia, and low arterial pressure. About 57% of patients in the hospital and 40% outpatients with chronic liver illness have hyponatremia, which is a prevalent abnormality. An increase in extracellular fluid volume causes hypervolemic (dilutional) hyponatremia in 90% of patients with cirrhosis, whereas hypovolemic hyponatremia (usually due to overdiuresis) occurs in 10% of patients. Baroreceptor-mediated non-osmotic activation of vasopressin release is thought to be caused by a decrease in effective circulation volume in patients with cirrhosis. Low sodium supply to the distal tubule because of lower glomerular filtration rate and/or increased proximal tubule sodium reabsorption are two further possible contributors to hyponatremia in cirrhosis. More patients with 130 mmol/L of blood sodium had more refractory ascites, less weight change response, a greater need for large-volume paracentesis, and shorter intervals between paracentesis, Angeli et al. found. In individuals with a blood sodium concentration between 131 and 135 mmol/L, there are symptoms of poor ascites response. Hyponatremia caused by a decreased clearance of solute-free water was a significant predictive factor in patients with
liver cirrhosis when hyponatremia was included in the MELD score, according to recent research.\textsuperscript{10,14} Patients with hyponatremia have a worse prognosis than those who do not suffer from the condition.\textsuperscript{13,15} Serum sodium levels and severity of sequelae in cirrhotic patients in Bangladesh have not been studied extensively. So, the study’s goal was to investigate the association of serum sodium levels and the severity of complications of liver cirrhosis.

### Methods

In the period of April 2019 to September 2020, this cross-sectional research was carried out in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. By using consecutive sampling, a total of 96 patients of liver cirrhosis ≥18 years of both sexes were included in the research. Told permission was gained from all participants or their care providers after they were informed about the aims and purpose of the research in a clear and understandable manner in their native language. The protocol for the study was approved by the Institutional Review Board of BSMMU. Participants in the research were those who had been diagnosed with cirrhosis by clinical, biochemical and ultrasonographic results, as well as endoscopic findings of esophageal varices and if inconclusive in those investigations cirrhotic alterations on liver biopsy. Patients with intrinsic renal disease (characterized by urinary protein > 500 mg/day, urinary RBC >50/HPF, parenchymal renal disease on ultrasound & obstructive pathology in urinary tract), hepatocellular carcinoma, or intra-abdominal malignancy and those taking diuretics for last 3 days with the exception of those with refractory ascites were excluded from the study. Other than Hepatitis B and Hepatitis C, were classed as ‘others’ as the etiology of cirrhosis. Patients were divided into three groups based on their Child-Pugh scores: class A, class B, and class C. The complications of cirrhosis were labeled as grade 1, grade 2, and grade 3 ascites, refractory ascites, hepatorenal syndrome, and spontaneous bacterial peritonitis. Furthermore, patients with hepatic encephalopathy (HE) were categorized into No hepatic encephalopathy, moderate (grades I and II), and severe (grades III and IV) hepatic encephalopathy according to the West Haven criteria. Upper endoscopy was performed on all research participants in order to determine the existence of esophageal varices and the severity of the varices (I, II, III, and IV). Patients were recommended to follow a “no added salt” diet, which corresponded to a sodium consumption of around 88 mmol/day. Patient’s blood samples were sent to the BSMMU department of biochemistry and molecular biology for the purpose of analyzing serum sodium levels. The normal sodium levels in the blood are between 135 and 145 mmol/L. Hyponatremia in cirrhosis is arbitrarily defined as a fall in blood sodium concentration below 130 mmol/L.\textsuperscript{6} However, declines below 135 mmol/L should also be considered hyponatremia in general patient populations according to hyponatremia treatment guideline 2007.\textsuperscript{15} This study was conducted using the statistical program for social science (SPSS) version 23.0 for data input and analysis. Results of serum sodium level were expressed as mean ± SD. Associations of serum sodium with complications of cirrhosis was tested by using ANOVA test between groups. A p-value of less than 0.05 was considered statistically significant.

### Results

According to the prevalence of child-pugh score of liver cirrhosis, the majority studied patients (40%) in class-A were in the age group (e”61) years, then maximum (34.38%) in class-B were in the same age group and (33.90%) found in class-C were in the age group (51-60). Mean age in class-A was 53 ±11.66 years, in class-B was 52.81±11.11 years and 52.80 ±10.59 years in class-C respectively. In all classes males were predominant, 60% in class-A, 78.13% in class-B and 69.49% in class-C. The main etiology was Hepatitis B found 80.00% in class-A, 65.63% in class-B and 54.24% in class-C. Hepatitis C was found 9.38% in class-B, 62.71% in class-C and no patient was found in class-A. Other etiological factors were found in 20.00% in class-A, 18.75% in class-B and 23.73% in class-C. (Table-I)

| Variables | Class-A | Class-B | Class-C | Total |
|-----------|---------|---------|---------|-------|
| Number    | 6(6.25%)| 32(33.33%)| 58(60.42%)| 96(100%) |
| Age       | 18-40   | 1(20.00%)| 6(18.75%)| 10(16.95%)| 17(17.71%) |
|           | 41-50   | 1(20.00%)| 6(18.75%)| 11(18.64%)| 18(18.75%) |
|           | 51-60   | 1(20.00%)| 9(28.13%)| 20(33.90%)| 30(31.25%) |
|           | ≥61     | 2(40.00%)| 11(34.38%)| 18(30.51%)| 31(32.29%) |
| Mean ± SD | 53±11.66| 52.81±11.11| 52.80±10.59| 52.81±10.82 |
| Gender    | Male    | 3(60.00%)| 25(78.13%)| 41(69.49%)| 69(71.88%) |
|           | Female  | 2(40.00%)| 7(21.88%)| 18(30.51%)| 27(28.13%) |
| Aetiology | Hepatitis B | 4(80.00%)| 21(65.63%)| 32(54.24%)| 57(59.38%) |
|           | Hepatitis C | 0(0.00%)| 3(9.38%)| 37(62.71%)| 40(41.67%) |
|           | Others  | 1(20.00%)| 6(18.75%)| 6(10.36%)| 13(13.51%) |

Table-I Distribution of Baseline Characteristics based on the Child-Pugh score (N=96).
In child pugh class A, mean serum sodium level was 138±4.53 mmol/L and in class B, 131±4.85 mmol/L, in class C, 125.98 ±5.76 mmol/L respectively which was statistically significant (P<0.0001) (Table-II).

The severity of ascites was graded as mild, moderate & severe ascites which was observed in 9(9.4%), 19(19.8%), 20(20.8) of study subjects. The mean serum sodium level was 132±1.73, 127.63±1.80, 122±1.47 respectively (p=0.000) which indicated that, as the severity of ascites increased serum sodium level significantly decreased. Complications of ascites were refractory ascites, hepatorenal syndrome and spontaneous bacterial peritonitis found in 16(16.7%), 13(13.5%) and 19(19.8%) of patients and the mean serum sodium level was 122.31±7.43, 125.85±4.32, 126.37±4.09 (mmol/L) respectively (p=0.091) which indicated that serum sodium level was low in these complications but there was no significant difference among them. (Table-III)

No hepatic encephalopathy (HE), Grade I & II, Grade III & IV HE was observed in 63(66.62%), 21(21.67%) and 12(12.5%) and the mean serum sodium level was 138±4.31, 131±4.29 and 126.03±6.46 (mmol/L) respectively (p=0.000). As the grading of hepatic encephalopathy increased, serum sodium level decreased significantly. No esophageal varices, Grade I & II, Grade III & IV was observed in 40(41.66%), 26(27.08%) and 30(31.25%) and the mean serum sodium level was 134.64±4.61, 133.46±4.17 and 133.26±3.67 (mmol/L) respectively (P=0.336). No statistically significant difference of serum sodium level was found among patients with different grades of esophageal varices. (Table-III)

| Variable(n) | Serum sodium (mmol/L) | P value |
|-------------|------------------------|---------|
| Child-Pugh class | Class A 138±4.53 | <0.0001 |
|              | Class B 131±4.85 |         |
|              | Class C 125.98±5.76 |         |

ANOVA test was done to compare between groups
Discussion

In our study, we enrolled a total of 96 liver cirrhosis patients. The enrolled patients were mainly classified in child pugh classes\textsuperscript{16} to observe the severity of cirrhosis. In our study, the mean age of the study people was 52.81±10.82. In the study of Angeli P\textsuperscript{2}, Kim et al\textsuperscript{4}, Gupta GK et al\textsuperscript{17}, Mahmoud HS\textsuperscript{18} illustrated almost the same mean age. In their study, they observed the mean age of the patients was 58.6±11.3, 55.8±11.6, 43.58±13.09 and 49.89±11.41 respectively. In all classes, the majority studied patients were male where 60% in class-A, 78.13% in class-B and 69.49% in class-C. Majority of the patients had Hepatitis B in all classes followed by hepatitis C and others. This finding was consistent with the study done by Al Mamun et al\textsuperscript{19}.

In our study, we observed, the mean serum sodium in class A was 138 mmol/L, in class B was 131 mmol/L and in class C was 125.98 mmol/L which was decreasing from child class A to B to C and there was significant difference among them (P<0.0001). Decrease in serum sodium level with more increase in the child pugh score also observed in the study of Mahmoud HS\textsuperscript{18} (p=0.02). Al Mamun et al\textsuperscript{20} conducted a study and found neither association nor correlation of hyponatremia with Child Pugh score. This finding was probably due to small sample size.

In this present study, we found a significant lower level of serum sodium with more increases in ascites, as mild, moderate & severe ascites (p=0.000). Similar findings also observed in the study of Gupta GK et al\textsuperscript{17} (P=0.02). In our study, we observed the mean serum sodium level was low (<130mmol/L) in the patients with refractory ascites, hepatorenal syndrome and spontaneous bacterial peritonitis but no significant difference among them (P=0.091). In the study of Gupta GK et al\textsuperscript{17} found a significant relationship of serum sodium with spontaneous bacterial peritonitis (P=0.04), hepatorenal syndrome (P=0.001) and refractory ascites (P=0.02) which was consistent to our findings but in their study they did not explore the relationship of serum sodium among groups.

In this current study, we found lower level of serum sodium with more progression of hepatic encephalopathy significantly (p=0.000). The same result reported by Kim et al\textsuperscript{4}, where they found the more the increase in the HE grades the more the decrease in serum sodium level (p=0.003). Hyponatremia has been associated with a reduction in brain organic osmolytes, particularly myoinositol, suggesting that it may play a role in the pathogenesis of hepatic encephalopathy.\textsuperscript{2,12} In Esophageal varices, we did not find any significant relationship of mean serum sodium level with different grades of varices (p=0.336). Angeli et al\textsuperscript{2} (p=0.223); Mahmoud HS\textsuperscript{18} (p=0.05) reported similar findings. The formation of esophageal varices is dependent on histological alterations rather than an excess of body water, hence there was no correlation between their existence and severity in the serum sodium concentrations.\textsuperscript{4}

The findings of this research were inadequate to show a definite link between low serum sodium levels and cirrhosis problems, which is a drawback. Cirrhosis consequences such as hepatic hydrothorax, infection, and gastric varices were not included in the research. Nonetheless, the results may not be representative of the whole population since the research was done in a hospital.

Conclusion

Low level of serum sodium level may indicate the existence of severe liver disease and complications in liver cirrhosis. Further large-scale meticulous studies may be needed to establish the causal relationship between severity of liver diseases and serum sodium.

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