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A Study on Correlation of Serum Sodium with the Complications of Chronic Liver Disease

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Abstract **Original Research Article**

Introduction*:** Cirrhosis is mostly initiated by alcoholism and hepatitis C, however certainly has many other possible reasons, such as Wilson's disease, hemochromatosis, autoimmune hepatitis, and non-alcoholic fatty disease. Hyponatremia occurs when serum sodium concentration in the blood is less than 135mmol/L, with severe hyponatremia being below 120 mmol/L. In the current study, lower serum sodium levels were associated with improved complications of decompensated chronic liver and mortality leading to the integration of sodium. ***Aim of the Study: The study aimed to investigate the correlation of serum sodium with the complications of chronic liver disease. ***Methods:*** A Prospective cross-sectional study was carried out Department of Gastroenterology and Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shabagh, Dhaka, from March 2014 to February 2015. A total of 100 patients (N=100) for one year were enrolled in this study following the inclusive criteria. Data were collected using the predesigned semi- structured questionnaire. Verbal consent was taken before recruiting the study population. Completed data forms were reviewed, edited, and processed for computer data entry. ***Result:*** Among hundred patients (N=100) with decompensated chronic liver disease observe the impact of hyponatremia with the severity of complications. Of them, it was observed that more than one-third of the patients (37,37.0%) belonged to age 31-40 years. The mean age was found 42.2±SD years. It was observed that almost two-thirds of the patients (63,63.0%) were male and thirty-seven (37,37.0%) patients were female. Among the study population, the majority of the patients (90,90.0%) belonged to serum sodium ≤135 mmol/l (Hyponatremia). The mean serum sodium was found 124.7±SD mmol/l. The majority of patients (57,57.0%) had moderate ascites, nineteen patients (19,19.0%) had mild and about one-fourth of the patients (24,24.0%) had severe ascites. In his current analysis, a negative significant correlation was observed between serum sodium level with encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, and CTP score. But no correlation was found between serum sodium with varices. ***Conclusion:*** Cirrhotic patients with chronic hepatitis infections have a variable presence of low sodium levels and <130 meq/L were associated with maximum morbidity and mortality rate.

Keywords: Liver, Serum Sodium, Ascites, Cirrhosis.

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INTRODUCTION

Cirrhosis is a result of chronic liver disease or hepatic cirrhosis and a condition in which liver tissue is replaced by fibrotic scar, and regenerative nodules leading to progressive loss of liver function [1, 2]. Cirrhosis is mainly caused by alcoholism and hepatitis C, however certainly have many other possible causes, such as Wilson's disease, hemochromatosis, autoimmune hepatitis, and non-alcoholic fatty disease [3]. The name cirrhosis was first recommended by Rene Laennec in the year 1819 [4]. Cirrhosis is one of the prime reasons for mortality and morbidity around the world and is the 11th foremost reason for death and the 15th major cause for morbidity, clarifying 2.2% of

deaths and 1.5% of disability-adjusted life years in 2016 nationwide [5]. In 2017, chronic liver disease caused around two-thirds of death among men and one-third among women [6]. In Bangladesh, the prevalence of chronic diseases is very substantial and approximately more than 10% of patients are treated for liver diseases in Bangladesh [7, 8]. The experimental course of cirrhosis has been typically described as a compensated and decompensated state based on the lack or the occurrence of ascites, bleeding, jaundice, and encephalopathy [9]. Decompensated chronic liver disease is complicated by hyponatremia in cirrhosis which is low sodium concentration in the blood [10]. It has been stated that hyponatremia occurs when serum sodium concentration in the blood is less than 135mmol/L, with severe hyponatremia being below 120 mmol/L [11, 12]. The threat of mortality is increased by around 12% for every unit of decrease in the serum sodium level [13]. Patients with hyponatremia have a higher risk of early death before transplantation and have a greater rate of mortality compared to those patients without hyponatremia [14]. Chronic liver disease is complicated by many factors such as intractable ascites, severe hyponatremia, and decreased arterial pressure. Advanced cirrhosis occurs as a progress of high serum levels of renin owing to portal hypertension, a reduced vascular reaction to vasoactive drugs, and a lessened solute-free water clearance [15]. Based on the American Association for the Study of Liver Diseases (AASLD), newly identified cirrhotics for the diagnosis of esophageal and gastric varices should undergo screening esophagogastroduodenoscopy and if it reveals no varices then it should be reversed in 2-3 years [16]. Decompensated cirrhosis is a composite complaint affecting several systems which needs a systematic method for its management. British Society of Gastroenterology certifies a 'care bundle' guideline to manage patients with decompensated cirrhosis for the 1st 24 hours [17]. In the current study, lower serum sodium levels were associated with increased complications of decompensated chronic liver and mortality leading to the integration of sodium. The study aimed to investigate the correlation of serum sodium with the complications of chronic liver disease.

OBJECTIVES

General Objective

- To see the correlation of serum sodium with the complications of chronic liver disease.

METHODS

A Prospective cross-sectional study was carried out Department of Gastroenterology and Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shabagh, Dhaka, from March 2014 to February 2015. A total of 100 patients (N=100) over one year were enrolled in this study following the inclusive criteria. Data were collected using the predesigned semi-structured questionnaire. A consecutive sampling technique was used. Verbal consent was taken before recruiting the study population. Ethical clearance was taken from the IRB Ethical Review Committee of BSMMU, Dhaka. The information was kept confidential only to be used for the study purpose.

Inclusion Criteria

- Patients ≥18 years old presented with decompensated cirrhosis.

Exclusion Criteria

- Patients with several chronic diseases, intrinsic renal disease, intrinsic central nervous system, congestive heart failure
- Patients who showed unwillingness to participate in the study.

Data Analysis

The study coordinators performed random checks to verify data collection processes. Completed data forms were reviewed, edited, and processed for computer data entry. Frequencies, percentages, and cross-tabulations were used for descriptive analysis. χ 2 test was used to analyze statistical significance. The data analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 25.0 and the ANOVA test. The significance level of 0.05 was considered for all tests.

RESULT

Among hundred patients (N=100) with decompensated chronic liver disease observe the impact of hyponatremia with the severity of complications. Of them, it was observed that more than one-third of the patients (37,37.0%) belonged to age 31-40 years. The mean age was found 42.2±SD years. It was observed that almost two-thirds of the patients (63,63.0%) were male. The majority of patients (27,27.0%) were service holders. Forty-two patients (42,42.0%) have an income of <5000 taka/month. Almost half of the patients (47,47.0%) had HBV, twenty-seven (27,27.0%) had HCV, six (6,6.0%) had Wilson, five (5,5.0%) had NASH and fifteen patients (15,15.0%) had unknown etiology [Table 1]. Among the study population, the majority of the patients (90,90.0%) belonged to serum sodium ≤135 mmol/l (Hyponatremia). The majority of patients (57,57.0%) had moderate ascites. Based on encephalopathy, the majority of the patients (58,58.0%) were grade I. It was observed that nine patients (9,9.0%) were found with hepatorenal syndrome and ninety- one patients (91,91.0%) were without the hepatorenal syndrome, twenty-two patients (22,22.0%) were found with spontaneous bacterial peritonitis, the majority of patients (58,58.0%) was found medium-sized varices and almost half patients (47,47.0%) was found CTP >9 scores [Table 2]. It was observed that mild ascites were found in eleven hyponatremic patients

(11,12.2%), moderate ascites were found in fifty-five hyponatremic patients (55,61.1%) and severe ascites were found in twenty-four hyponatremic patients (24,26.7%). Encephalopathy grade 0 was found in around one-fifth of the hyponatremic patients (19,21.1%), encephalopathy grade I was found in more than half of hyponatremic patients (51,56.7%), encephalopathy grade II & grade III was found in seventeen hyponatremic patients (17,18.9%) & three hyponatremic patients (3,3.3%) respectively. Medium varices were found in a majority of the hyponatremic patients (52,57.8%) & large varices were found in thirty-seven hyponatremic patients(37,41.1%), CTP 7-9 score was found in thirty-five hyponatremic patients (35,38.9%) & CTP>9 scores were found in half of the hyponatremic patients (45,50.0%) [Table 3]. Mean serum sodium was found 132.0±2.9, 123.2±5.8, 119.7±7.3 mmol/L in mild, moderate, and severe ascites respectively, mean serum sodium was found 126.1±6.5, 124.5±6.4, 119.6±5.6, 112.0±5.3 mmol/L in grade 0, grade I, grade II, grade III respectively, mean serum sodium was found 120.0±0.0, 123.7±7.0, 122.8±7.0 mmol/L in small, medium, large varices respectively and mean serum sodium was found 130.1±4.4, 125.0±6.3, 120.5±6.4 mmol/L respectively [Table 4]. Mild ascites were found in eleven patients among them two patients (2,18.2%) were found with a serum sodium level of 120-130 mmol/L. Moderate ascites were found in fifty-five patients, among them, thirteen (13,23.6%) was found with serum sodium level <120 mmol/L. Severe ascites were found in twenty-four patients among them twelve (12,50.0%) were found with serum sodium levels <120 mmol/L with the difference being statistically significant($p<0.05$) among the three groups. It was observed that encephalopathy grade I was found in fifty-one patients, among them thirteen patients (13,25.5%) found with a serum sodium level of 131-135 mmol/L, grade II was found in seventeen patients among them eight patients (8,47.1%) found serum sodium level of 120-130 mmol/L, grade III was found in three patients among them all of them (3,100.0%) was found serum sodium level <120 mmol/L with the difference was statistically significant ($p<0.05$) among three groups, a small variance was found in one patient among them one patient (1,100.0%) was found serum sodium level 120-130 mmol/L, a medium variance was found in fifty-two patients among them twelve (12,23.1%) was found serum sodium level 131-135 mmol/L, large varices was found in thirty-seven patients among them seven (7,18.9%) was found serum sodium level 131-135 mmol/L with the difference was not statistically significant($p>0.05$) among three groups CTP <7 scores was found in ten patients among them six patients (6,60.0%) was found serum sodium level of 131-135 mmol/L, CTP 7-9 score was found in thirty-five patients among them ten patients (10,28.6%) were found serum sodium level of 131-135 mmol/L, with CTP >9 score found in forty-five patients among them three (3,6.7%) was found serum sodium level 131-135 mmol/L with the difference was statistically significant ($p<0.05$) among three groups [Table 5].

Table 1: Distribution of study population based on characteristics (N=100)

Characteristics	**(N, %)**
Age, Mean age: 42.2±SD	
≤30	11, 11.0%
31-40	37, 37.0%
41-50	36, 36.0%
51-60	14,14.0%
>60	2, 2.0%
Sex	
Male	63,63.0%
Female	37,37.0%
Occupational Status	
Service	27,27.0%
Cultivator	21,21.0%
Housewife	18,18.0%
Business	16,16.0%
Others	18,18.0%
Monthly Income	
<5000/month	42,42.0%
5000-20,000/month	38,38.0%
>20,000/month	20,20.0%
Etiology	
HBV	47,47.0%
HCV	27,27.0%
Unknown	15,15.0%
Wilson	6,6.0%
NASH	5,5.0%

Table 2: Distribution of study population based on Epidemiology (N=100)

Epidemiology	**(N, %)**
Serum sodium (mmol/L), Mean: 124.7±7.8	
≤135 (Hyponatraemia)	90,90.0%
>135 (Normal)	10,10.0%
Ascites	
Mild	19,19.0%
Moderate	57,57.0%
Severe	24,24.0%
Encephalopathy	
Grade 0	22,22.0%
Grade I	58,58.0%
Grade II	17,17.0%
Grade III	3,3.0%
Syndrome	**(N, %)**
Hepatorenal syndrome	
Absent	91,91.0%
Present	9,9.0%
Spontaneous bacterial peritonitis	
Absent	78,78.0%
Present	22,22.0%
Varices	
Small	2,2.0%
Medium	58,58.0%
Large	40,40.0%
CTP score	
<7	13,13.0%
7-9	40,40.0%
>9	47,47.0%

Table 3: Distribution of study population based on Serum sodium level in hyponatremia & normal patients (N=100)

Ascites	**Serum sodium (mmol/L)**	
	Hyponatremia (n=90)	**Normal (n=10)**
Mild	11,12.2%	8,80.0%
Moderate	55,61.1%	2,20.0%
Severe	24,26.7%	0,0.0%
Encephalopathy		
Grade 0	19,21.1%	3,30.0%
Grade I	51,56.7%	7,70.0%
Grade II	17,18.9%	0,0.0%
Grade III	3,3.3%	0, 0.0%
Varices		
Small	1,1.1%	1,10.0%
Medium	52,57.8%	6,60.0%
Large	37,41.1%	3,30.0%
CTP score		
<7	10,11.1%	3,30.0%
7-9	35,38.9%	2,20.0%
>9	45,50.0%	5,50.0%

Table 4: Distribution of study population based on mean Serum sodium level in hyponatremia patients based on complications (n=90)

Ascites	Serum sodium (mmol/L)		*p-value*
	Mean ± SD Range (min, max)		
Mild	132.0±2.9	127,135	0.001^{S}
Moderate	123.2±5.8	108,135	
Severe	119.7±7.3	108,134	
Encephalopathy			
Grade 0	126.1±6.5	116,135	0.001^{S}
Grade I	124.5±6.4	110,135	
Grade II	119.6±5.6	108,128	
Grade III	112.0±5.3	108,118	
Varices			
Small	120.0±0.0	120,120	0.001^{S}
Medium	123.7±7.0	108,135	
Large	122.8±7.0	108,135	
CTP score			
<7	130.1±4.4	120,135	0.001^{S}
7-9	125.0±6.3	110,135	
>9	120.5±6.4	108,135	

Table 5: Distribution of study population based on an association between Serum sodium level with complications in hyponatremia patients (n=90)

Serum sodium (mmol/L)	Ascites				*p-value*
	Mild (n=11)		**Moderate (n=55)**	**Severe (n=24)**	
131-135(mild)	9,81.8%		7,12.7%	3,12.5%	0.001^{S}
120-130(moderate)	2,18.2%		35,63.7%	9,37.5%	
<120(severe)	0,0.0%		13,23.6%	12,50.0%	
	Encephalopathy				
	Grade 0 (n-19)	**Grade I (n=51)**	**Grade II (n=17)**	**Grade III (n=3)**	
131-135(mild)	6,31.6%	13,25.5%	0,0.0%	0,0.0%	0.002^{S}
120-130(moderate)	10,52.6%	29,56.9%	8,47.1%	0,0.0%	
<120(severe)	3,15.8%	9,17.6%	9,52.9%	3,100.0%	
	Varices				
	Small (n=1)		**Medium (n=52)**	**Large (n=37)**	
131-135(mild)	0,0.0%		12,23.1%	7,18.9%	0.875^{ns}
120-130(moderate)	1,100.0%		26,50.0%	19,51.4%	
<120(severe)	0,0.0%		14,26.9%	11,29.7%	
	CTP score				
	<7 (n=10)		**7-9 (n=35)**	**>9 (n=45)**	
131-135(mild)	6,60.0%		10,28.6%	3,6.7%	0.001^{S}
120-130(moderate)	4,40.0%		19,54.3%	23,51.1%	
<120(severe)	0,0.0%		6,17.1%	19,42.2%	

DISCUSSION

Advanced cirrhosis in patients presents with clinical appearances such as intractable ascites, severe hyponatremia, and reduce arterial blood pressure. Hyponatremia patients do have not a better prognosis compared to those who do not suffer from this state [18]. Around 997 cirrhotic patients showed an occurrence of serum sodium levels less than 130 mmol/L of21.6% in 2006 [19]. This current prospective study was conducted to find out the association between serum sodium and the severity of complications of decompensated chronic liver.

In this current examination, more than one-third of the patients (37,37.0%) belonged to age 31-40 years. The mean age was found 42.2±SD years. A related article found that the mean age of the patients was 46.8± SD years, which is comparable with the current study [20]. Another similar study found that the mean age of the patients was 44±SD years [21]. On the other hand, the mean age was 59±SD years with the range from 39to 75 years found in another article [22]. Cirrhosis is more common in adults ages 45 to 54 and about 1 in 200 adults has cirrhosis [23].

In this current study, it was observed that almost two third (63.0%) of patients were male and 37(37.0%) patients were female which indicates that chronic liver disease is predominant in male subjects. Another linked study stated that women had a lower percentage of cirrhosis deaths caused by liver diseases [24]. Another study found that men were 2-fold more likely to die from chronic liver disease and cirrhosis compared to women [25].

Regarding the etiology of chronic liver disease, it was observed in this series that HBV and HCV were most common, which were 47.0% and 27.0% respectively. However, 15.0% had unknown etiology, 6.0% had Wilson and 5.0% had NASH. Another related article found suggested that, in chronic Hepatitis B, the threat of cirrhosis depends to a large extent on the burden of viral infection and in chronic Hepatitis C, progression to cirrhosis depends primarily on the patient's age [26]. Another study suggested that the Hepatitis C virus was seen in 45.9% of patients [22]. In another study, the author depicted that the etiology of cirrhosis was alcoholic in 19.0%, virus related in around three-fifths of the patients, and unknown in 6.0%, and in 3.0% of cases, a double etiology was recognized. No patient had primary biliary cirrhosis, Wilson's disease, or hemochromatosis [27]. Another study suggested that cirrhosis was alcohol-related in 50.3% of patients, Hepatitis C related in 32.4%, and Hepatitis B related in 9.8% of patients. Patients in Central Europe were more likely to have alcohol abuse as an etiology of cirrhosis whereas Hepatitis C was most common in Western Europe [28].

In this current study, it was observed that the majority (90.0%) of patients belonged to serum sodium ≤135 mmol/l (Hyponatremia). The mean serum sodium was found 124.7±7.8 mmol/L. Another linked study showed that 3.5% of patients presented severe hyponatremia with serum sodium concentration ≤127 mmol/L at the time of surgery and half of the patients developed neurological complications in the early postoperative period [29] Another study found that, in a population survey of 997 patients with cirrhosis, 486(49.6%) and 211(21.6%) had serum sodium <135 mequ/L and <130 meq/L respectively [30].

In this present study, it was observed that almost half (47.0%) of patients were found CTP score >9, 13.0% had a <7 score and 40.0% had a 7 -9 score. A relevant study showed that cirrhosis at the time of referral was relatively advanced, with a mean ±SD CTP score of 9.4±2.4; 49.0% were CTP class C, 40.0% were class B, and 11.0% were class A, which is comparable with the current study [31].

In this current study, it was observed that most of the patients (57.0%) were found moderate levels of ascites, 19.0% were mild and 24.0% were severe. Another study revealed that moderate ascites was 37.8%, severe was at 53.5% and refractory ascites at 8.7%, which differ from the current study, may be due to injudicious use of diuretics and free water intake [32].

In this present analysis, it was observed that the majority (58.0%) of patients were in Encephalopathy grade I, 22.0% in grade 0, 17.0% in grade II, and 3.0% in grade III. Another similar study found that severe recurrent or refractory encephalopathy was present in 15.0%, which is comparable with the current study [33].

In this series, it was observed that nine patients (9,9.0%) were found with hepatorenal syndrome and ninety-one patients (91,91.0%) were without the hepatorenal syndrome. Another study suggested that refractory ascites were a common complication of advanced cirrhosis and were related to hepatorenal syndrome and hepatic hydrothorax [34].

In this series, the mean serum sodium level significantly ($p<0.05$) declined according to the severity of ascites. Another author observed that 58 patients with low serum sodium were in Class B ($p=0.001$). A more severe grade of ascites was present in patients with low serum sodium needing frequent paracentesis and higher dosages of diuretics [32].

In this current study, it was observed that a negative significant correlation ($r=-0.414$:$p=0.001$) was found between low serum sodium levels with encephalopathy. Hepatic encephalopathy was more frequent in patients with serum sodium <130 meq/Cirrhosis-related complications were also significantly increased in patients with mild hyponatremia than in patients with normal serum sodium depicted in another article [32]. Another study revealed that there was a clear inverse relationship between serum sodium levels and the frequency of hepatic encephalopathy [28].

In this study, the mean serum sodium level was considerably ($p<0.05$) and declined with an increased CTP score. The severely low level of serum sodium was significantly ($p<0.05$) associated with increased CTP score. In his current analysis, a negative significant correlation was observed between serum sodium level with encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, and CTP score. But no correlation was found between serum sodium with varices.

CONCLUSION

A low concentration of sodium may indicate the presence of severe liver complications in cirrhosis and many chronic liver diseases. Cirrhotic patients with chronic hepatitis infections have a variable presence of

low sodium levels and <130 meq/L were associated with maximum morbidity and mortality rate.

Limitations

- The study population was selected from one selected hospital in Dhaka city, so the results of the study may not reflect the exact picture of the country.
- The present study was conducted in a very short period.
- The small sample size was also a limitation of the present study. Therefore, in the future, further study may be undertaken with a large sample size.

RECOMMENDATIONS

There is a necessity for setting a screening docket to cover all age groups for early detection and treatment of cases. Furthermore, strategies should be implemented to accelerate government programs. Further studies should be undertaken by including a large number of patients.

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Conflict of Interest: None declared.

Ethical Approval: The study was approved by the Institutional Ethics Committee.

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