ORIGINAL ARTICLE

Prevalence of hyponatremia and its significance among patients with liver cirrhosis

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ABSTRACT

BACKGROUND: Hyponatraemia in cirrhosis largely occurs in the setting of expanded extracellular fluid volume. The relationship between hyponatremia and severity of cirrhosis is evidenced by its close association with the occurrence of complications like hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis. Serum sodium concentration is also included in the prognostic model for end-stage liver disease (MELD). **AIM:** To assess the prevalence of hyponatremia and to correlate hyponatraemia with the severity of liver disease among the patients with cirrhotic liver disease. **METHODOLOGY:** A cross sectional observational study was conducted among 100 consecutive patients with cirrhosis of liver admitted in our hospital during the period of June 2015 to May 2016. Patients were recruited for the study based on the diagnosis of cirrhosis which was confirmed by clinical, biochemical, and ultrasonographic findings and for few cases endoscopic findings of oesophageal varices was made. Based on the biochemical parameters the severity of cirrhosis was assessed according to Child-Pugh score. A total score from 5-6, 7-9 and 10-15 were classified as class A, B and C respectively. In our study chronic hyponatremia was defined as serum level of sodium < 130 meq/L. **RESULTS:** The serum sodium levels of the study subjects had shown that 48% of them had normal sodium levels and 21% had mild hyponatremia and the remaining 31% had severe hyponatremia. Based on the child pugh score of liver cirrhosis class B patients had the mean sodium levels of 133.5 meq/L whereas class C patients sodium levels were 124.8 meq/L and the difference was found to be statistically significant. The correlation between the mean MELD score and the serum sodium levels had shown a strong negative correlation between them. **CONCLUSION:** Our study had proven a strong association of hyponatremia among patients with liver cirrhosis. Further prospective studies are needed to determine the clinical significance of hyponatremia and identify its correlation with the incidence of possible complications.

Keywords: Hyponatremia, liver cirrhosis, MELD score.

INTRODUCTION

Hyponatraemia is defined as a serum sodium level ≤136 mEq/L while, in cirrhosis, it has classically been considered relevant only at a serum sodium level <130 mEq/L.[1]Generally, hyponatraemia is divided into three clinical types: hypovolemic, euvolemic and hypervolemic and some patients have a mixed picture of all the three. In liver cirrhosis hyponatraemia occurs in the Setting of a hypotonic serum with increased extracellular fluid volume, or so-called 'dilutionalhyponatraemia'. In this instance, there is a distinct impairment of free water excretion in the presence of excessive anti-diuretic hormone (ADH). Diseases associated with this of this type of hyponatraemia include cirrhosis, congestive heart failure, certain types of Renal failure and nephritic syndrome.[2] Hyponatraemia in cirrhosis largely occurs in the setting of expanded extracellular fluid volume. There are of course important instances where a patient will present with hypovolemic hyponatraemia in the setting of diuretic use or gastrointestinal losses. When evaluating a cirrhotic patient with low serum sodium, it is important to exclude and treat these causes as the sole or major contributing

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factor.[3,4] Although hyponatremia can be found in patients with early or moderately advanced cirrhosis belonging to classes A and B of Child-Pugh classification, in most cases it occurs in an advanced disease (Child-Pugh class C).[5] The relationship between hyponatremia and severity of cirrhosis is further evidenced by its close association with the occurrence of complications like hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis.[6] Severe hyponatremia, that require immediate and specific treatment, is relatively rare in cirrhosis. Therefore, the occurrence of mild to moderate hyponatremia has mainly to be appraised for its clinical meaning. In fact, the occurrence of hyponatremia represents an independent outcome predictor for the development of hepatorenal syndrome, hepatic encephalopathy and survival.[7-9] Such an important prognostic power has led serum sodium concentration to be included in the prognostic model for end-stage liver disease (MELD),[10] widely used to establish the need for liver transplantation (OLT) and prioritize patients on the waitlist, with the aim of improving its prognostic ability, especially in patients with cirrhosis and ascites. Biggins*et al.*[11] proposed the MELD-Na score by integrating serum sodium concentration into the MELD equation. To date in India no studies have been conducted to evaluate the prevalence of hyponatremia in any hospitalized patients with liver cirrhosis. In fact, very few studies done in abroad had evaluated the correlation between serum sodium levels and severity of liver disease in cirrhotic patients. Given the need for further studies regarding this relationship, we conducted this study to evaluate the prevalence of hyponatremia and to correlate hyponatraemia and severity of liver disease in cirrhosis.

AIM & OBJECTIVE

To assess the prevalence of hyponatremia and to correlate hyponatraemia with the severity of liver disease among the patients with cirrhotic liver disease.

MATERIALS AND METHODS

A cross sectional observational study was conducted among 100 consecutive patients with cirrhosis of liver admitted in our hospital during the period of June 2015 to May 2016. All the patients were recruited after getting their free, fair and full written consent. The study protocol was approved by the institutional ethical committee. Patients were recruited for the study based on the diagnosis of cirrhosis which was confirmed by clinical, biochemical, and ultrasonographic findings and for few cases endoscopic findings of oesophageal varices was made. The patients with hepatocellular carcinoma (HCC), exudative ascites, hypovolemic and hypervolaemic causes of hyponatraemia and using diuretic within one month were excluded from the study. The cause of cirrhosis other than Hepatitis B, Hepatitis C, and Wilson's disease were classified as 'others'. In our study chronic hyponatremia was defined as serum level of sodium < 130 meq/L.During hospital stay the dietary sodium was restricted to 70 meq per day for patients with ascites. In patients with mild hyponatraemia, the water intake was restricted to 1000 ml/day and in those with severe hyponatraemia to750 ml/day. The following were the biochemical tests carried out in the patients; serum electrolytes, serum creatinine, LFT, serum albumin, prothrombin time and viral marker, 24 hour urinary copper were estimated in all patients. Based on the biochemical parameters the severity of cirrhosis was assessed according to Child-Pugh score. A total score from 5-6, 7-9 and 10-15 were classified as class A, B and C respectively. The quantitative data were presented as their means ± SD, while categorical or nominal data were expressed in percentage. The t-test was used to compare quantitative data, the chi-square test used for categorical data and bivariate correlation test were done to find correlation between variables. All analyses were carried out using SPSS software version 16 (SPSS, Inc. Chicago). P values of less than 0.05 were considered statistically significant.

RESULTS

The age and sex wise distribution of study population was shown in table 1.

Table 1: Age and sex wise distribution of the study population

Age group (in years)	Gender		Total
	Male	Female	
30 – 40	12	0	12
41 – 50	48	4	52
51 – 60	22	2	24
61 – 70	7	1	8
>70	4	0	4
Total	93	7	100
Mean age ± SD	47.8 ± 5.8	45.7 ± 6.2	

A total of 100 subjects were included in the study of which 93 were males and 7 were females and the mean age was 47.8 years for males and 45.7 years for females. A detailed biochemical and ultrasonographic investigation was made on all subjects and it was found that among males alcoholism was found to be the major cause for cirrhosis of liver and among females hepatitis B and C were found to be the cause for development of liver cirrhosis (table 2).

Table 2: Distribution of the study population based on causes for liver cirrhosis

Causes for liver cirrhosis	Gender		Total	P value
	Male	Female		
Alcoholic	83	0	83	<.0001
Hepatitis B	6	4	10	<.001
Hepatitis C	4	3	7	<.001
Total	93	7	100	

P value derived by applying Chi-square test

The serum sodium levels of the study subjects had shown that 48% of them had normal sodium levels and 21% had mild hyponatremia and the remaining 31% had severe hyponatremia (table 3).

Table 3: Distribution of the study population based on their serum sodium levels.

Sodium levels	Frequency	Percentage
108 to 130	31	31%
131 to 135	21	21%
135 to 145	48	48%

Based on the child pugh score of liver cirrhosis class B patients had the mean sodium levels of 133.5 meq/L whereas class C patients sodium levels were 124.8 meq/L and the difference was found to be statistically significant (table 4).

Table 4: Mean sodium levels among the study population based on their Child Pugh score

Child pugh score	Mean sodium levels	SD	P value
Class B	133.5	4.68	<.0001
Class C	124.8	5.84	

This proves that the serum sodium levels start decreasing as the disease condition worsens. Among the various complications encountered by the patients like hepatic encephalopathy, variceal bleeding, coagulopathy and hepatorenal syndrome had shown a strong significant association with severe hyponatremia (table 5).

Table 5: Comparison of sodium levels with the various complications developed among the study subjects

Complications (n)	Sodium <130 meq/L	Sodium 131to 135 meq/L	Sodium >135 meq/L	Chi Square	P value
Ascites (95)	31(32.6%)	21 (22.1%)	43(45.2%)	5.7	0.058
Portal Hypertension (98)	31 (31.6%)	21 (21.4%)	46(46.9%)	2.21	0.331
Hepatic encephalopathy (33)	20 (60.6%)	10(30.3%)	3 (9%)	31.49	<0.001
Variceal Bleeding (28)	11(39.2%)	10(35.7%)	7 (25%)	9.16	0.06
Coagulopathy (17)	10 (58.8%)	2 (11.7%)	5 (29.4%)	7.42	0.024
Hepto renal Syndrome (9)	7 (77.7%)	2 (22.2%)	0	11.14	0.003

The correlation between the mean MELD score and the serum sodium levels had shown a strong negative correlation between them, as the serum sodium level decreases the mean MELD score increases, which indicated the poor prognosis of the disease (table 6).

Table 6: Correlation between MELD score and the sodium levels

Sodium Level (Meq/L)	Mean MELD Score	Correlation value (r value)
<130	27.45±9.24	-0.0316
131 to 135	24.76±6.86	
>136	18.38±5.46	

DISCUSSIONS

The present study had shown that alcoholism was the most common cause for cirrhosis followed by hepatitis B and C which found to be more common in females developing liver cirrhosis. The results shown by Eric Levesque etal was almost in par with our study quoting the prevalence of alcoholic cirrhosis as 68%, HBV and HCV were the cause of cirrhosis for 14% and 4% of patient.[12] Reduced

concentration of serum sodium is a very common electrolyte disorder in patients who have cirrhosis.[13] In our study, the prevalence of hyponatremia in liver cirrhosis was 52% of which 21% had mild hyponatremia and 31% of patients had severe hyponatremia. Angeli and his colleagues found that serum sodium levels of ≤135 meq/L occurred in 49.4% in their cirrhotic patients.[14] Also, Jong Hoon Kim et al revealed that the prevalence of dilutional hyponatremia, classified as serum sodium concentrations of ≤135 mmol/L, ≤130 mmol/L, and ≤125 mmol/L, were 20.8%, 14.9%, and 12.2%.[15] In the study by Shaikh*et al.*[16] conducted on 217 cirrhotic ascitic patients the prevalence of hyponatremia was 51.6%. Khalil *et al.*[17] showed a prevalence of hyponatremia of 65.5% among 200 decompensated cirrhotic patients. So our results were almost in par with the above mentioned studies.A recent study study done by Mamun AAetal in Bangladesh had shown the prevalence of chronic hyponatremia was 35% among the liver cirrhosis patients.[18] In our study we considered chronic hyponatremia those who had serum sodium level >130 meq/L and taking this level as cut-off point we found about 35% patient with Cirrhosis had hyponatremia. The percentage of hyponatremia sought in this study more or less conforms to study done by Gines et al.[19] The percent of people with cirrhosis affected by chronic hyponatremia increases to 50 percent if a cutoff for serum sodium concentration of 135 meq/L, the lower limit of normal, is used.[19] Although the prevalence of hyponatremia was associated with decompensated cirrhosis, this association increased markedly in certain major cirrhosis complications - for example, among patients with hepatic encephalopathy about 60.6% were hyponatremic; among patients with HRS (hepato-renal syndrome) about 77.7% were hyponatremic; and among patients with coagulopathy about 58% were hyponatremic; among patients with variceal bleeding, hyponatremic patients constituted about 39.2%. These associations was investigated by several researchers like Angeli*et al*. [14] ,Shaikh*et al.*[16], Kim *et al*[15] , and Khalil *et al.*[17] The relationship between hepatic encephalopathy and serum levels may be explained on the basis of more severe liver failure among patients with serum sodium less than 130 mEq/l, and the possibility that the two events may be pathophysiologically linked. Low serum sodium levels in patients with cirrhosis are associated with a remarkable reduction in the cerebral concentration of organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling.[20]The pathophysiology of association between HRS, refractory ascites, and hyponatremia can be explained by increased body fluid resulting from the impairment of solute-free water excretion. This increased risk for HRS may be related to a more severe circulatory dysfunction in patients with hyponatremia compared with patients without hyponatremia.[21] The most common reason for chronic hyponatremia in cirrhosis is impairment in renal solute-free water secretion due to increased antidiuretic hormone secretion and decreased effective arterial volume. The brain is able to compensate for the increased osmolar pressure (which leads to cerebral edema) in chronic hyponatremia by extruding intracellular osmolytes, such as potassium, glutamine and myoinositol, which can take 48 hours for full effect.[22]This adaptive mechanism explains why patients with chronic hyponatremia and serum sodium concentrations above 120 meq/L are often asymptomatic. The correlation between the mean MELD score and the serum sodium levels had shown a strong negative correlation ($r = -0.0316$, with $P < 0.05$). In agreement with this study, Khalil *et al.*[17] and Wang *et al.*[18] demonstrated a significant correlation between serum sodium and MELD score in decompensated cirrhotic patients. As arginine vasopressin release is a primary cause of hyponatremia in cirrhosis, several vasopressin receptor antagonists have been evaluated in treating hyponatremia in patients with cirrhosis/ESLD and other conditions characterized by hypervolemia

- for example, heart failure. These include the intravenous dual V1A/V2-receptor antagonist conivaptan, and the oral V2-receptor antagonistslixivaptan (VPA-985), satavaptan, and tolvaptan. Currently, only conivaptan and tolvaptan are approved for increasing serum sodium in patients with hypervolemic or euvolemic hyponatremia in the USA.[24] The only limitation of this study was that it did not assess the effect of serum sodium concentration on the risk for developing complications but simply examined the concurrent presence of complications and sodium levels in a retrospective analysis.

CONCLUSION

In our study, the prevalence of hyponatremia in liver cirrhosis was 52% of which 21% had mild hyponatremia and 31% of patients had severe hyponatremia. It had proven a strong association of hyponatremia in liver cirrhosis. A strong negative correlation was seen between mean MELD scores and the serum sodium levels. Further prospective studies are needed to determine the clinical significance of hyponatremia and identify its correlation with the incidence of possible complications. Management of hyponatremia may decrease the incidence and severity of liver cirrhosis complications and improve the quality of life of the patients.

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