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Original Article

Prevalence of Hyponatremia in Chronic Liver Disease Patients and Its Correlation with the Severity of the Disease

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Abstract

Background: Hyponatremia has been most common electrolyte abnormality found among the patients with advanced cirrhosis indicating a poor prognosis. The present study was conducted to estimate the prevalence of hyponatremia in chronic liver disease (CLD) patients and to assess the correlation of hyponatremia with the severity of the CLD.

Materials and Methods: This was a cross-sectional study conducted among CLD patients admitted in a tertiary care hospital. The sociodemographic data, clinical history, and details about the risk factors of CLD were collected using a semi-structured questionnaire by interview method. Blood investigations were performed along with upper GI endoscopy. Severity of cirrhosis was assessed according to Child-Pugh score. Data were analyzed using SPSS version 18.0. $P < 0.05$ was considered statistically significant.

Results: The mean age of the study subjects was 45.19 ± 10.01 years and 92.0% were male. The prevalence of hyponatremia was 75.0% at the cut off of ≤135 mEq/L and it was 52.0% at the cut off of ≤130 mEq/L. Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia (76.6% vs. 50.0%), but it was not statistically significant ($P > 0.05$). Significantly higher proportions of those with hyponatremia had hepatic encephalopathy (85.4%) compared to those with no hyponatremia (67.8%) ($P < 0.05$).

Conclusion: The prevalence of hyponatremia was noted to be 75.0%, but the severity as per Child-Pugh score had no association with hyponatremia. However, hepatic encephalopathy was significantly associated with hyponatremia.

Keywords: Child-Pugh score, Chronic liver disease, *Hyponatremia*

INTRODUCTION

Chronic liver disease (CLD) is a progressive disease of the liver with deterioration of liver functions for more than 6 months. Such liver functions include detoxification of harmful products of metabolism, excretion of bile and the synthesis of clotting factors, and other proteins. It is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, leading to fibrosis and cirrhosis. The final stage of CLD, the cirrhosis, results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix.[1]

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Cirrhosis is ranked as 11th leading cause of death and 15th leading cause of morbidity. It contributes for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide as in 2016. 1.32 million deaths in 2017, nearly two-thirds among men and one-third among women are due to CLD.[2] According to the latest WHO data published in 2018, liver disease deaths, in India, are recorded as 3.0% of total deaths corresponding to 264,193 deaths. The age adjusted death rate being 23.0 per 100,000 population, it ranks India at 62nd position in the world.[3]

There is a wide-ranging spectrum of etiologies for CLD such as toxins, chronic alcohol abuse, infection with Hepatitis B and C, autoimmune diseases, and genetic and

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metabolic disorders.[1] Alcohol has been the most common etiology of cirrhosis, while hepatitis B virus was most common in the non-cirrhotic CLD and Hepatocellular carcinoma.[4] The signs and symptoms are nonspecific, which are anorexia, fatigue, and weight loss, or it depends on the complication that the patient would have developed. The three important complications of CLD are portal hypertension (esophageal varices and ascites), hepatocellular insufficiency (e.g., jaundice and hepatic encephalopathy), and hepatocellular carcinoma.[1]

Hyponatremia is decreased serum sodium below 130 mmol/L and is a common finding in patients with decompensated cirrhosis due to an abnormal regulation of body fluid homeostasis. It can be either be due to hypovolemia due to loss of extracellular fluid as a result of use of diuretics or due to expanded extracellular fluid volume due to the inability of the kidneys to excrete solute-free water proportionate to the amount of free water ingested.[5] A number of recent studies have shown the association of hyponatremia with greater severity of complications of cirrhosis, namely, difficult-to-control ascites, and greater frequency of complications post-transplant including neurologic disorders, renal failure, and infectious complications.[6] Hyponatremia is also found to be associated with increased morbidity and mortality in patients with cirrhosis.[5] As there were no studies on the effect of hyponatremia in CLD in the present study setting, this study was conducted to estimate the prevalence of hyponatremia in CLD patients and to assess the correlation of hyponatremia with the severity of the CLD in the present study setting.

MATERIALS AND METHODS

This was a cross-sectional study conducted for 18 months from November 2019 to May 2021 among CLD patients admitted in wards of the Department of Medicine of a tertiary care hospital situated in Bangalore after obtaining ethical clearance from the Institutional Ethics committee. From the previous study, considering prevalence of hyponatremia in liver cirrhosis as 52%,[7] estimated sample size was 99 ≈ 100 with 5% alpha error, 5% absolute precision, and considering 5% non-compliance using the formula $n = z^2(pq/L^2)$. After obtaining written informed consent, 100 patients with CLD admitted in the hospital were included in the study by purposive sampling. The sociodemographic data, clinical history, and details about the risk factors of CLD were collected using a semi-structured questionnaire by interview method. Clinical history included age, sex, and history of alcohol intake. Clinical examination included vitals, general examination, and systemic examination which were done. Venous blood samples were drawn at the time of admission before initiation of treatment. All blood samples were processed within 30 min of blood collection using an autoanalyzer. Investigations included complete hemogram, serum electrolytes, serum urea and creatinine, liver function test, serum albumin, and prothrombin time. Upper GI endoscopy was performed on all the patients. Severity of cirrhosis was assessed according to Child-Pugh score.

The Child-Pugh scoring system[8] (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. The original scoring system conceptualized by Child and Turcotte in 1964 used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status. The scoring system was modified later by Pugh *et al.*, substituting prothrombin time for clinical nutrition status. In addition, they introduced variable points for each criterion based on increasing severity:

- Encephalopathy: None = 1 point, Grades 1 and 2 = 2 points, and Grades 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, and moderate = 3 points
- Bilirubin: under 2 mg/ml =1 point, 2–3 mg/ml =2 points, and over 3 mg/ml =3 points
- Albumin: >3.5 mg/ml =1 point, 2.8–3.5 mg/ml =2 points, and <2.8 mg/ml =3 points
- Prothrombin Time* (sec prolonged): <4 s = 1 point, 4–6 s = 2 points, and over 6 s = 3 points.

*Frequently, INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7–2.2 = 2 points, and INR above 2.2 = 3 points.

The severity of cirrhosis classified as:

- Child-Pugh A: Good hepatic function – 5–6 points
- Child-Pugh B: Moderately impaired hepatic function – 7–9 points
- Child-Pugh C: Advanced hepatic dysfunction – 10–15 points.

Operational definition

Hyponatremia was considered at the serum sodium levels of cut off of ≤135 mEq/L.

Statistical analysis

Data were entered in excel and the categorical data were presented as proportions and the continuous data were presented in mean ± SD. The categorical variables were analyzed using Chi-square test and Fisher's exact test. The means were compared among the groups of Child-Pugh class using one-way ANOVA. SPSS Statistics version 18.0 (IBM Corp., USA). $P < 0.05$ was considered statistically significant.

RESULTS

Majority of the study subjects, that is, 39.0% were in the age group of 46–55 years and almost all (92.0%) were male. The mean age of the study subjects was 45.19 ± 10.01 years and the age ranged from 25 years to 73 years. The most common etiology of CLD being alcohol (94.0%) were chronic alcohol drinkers for more than 10 years (72.9%) and nearly more than half, that is, 63.5% were consuming an alcohol of more than 60 g per day [Table 1].

The average levels of total protein and albumin levels in g/day were 5.7 and 2.2, respectively. The median total bilirubin and direct bilirubin levels were 4.95 mg/dL and 3.00 mg/dL, respectively. The median serum glutamic oxaloacetic transaminase levels were 92.0 U/L, serum glutamic pyruvic transaminase was 44.5 U/L, and alkaline phosphatase was 124 U/L [Table 2].

Most of them (90.0%) had ascites, 56.0% had splenomegaly, 41.0% had hepatic encephalopathy of varied severity, and higher proportions of study subjects had developed portal hypertension (93.0%). Majority of the study subjects (77.0%) had advanced hepatic dysfunction according to Child-Pugh classification [Table 3].

The prevalence of hyponatremia was noted to be 75.0% considering the cut off of ≤135 mEq/L and it was 52.0%, when the cut off of ≤130 mEq/L was considered. However, 78.7% of those with hyponatremia had advanced hepatic dysfunction as per Child-Pugh Score. The mean sodium levels was 130.93 ± 6.12 mEq/L and the minimum and maximum levels of sodium among the study subjects were 113 mEq/L to 146 mEq/L [Table 4].

Among various sociodemographic such as age, gender, and alcohol intake and complications of CLD such as ascites, hepatic encephalopathy, and portal hypertension, significantly higher proportions of those with hyponatremia had hepatic encephalopathy (85.4%) compared to those with no hyponatremia (67.8%) ($P < 0.05$).

Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia (76.6% vs. 50.0%), but it was not statistically significant ($P > 0.05$).[Table 5]

Table 1: Sociodemographic and clinical details of the study subjects (*n*=100)

Variables	Frequency, *n* (%)
Age-group (years)	
≤35	21 (21.0)
36–45	27 (27.0)
46–55	39 (39.0)
>55	13 (13.0)
Gender	
Males	92 (92.0)
Females	8 (8.0)
Etiology of chronic liver disease	
Alcohol	94 (94.0)
Infective (Hep B)	2 (2.0)
Both	4 (4.0)
Alcoholic (g/day) (*n*=96)*	
≤60	35 (36.5)
61–120	46 (47.9)
121–180	15 (15.6)
Duration of alcoholism (years) (*n*=96)*	
≤10	26 (27.1)
11–20	58 (60.4)
>20	12 (12.5)

*04 are non-alcoholics

Table 2: Average levels of different blood parameters (*n*=100)

Blood parameters	Median (range)
Total protein (g/dL)	5.70 (3.50–8.00)
Total albumin (g/dL)	2.20 (1.10–4.80)
Total bilirubin (mg/dL)	4.95 (0.50–34.40)
Direct bilirubin (mg/dL)	3.00 (0.1–25.10)
SGOT (U/L)	92.0 (15–1405)
SGPT (U/L)	44.5 (10–1642)
Alkaline phosphatase (U/L)	124.0 (13.0–430.0)

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 3: Signs of chronic liver disease and severity of liver disease according to Child-Pugh class (*n*=100)

Variables	Frequency, *n* (%)
Ascites	
Yes	90 (90.0)
No	10 (10.0)
Splenomegaly	
Yes	56 (56.0)
No	44 (44.0)
Hepatic encephalopathy	
0	59 (59.0)
1	6 (6.0)
2	15 (15.0)
3	9 (9.0)
4	11 (11.0)
Portal hypertension	
Yes	93 (93.0)
No	7 (7.0)
Child-Pugh class	
A	6 (6.0)
B	17 (17.0)
C	77 (77.0)

Table 4: Prevalence of hyponatremia

Hyponatremia	Child-Pugh class			Total
	Class A	Class B	Class C	
Yes	3 (4.0)	13 (17.3)	59 (78.7)	75 (75.0)
No	3 (12.0)	4 (16.0)	18 (72.0)	25 (25.0)

Table 5: Association of hyponatremia with sociodemographic, complications, and severity of chronic liver disease (*n*=100)

Variables	Hyponatremia		χ^2 (*P*)
	Yes	No	
Age-group (years)			
≤45	38 (79.2)	10 (20.8)	0.86 (0.36)
>45	37 (71.2)	15 (28.8)	
Gender¥			
Males	68 (74.7)	23 (25.3)	(1.00)
Females	7 (77.8)	2 (22.2)	
Alcohol intake¥			
Yes	71 (74.0)	25 (26.0)	(0.57)
No	4 (100.0)	0 (0.0)	
Ascites			
Yes	67 (74.4)	23 (25.6)	(1.00)
No	8 (80.0)	2 (20.0)	
Hepatic encephalopathy			
Yes	35 (85.4)	06 (14.6)	3.98 (0.04)*
No	40 (67.8)	19 (32.3)	
Portal hypertension			
Yes	70 (75.3)	23 (24.7)	(1.00)
No	5 (71.4)	2 (28.6)	
Child-Pugh class			
Class A	3 (50.0)	3 (50.0)	(0.16)
Class B/C	72 (76.6)	22 (23.4)	

*Indicates statistically significant association, ¥Fisher's exact test applied

The mean levels of sodium were lesser in Class B (130.53 mEq/L) and Class C (130.82 mEq/L) severity of CLD compared to Class A (133.50 mEq/L) as per Child-Pugh score ($P > 0.05$).

DISCUSSION

CLD is a condition with deranged hepatic functions and hyponatremia is noted to be common in about half of the hospitalized patients.[9,10] Understanding the prevalence of hyponatremia and its association with the CLD in the present study, setting would help in the better management of advanced liver disease. Hence, the present study was conducted.

Malani *et al.* have reported a mean age of 58 years and majority were male with most common etiology of CLD being alcohol which are almost in line with the present study findings, but for the mean age which was lesser in ours (45 years) and also the proportions which were more in our study setting. The differences in the distribution of patients might be due to the different study settings.[9] However, the distribution of the patients with respect to age and gender and also the etiology of CLD according to Nareddy *et al.* was same as our study findings.[10] Nearly 3/4th (72.9%) of our study subjects were chronic alcoholics for more than 10 years and nearly more than half, that is, 63.5% were consuming an alcohol of more than 60 g per day.

Kumar and Ashok had found ascites among all the patients and hepatic encephalopathy among 18% of them, whereas 90.0% of our study subjects had ascites and 41.0% of them had hepatic encephalopathy.[11] Portal hypertension was reported among 93.0% of our subjects and it is postulated that splenomegaly can manifest following portal hypertension and it also contributes to the progression to cirrhosis, where 56.0% of our subjects had splenomegaly in the current study.[12] Dhanorkar and Galande found hepatic encephalopathy Grades I, II, III, and IV among 24.0%, 27.0%, 30.0%, and 39.0% in patients with liver cirrhosis, respectively, and 6.0%, 15.0%, 9.0%, and 11.0% in ours had, respective hepatic encephalopathy of Grades I, II, III, and IV which were relatively lesser in our subjects indicating relatively lesser complications compared to theirs.[13]

Majority of the study subjects (77.0%) had advanced hepatic dysfunction according to Child-Pugh classification in our study. Similarly, Nareddy *et al.* have reported that majority of their patients (72.6%) belonged to Child-Pugh C (72.6%).[10]

About 49.4% of those with liver cirrhosis had hyponatremia as per Singh *et al.*[14] and it was 53.0% as per Reddy *et al.*[15] The prevalence of hyponatremia was noted to be 75.0% which was higher among our study subjects and is dependent on other factors such as release of arginine vasopressin, production of solute-free water, and resorption of sodium in proximal tubule and is also said to be associated with many complications such as severe ascites and hepatic encephalopathy.[6] Nareddy *et al.* found 34.7% to have hyponatremia when the cut-off of ≤ 130 mEq/L was considered and 52.0% were affected in ours and as said earlier, it is dependent on other factors.[6,10] Based on the findings of Malani *et al.*, 20.0%, 23.8%, and 91.7% of the patients belonging to Child-Pugh Scores A, B, and C, respectively, had with hyponatremia; however, in ours, the proportions were higher and it was 50.0%, 76.5%, and 76.6% except for Class C which was higher in theirs.[9]

In our study, the overall mean sodium levels were 130.93 ± 6.12 mEq/L and the levels were lesser in Class B (130.53 mEq/L) and Class C (130.82 mEq/L) compared to Class A (133.50 mEq/L) as per Child-Pugh scores. Similarly Raja *et al.* recorded mean sodium levels of 133.5 meq/L in Class B patients and Class C patients sodium levels were 124.8 meq/L based on Child-Pugh scores and the difference was found to be statistically significant; however, the significance could not be established in ours as the levels were nearly same in Class B and C which depends on the severity of the liver disease.[7] Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia

(76.6% vs. 50.0%), but it was not statistically significant. However, Nareddy *et al*. have found the significant association of hyponatremia with advanced liver disease as per Child-Pugh Class C [10]. Hyponatremia were associated with increased frequency of hepatic encephalopathy according to Gupta *et al*. and Gadhwal and Arif; similarly, in ours, it was significantly associated.[16,17] Younus A *et al*. also have established similar association.[18] Hyponatremia is known to affect the brain function and hence is said to predispose hepatic encephalopathy [14].

Further in-depth study in a larger setting may help us to get a deeper insight in eliciting the causal relationship between severity of liver disease and hyponatremia.

CONCLUSION

The prevalence of hyponatremia was seen in 3/4th (75.0%) of those with CLD in our study. However, the proportions of those with hyponatremia increased with severity of CLD, but for the significance, the levels of sodium did not differ much with severity of liver diseases as per the Child-Pugh classification. However, our study highlights a significant association of an important complication of hepatic encephalopathy with hyponatremia. Hence, serum sodium levels might indicate the complication in CLD.

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