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An observational cross-sectional study of the serum sodium levels and their association with severity in chronic liver disease patients in a tertiary care center in Haryana

Navtej Singh[1], Tarun[2], Ankit Chamoli[3]

[1]Professor and Head, [2]Associate Professor, [3]Postgraduate Resident, Department of General Medicine, Bhagat Phool Singh Government Medical College for Women, Sonipat, Haryana, India

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ABSTRACT

Background: Chronic liver diseases (CLDs) cause significant morbidity and mortality worldwide. Reduced serum sodium concentration is a common finding in patients with cirrhosis, being the most common electrolyte disorder in this setting. **Aims and Objectives:** The objectives of the study were as follows: (1) To find the association of altered serum sodium levels with the disease severity (as per Child-Pugh Score [CPS] and Model for End-Stage Liver Disease [MELD]) and (2) to assess for the type of dysnatremias commonly found in CLD and its association with complications of CLD. **Materials and Methods:** It is an observational cross-sectional study. It was done for 18 months (June 2019 till May 2020) in the Department of General Medicine of Bhagat Phool Singh Government Medical College for Women, Khanpur Kalan, Sonipat, Haryana. **Results:** Among all patients with CLD, 30.8% had serum sodium levels ≤130 mEq/L), 32.5% had 131–135 mEq/L, and 36.7% had ≥136 mEq/L. Thus, hyponatremia was observed in 63.3% of the patients. Mean MELD score and mean CPS were significantly higher in patients with reduced serum sodium levels. In addition, Child-Pugh Class C was significantly more common in patients with serums sodium levels ≤130 mEq/L as compared to other patients. Hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were found to occur significantly more common in patients with serums sodium levels ≤130 mEq/L. **Conclusion:** Hyponatremia is very common among patients with CLD. Low serum sodium level was associated with more severe liver disease, more complications, and higher mortality.

Key words: Ascites; Hepatorenal syndrome; Hyponatremia; Liver cirrhosis; Prognosis

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INTRODUCTION

Chronic liver diseases (CLDs) cause significant morbidity and mortality worldwide. Multiple etiological factors lead to a similar clinicopathological syndrome in CLDs, although the rates of progression and clinical course may be different.[1] Most of the increase in CLD mortality has been reported from the low- and low-middle-income countries (LMICs) of Asia and Africa. LMICs are experiencing a demographic and epidemiologic transition in disease burden. India is one of the epicenters of this change.[2] It may occur due to a wide variety of CLDs such as infections viral (HBV, HCV, and HDV), toxic (alcohol and arsenic), metabolic, biliary disorders, and vascular lesions like Budd-Chiari syndrome.

Reduced serum sodium concentration is a common finding in patients with cirrhosis,[3] being the most common electrolyte disorder in this setting. Indeed, about 20% of patients have values lower than 130 mmol/L, which is the current definition of hyponatremia in cirrhosis. However, even though patients with cirrhosis and serum sodium concentration between 130 and the lower normal limit of 135 mmol/L could not be considered as hyponatremic according to this definition, they

Address for Correspondence:
Dr. Tarun, Associate Professor, Department of General Medicine, Bhagat Phool Singh Government Medical College for Women, Sonipat – 131 305, Haryana, India. **Mobile:** +91-9812208111. **Email:** drtarun7@gmail.com

present pathogenic and clinical features similar to those with serum sodium lower than 130 mmol/L. With the cutoff of 135 mmol/L, the prevalence of hyponatremia rises to almost 50%. Instead, the occurrence of severe hyponatremia, that is, serum sodium concentration lower than 126 mmol/L, is rare and its prevalence is 6%.

In cirrhosis, hyponatremia generally develops slowly and gradually. Therefore, the brain can adjust to hypo-osmolality and hypotonicity of the extracellular fluid so that the incidence of neurological manifestations directly attributable to hyponatremia is relatively low. However, since hyponatremia occurs in the setting of end-stage liver disease, it is often difficult to define to what extent the clinical manifestations are due to reduced serum sodium concentration or to hepatic encephalopathy.

The relationship between hyponatremia and severity of cirrhosis is further evidenced by its close association with the occurrence of complications: Indeed, the prevalence of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis is substantially higher in patients with serum sodium concentration ≤130 mmol/L than in those with higher levels. Studies indicate that hyponatremia is a key accomplice in the pathophysiology of hepatic encephalopathy in cirrhosis and not just an innocent bystander.[4] Recent studies have concluded that hyponatremia is a key prognostic factor in patients with CLD. Moreover, the patients with hyponatremia have poor survival rates as compared to those without hyponatremia.[5]

Aims and objectives

The objectives of the study were as follows:

1. To find the association of altered serum sodium levels with the disease severity (as per Child-Pugh Score [CPS] and Model for End-Stage Liver Disease [MELD]).
2. To assess for the type of dysnatremias commonly found in chronic liver disease and its association with complications of chronic liver disease.

MATERIALS AND METHODS

It was an observational cross-sectional study conducted on patients admitted to General Medical Department of BPS Government Medical College and Hospital for Women, Sonipat, Haryana, for 18 months from June 2019 to May 2020.

All the patients presenting with CLD in said interval of time, fulfilling inclusion and exclusion criteria were included in the study.

Using n-Master 22 software taking the prevalence of CLD 1.28% and 6% precision with a 95% confidence interval, the required sample size was 120.

Inclusion criteria

The following criteria were included in the study:

1. Patients lying in the age group of 18–65 years, irrespective of gender.
2. Patients diagnosed with chronic liver disease.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients diagnosed with comorbid cardiac failure.
2. Patients diagnosed with comorbid chronic kidney disease
3. Patients on drugs that alter serum sodium levels such as SSRIs, TCA, MAO inhibitors, and cytotoxic drugs.

The analysis included profiling of patients on different demographic, laboratory, and clinical parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute numbers and percentages. Patients were classified into three groups (Groups A, B, and C) based on the serum sodium level to assess the association between serum sodium levels and patient characteristic complications and severity of disease as calculated by MELD and CPS. $P<0.05$ is considered statistically significant.

MELD[6]

It is calculated based on the variables: Serum bilirubin, serum creatine, and INR values. They are used to predict the mortality rate depending on the score. It is used to prioritize patients for liver transplantation and transjugular intrahepatic port systemic shunts.

MELD SCORE = 3.78 ($\log_e$ serum bilirubin [mg/dl]) + 11.2 (loge INR) + 9.57 ($\log_e$ serum creatinine [mg/dl]) + 6.43

CPS

The score was developed by Child and Turcotte in 1964. It includes serum bilirubin, serum albumin, ascites, clinically apparent encephalopathy, and malnutrition.[7] Each variable was given points according to the severity or based on cutoff ranges. Further patients were classified into three groups of worsening severity (A, B, and C). A modification of this score was made by Child-Pugh later to predict the outcome from surgical procedures used to reduce portal hypertension and to treat esophageal varices.[8]

FACTOR	1 POINT	2 POINTS	3 POINTS
ENCEPHALOPATHY	NONE	MINIMAL	ADVANCED
ASCITES	ABSENT	CONTROLLED	REFRACTORY
BILIRUBIN (mg/dl)	<2	2-3	>3
ALBUMIN (g/l)	>3.5	3.5-2.8	<2.8
PROTHROMBIN (s)	<4	4-6	>6

	CHILD A	CHILD B	CHILD C
TOTAL POINTS	5-6	7-9	10-15

Serum sodium levels groups:
Group A: Those with serum sodium levels ≤130 meq/l
Group B: Those with serum sodium levels between 131 and 135 meq/l
Group C: Those with serum sodium levels ≥136 meq/l.

RESULTS

In the present study, 120 patients were included. It was observed that 30.8% were in Group A (≤130 mEq/L), 32.5% were in Group B (131–135 mEq/L), and 36.7% were in Group C (≥136 mEq/L). Thus, hyponatremia was observed in 63.3% of the patients. (Figure. 1)

The age of the patients was not associated with serum sodium levels. The mean age of Group A patients was 49.7±11.78 years, for patients from Group B, it was 47.8±10.58 years, and 49.5±10.92 years for Group C patients. (Figure. 2)

Overall, 12.5% of the patients were female and the rest were male. The gender of the patients was not significantly associated with serum sodium levels. (Table. 1)

Portal hypertension was observed in 95.8%, hepatic encephalopathy in 18.3%, hepatorenal syndrome in 13.3%, spontaneous bacterial peritonitis in 6.7%, and coagulopathy in 16.7%. Of these, hepatic encephalopathy (P<0.01), hepatorenal syndrome (P<0.01), and coagulopathy (P<0.01) were found to occur significantly more commonly among patients from Group A, as compared to those in patients from Group B or C. (Figure. 3)

We observed that the mean MELD score was significantly higher among Group A patients (17.87±6.61) as compared to those with Group B (13.41±5.13) and Group C (11.84±4.3).(Figure. 4)

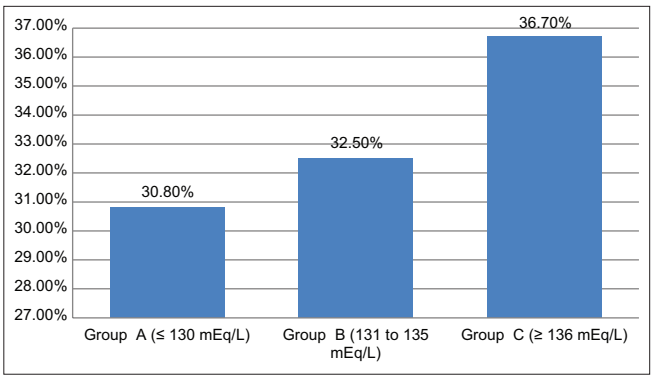

Figure 1: Distribution of patients according to their serum sodium levels

It was observed that Child-Pugh Class C was significantly more common in Group A patients (45.9%) as compared to those with Group B (25.6%) and Group C (11.4%). (Table. 2)

Overall, 10.8% of the patients expired. It was observed that mortality was 29.7% among Group A patients, which was significantly higher than that of Group B patients (5.1%) or Group C patients (0%). (Figure. 5)

DISCUSSION

In this observational cross-sectional study, we aimed to study the serum sodium levels in CLD patients and establish its association with the severity of disease in such patients. We included adult patients diagnosed with CLD and assessed their serum electrolytes, along with other biochemical parameters. The severity of liver disease was assessed

Table 1 : Distribution of patients according to their gender

Gender	Group A	Group B	Group C	Total
Female				
N	3	3	9	15
%	8.10	7.70	20.50	12.50
Male				
N	34	36	35	105
%	91.90	92.30	79.50	87.50
Total				
N	37	39	44	120
%	100.00	100.00	100.00	100.00
		*P=0.13		

*Analyzed using Chi-square test

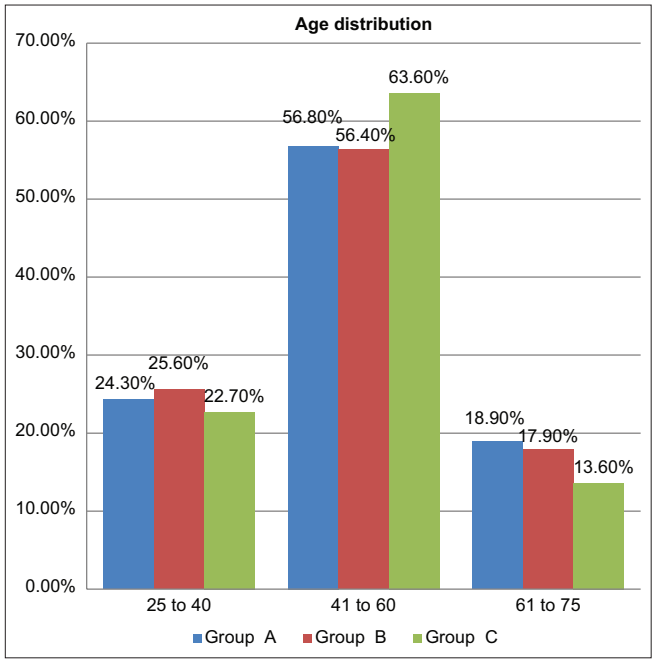

Figure 2: Distribution of patients according to their age

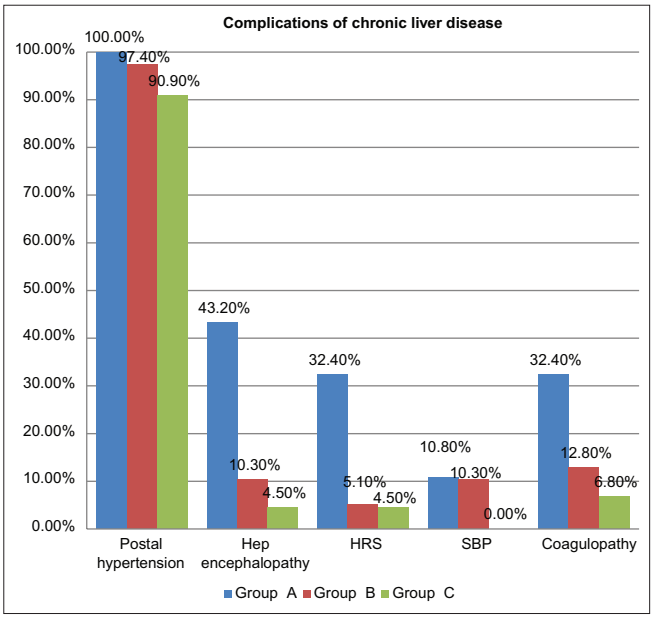

Figure 3: Distribution of patients according to their complications

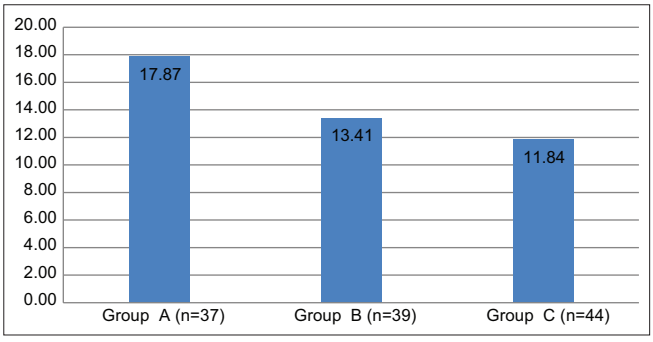

Figure 4: Description of patients according to their MELD score

Table 2: Distribution of patients according to their Child-Pugh class

Child-Pugh Class	Group A	Group B	Group C	Total
A				
N	1	3	10	14
%	2.70	7.70	22.70	11.70
B				
N	19	26	29	74
%	51.40	66.70	65.90	61.70
C				
N	17	10	5	32
%	45.90	25.60	11.40	26.70
Total				
N	37	39	44	120
%	100.00	100.00	100.00	100.00
		*P<0.001		

*Analyzed using Chi-square test

using CPS and MELD. Those with serum sodium levels <130 mEq/L were classified as Group A, 131–135 mEq/L as normal Group B, and greater or equal to 136 mEq/L as Group C. We discuss the findings of our study as follows.

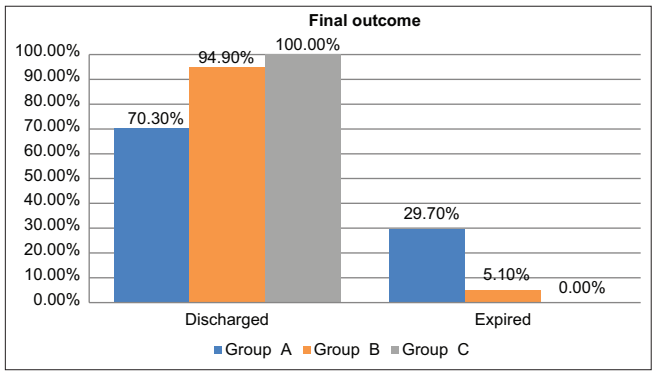

Figure 5: Association of clinical outcome with dysnatremia

Dysnatremia

In the present study, 120 patients were included. It was observed that 30.8% were in Group A (≤130 mEq/L), 32.5% were in Group B (131–135 mEq/L), and 36.7% were in Group C (≥136 mEq/L). Thus, hyponatremia was observed in 63.3% of the patients.

Meganathan and Kumar established the prevalence of hyponatremia in cirrhosis and to investigate if hyponatremia predicts an increased rate and severity of complications in cirrhosis.[9] They reported hyponatremia in 44%, normal serum sodium in 26%, and hypernatremia in 30% of the patients. In another study, Umemura et al., evaluated mortality in cirrhosis patients taking conventional diuretics and identified associations between serum sodium level and clinical characteristics.[10] In their study, 26 of 171 patients (15.2%) had sodium values below the lower limit of the normal range (135 mEq/L) and eight of 171 patients (4.7%) had Na of 130 mEq/L or less, which is the cutoff value commonly used to define hyponatremia. This study suggests that the frequency of hyponatremia in patients with cirrhosis is also relatively low in the Japanese population. This may reflect variations in patient selection, sample size differences, or ethnic variability.

Demographic characteristics

We observed that the mean age of Group A patients was 49.7±11.78 years, for patients from Group B, it was 47.8±10.58 years, and 49.5±10.92 years for Group C patients. Overall, 12.5% of the patients were female and the rest were male. Neither age nor gender was associated with serum sodium levels.

Elkady et al., reported the mean age of patients with a mean serum sodium <125 mEq/L to be 59 years and that of 56 years for those with mean serum sodium level more than 125 mEq/L.[11] Both age and gender were not found to be significantly associated with serum sodium levels.

Complications

In the present study, hepatic encephalopathy (P<0.01), hepatorenal syndrome (P<0.01), and coagulopathy

(P<0.01) were found to occur significantly more commonly among patients from Group A, as compared to those in patients from Group B or C. In a similar study by Meganathan and Kumar, the majority of the hyponatremic patients had the hepatorenal syndrome.[9] The incidence of portal hypertension was 95% in patients with severe hyponatremia. About 84% of the hyponatremic patients had the hepatorenal syndrome. It was seen that the incidence of complications such as hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, and portal hypertension is more in severe hyponatremia. In another study by Elkady et al., hepatic encephalopathy was observed in 91% and upper gastrointestinal bleeding was present in 50% of those with serum sodium levels <125 mEq/L, which was significantly higher as compared to those with serum sodium levels of more than 125 mEq/L.[11] In the study by Jenq et al., a significantly higher proportion of patients with sodium level ≤135 mEq/L had hepatic encephalopathy (52/67) as compared to those with sodium >135 mEq/L (35/59).[12] However, esophageal variceal bleeding, peptic ulcer bleeding, and presence of hepatocellular carcinoma were not significantly associated with serum sodium levels. The existence of putative mechanisms implicated in impaired free-water excretion (e.g., prostaglandins and arterial natriuretic peptide), which is irrelevant to gastrointestinal bleeding, may explain this phenomenon.

MELD score

In our study, the mean MELD score was significantly higher among Group A patients (17.87±6.61) as compared to those with Group B (13.41±5.13) and Group C (11.84±4.3). In another study by Meganathan and Kumar, the mean MELD score was 27.7±6.7 for patients with hyponatremia, which was significantly higher as compared to those with normal serum sodium levels and hypernatremia.[9] Elkady et al., also reported the mean MELD score to be 18.19±5.3 among patients with serum sodium ≤125 mEq/L as compared to 16.17±6.2 in patients with serums odium more than 125 mEq/L.[11]

Child-Pugh score and class

We observed that the Child-Pugh score was significantly higher among Group A patients (9.7±2.04) as compared to those with Group B (8.64±1.68) and Group C (7.71±1.8). In addition, Child-Pugh Class C was significantly more common in Group A patients (45.9%) as compared to those with Group B (25.6%) and Group C (11.4%). In a similar study by Jenq et al., CPS was significantly higher in patients with serum sodium level ≤135 mEq/L (12.4±2.3) as compared to those with serum sodium level >135 mEq/L (11.1±2.1).[12] In the study by Kim et al., mean CPS was significantly higher in patients with hyponatremia (10.5±1.6) as compared to those with normal serum sodium level (9.8±1.7) and hypernatremia (8.7±1.6), P<0.001.[13]

Mortality

In our study, overall, 10.8% of the patients expired. It was observed that mortality was 29.7% among Group A patients, which was significantly higher than that of Group B patients (5.1%) or Group C patients (0%). In another study by Eklady et al., three mortalities were 26.4% among patients with serums sodium ≤125 mEq/L and 15.9% among patients with serum sodium more than 125 mEq/L.[11] The difference was not statistically significant. Jenq et al., reported that differences in serum sodium level between survivors and non-survivors (137.2±7.4 mmol/L vs. 133.7±8.0 mmol/L, respectively) were statistically significant (P=0.02).[12] In a similar study by Kim et al., 3-year survival rate was 47.2% in patients with a serum sodium ≥136 mmol/L, 16.6% in patients with a serum sodium of 131–135 mmol/L, and 33.3% in patients with a serum sodium ≤130 mmol/L and the association was statistically significant (P<0.001).[13]

Limitations of the study

There are a few limitations of this study:

- First, the subjects were enrolled from just one institution; consequently, the results may not be directly extrapolated to other patient populations.
- Second, measurement of serum sodium level was performed only on the 1st day of admission. Sequential measurement of serum sodium concentrations (e.g., daily or weekly) may reflect the dynamic aspects of clinical diseases and thus provide complete data for mortality risk.

CONCLUSION

Hyponatremia is very common among patients with CLD. Low serum sodium level was associated with more severe liver disease, more complications, and higher mortality. Thus, we recommend:

1. Serum sodium levels should be monitored regularly in patients with CLD.
2. Those with hyponatremia should be prioritized to receive intensive care.
3. Future studies should be planned to assess how much reduction in complications and mortality can occur after correcting serum sodium levels.

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Authors Contribution:
NS- Concept and design of the study, statistical analysis and interpretation, and revision of the manuscript; **T-** Concept, coordination, statistical analysis, and interpretation; and **AC-** Statistical analysis and interpretation, reviewed the literature, and prepared first draft of manuscript.

Work attributed to:
Bhagat Phool Singh Government Medical College for Women, Sonipat - 131 305, Haryana, India.

Orcid ID:
Dr. Navtej Singh - https://orcid.org/0000-0002-0348-6822
Dr. Tarun - https://orcid.org/0000-0003-1201-5990
Dr. Ankit Chamoli - https://orcid.org/0000-0002-4837-0962

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