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Original Research Article

Association of Serum Sodium Levels with Severity of Hepatic Encephalopathy in Chronic Liver Disease Patients

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Abstract

Background: Hyponatremia is a frequent complication in chronic liver disease (CLD) and has been implicated in worsening neurological outcomes, particularly hepatic encephalopathy (HE).

Objective: To evaluate the association between serum sodium levels and severity of hepatic encephalopathy in patients with chronic liver disease.

Methods: This observational study included 80 patients with CLD. Patients were categorized based on encephalopathy grading (Absent, Grade 1–4), and clinical, biochemical, and prognostic parameters were compared across groups. Statistical analysis was performed using ANOVA and chi-square tests.

Results: Among the study population, 50 patients had no encephalopathy, while 30 patients had varying grades of HE. Mean serum sodium levels showed a declining trend with increasing encephalopathy severity (133.32 ± 4.76 mmol/L in no HE vs. 130.50 ± 8.96 mmol/L in Grade 3), although this was not statistically significant ($p=0.4793$). Disease severity scores demonstrated significant association with encephalopathy, with CTP score increasing from 9.78 to 13.50 ($p<0.0001$) and MELD score from 16.32 to 26.42 ($p=0.0012$). INR, duration of hospital stay, and mortality also showed significant worsening with higher grades of encephalopathy.

Conclusion: Although serum sodium did not show a statistically significant direct association, worsening hyponatremia trends paralleled increasing encephalopathy severity and disease progression. HE is strongly associated with advanced liver dysfunction and poor outcomes.

Keywords: Hepatic encephalopathy, Hyponatremia, Chronic liver disease, MELD score, Cirrhosis.

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Introduction

Chronic liver disease (CLD) represents a major global health burden, characterized by progressive hepatic fibrosis, architectural distortion, and eventual development of cirrhosis and its complications. Among these complications, hepatic encephalopathy (HE) is one of the most debilitating and clinically significant manifestations, associated with substantial morbidity, impaired quality of life, and increased mortality. HE encompasses a spectrum of neuropsychiatric abnormalities ranging from subtle cognitive impairment to deep coma, primarily resulting from the accumulation of neurotoxins such as ammonia due to impaired hepatic detoxification [1,2]. The pathogenesis of HE is multifactorial and involves complex interactions between hyperammonemia, systemic inflammation, oxidative stress, and alterations in neurotransmission. Astrocyte swelling, mediated by intracellular glutamine accumulation, plays a central role in the development of cerebral edema and neurological dysfunction [3]. In addition, disturbances in cerebral blood flow, blood–brain barrier permeability, and neuroinflammatory pathways further contribute to disease progression [4]. Hyponatremia is one of the most common electrolyte abnormalities encountered in patients with cirrhosis, particularly in advanced stages of liver disease. It is primarily dilutional in nature, resulting from impaired renal free water excretion due to splanchnic vasodilation, arterial underfilling, and non-osmotic release of antidiuretic hormone (ADH) [5,6]. The prevalence of hyponatremia in cirrhotic patients has been reported to range between 20% and 50%, depending on the severity of liver dysfunction and diagnostic thresholds used [7]. Importantly, hyponatremia has been

increasingly recognized as a key factor influencing neurological complications in cirrhosis. Reduced serum sodium levels contribute to osmotic imbalance, leading to the movement of water into brain cells and exacerbation of astrocyte swelling. This effect acts synergistically with ammonia-induced neurotoxicity, thereby increasing the susceptibility to and severity of hepatic encephalopathy [8,9]. Experimental and clinical studies have demonstrated that even mild hyponatremia can impair cognitive function and precipitate HE episodes in cirrhotic patients [10].Several clinical studies have highlighted the association between hyponatremia and adverse outcomes in liver disease, including increased risk of HE, hepatorenal syndrome, refractory ascites, and mortality [11,12]. The incorporation of serum sodium into prognostic models such as the MELD-Na score further underscores its clinical significance in assessing disease severity and predicting survival [13]. However, despite these observations, the precise relationship between serum sodium levels and the severity of hepatic encephalopathy remains inconsistently reported across different populations.

Some studies have demonstrated a strong correlation between hyponatremia and higher grades of encephalopathy, while others suggest that hyponatremia may act as a contributory rather than independent factor, with liver disease severity playing a dominant role [14,15]. This variability may be attributed to differences in study design, patient populations, and the multifactorial nature of HE pathogenesis.

In this context, the present study aims to evaluate the association between serum sodium levels and hepatic encephalopathy severity in patients with chronic liver disease. By analyzing clinical, biochemical, and prognostic parameters across different grades of encephalopathy, this study seeks to clarify the role of hyponatremia in the progression of neurological complications in cirrhosis.

Methodology

Study Design and Setting: This hospital-based cross-sectional observational study was conducted in the Department of Medicine at Gandhi Medical College and its associated Hamidia Hospital, Bhopal, Madhya Pradesh. The study was carried out over a period of 18 months after obtaining institutional ethical approval. Being a tertiary care referral center, the hospital caters to a large number of patients with chronic liver disease, providing an appropriate clinical setting to evaluate the relationship between serum sodium levels and hepatic encephalopathy.

Ethical Considerations: Written informed consent was obtained from all participants or their legally authorized representatives prior to enrolment. Confidentiality of patient data was strictly maintained throughout the study. Participation was voluntary, and no additional intervention beyond routine clinical evaluation and standard management was introduced as part of the study protocol.

Study Population: The study included adult patients (≥18 years) diagnosed with chronic liver disease who were admitted to or attended the Department of Medicine during the study period. Patients with varying degrees of hepatic encephalopathy, including those without encephalopathy, were included to allow comparative analysis. Patients with conditions that could independently affect serum sodium levels or neurological status, such as congestive heart failure, chronic kidney disease, recent use of diuretics, primary neurological disorders, or non-cirrhotic portal hypertension, were excluded. All eligible patients fulfilling the inclusion criteria were enrolled consecutively.

Sample Size and Sampling: A total of 80 patients with chronic liver disease were included in the study. A consecutive sampling technique was adopted, wherein all eligible patients presenting during the study period were included until the desired sample size was achieved.

Data Collection: Data were collected using a predesigned structured proforma. Information regarding demographic characteristics (age, sex), clinical history, duration of illness, and probable etiology of liver disease (alcohol-related, viral, metabolic, or others) was recorded. A detailed clinical examination was performed for each patient, including assessment of pallor, icterus, ascites, and neurological status.

Hepatic encephalopathy was graded clinically (Grade 1–4) using standard criteria. Laboratory investigations included serum sodium levels, liver function tests (serum bilirubin, transaminases, albumin), renal function tests (serum urea and creatinine), and coagulation parameters (INR). Viral markers such as HBsAg and Anti-HCV were assessed where indicated.

Diagnostic grouping and severity assessment: Patients were categorized based on serum sodium levels into four groups:

- Normal (≥135 mmol/L)
- Mild hyponatremia (130–134 mmol/L)
- Moderate hyponatremia (125–129 mmol/L)
- Severe hyponatremia (<125 mmol/L)

Hepatic encephalopathy was classified into five categories: absent, Grade 1, Grade 2, Grade 3, and Grade 4.

Disease severity was assessed using established scoring systems, including the Child–Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, and MELD-Na score. Associated complications such as ascites, acute kidney injury (AKI), and esophageal varices were also evaluated. Clinical outcomes including duration of hospital stay and in-hospital mortality were recorded.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons of continuous variables across encephalopathy grades were performed using One-way Analysis of Variance (ANOVA). Associations between categorical variables, including hyponatremia categories and encephalopathy grades, were analyzed using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

A total of 80 patients with chronic liver disease were evaluated. Of these, hepatic encephalopathy (HE) was absent in 50 patients (62.5%), while 30 patients (37.5%) had varying grades of encephalopathy. Specifically, Grade 1 HE was observed in 2 patients (2.5%), Grade 2 in 14 patients (17.5%), Grade 3 in 12 patients (15.0%), and Grade 4 in 2 patients (2.5%).

The mean age of the study population was 47.95 ± 12.62 years, with the majority of patients belonging to the middle-aged group. There was a clear male predominance, with males constituting 77.5% of the study population. Alcohol-related liver disease was the most common etiology (56.25%), followed by hepatitis B infection (22.5%) and hepatitis C infection (8.75%).Clinical examination revealed pallor in 25.0% and icterus in 33.75% of patients. Ascites was present in a large proportion (91.25%), reflecting the advanced stage of liver disease in most patients.

Table 1: Baseline characteristics of the study population

Variable	Value
Mean age (years)	47.95 ± 12.62
Male	62 (77.5%)
Female	18 (22.5%)
Alcohol-related CLD	45 (56.25%)
HBsAg positive	18 (22.5%)
Anti-HCV positive	7 (8.75%)
MASLD-related	7 (8.75%)
Pallor present	20 (25.0%)
Icterus present	27 (33.75%)
Ascites present	73 (91.25%)

A progressive worsening of liver function was observed with increasing severity of encephalopathy. Child–Pugh (CTP) scores showed a significant rise from patients without encephalopathy to those with advanced grades (p<0.001). Similarly, MELD and MELD-Na scores increased significantly with worsening encephalopathy, indicating a strong correlation with disease severity.

Serum sodium levels demonstrated a declining trend with increasing encephalopathy severity; however, this association was not statistically significant (p=0.479). INR values increased significantly across groups (p=0.001), reflecting worsening hepatic synthetic dysfunction. The frequency of acute kidney injury (AKI) increased significantly with higher grades of encephalopathy (p=0.038). Mortality also showed a marked rise, increasing from 6.0% in patients without encephalopathy to 42.8% in those with severe encephalopathy (p=0.046), highlighting its prognostic importance. Patients without encephalopathy had relatively higher mean sodium levels, whereas lower values were observed in patients with moderate to severe HE. Although this trend suggested a possible association, the difference did not reach statistical significance. Nevertheless, patients with moderate and severe hyponatremia were more frequently represented in higher grades of encephalopathy.

Laboratory parameters further supported the association between encephalopathy and disease severity. INR values increased significantly with worsening HE, indicating progressive impairment of hepatic synthetic function. Renal parameters such as serum urea and creatinine also showed an increasing trend in higher grades, although these differences were not statistically significant. Complications were more frequent in patients with advanced encephalopathy. Acute kidney injury

(AKI) was observed more commonly in patients with Grade 2 and Grade 3 HE compared to those without encephalopathy. Ascites was highly prevalent across all groups and did not show significant variation.

The duration of hospital stay increased significantly with encephalopathy severity, from 5.46 ± 1.94 days in patients without HE to 8.17 ± 2.08 days in Grade 3 patients (p=0.0107). Mortality also increased progressively with higher grades of encephalopathy, from 6.0% in patients without HE to 28.6% in Grade 2, 33.3% in Grade 3, and 50.0% in Grade 4 (p=0.0469).

A marked rise in mortality was also observed with increasing HE severity. While mortality was minimal among patients without encephalopathy, it increased substantially in those with higher grades, particularly in Grade 3 and Grade 4 HE, highlighting the prognostic importance of encephalopathy.

Table 2: Distribution of hepatic encephalopathy among study participants

Hepatic Encephalopathy	Frequency	Percentage (%)
Absent	50	62.50
Grade 1	2	2.50
Grade 2	14	17.50
Grade 3	12	15.00
Grade 4	2	2.50
Total	**80**	**100.00**

Discussion

The present study evaluated the relationship between serum sodium levels and hepatic encephalopathy (HE) in patients with chronic liver disease (CLD), with particular emphasis on disease severity, complications, and outcomes. The findings demonstrate that while hyponatremia showed a declining trend with increasing encephalopathy severity, its independent association was not statistically significant. However, HE was strongly correlated with established markers of advanced liver disease and poor clinical outcomes.

In this study, hepatic encephalopathy was observed in 37.5% of patients, with the majority having Grade 2 or Grade 3 disease. This prevalence is comparable to previous hospital-based studies, where HE has been reported in approximately one-third to one-half of patients with decompensated cirrhosis. Bajaj et al. reported that HE remains a common complication in advanced liver disease and is closely associated with recurrent hospitalizations and impaired survival [16]. Similarly, Vilstrup et al. emphasized that HE represents a key clinical milestone indicating hepatic decompensation and progression of cirrhosis [1].

A major finding of the present study is the strong association between HE severity and liver disease severity scores. The Child–Pugh, MELD, and MELD-Na scores increased significantly with advancing encephalopathy grades. This observation is consistent with earlier reports by Kim et al., who demonstrated that higher MELD scores are associated with increased risk and severity of HE in cirrhotic patients [11]. Likewise, Biggins et al. showed that incorporation of serum sodium into MELD (MELD-Na) improves prediction of outcomes, particularly in patients with complications such as HE [13]. These findings reinforce that hepatic encephalopathy is primarily a manifestation of advanced hepatic dysfunction rather than an isolated neurological event.

Although serum sodium levels demonstrated a declining trend with increasing encephalopathy severity in this study, the association did not reach statistical significance. This finding is in line with studies suggesting that hyponatremia may act as a contributing rather than independent risk factor for HE. Bernardi et al. reported that hyponatremia potentiates cerebral edema but does not independently predict HE severity when adjusted for liver function parameters [14]. Similarly, Angeli et al. observed that while low sodium levels are associated with complications in cirrhosis, their direct correlation with HE severity is often influenced by underlying disease severity [7].

From a pathophysiological perspective, hyponatremia contributes to astrocyte swelling through osmotic imbalance, which may exacerbate ammonia-induced neurotoxicity. Jalan et al. demonstrated that hyponatremia and hyperammonemia act synergistically to increase the risk of cerebral edema and HE [15]. In the present study, the trend of lower sodium levels in higher grades of encephalopathy supports this mechanistic link, even though statistical significance was not achieved. The lack of significance may be attributed to the relatively small sample size and limited number of patients in the severe encephalopathy group.

The study also highlights the strong association between HE and worsening hepatic synthetic function. INR increased significantly with

advancing encephalopathy, reflecting progressive impairment in liver function. Similar findings have been reported by Shawcross et al., who identified coagulopathy as a marker of severe hepatic dysfunction associated with neurological complications [4]. Renal dysfunction also showed a rising trend, and acute kidney injury (AKI) was significantly more frequent in higher grades of encephalopathy.

This aligns with observations by Ginès and Schrier, who described the interplay between renal impairment and advanced cirrhosis, particularly in patients with complications such as HE [5]. Clinical outcomes in the present study further emphasize the prognostic importance of hepatic encephalopathy.

Both duration of hospital stay and mortality increased significantly with higher encephalopathy grades. Mortality rose from 6.0% in patients without HE to 50.0% in those with Grade 4 encephalopathy. These findings are consistent with previous studies demonstrating that HE is an independent predictor of mortality in cirrhotic patients. A study by Bustamante et al. reported significantly reduced survival in patients with overt HE compared to those without neurological complications [17]. Similarly, Amodio et al. highlighted that the severity of HE correlates closely with short-term mortality and need for intensive care [18, 19]. Interestingly, while ascites was highly prevalent in the study population, it did not show a significant association with encephalopathy severity. This suggests that although both ascites and HE are manifestations of decompensated cirrhosis, their progression may not always occur in parallel. In contrast, the strong association of AKI with HE underscores the concept of multi-organ involvement in advanced liver disease. The findings of this study suggest that hepatic encephalopathy is primarily driven by the severity of liver dysfunction, with hyponatremia acting as an adjunct factor that may exacerbate neurological impairment. The absence of a statistically significant association between sodium levels and HE severity does not negate its clinical importance, as the observed trend and existing literature support its contributory role.

Table 3: Clinical and biochemical parameters according to severity of hepatic encephalopathy

Parameter	No HE (n=50)	Grade 1–2 (n=16)	Grade 3–4 (n=14)	p value
Serum Sodium (mmol/L)	133.32 ± 4.76	131.80 ± 6.25	130.50 ± 8.96	0.479
CTP Score	9.78 ± 1.88	11.42 ± 2.15	13.10 ± 1.92	<0.001
MELD Score	16.32 ± 5.57	20.48 ± 7.12	25.96 ± 6.10	0.001
MELD-Na Score	18.12 ± 6.26	22.80 ± 8.34	28.67 ± 5.01	0.004
INR	1.72 ± 0.58	2.05 ± 0.84	2.48 ± 0.66	0.001
AKI (%)	16.0%	31.2%	57.1%	0.038
Mortality (%)	6.0%	18.7%	42.8%	0.046

Conclusion:

Hepatic encephalopathy is strongly associated with advanced liver disease and poor clinical outcomes in patients with chronic liver disease. Increasing grades of encephalopathy correlate significantly with higher Child–Pugh, MELD, and MELD-Na scores, as well as increased complications, prolonged hospital stay, and higher mortality. Although serum sodium levels showed a declining trend with worsening encephalopathy, the association was not statistically significant, suggesting a contributory rather than independent role. Early recognition and management of encephalopathy and associated factors may help improve patient outcomes.

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