

HYPONATREMIA IN HEPATIC ENCEPHALOPATHY: PREVALENCE AND RELATIONSHIP WITH LIVER DISEASE SEVERITY

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Abstract

Background: Hyponatremia is a frequent complication of cirrhosis, as well as a significant cause of the development and progression of hepatic encephalopathy (HE). A deficiency in serum sodium augments brain edema and worsens the dysfunction of the nervous system. Even though the clinical significance of hyponatremia is high, most studies have not studied the prevalence of this disease and how it correlates with the extent of liver disease.

Objectives: To establish the frequency of hyponatremia in patients with hepatic encephalopathy and the correlation between hyponatremia and the severity of liver disease in the Child-Pugh classification and in the MELD-Na scores.

Methods: This was a cross-sectional study that entailed the analysis of adult patients who were admitted to the hospital with hepatic encephalopathy and had cirrhosis. The demographic, clinical, and laboratory data were collected, including serum sodium, bilirubin, INR, creatinine, and albumin. Hyponatremia was defined as less than 135mmol/L of serum sodium and was characterized as mild (130-134 mmol/L), moderate (125-129 mmol/L), or severe (<125 mmol/L). West Haven criteria were applied to score HE, and the severity of the liver disease was established with the assistance of the Child-Pugh class and the MELD-Na as disease-severity scores. The statistical tests were chi-square, ANOVA, Kruskal-Wallis, Spearman's correlation, and logistic regression.

Results: Hyponatremia was present in 197 of 338 patients (58.3%; 95% CI: 53.0%-63.4%). Hyponatremia was not significantly associated with West Haven HE grade (chi-square = 2.277, df = 3, p = 0.517; Cramer's V = 0.082) or Child-Pugh class (chi-square = 2.649, df = 2, p = 0.266; Cramer's V = 0.089). MELD-Na scores differed significantly across sodium categories (ANOVA F(3,334) = 51.986, p < 0.001; Kruskal-Wallis H = 104.513, p < 0.001), and serum sodium showed a significant inverse correlation with MELD-Na (Spearman rho = -0.605, p < 0.001). Multivariable logistic regression did not identify any statistically significant independent predictors of moderate-severe hyponatremia (all p > 0.05).

Conclusion: Hyponatremia was common among cirrhotic patients with hepatic encephalopathy, affecting more than half of the study population. The present data did not demonstrate a significant association of hyponatremia with either HE grade or Child-Pugh class. Serum sodium was inversely associated with MELD-Na, while no statistically significant independent predictors of moderate-severe hyponatremia were identified in multivariable analysis.

Keywords: Hyponatremia, Hepatic Encephalopathy, Cirrhosis, MELD-Na, Child-Pugh, Liver Disease Severity.

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Introduction

Cirrhosis of the liver is an insidious disease that is characterized by deformity of the hepatic architecture and portal hypertension. The large range of common occurrences of chronic liver attacks is the commonality: chronic viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and autoimmune or metabolic attacks. Decompensating events frequently occur in patients with cirrhosis, and they are ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Hepatic encephalopathy (HE) is one of these complications, and it is not only one of the most debilitating complications but also leads to neuropsychiatric impairment, repeated hospitalizations, and a high mortality rate (Tauseef, 2025).

Hepatic encephalopathy is a scale of reversible neurocognitive dysfunction, evident in the setting of severe liver disease, and no other neurological dysfunction. The presence of gut-derived neurotoxins, particularly ammonia, and insufficiency of hepatic clearance and malfunction of the blood-brain barrier have been thought to lead to it. Clinically, HE is graded according to the West Haven criteria, with grade 1 having mild cognitive changes and grade 4 having profound coma. Some of the risks that are associated with the incidence of HE include poor prognosis, poor quality of life, and high healthcare burden (Khattak et al., 2025).

Among the causes that lead to the risk and severity of HE is the presence of electrolyte imbalances, and the most severe is hyponatremia. The case of hyponatremia describes the accurate level of serum sodium level of less than 135 mmol/L and is a typical occurrence in a patient with advanced cirrhosis. It develops as a consequence of splanchnic vasodilatation, the activation of the renin-angiotensin-aldosterone system, sympathetic overactivity, and non-osmotic renin-vasopressin release, which all damage renal free water excretion. The hyponatremia that develops as a result of the dilution contributes to water loss to the brain, which causes low-grade cerebral edema and predisposes the body to ammonia-related neurotoxicity (Samejo et al., 2025).

Some of the studies have shown that hyponatremia is not only prevalent, but also an independent risk factor for the incidence of HE. More prone to encephalopathy of a severe type, the course of such patients is repeated. In

addition, hyponatremia was also found to be associated with extended hospital stay, the need for intensive care, and even death in the hospital. It is worth noting that serum sodium has been incorporated in the MELD-Na score, which has been shown to augment the prognostic value of liver transplantation awaiting patients with cirrhosis (Priya et al., 2025).

Even though some pathophysiological relationships have already been established, the incidence of hyponatremia in patients with HE was reported to vary among studies and in diverse populations, with an average prevalence of 30 or above. This may be due to dissimilarities in the choice of patients, the etiology of cirrhosis, access to care, and diuretics. Moreover, no local data on the occurrence in patients admitted with cirrhosis and HE and its correlations with the most popular severity scales, such as Child-Pugh class and MELD-Na score, are available. The purpose for which this relationship should be created is explained by the fact that it can help predict the early stratification of risk, help anticipate complications, and develop therapeutic strategies allowing for the restoration of the level of sodium (Zhou et al., 2025).

Literature Review

Hepatic encephalopathy (HE) refers to a neuropsychiatric complication of severe hepatic disease that has been extensively studied in terms of morbidity, mortality, and quality of life. It is a continuum of cognitive impairment that extends from mild neurocognitive impairments to a coma. The incidence of overt HE in cirrhotic patients has been reported internationally as 30-45 per cent, where less than 80 per cent may also have minimal cases. The pathogenesis of HE is a complex mechanism that comprises disrupted ammonia metabolism, inflammation in the system, neuroinflammation, and modifications to the blood-brain barrier. Some of the precipitating factors include electrolyte abnormalities, particularly hyponatremia, which have been progressively reported to be central to the development and progression of HE (Kumari et al., 2025).

The most common of all the electrolyte disorders observed in cirrhotic patients is hyponatremia, which is characterized by a serum sodium level that is below 135 mmol/L. Studies show that 30-50

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percent of patients with a high grade of cirrhosis in hospitals develop some form of hyponatremia, and its existence is directly correlated with poor clinical outcomes. This mechanism is primarily the dilutional one, mostly due to the non-osmotic secretion of arginine vasopressin as a reaction to the advancement of systemic vasodilation and efficient hypovolemia. The impact of this is a decrease in renal free water excretion, and this leads to water retention and sodium dilution. Not only does hyponatremia worsen the hemodynamic condition of patients with cirrhosis, but it directly causes cerebral degradation due to the formation of low-grade cerebral edema and enhanced brain sensitivity to ammonia (Shahinuzzaman et al., 2025).

Some of the researchers have reported the association of hyponatremia and hepatic encephalopathy. It has been demonstrated by Guevara et al that patients with low sodium concentration were more likely to develop HE as compared to normonatremic patients, irrespective of ammonia level. Similarly, studies in North America and Europe have yielded a reliable result that hyponatremia is associated with augmented and more severe manifestations of HE, prolonged hospital stay, and intensive care treatment. A prospective study showed that the risk of overt HE was nearly two times greater in patients with a serum sodium level of less than 130 mmol/L, as compared to the risk of overt HE in patients with a serum sodium level greater than 135 mmol/L. The results of the latter point to the importance of the interactions of ammonia and hyponatremia in the emergence of neurological dysfunction (Kumari & Naidu, 2025).

In the relationship with HE, hyponatremia has a stronger prognostic value. Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score are historically used to determine the severity of cirrhosis. However, the indices contained serum sodium. Early 2000s studies had confirmed that low serum sodium was prognostic of survival among cirrhotic patients on the liver transplant waiting list. This has resulted in the development of the MELD-Na score that adds serum sodium to the current MELD formula, which will add more stratification and prioritization of risky patients according to transplantation. The past studies that have confirmed the utility of MELD-Na have always found it to be superior to its counterpart, MELD, in patients with ascites, renal dysfunction, or frequent HE (Flores et al., 2025).

The local and regional literature also describes the fact that the hyponatremia burden is also great in the cirrhotic population. It has been observed that as many as 40 percent of patients with cirrhosis in the South Asian context present with hyponatremia in the hospital environment, with a higher occurrence in patients with ascites and those with HE. A research study conducted in Pakistan also indicated that hyponatremia was significantly more common in patients with high Child-Pugh class (B and C) and that hyponatremia was strongly associated with higher degrees of encephalopathy. This has also been reported in India, as it was noted that patients with a serum sodium below 130 mmol/L had a high degree of mortality compared to the patients whose serum sodium was normal. The above facts suggest that hyponatremia is not only common but a major prognostic variable within a broad spectrum of the population (Shekar et al., 2025).

Other than prevalence studies, neuroimaging and experimental models have been able to acquire mechanistic knowledge. Magnetic resonance spectroscopy analysis has proven that hyponatremia exacerbates neuro-tissue edema by limiting the osmotic regulation of the astrocyte in the scenario of hyperammonemia. This is why patients who have combined hyponatremia and hyperammonemia experience severe HE in comparison with hyperammonemia. The concept can also be supported by animal studies that demonstrate that the chronic hyponatremia condition predisposes the brain to the influence of ammonia toxicity and accelerates the development of the encephalopathy (Rudler et al., 2025).

Therapeutic implications have also been covered in the recent literature. The hyponatremia is reversible and has been discovered to be corrected by meticulously administering fluids, administering albumin, or administering vasopressin receptor antagonists (vaptans), which ensure that the neurological status of the chosen patients is improved. Vaptans are neither cost-effective nor safe, though, which makes their use limited. The current clinical practice suggests that the sodium levels of cirrhotic patients should be observed in detail and that abrupt correction is not to be performed due to the likelihood of osmotic demyelination. Nevertheless, such outcomes make the application of sodium optimization in the general treatment of HE justifiable (Semeya et al., 2025).

Although the relationship between hyponatremia and HE has significant evidence, there exist critical literature gaps. Most of the studies have been conducted among Western populations, and minimal data concerning the low- and middle-income nations have been gathered. In addition, the discrepancies in prevalence and effect of hyponatremia in the locations suggest that local disparities in the etiology of cirrhosis, diet, and access to healthcare can also have some impact. In addition to that, the causal relationship between hyponatremia and HE is already established, although the cause-and-effect relationship is debatable, since hyponatremia can either lead to the development of encephalopathy or it can be simply a symptom of more severe liver disease with increased susceptibility to encephalopathy (Diwan et al., 2025).

CHAPTER 3: RESEARCH METHODOLOGY

Study Design

This analysis was a cross-sectional analytical study conducted to determine the prevalence of hyponatremia in patients with hepatic encephalopathy (HE) and its relationship with liver disease severity. A cross-sectional design was selected because it allowed concurrent measurement of exposure (serum sodium level) and outcomes (encephalopathy grade and liver disease scores).

Study Setting and Duration

The study was conducted in the Department of Medicine/Gastroenterology at a tertiary care teaching hospital in Pakistan. Data were collected over six months from eligible patients admitted with hepatic encephalopathy.

Study Population

The target population consisted of adult patients aged 18 years and above who had a known history of cirrhosis and were admitted with hepatic encephalopathy of any grade. Both male and female patients were included.

Inclusion Criteria

- The patients were aged 18 years and above.
- Diagnosis of cirrhosis was identified using clinical, biochemical, and radiological evidence.
- Admitted patients had hepatic encephalopathy (West Haven grades I-IV).
- Informed consent was obtained either from the patient or the attendant.

Exclusion Criteria

- Patients with acute liver failure.
- Patients with chronic kidney disease (stage 4-5) and dialyzed patients.
- Patients who underwent large-volume paracentesis without albumin replacement within the preceding 48 hours.
- Patients who experienced severe hyperglycemia (>400 mg/dL) or a disorder that causes pseudohyponatremia.

Sampling Technique and Sample Size

Patients were recruited using consecutive sampling and fulfilled the eligibility criteria. The calculated target sample size was 380 patients. Complete data from 338 patients were available and included in the final analysis.

Data Collection Procedure

The data collection tool was a structured proforma/questionnaire. Demographic and clinical variables available in the study dataset included age, sex, etiology of cirrhosis, ascites, diuretic use, precipitating factor, and hepatic encephalopathy grade according to the West Haven classification. Laboratory parameters measured within 24 hours of admission included serum sodium, potassium, bilirubin, albumin, INR, creatinine, blood glucose, and ammonia. Liver disease severity was assessed using Child-Pugh class (A, B, or C) and the MELD-Na score. Length of hospital stay, ICU admission, and in-hospital mortality were also recorded.

Operational Definitions

- **Hyponatremia:** Serum sodium less than 135 mmol/L. It was divided into mild (130-134), moderate (125-129), and severe (<125 mmol/L).
- **Hepatic Encephalopathy:** West Haven graded I-IV.
- **Liver Disease Severity:** Child-Pugh class (A, B, C) and MELD-Na score.

Data Analysis

The data were entered and analyzed using SPSS version 26. Continuous variables were summarized as mean and standard deviation, with median and interquartile range additionally reported where appropriate; categorical variables were summarized as frequencies and percentages. Hyponatremia was defined as serum sodium <135 mmol/L and was categorized as mild (130-134 mmol/L), moderate (125-129 mmol/L), or severe (<125 mmol/L). The chi-square test was used to assess the association of hyponatremia status with West Haven HE grade and Child-Pugh

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class. MELD-Na scores across the four sodium categories (<125, 125-129, 130-134, and ≥ 135 mmol/L) were compared using one-way ANOVA, with Tukey HSD for pairwise comparisons, and the Kruskal-Wallis test as a non-parametric confirmation. Spearman correlation was used to assess the association between serum sodium and MELD-Na score. Multivariable logistic regression evaluated predictors of moderate-severe hyponatremia (<130 mmol/L), including age, sex, ascites, diuretic use, creatinine, INR, bilirubin, and HE grade. A two-sided p-value <0.05 was considered statistically significant; values smaller than 0.001 were reported as $p < 0.001$.

Ethical Considerations

Approval was obtained from the Institutional Review Board (IRB). Informed consent was obtained from the patient or the person responsible for their care. Confidentiality was maintained through study codes that replaced patient names. The risk to participants was low because the study was observational and involved routine investigations.

CHAPTER 4: RESULTS

Study Population

A total of 338 patients had complete data and were included in the final analysis. The mean age was 51.67 $\pm$ 11.36 years; 228 (67.5%) were male, and 110 (32.5%) were female. Child-Pugh class B was the most frequent severity class (155, 45.9%), followed by class C (115, 34.0%) and class A (68, 20.1%). West Haven HE grade II was most common (128, 37.9%), followed by grade III (86, 25.4%), grade I (77, 22.8%), and grade IV (47, 13.9%). Mean serum sodium was 133.15 $\pm$ 5.61 mmol/L and mean MELD-Na score was 22.29 $\pm$ 5.59.

Prevalence and Severity of Hyponatremia

Table 1. Distribution of serum sodium status and prevalence of hyponatremia

Serum sodium category	n	% of total
Normonatremia (≥ 135 mmol/L)	141	41.7
Mild hyponatremia (130-134	96	28.4

Serum sodium category	n	% of total
mmol/L)		
Moderate hyponatremia (125-129 mmol/L)	77	22.8
Severe hyponatremia (<125 mmol/L)	24	7.1
Any hyponatremia (<135 mmol/L)	197	58.3

Hyponatremia was present in 197 of 338 patients, corresponding to a prevalence of 58.28% (Wilson 95% CI: 52.96%-63.42%). Mild, moderate, and severe hyponatremia accounted for 96 (28.4%), 77 (22.8%), and 24 (7.1%) patients, respectively.

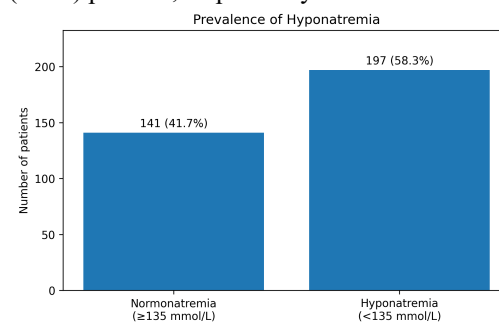


Figure 1. Prevalence of hyponatremia in the study population.

Association between Hyponatremia and HE Grade

Table 2. Hyponatremia status according to West Haven HE grade

HE grade	Normonatremia, n (%)	Hyponatremia, n (%)	Total
I	36 (46.8)	41 (53.2)	77
II	48 (37.5)	80 (62.5)	128
III	35 (40.7)	51 (59.3)	86
IV	22 (46.8)	25 (53.2)	47
Total	141 (41.7)	197 (58.3)	338

The proportion of patients with hyponatremia ranged from 53.2% in grades I and IV to 62.5% in grade II. The association between West Haven HE grade and hyponatremia status was

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not statistically significant (chi-square = 2.277, df = 3, p = 0.517). Cramer's V was 0.082, indicating a very small association.

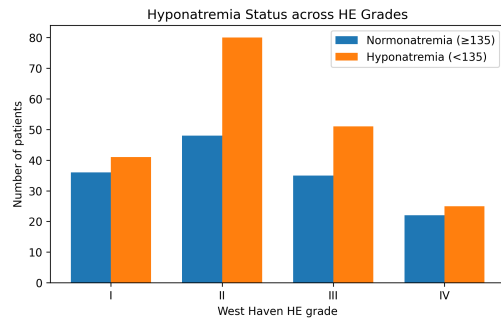


Figure 2. Distribution of normonatremia and hyponatremia across West Haven HE grades.

Association between Hyponatremia and Child-Pugh Class

Table 3. Hyponatremia status according to Child-Pugh class

Child-Pugh class	Normonatremia, n (%)	Hyponatremia, n (%)	Total
A	23 (33.8)	45 (66.2)	68
B	65 (41.9)	90 (58.1)	155
C	53 (46.1)	62 (53.9)	115
Total	141 (41.7)	197 (58.3)	338

Hyponatremia was present in 66.2% of Child-Pugh class A, 58.1% of class B, and 53.9% of class C patients. The association between Child-Pugh class and hyponatremia status was not statistically significant (chi-square = 2.649, df = 2, p = 0.266). Cramer's V was 0.089, indicating a small association. Therefore, this dataset does not support a claim that higher Child-Pugh class was associated with a greater frequency of hyponatremia.

MELD-Na Scores across Sodium Categories

Table 4. MELD-Na score according to serum sodium category

Sodium category (mmol/L)	n	MELD-Na, mean +/- SD	Median (IQR)
<125	24	28.83 +/- 5.23	28 (26-32)

Sodium category (mmol/L)	n	MELD-Na, mean +/- SD	Median (IQR)
125-129	77	25.49 +/- 4.51	26 (22-29)
130-134	96	22.89 +/- 4.41	23 (20-26)
≥135	141	19.03 +/- 4.75	18 (16-22)

MELD-Na scores differed significantly across the four sodium categories. One-way ANOVA showed $F(3,334) = 51.986$, $p < 0.001$, with eta-squared = 0.318. The Kruskal-Wallis test confirmed the group difference ($H = 104.513$, $df = 3$, $p < 0.001$). Tukey HSD showed significant pairwise differences between all sodium categories: severe versus moderate $p = 0.012$, moderate versus mild $p = 0.002$, and all remaining pairwise comparisons $p < 0.001$. Mean MELD-Na decreased stepwise as the sodium category increased.

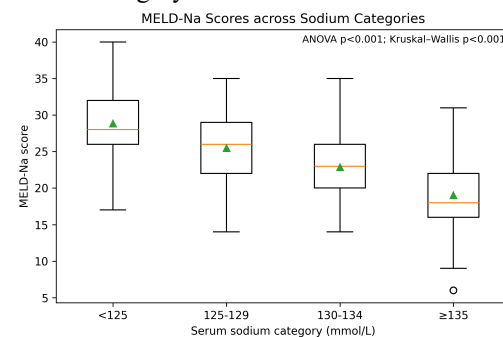


Figure 3. MELD-Na distribution across four serum sodium categories. The boxplot is generated from the raw study data.

Correlation between Serum Sodium and MELD-Na

Table 5. Spearman correlation between serum sodium and MELD-Na score

N	Spearman rho	p-value
338	-0.605	<0.001

Serum sodium was significantly and inversely correlated with MELD-Na score (Spearman $\rho = -0.605$, $p < 0.001$), indicating that lower sodium values were associated with higher MELD-Na scores.

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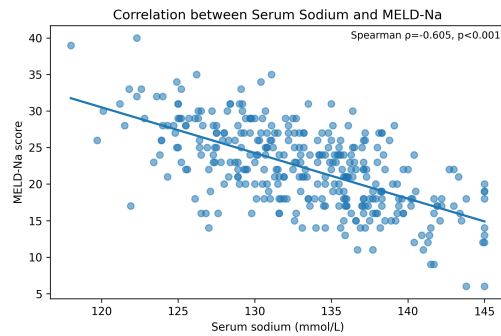


Figure 4. Scatter plot of serum sodium and MELD-Na score.

Predictors of Moderate-Severe Hyponatremia

Table 6. Multivariable logistic regression for moderate-severe hyponatremia (<130 mmol/L)

Predictor	Adjusted OR	95% CI lower	95% CI upper	p-value
Male sex	0.95	0.57	1.57	0.840
Ascites	0.73	0.41	1.31	0.295
Diuretic use	1.06	0.62	1.82	0.829
Age (per year)	1.01	0.99	1.03	0.250
Creatinine	1.15	0.70	1.88	0.584
INR	0.68	0.41	1.14	0.144
Bilirubin	0.93	0.86	1.02	0.107
HE grade (per grade)	1.15	0.90	1.47	0.249

None of the evaluated variables was a statistically significant independent predictor of moderate-severe hyponatremia after adjustment (all $p > 0.05$). The confidence intervals for all adjusted odds ratios included 1.0.

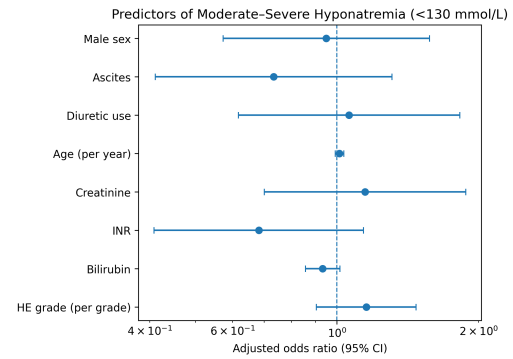


Figure 5. Adjusted odds ratios with 95% confidence intervals for predictors of moderate-severe hyponatremia.

Discussion

The present study showed that hyponatremia was highly prevalent among patients with hepatic encephalopathy, affecting more than half of the study population (58.3%). This observation is comparable to previous reports describing hyponatremia as a common electrolyte disorder in advanced cirrhosis, related to impaired renal free-water clearance in portal hypertension, activation of the renin-angiotensin-aldosterone system, and non-osmotic release of vasopressin. The high prevalence observed in this study supports regular assessment of serum sodium in patients with cirrhosis and encephalopathy (Kowshik et al., 2023).

In the present study, hyponatremia was observed across all West Haven grades; however, the association between HE grade and hyponatremia was not statistically significant ($\chi^2 = 2.277$, $p = 0.517$). Cramér's V of 0.082 indicated only a very small association. Although previous studies have reported relationships between low serum sodium and hepatic encephalopathy severity, the current data did not demonstrate a statistically significant relationship between HE grade and hyponatremia status (SADIQ et al., 2022).

With respect to liver disease severity, the present data did not demonstrate a statistically significant association between hyponatremia and Child-Pugh class (chi-square = 2.649, $df = 2$, $p = 0.266$; Cramer's $V = 0.089$). Hyponatremia occurred in 66.2% of class A, 58.1% of class B, and 53.9% of class C patients; therefore, the current dataset does not support an increasing frequency of hyponatremia with worsening Child-Pugh class. In contrast, MELD-Na differed significantly across sodium categories, and serum sodium was inversely correlated with MELD-Na (Spearman $\rho = -0.605$, $p < 0.001$).

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Because serum sodium is included in the MELD-Na calculation, this relationship should be interpreted with appropriate caution (Yau & Buchkremer, 2024).

The multivariable logistic regression analysis did not identify any statistically significant independent predictors of moderate-severe hyponatremia. HE grade, bilirubin, INR, creatinine, ascites, diuretic use, age, and gender all had p-values greater than 0.05. Although these factors may be clinically relevant in cirrhosis and sodium imbalance, the present analysis did not provide sufficient statistical evidence to classify them as independent predictors.

Overall, this study demonstrated that hyponatremia was prevalent among patients with hepatic encephalopathy. However, the current findings did not establish statistically significant associations of hyponatremia with either West Haven HE grade or Child-Pugh class. A strong inverse association was observed between serum sodium and MELD-Na, while multivariable analysis did not identify statistically significant independent predictors of moderate-severe hyponatremia.

These findings should be interpreted in the context of certain methodological considerations. First, the final analysis included 338 patients compared with the calculated target sample size of 380, which may have reduced the statistical power to detect smaller associations. Second, serum sodium is incorporated into the calculation of the MELD-Na score; therefore, the observed association between serum sodium and MELD-Na may partly reflect this mathematical relationship and should be interpreted with caution.

Conclusion

This study demonstrates that hyponatremia was common among patients with hepatic encephalopathy, affecting 58.3% of the study population. Hyponatremia was not significantly associated with West Haven HE grade ($p = 0.517$) or Child-Pugh class ($p = 0.266$). Serum sodium showed a significant inverse relationship with MELD-Na score (Spearman $\rho = -0.605$, $p < 0.001$), indicating that lower sodium values were associated with higher MELD-Na scores.

The multivariable logistic regression analysis did not identify any statistically significant independent predictors of moderate-to-severe hyponatremia. HE grade, renal function, bilirubin, INR, ascites, diuretic use, age, and gender all had p-values greater than 0.05. Therefore, these variables should not be interpreted as independent predictors on the basis of the present model.

Routine monitoring and timely management of serum sodium may be considered an important component of care in cirrhotic patients with hepatic encephalopathy, particularly because hyponatremia was common and was significantly associated with higher MELD-Na scores in this study.

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