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ORIGINAL ARTICLE

Correlation Between Serum Sodium and Worsening of Hepatic Encephalopathy

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ABSTRACT

Introduction: Hepatic encephalopathy (HE) is a severe neuropsychiatric complication in patients with liver cirrhosis, and hyponatremia is a critical factor influencing its progression. This study aims to evaluate the role of serum sodium levels in predicting the severity and outcomes of HE. **Methodology:** This observational study was conducted at A.J. Institute of Medical Sciences, Mangalore, over two years, including 97 HE patients aged 21 and above. Patients with Grade 2-4 HE, as per the West Haven criteria, were included. Sodium levels were measured on Days 0, 2, 4, and 7, and statistical analyses were performed to assess changes in sodium levels and their association with clinical outcomes. **Results:** The mean sodium level decreased from 126.79 mEq/L on Day 0 to 122.20 mEq/L on Day 7. Patients discharged against medical advice (DAMA) showed a mean sodium decrement of 6.00 mEq/L, while those who expired had a larger decrease of 10.59 mEq/L. In contrast, improved patients exhibited a mean sodium increase of 12.70 mEq/L. The variation in sodium levels across these groups was statistically significant ($p<0.001$). Lower sodium levels were associated with poorer outcomes, while rising sodium levels correlated with recovery. **Conclusion:** This study highlights that serum sodium levels are a significant predictor of morbidity and mortality in HE patients. Regular monitoring and timely correction of sodium imbalances are crucial for improving patient outcomes. Future research should focus on therapeutic strategies to manage hyponatremia and its systemic effects in HE patients.

Keywords: Hepatic encephalopathy; Hyponatremia; Serum sodium; Liver cirrhosis; Patient outcomes; Morbidity; Mortality

INTRODUCTION

It is estimated that diseases of the liver account for nearly 2 million deaths globally. Studies have also shown that there has been an increase in the age standardised incidence of patients who suffer from decompensated cirrhosis of the liver[1,2]. The morbidity and mortality of the patients who suffer from cirrhosis of the liver is much lower than those patients who have hepatic decompensation along with cirrhosis of the liver. It is estimated that the one-year mortality may reach up to 50% in these patients. Also, it is noted that hepatic decompensation is one of the most important causes of hospitalization in patients with cirrhosis[3–5]. Hepatic encephalopathy is the term used to describe the complex and variable changes in neuropsychiatric status that complicate liver disease. The defining feature is fulminant hepatic failure, and the multitude of metabolic abnormalities caused by loss of functioning hepatocyte mass[6,7]. There is evidence that overt hepatic encephalopathy and hyponatremia both have a higher mortality in patients who have cirrhosis of the liver[8]. In comparison, hyponatremia is considered another important complication of decompensated liver cirrhosis and is said to be present in at least half of the patients who have been hospitalized for cirrhosis of liver hepatic decompensation. Studies have also shown that hyponatremia can be an independent predictor of mortality not only in patients who have cirrhosis of the liver that is decompensated but also in those patients who are acute on chronic liver[9]. Sodium variations are a common electrolyte abnormality encountered in patients with chronic liver disease and more so when they develop, overt hepatic encephalopathy. A majority of patients with ethanol-related chronic liver disease progress to the decompensated state thereby developing hepatic encephalopathy either due to

continued ethanol consumption, superadded infection or blood loss, etc., Analysis of the course and variation in the biochemical parameters during the disease process might help better understand and manage the disease process [10,11].

In chronic liver disease owing to hepatic dysfunction patients develop hypoproteinaemia and thereby also progress to a state of fluid overload leading to dilutional hyponatraemia. As a feature of worsening hepatic dysfunction patients develop hepatic encephalopathy due to failure of degradation activity of the liver leading to the accumulation of toxic metabolites. Serum sodium levels in previous studies have been shown to be worse in a decompensated state when compared to compensated chronic liver disease. This study has been done to observe the fluctuations of serum sodium values in various grades of hepatic encephalopathy and also in patients with chronic liver disease, to ascertain the use of serum sodium as an indicator to the severity of hepatic encephalopathy and to observe the nominal variations in patients with chronic liver disease without the complication.

The aim of the study was to ascertain the use of serum sodium as an indicator to the severity and morbidity of hepatic encephalopathy and to observe the nominal variation in serial serum sodium levels during hepatic encephalopathy.

The objective of the study was to ascertain the association of serum sodium values as an indicator to the recovery and deterioration of hepatic encephalopathy.

MATERIAL AND METHODS

This observational study was conducted at A.J. Institute of Medical Sciences and Research Centre, Mangalore, over a period of two years from 2022 to 2024. The study population included patients diagnosed with hepatic encephalopathy (HE), admitted to the Medicine Department in a decompensated state, i.e., Grade 2-4 as per West Haven criteria [12].

Inclusion and Exclusion Criteria

The study included patients above 21 years of age, of both sexes, who were admitted to the ICU and wards with a diagnosis of hepatic encephalopathy (Grade 2-4). Exclusion criteria were patients with acute intracerebral events such as infarcts or hemorrhage, patients in sepsis with positive blood cultures, patients with a history of drug intake (e.g., narcotics, valproic acid), and those developing hepatorenal syndrome or massive ascites.

Sample Size Estimation

The study aimed to include 97 cases of diagnosed hepatic encephalopathy. The sample size was estimated based on the prevalence of hyponatremia (serum sodium $\leq$ 130 mEq/L), which is around 70% in HE patients associated with decompensated chronic liver disease (DCLD). A 95% confidence level and an absolute variability of 20% were considered to calculate the sample size. The sampling technique used was convenience sampling.

Data Collection

Following ethics approval from the Institutional Ethics Committee (IEC) and after obtaining informed written consent from each patient, data was collected from patients admitted with hepatic encephalopathy and hyponatremia at AJ Institute of Medical Sciences and A.J. Hospital and Research Centre. Additional data were extracted from patients' medical records and case sheets when necessary to ensure completeness of the information. The statistical analysis was done using SPSS version 23.0.

RESULTS

This observational study analyzed a total of 97 patients diagnosed with HE admitted in a decompensated state. Among the hepatic encephalopathy patients, 38.1% were aged 25-44 years, 44.3% were aged 45-64 years, 15.5% were aged 65-84 years, and 2.1% were aged 85 and above. Females constituted 24.7% & males 75.3% of the study participants.

In the study of hepatic encephalopathy patients, 74.2% were diagnosed with alcoholic cirrhosis, while 14.4% had HBV-associated cirrhosis. Autoimmune hepatitis and NASH each accounted for 3.1% of cases, with alcoholic hepatitis and HCV-associated cirrhosis both contributing 2.1% each. Wilson's disease was the least common, representing 1.0% of the patients (Figure 1).

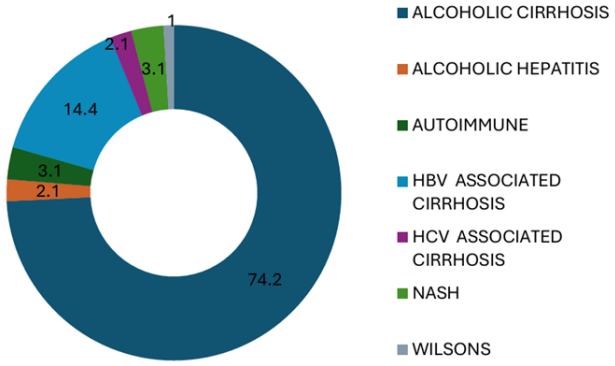

Fig. 1: Cause of hepatic encephalopathy among the participants

Table 1 presents the serial changes in mean sodium levels from Day 0 to Day 7 in patients with hepatic encephalopathy. On Day 0, the mean sodium level was 126.794 $\pm$ 7.769mEq/L, which progressively decreased over time. By Day 2, the mean sodium level dropped to 124.588 $\pm$ 9.684 mEq/L, further declining to 123.392 $\pm$ 11.371 mEq/L on Day 4. On Day 7, the mean sodium level reached

its lowest point at 122.196 ± 13.106 mEq/L. The analysis shows a significant decrease in sodium levels over the course of the study, with an F value of 49.24 and a p value of less than 0.001, indicating that the changes in sodium levels were statistically significant over time. This suggests that worsening hyponatremia is associated with disease progression in hepatic encephalopathy.

Table 1: Serial changes in mean sodium levels over time

Sodium Level	Mean	Std. Deviation	F Value	p Value
Sodium Level Day 0	126.794	7.769		
Sodium Level Day 2	124.588	9.684	49.24	p < 0.001
Sodium Level Day 4	123.392	11.371		
Sodium Level Day 7	122.196	13.106		

Figure 2 shows the trends in serum sodium levels across patient outcomes. In patients discharged against medical advice (DAMA), the mean sodium levels showed a significant decline, dropping from 118.96 ± 0.92 on Day 0 to 112.96 ± 0.92 by Day 7. Similarly, in the expired group, the mean sodium level began at 123.38 ± 3.59 on Day 0 and gradually decreased to 112.78 ± 4.45 by Day 7. In contrast, patients in the Improved group exhibited a consistent increase in sodium levels, rising from 136.50 ± 1.54 on Day 0 to 139.50 ± 1.54 on Day 7. These findings underscore a clear pattern: while patients who either expired or left against medical advice experienced a progressive decline in sodium levels, those who showed clinical improvement demonstrated a steady increase. This suggests that rising sodium levels may be associated with better recovery outcomes, whereas declining sodium levels may indicate a worsening prognosis.

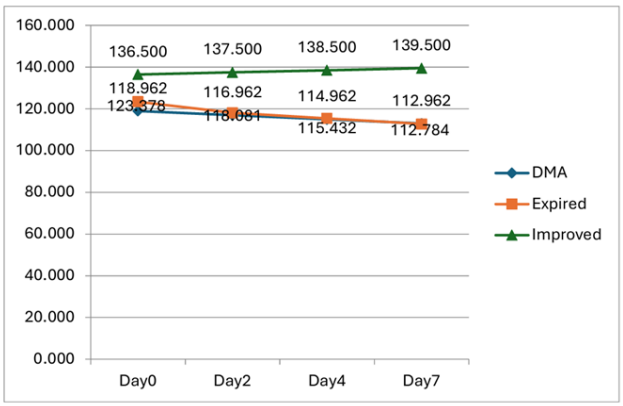

Fig. 2: Trends in serum sodium levels across patient outcomes

Patients who improved showed an increase in sodium levels, while those who expired or were discharged against medical advice (DAMA) exhibited decreasing sodium levels (Table 2).

Table 2: Comparing changes taken place in sodium from day 0 to day 7 between the outcome

Status	Average Change (Mean)	Mean	SD	F value	p value
DAMA	Average decrement	6	0.00	51.0	p < 0.001
Expired	Average decrement	10.59	2.11		
Improved	Average increment	12.7	2.08		

Table 2 indicates significant changes in values from Day 0 to Day 7 across different outcomes. For those with DAMA (Discharged Against Medical Advice), the average decrement is 6.00 ± 0.00. In the expired group, the average decrement is 10.59 ± 2.11, reflecting a notable decrease. Conversely, the Improved group shows an average increment of 12.70 ± 2.08, indicating a significant increase in values. These findings highlight a clear pattern of reduction for DAMA andExpired outcomes, and an increase for those who improved (with an F value of 51.0 and a p-value less than 0.001)

DISCUSSION

Our study observed that 44.3% of HE patients were aged 45-64 years, 38.1% were aged 25-44 years, 15.5% were aged 65-84 years, and 2.1% were aged 85 and above. Males constituted 75.3% of the patients, while females accounted for 24.7%. This age distribution is consistent with the findings of Kim et al., who reported a significant prevalence of HE in middle-aged to older adults[13]. Furthermore, the higher incidence of HE among males aligns with the observations of Lars Bosen et al., who noted a greater prevalence of HE in men[10].

Alcoholic cirrhosis was identified as the most common cause of HE in our study, accounting for 74.2% of cases. This was followed by HBV-associated cirrhosis (14.4%), with autoimmune hepatitis and NASH each contributing 3.1% of cases. Alcoholic hepatitis and HCV-associated cirrhosis each accounted for 2.1%, while Wilson's disease was the least common cause, representing 1.0% of the patients. These findings align with the study by Maqsood et al., which identified alcohol-related liver disease as the predominant cause of HE and highlighted the significance of hepatitis B and C as etiological factors[14].

Our study revealed a significant decrease in serum sodium levels over time in patients with hepatic encephalopathy (HE). The mean sodium level on Day 0 was 126.79 mEq/L, which dropped to 122.20 mEq/L by Day 7. The trends in sodium levels varied markedly across different patient outcomes. Patients discharged against medical advice (DAMA) had a mean sodium decrement of 6.00 mEq/L, while those who expired exhibited a greater decline, with a mean reduction of 10.59 mEq/L. In contrast,

patients who improved showed an average sodium increase of 18.925 mEq/L. These findings highlight a statistically significant difference in sodium level changes across outcomes, with a p-value of less than 0.001.

This result aligns with a study by Guevera et al., which demonstrated that hyponatremia (serum sodium < 130 mEq/L) is a significant risk factor for developing overt HE in cirrhosis patients. The study suggested that hyponatremia is associated with lower brain concentrations of organic osmolytes, particularly myo-inositol, which are critical for brain function. Patients with reduced brain myo-inositol levels were more likely to develop overt HE, emphasizing the critical role of sodium levels in the pathogenesis and progression of HE[15]. Similarly, Jong Hon Kim et al. found that even mild hyponatremia (serum sodium 131-135 mEq/L) was linked to severe complications such as higher HE grades, spontaneous bacterial peritonitis, and hepatic hydrothorax. Their study demonstrated that lower sodium levels were closely associated with impaired liver function, as indicated by higher Child-Pugh and MELD scores, and predicted worse clinical outcomes[12].

The sodium level decline observed in non-survivors and DAMA patients may be attributed to several factors. As liver disease progresses, the liver's capacity to regulate electrolytes diminishes, leading to sodium and water imbalances. Advanced liver disease is commonly associated with complications like ascites, which exacerbates sodium retention and dilutional hyponatremia. Hepatorenal syndrome, a severe complication of liver cirrhosis, results in renal vasoconstriction and reduced renal perfusion, impairing the kidneys' ability to excrete free water, which further contributes to hyponatremia. The use of diuretics to manage ascites and edema also contributes to sodium imbalances, further reducing serum sodium levels. Additionally, hyponatremia leads to a reduction in brain organic osmolytes, particularly myo-inositol, which are crucial for maintaining neuronal cell volume and function, thus worsening the neurological symptoms of HE.

Sodium levels among HE patients showed a significant association with clinical outcomes. Patients who improved exhibited a steady increase in sodium levels from Day 0 to Day 7, while those who expired or were discharged against medical advice (DAMA) experienced a continuous decline. Specifically, the mean sodium levels on Day 0 were 118.96 mEq/L for DAMA patients, 123.38 mEq/L for those who expired, and 120.575 mEq/L for those who improved. By Day 7, these values had decreased to 112.96 mEq/L for DAMA patients and 112.78 mEq/L for expired patients, while those who improved showed an increase to 139.50 mEq/L. This significant variation in sodium levels across the different groups correlates directly with their clinical outcomes, suggesting that sodium levels are a key prognostic factor.

This association between sodium levels and patient outcomes is supported by a study by Lars Bosen et al., which found that lower serum sodium levels at admission were associated with higher rates of HE and increased mortality[10]. Their study emphasized that the hazard for HE increases linearly with each mmol/L decrease in serum sodium, underscoring the crucial role of sodium levels in predicting HE severity and patient survival. Similarly, findings by Vishwadeep Ahluwalia et al. highlight that hyponatremia significantly impacts the health-related quality of life in cirrhotic patients[16]. Their research showed that patients with hyponatremia, irrespective of HE presence, experienced worse physical and psychosocial health-related quality of life scores, reflecting the broader impact of sodium imbalances on patient well-being.

Hyponatremia in HE patients is often caused by impaired renal water excretion, a condition exacerbated by the use of diuretics commonly prescribed to manage ascites and edema in cirrhotic patients. The progressive decline in sodium levels observed in non-survivors and DAMA patients reflects the severity of liver and renal dysfunction. As liver disease progresses, the kidneys' ability to excrete free water diminishes, leading to water retention and dilutional hyponatremia. Diuretic use further disrupts the electrolyte balance by promoting sodium excretion while reducing fluid overload. In contrast, the improvement in sodium levels among survivors may be attributed to successful medical interventions, including careful fluid management, diuretic adjustments, and treatment of underlying infections or complications that exacerbate hyponatremia. Nutritional support and medications that enhance renal perfusion may also contribute to improved sodium levels and patient outcomes. Therefore, regular monitoring and timely intervention for hyponatremia are critical in managing HE patients, as evidenced by the significant differences in sodium level trends among the DAMA, expired, and improved groups.

CONCLUSION

This study highlights the crucial role of serum sodium levels in predicting the severity and outcomes of hepatic encephalopathy (HE). The data demonstrated that lower sodium levels are strongly associated with higher morbidity and mortality, particularly in patients who were discharged against medical advice or expired. This finding supports existing literature that highlights hyponatremia as a key factor in the progression of HE. In contrast, patients who improved showed a steady increase in sodium levels, suggesting effective management of their condition. The study emphasizes the importance of regular monitoring and timely intervention for hyponatremia, along with other biochemical abnormalities such as elevated bilirubin, hypoalbuminemia, and elevated liver enzymes, which were common among our study population. These findings reinforce the need

for targeted therapeutic strategies to correct electrolyte imbalances and improve patient outcomes. Overall, our study provides valuable insights into the biochemical profiles of HE patients and highlights the critical need for comprehensive management of both liver dysfunction and its systemic complications to enhance survival rates and quality of life for these patients.

Conflict of Interest

None.

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None.

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