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**RESEARCH PAPER**

# Prevalence of hyponatremia in Cirrhosis and its correlation with severity of the disease

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***Background and aims:*** *Clinical manifestations of cirrhosis result from pathophysiological changes and also reflect the severity of the disease regardless the etiology. Portal hypertension is a major complication of cirrhosis which leads to development of ascites and esophageal varices.[1]* ***Method:*** *232 cirrhotic patients were included in this study from November 2017 to December 2018. Hyponatremia was defined as serum sodium level <135mEq/L and was classified as severe, moderate and mild. Disease severity was described using Child-Pugh Score (CPS) and Model for End-Stage Liver Disease (MELD) score. Association between categorical variables were tested using the Chi-square test. Correlation between variables was assessed using the Pearson correlation coefficient. Statistical analysis was performed with IBM SPSS Statistics version 21 Software. A p-value less than or equal to 0.05 was considered significant.* ***Results:*** *Out of 232 patients 33.62% (n=78) had normal sodium levels while 154 patients had hyponatremia among whom 19% (n=46), 15.52%, (n=36), 31.62 % (n=72) patients had severe, moderate and mild hyponatremia respectively. Sodium level was negatively correlated (r= -0.254) with MELD score (p <0.0). The majority of the patients had hyponatremia in CPS class C, followed by Class B and Class A in different hyponatremia groups.* ***Conclusion:*** *Hyponatremia is a prevalent finding in Cirrhosis of the liver, especially in an advanced stage. The severity of hyponatremia correlates with the severity of liver disease and complications in the majority of the cases.*

*Keywords: Cirrhosis, Hyponatremia, Disease severity, Child-Pugh Score, MELD Score*

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## INTRODUCTION

Cirrhosis of the liver is defined by diffuse hepatic fibrosis, where regenerative and degenerative nodules replace the typical architecture of the liver.[1] Clinical manifestations of cirrhosis result from pathophysiological changes and also reflect the severity of the disease regardless the etiology. Portal hypertension is a major complication of cirrhosis which leads to development of ascites and esophageal varices.[1] Variceal bleeding, ascites, encephalopathy, jaundice, SBP, hepatorenal syndrome (HRS), coagulopathy, and hepatocellular carcinoma are the complications in decompensated Cirrhosis, some of which are life-threatening. Electrolyte imbalances like hyponatremia and hypokalemia are frequent manifestations of decompensated Cirrhosis.

In hospitalized patients, hyponatremia is a widespread manifestation, occurs in up to 22% of the cases.[2] Hyponatremia is generally defined as a serum sodium level < 135mEq/l. While in the case of cirrhotic patients, serum sodium< 130 mEq/l is considered hyponatremia and is found in up to 20-30% of the cases.[2-4] Hyponatremia in cirrhotic patients are usually asymptomatic, but in some cases, it may develop nausea, vomiting, anorexia, lethargy and rarely seizure.

Hyponatremia in Cirrhosis may be due to hypovolemia or, more commonly, hypervolemia. Hypovolemic hyponatremia, representing 10% of all patients with Cirrhosis of the liver,[5] results from a substantial loss of extracellular fluid over sodium, either from the kidney due to high diuretics or high diuretics the gastrointestinal tract due to diarrhoea or vomiting.

Hyponatremia in cirrhotic patients is hypervolemic or dilutional hyponatremia.[6] Pathogenesis of hyponatremia in Cirrhosis is nonosmotic hypersecretion of arginin vasopressin from neurohypophysis related to circulation dysfunction. It is associated with increased mortality and morbidity from HRS and hepatic encephalopathy. It is also connected with the increased likelihood of complications in hepatic transplantation in the form of reduced short time survival.

Hyponatremia occurs due to impaired circulatory volume, primarily due to peripheral vasodilatation, leading to secretion of AVD and reduction in renal perfusion and GFR(glomerular filtration rate). Ultimately, there is impaired free water clearance.[7]

Hyponatremia in cirrhotic patients has been associated with a reduction in myoinositol, a brain organic osmolyte, which may play an essential role in the genesis of hepatic encephalopathy.[6] The mainstay of managing hyponatremia is fluid restriction and salt restriction, potassium correction and the use of diuretics. Intravenous albumin infusion may be effective for a short duration.[8]

Hyponatremia is a predictor of reduced survival in cirrhotic patients with ascites (9,10) regardless of the aetiology and a significant risk factor for life-threatening complications like HRS and hepatic encephalopathy. (4,5) So, early detection and proper management are essential in treatment perspectives.

Alcoholic liver disease and Cirrhosis are widespread due to high alcohol intake in this part of the country. However, the prevalence of hyponatremia in cirrhotic patients has not been studied widely. Therefore the present study has investigated the prevalence of hyponatremia in cirrhotic patients and its correlation with the severity of the disease and its complications.

## MATERIAL AND METHODS

It was a cross-sectional hospital-based observational study conducted in our hospital. According to the study criteria, 232 randomly selected cirrhotic patients were included from November 2017 to December 2018.

All patients with Cirrhosis were included. If available, the diagnosis of Cirrhosis of the liver was made by clinical examination, laboratory investigations, USG and histopathological report. Cirrhotic patients with heart failure, chronic kidney diseases, hepatocellular malignancy and drugs therapy (SSRI, TCA, MAO inhibitors) were excluded from the study. Patients were examined clinically and by laboratory investigations, including complete blood count, urine analysis, renal function test, serum sodium and potassium, liver function tests, blood glucose, prothrombin time(PT), INR, ultrasound abdomen, UGI endoscopy, chest x-ray and ascitic fluid analysis, wherever indicated. Informed consent was taken from the patients.

Hyponatremia was defined as serum sodium level < 135mEq/l and was subdivided into three different groups like severe (<125mEq/l)A serum sodium level >136mEq/l is considered normal.. A serum sodium level >136mEq/l is considered normal. CPS (class A, B and C) and MELD scores describe disease severity. The MELD score was divided into subgroups like<10, 11-20, 21-30 and 31-40.

### Statistical analysis

Pearson's chi-square test was used to test any association between categorical variables**.** To assess the correlation between variables, the Pearson correlation coefficient was used. Statistical analysis was performed with IBM SPSS Statistics version 21 Software. A p-value less than or equal to 0.05 was considered significant.

## RESULTS

A total of 232 patients were included in this study, among whom the majority were alcoholic Cirrhosis (93.10%), followed by HBV infection and alcohol plus HBV infection (**Figure 1**).

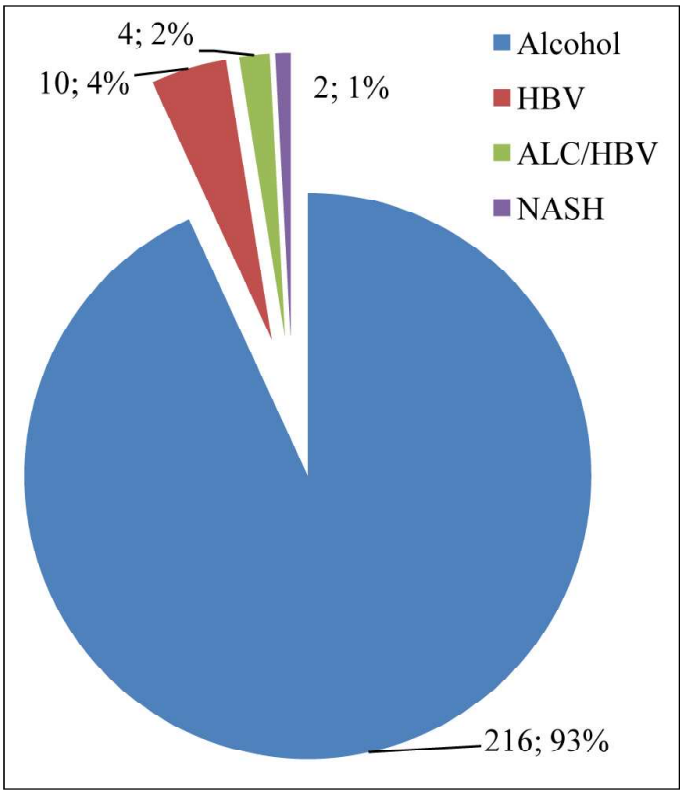


**Figure 1** Aetiology

Out of 232 patients, 209 were male, and 23 were female. The age range of the patients was 28 to 78 years with a mean (±S.D.) age of 47.34(± 10.26) years. The most common presenting features of Cirrhosis were ascites

(78.45%), jaundice (50.86%) and pain abdomen (43.97%). Hepatic encephalopathy (24.14%), UGI bleeding(20.6%), tense ascites(18.10%), SBP (16.81%) and hepatorenal syndrome(10.34%) were also observed in few cases (**Table1**).

**Table 1** Basic Characteristics of Cirrhotic patients (n = 232)

| Characteristics | | |
|---|---|---|
| | Mean ± S.D | Range |
| Age (in years) | 47.34 ± 10.26 | 28–78 |
| Sex: | Number (n) | Percentage (%) |
| Male | 209 | 90.09 |
| Female | 23 | 9.91 |
| Presenting Features | Number (n) | Percentage (%) |
| Ascites/ Distension of Abdomen | 182 | 78.45 |
| Jaundice | 118 | 50.86 |
| Pain Abdomen | 102 | 43.97 |
| Bacterial Infection | 84 | 36.21 |
| Fever | 80 | 34.48 |
| Hepatic Encephalopathy | 56 | 24.14 |
| UGI Bleeding | 48 | 20.69 |
| Tense Ascites | 42 | 18.10 |
| SBP | 39 | 16.81 |
| Hepatorenal Syndrome | 24 | 10.34 |

Out of 232 patients, 33.62% (n=78) had normal sodium level. The overall prevalence of hyponatremia was 66.38%, with 19.83% of patients having mild, 15.52% having moderate and 31.03% having severe hyponatremia (**Fig. 2**).

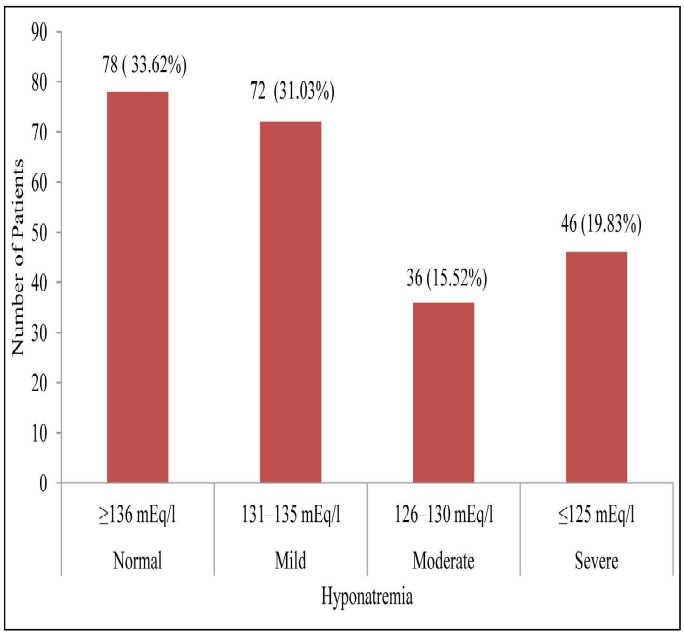


**Figure 2** Prevalence of Hyponatremia among patients with Cirrhosis

The mean(±S.D.) MELD score of the patients was 24.16 (± 7.78). Serum sodium level (mEq/l) was found to be negatively correlated (r=-0.254) with MELD score (p <0.001), suggesting that patients with lower sodium levels had more severe disease (Table 2).

**Table 2 Correlation between MELD score and the sodium levels**

| Sodium (mEq/l) | MELD Score (Mean ± S.D) | *r value* | *p value* |
|---|---|---|---|
| ≥136 | 21.59 ± 8.15 | -.254 | <0.001 |
| 131–135 | 23.31 ± 6.51 | | |
| 126–130 | 24.33 ± 7.29 | | |
| ≤125 | 29.70 ± 6.70 | | |
| Overall | 24.16 ± 7.78 | | |

Based on the MELD score, patients were assigned to 4 groups, <10, 11-20, 21- 30 and 31- 40. These scores indicated that as hyponatremia became more severe, the MELD score increased, suggesting an association of declined liver function with a degree of hyponatremia (**Table 3**).

**Table 3** MELD Score

| MELD Score | Sodium (mEq/l) | | | | Total (n = 232) | *p value* |
|---|---|---|---|---|---|---|
| | ≤125 (n = 46) | 126–130 (n = 36) | 131–135 (n = 72) | ≥ 136 (n = 78) | | |
| ≤10 | 0 | 0 | 0 | 6 (7.69%) | 6 (2.59%) | 0.007* |
| 11–20 | 2 (4.35%) | 12 (33.33%) | 18 (25.00%) | 28 (35.90%) | 60 (25.86%) | 0.001* |
| 21–30 | 28 (60.87%) | 18 (50.00%) | 42 (58.33%) | 34 (43.59%) | 122 (52.59%) | 0.183 |
| 31–40 | 16 (34.78%) | 6 (16.67%) | 12 (16.67%) | 10 (12.82%) | 44 (18.97%) | 0.021* |

In this study, most of the patients (60%) had a CPS score of C followed by CPS score B (32.76%), and only 6.9% of the patients had a CPS score A. In every range of hyponatremia, the majority of the patients had CPS class C followed by Class B and Class A. These scores indicate that as hyponatremia became more severe, liver function declined (**Table 4**).

**Table 4** Child-Pugh Score

| Child–Pugh | Sodium (mEq/l) | | | | Total (n = 232) | *p value* |
|---|---|---|---|---|---|---|
| | ≤125 (n = 46) | 126–130 (n = 36) | 131–135 (n = 72) | ≥ 136 (n = 78) | | |
| A (5–6) | 0 | 2 (5.56%) | 2 (2.78%) | 12 (15.39%) | 16 (6.90%) | 0.003* |
| B (7–9) | 6 (13.04%) | 10 (27.78%) | 24 (33.33%) | 36 (46.15%) | 76 (32.76%) | 0.002* |
| C (10–15) | 40 (86.96%) | 24 (66.67%) | 46 (63.89%) | 30 (38.46%) | 140(60.35%) | 0.000* |

The chi-square test revealed significant associations of the number of patients having various complications of Cirrhosis with the severity of hyponatremia. As seen from Table 3, hepatic encephalopathy and HRS, two significant complications of Cirrhosis, were significantly associated with severe hyponatremia (p-value<0.05). Out of 56 patients with hepatic encephalopathy, 20 (43.48%) had a serum

Sodium level<125mEq/l, while among the 24 patients with Hepatorenal syndrome, 20 had severe hyponatremia. Except for bacterial infections and UGI bleeding, the occurrence of other complications like ascites, Tense Ascites and SBP were also found to be significantly associated with the degree of hyponatremia (p-value<0.05). While ascites and UGI bleeding were found to occur among patients with any level of hyponatremia, the other complications were found to occur more among patients with serum sodium Level <125mEq/l. It was observed that patients with a Serum sodium concentration <135mEq/l had a significantly increased risk of developing complications than Patients with serum sodium >136mEq/l. Among patients with hyponatremia, the risk of developing complications was higher among those with severe hyponatremia than moderate and mild hyponatremia cases (Table 5).

**Table 5** Frequency of complications of Cirrhosis in different serum sodium level groups

| | Sodium (mEq/L) | | | Normal ≥136(mEq/L) (n = 78) | p-Value |
|---|---|---|---|---|---|
| | ≤125 (n = 46) | 126–130 (n = 36) | 131–135 (n = 72) | | |
| Ascites (182) | 26 (56.52%) | 30 (83.33%) | 60 (83.33%) | 66 (84.62%) | 0.001* |
| Bacterial Infection (84) | 24 (52.17%) | 12 (33.33%) | 22 (30.56%) | 26 (33.33%) | 0.090 |
| Hepatic Encephalopathy (56) | 20 (43.48%) | 8 (22.22%) | 14 (19.44%) | 14 (17.95%) | 0.007* |
| Hepatorenal Syndrome (24) | 20 (43.48%) | 2 (5.56%) | 0 (0.00%) | 2 (2.56%) | <0.001 * |
| Tense Ascites (42) | 18 (39.13%) | 6 (16.67%) | 8 (11.11%) | 10 (12.82%) | 0.001* |
| SBP (39) | 14 (30.43%) | 9 (25.00%) | 8 (11.11%) | 8 (10.26%) | 0.008* |
| UGI Bleeding (48) | 8 (17.39%) | 10 (27.78%) | 18 (25.00%) | 12 (15.38%) | 0.313 |

## DISCUSSION

Cirrhosis of the liver is very common due to the high prevalence of alcohol intake in this part of the country. In the advanced stage of liver disease, along with other complications, hyponatremia is also a widespread manifestation associated with increased mortality.

In the present study, the overall prevalence of hyponatremia was 66.38%. Out of 232 patients, 78 patients (33.62%) had average serum sodium level, whereas 72 patients (31.03%), 36 patients (15.52%), and 46 patients (19.83%) had mild, moderate and severe hyponatremia, respectively. The findings are concordant with similar other studies.[7,11-15] However, in the present study, the prevalence of hyponatremia was a little higher due to the enrolment of patients irrespective of diuretics therapy.

In the present study, we have observed that hyponatremia more commonly occurs with CPS class C (60.34%) followed by CPS B (32.76%) and a high MELD score (mean 24.16 +/-7.78). The correlation between serum sodium concentrations and MELD score had shown a strong negative correlation with a correlation coefficient -0.254 (p-value <0.001). This finding was similar to another study.[11]

Of 232 patients, 60.35% had CPS class C followed by 32.76% and 6.90% patients in class B and class A, respectively. Out of 46 patients with severe hyponatremia, the majority, 40 patients (86.96%), were in CPS class C. Similarly, 24 out of 36 patients (66.67%) with moderate hyponatremia, 46 out of 72 patients (63.89%) with mild hyponatremia and 30 out of 78 patients (38.46%) with average sodium level were in class C of CPS. The association between CPS classes and serum sodium concentration was statistically significant (p-value<0.05). This finding was in agreement with various studies suggesting a significant correlation between the disease severity and hyponatremia.[11,16]

The association between the severity of hyponatremia and complications were also assessed in this study. Except for ascites and upper GI bleeding, it was observed that as the severity of the hyponatremia increases, the different complications increases. The proportions of patients with hepatic encephalopathy and HRS were significantly higher among patients with severe hyponatremia. Frequency of hepatic encephalopathy, hepatorenal syndrome, SBP, tense ascites was familiar with serum sodium<130mEq/l and specifically among those with Serum sodium level <125mEq/l. Other complications like bacterial infections, tense ascites. Spontaneous bacterial peritonitis(SBP) was more prevalent among patients with severe hyponatremia. Only ascites and upper GI bleeding affected patients with hyponatremia and those with average sodium levels. This finding agrees with similar other studies.[15,16]

Majority of the complications are believed to occur due to increased body fluid resulting from the impairment of solute free water excretion. Hyponatremia plays an essential role in the occurrence of hepatic encephalopathy. The extracellular fluid hypotonicity due to hyponatremia favours the osmotic effects of glutamine and cell swelling and cerebral oedema induced by increased ammonia levels. Moreover, hyperammonemia and hyponatremia alter the myo-inositol metabolism in the brain cells. So, hyponatremia accelerates the neurological effect of altered ammonia metabolism in Cirrhosis.[15,17]

**Limitation**: The current study is a single centred cross-sectional study. Patients were not being followed up.

## CONCLUSION

The present study shows that hyponatremia is a prevalent finding in Cirrhosis of the liver, especially in an advanced stage. Hyponatremia in Cirrhosis is usually associated with various complications. The severity of hyponatremia correlates with the severity of liver disease and difficulties in the majority of the cases.

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