## Original Article

# A Study of Hyponatremia in Patients of Liver Cirrhosis in a Tertiary Care Hospital of South Gujarat

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## ABSTRACT

**Introduction:** Hyponatremia is the most common electrolyte abnormality in patients with liver cirrhosis and associates with the poor prognosis and the complications like hepatorenal syndrome, ascites etc. To evaluate the association between hyponatremia and its complications in liver cirrhosis and its prognostic significance.

**Methods:** A retrospective study was done on 50 patients who were selected based on history, examination, laboratory investigations and imaging suggestive of the diagnosis of cirrhosis of liver . The presence of various complications and the outcome of the patients were monitored. The severity of the disease was calculated using MELD score and Child Pugh Score. In this study, which was conducted in a tertiary care hospital of South Gujarat, we enrolled 50 subjects who were known cases cirrhosis of liver .

**Result:** Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels are associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis etc. in the patients with hyponatremia, it ranged from 117-130 meq/l . hyponatremia was present in 26%. Complication of liver cirrhosis like GI Bleeding, Coagulopathy and Hepatorenal Syndrome with hyponatremia were found as 53.8 %, 46.1 % and 30.8 %.

**Conclusion:** Hyponatremia is associated with high morbidity and mortality in cirrhotic patients. Hence hyponatremia is a valuable marker that can be used to assess the prognosis in patients with cirrhosis of liver.

**Key words**: liver cirrhosis, hyponatremia, hepatic encephalopathy

## INTRODUCTION

Hyponatremia is defined as a serum sodium level <136 mEq/L while in cirrhosis, it has classically been considered relevant only at a serum sodium level <130 mEq/L.[1] Generally, hyponatremia is divided into three clinical types: hypovolemic, euvolemic and hypervolemic and some patients have a mixed picture of all the three. In liver cirrhosis hyponatremia occurs in the Setting of a hypotonic serum with increased extracellular fluid volume, or so-called 'dilutional hyponatremia'. In this instance, there is a distinct impairment of free water excretion in the presence of excessive anti-diuretic hormone (ADH).

Diseases associated with this type of hyponatremia include cirrhosis, congestive heart failure, certain types of Renal failure and nephritic syndrome.[2] Hyponatremia in cirrhosis largely occurs in the setting of expanded extracellular fluid volume. There are of course important instances where a patient will present with hypovolemic hyponatremia in the setting of diuretic use or gastrointestinal losses. When evaluating a cirrhotic patient with low serum sodium, it is important to exclude and treat these causes as the sole or major contributing factor.[3,4]

Although hyponatremia can be found in patients with early or moderately advanced cirrhosis belonging to classes A and B of Child-Pugh classification, in most cases it occurs in an advanced disease (Child-Pugh class C).[5] The relationship between hyponatremia and severity of cirrhosis is further evidenced by its close association with the occurrence of complications like hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis.[6] Severe hyponatremia, that require immediate and specific treatment, is relatively rare in cirrhosis. Therefore, the occurrence of mild to moderate hyponatremia has mainly to be appraised for its clinical meaning. In fact, the occurrence of hyponatremia represents an independent outcome predictor for the development of hepatorenal syndrome, hepatic encephalopathy and survival.[7,8]

| Variables | 1 point | 2 points | 3 points |
|---|---|---|---|
| **S. Bilirubin (mg/l)** | 2 | 2-3 | >3 |
| **S. Albumin (g/l)** | >35 | 28-35 | <28 |
| **INR** | <1.7 | 1.7-2.2 | >2.2 |
| **Ascites** | None | Mild | Moderate to severe |
| **Encephalopathy** | none | Grade 1-2 | Grade 3-4 |

Based on total points, Child A = 5–6 points, Child B = 7–9 points, Child C = 10–15 points

Such an important prognostic power has led serum sodium concentration to be included in the prognostic model for end-stage liver disease (MELD),[9] widely used to establish the need for liver transplantation and prioritize patients on the waitlist, with the aim of improving its prognostic ability, especially in patients with cirrhosis and ascites.

MELD = 3.78 [log serum bilirubin (mg/dl)] + 11.2 [loge INR] + 9.57 [loge serum creatinine (mg/dl)] + 6.43

MELD-Na*= MELD + 1.32 x (137 - Na) - [0.033 x MELD*(137 - Na)]

*Bigginset el.[10] proposed the MELD-Na score by integrating serum sodium concentration into the MELD equation.

## AIMS AND OBJECTIVES

The research was conducted to study the prevalence of hyponatremia in cirrhosis and to evaluate the association between hyponatremia and complications in cirrhosis and its prognostic significance.

## MATERIAL & METHOD

The study was conducted amongst outdoor & indoor patients of a tertiary care hospital of South Gujarat. All patients with Ultrasonography suggestive of cirrhosis of liver were included with excluding other causes of hyponatremia like Patients with cardiac failure , fluid overload states, trauma , burns , vomiting, diarrhoea , Patients with chronic kidney disease , gastrointestinal losses, CNS lesions leading to cerebral salt wasting , Patients on drugs such as diuretics, Selective serotonin reuptake inhibitors, Tricyclic anti- depressants, Monoamine oxidase inhibitors, cytotoxic drugs, steroids etc.

## RESULTS

This study, conducted in a tertiary care hospital of South Gujarat, on enrolled 50 subjects.

Patients were classified into four groups based on the serum sodium levels which are Normal (≥135 meq/L), Mild (130-134 meq/L), Moderate (125-129 meq/L) and Severe (<125 meq/L) hyponatremia. Based on the serum sodium levels, 26% of patients had serum sodium levels in Moderate hyponatremia (125-129 meq/L). 18% of patients had serum sodium levels in Mild hyponatremia (130-134 meq/L), while 56% of patients had Normal hyponatremia (≥135 meq/L). No patients (0%) had severe hyponatremia (<125 meq/L). Therefore, in this study we have classified patients based on serum sodium levels which are (≥135 meq/L), (130-134 meq/L) and <130meq/L.

In the present study, 44% of the patients were from 51-60 years age group followed by 26% of 41-50 years age group. Mean age of patients with sodium levels (≥135 meq/L) was 53.28 ± 8.86 years, while in those with serum sodium levels (130-134 meq/L) and (<130 meq/L) were 53.78 ± 9.24 years and 53.79 ± 8.8 years respectively.

Alcohol was the most common cause of cirrhosis of liver in this study followed by chronic hepatitis B and chronic hepatitis C. All patients presented with abdominal distension and lower limb swelling at the time of admission, while clinically detectable jaundice was found in around 36% of patients.

**Table 1: Type of hyponatremia in liver cirrhosis**

| Type of hyponatremia | Patients (%) |
|---|---|
| Normal (≥135 meq/L) | 28 (56%) |
| Mild (130-134 meq/L) | 9 (18%) |
| Moderate (125-129 meq/L) | 13 (26%) |
| Severe (<125 meq/L) | 0 (0%) |
| **Total** | **50 (100%)** |

**Table 2: Age wise distribution of study subjects**

| Age (yrs) | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) | Total |
|---|---|---|---|---|
| 31-40 | 2 (7.1%) | 1 (11.1%) | 1 (7.6%) | 4 (8%) |
| 41-50 | 5 (17.8%) | 4 (44.4%) | 4 (30.7%) | 13 (26%) |
| 51-60 | 13 (46.4%) | 3 (33.3%) | 6 (46.2%) | 22 (44%) |
| 61-70 | 8 (28.5%) | 1 (11.1%) | 2 (15.3%) | 11 (22%) |
| **Total** | 28 (100%) | 9 (100%) | 13 (100%) | 50 (100%) |
| **Mean Age** | 53.28 ±8.86 | 53.78 ± 9.24 | 53.79 ± 8.8 | 53.63 ± 8.96 |
| **P value** | 0.713 | | | |

**Table 3: Gender wise distribution in study subjects**

| Gender | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) | Total |
|---|---|---|---|---|
| Male | 21 (75%) | 6 (66.6%) | 11 (84.6%) | 38 (76%) |
| Female | 7 (25%) | 3 (33.3%) | 2 (15.4%) | 11 (24%) |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** | **50(100%)** |
| **P value** | **0.614** | | | |

**Table 4: Cause of cirrhosis in study subjects**

| Causes of cirrhosis | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) | Total |
|---|---|---|---|---|
| Alcohol | 27 (96.4%) | 8 (88.8%) | 10 (76.9%) | 45 (90%) |
| HBV | 1 (3.5%) | 1 (11.1%) | 2 (15.3%) | 4 (8%) |
| HCV | 0 | 0 | 1 (7.69%) | 1 (2%) |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** | **50 (100%)** |

**Table 5: Clinical presentation wise distribution of study subjects**

| Presentation | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) | Total |
|---|---|---|---|---|
| Abdominal Distension | 28 (100%) | 9 (100%) | 13 (100%) | 50 (100%) |
| Lower Limb Swelling | 28 (100%) | 9 (100%) | 13 (100%) | 50 (100%) |
| Jaundice | 12 (42.8%) | 2 (22.2%) | 4 (30.7%) | 18 (36%) |
| Altered Sensorium | 5 (17.8%) | 1 (11.1%) | 4 (30.7%) | 10 (20%) |
| Seizures | 1 (3.5%) | 0 | 1 (7.7%) | 2 (4%) |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** | **50 (100%)** |

**Table 6-Clinical complication in study subjects**

| Complication | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) | Total |
|---|---|---|---|---|
| Ascites | 28 (100%) | 9 (100%) | 13 (100%) | 50 (100%) |
| Portal Hypertension | 24 (85.7%) | 9 (100%) | 12 (92.3%) | 45 (90%) |
| Hepatic Encephalopathy | 2 (7.1%) | 5 (55.5%) | 9 (69.2%) | 16 (32%) |
| GI Bleeding | 1 (3.5%) | 2 (22.2%) | 7 (53.8%) | 10 (20%) |
| Coagulopathy | 1 (3.5%) | 1 (11.1%) | 6 (46.1%) | 8 (16%) |
| Hepatorenal Syndrome | 0 | 1 (11.1%) | 4 (30.8%) | 5 (10%) |
| SBP | 0 | 1 (11.1%) | 2 (15.3%) | 3 (6%) |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** | **50 (100%)** |

**Table 7: Biochemical parameters in study subjetcs**

| Biochemical parameters | Value (Mean ± SD) | | |
|---|---|---|---|
| | (≥135 meq/L) (n=28) | (130-134 meq/L) (n=9) | (<130 meq/L) (n=13) |
| S. Creatinine | 1.25 ± 1.28 | 1.96 ± 1.41 | 2 ± 1.45 |
| S. Urea | 60 ± 40.53 | 43.89 ± 41.18 | 52.92 ± 37.78 |
| Total Bilirubin | 4.27 ± 5.38 | 13.27 ± 5.49 | 12.37 ± 5.67 |
| Total Protein | 7.04 ± 1.13 | 6.94 ± 1.09 | 7.41 ± 1.04 |
| S. Albumin | 3.62 ± 1 | 3.45 ± 1.01 | 3.98 ± 1.03 |
| SGOT | 63.14 ± 21.97 | 68.33 ± 21.29 | 66.08 ± 21.42 |
| SGPT | 64.17 ± 19.54 | 77.77 ± 17.94 | 62.46 ± 19.3 |
| Prothrombine Time | 25.60 ± 15.35 | 28.55 ± 14.95 | 42.92 ± 16.87 |
| INR | 1.73 ± 0.89 | 1.84 ± 0.88 | 2.69 ± 0.97 |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** |

**Table 8: Score wise distribution in study subjects**

| Score | Mean ± SD | | |
|---|---|---|---|
| | (≥135 meq/L) (n=28) | (130-134meq/L) (n=9) | (<130 meq/L) (n=13) |
| MELD Score | 18.5 ± 8.24 | 28.66 ± 8.08 | 34.23 ± 8.3 |
| Child-Pugh Score | 7.42 ± 1.24 | 8.1 ± 1.3 | 8.53 ± 1.33 |
| **Total** | **28 (100%)** | **9 (100%)** | **13 (100%)** |

Around 20% patients presented with history of altered sensorium. While around 4% patients were found with seizures.

Hepatic encephalopathy was present in 32% while GI bleeding was found in 20% of patients. Coagulopathy and hepatorenal syndrome were found in 16% and 10%patients, while SBP was found in 6%.

In addition, there was significant difference in the occurrence of complications such as Hepatic Encephalopathy, GI Bleeding, coagulopathy spontaneous bacterial peritonitis and hepatorenal syndrome as seen in the chart with great variation inpercentage wise distribution of the complications among different range of Na+ level.

In the present study, due to biochemical parameters it was found that Total Bilirubin, Prothrombine Time and INR were found statistically significant between three groups while others parameters such as S. Creatinine, S. Urea, Total Protein, S. Albumin, SGOT, SGPT were statistically not significant.

Patients with serum sodium levels (≥135 meq/L), had a mean MELD score of 18.5 ± 8.24, while those with levels (130-134 meq/L), and (<130 meq/L) had mean scores of 28.66 ± 8.08 and 34.33 ± 8.33 respectively.

Moreover, Serum sodium levels had a strong association with severity of disease as calculated by Child-Pugh Score. Patients with serum sodium levels (≥135 meq/L), had a mean Child-Pugh Score score of 7.42 ± 1.24, while those with levels (130-134 meq/L), and (<130 meq/L) had mean scores of 8.1 ± 1.3 and 8.53 ± 1.33 respectively.

A significant proportion of patients with cirrhosis of liver have abnormal serum sodium concentration. Hyponatremia is the most common occurrence in our study. No patients presented with serum sodium levels greater than 145. 18% of patients had serum sodium levels less than 135, while 26% patients had serum sodium levels than 130. Serum sodium levels less than 125 were un-

common.

**Mortality wise distribution in study subjects:** Among 13 patients with serum sodium levels (<130 meq/L), 5 patients (38.4%) died. Among 9 patients with serum sodium levels (130-134 meq/L), 1 patient (11.1%)died. There were no deaths among patients with sodium levels (≥135 meq/L). The difference in mortality among these three groups was statistically significant.

## DISCUSSION

In the present study, Abdominal Distension and Lower Limb Swelling were in all patient while **S. Trikha et al[14]** have found 91% and 76% while jaundice was very high compare to current study 86% vs 36%.

The results of the present study extend the observations made by the above-mentioned studies that liver cirrhosis is associated with abnormal serum sodium concentration. In the present study, the number of patients with hyponatremia are not more than half, in contrast with other study such as **AV Christudhas et al[11], MK Raja et al12, OA Khalil et al[13]** have less than half of the patients defined as 44%,48%, and 45.5% were normal sodium level (≥135 meq/L)

**Table 9: comparison of studies for prevalence of hyponatremia**

| Studies | Prevalence of hyponatremia | | |
|---|---|---|---|
| | ≥135 meq/L | 130-134 meq/L | <130 meq/L |
| **Present study** | 56% | 18% | 26% |
| **AV Christudhas et al[11]** | 44% | 24% | 32% |
| **MK Raja et al[12]** | 48% | 21% | 31% |
| **OA Khalil et al[13]** | 45.5% | 20% | 34.5% |

**Table 10: Clinical Presentation**

| Presentation | Present Study | S. Trikha et al[14] |
|---|---|---|
| Abdominal Distension | 100% | 91% |
| Lower Limb Swelling | 100% | 76% |
| Jaundice | 36% | 86% |
| Altered Sensorium | 20% | 30% |
| Seizures | 4% | 1% |

**Clinical Complication:** In the present study, patients with serum sodium levels <130 meq/L had increased frequency 69.2% as of hepatic encephalopathy compared to the other two groups which was similar to other study such as **MK Raja et al[12], DK Reddy et al[15]** and **S Shaikh et al[16]** and have found 60.6%, 60%, and 25.8% respectively. Hence there is significant association between hepatic encephalopathy and hyponatremia, the results of this study were similar to the mentioned above studies. The relationship between hepatic encephalopathy and serum levels may be explained on the basis of more severe liver failure among patients with serum sodium less than 130 meq/L. Lowserum sodium levels in patients with cirrhosis are associated with a remarkable reduction in the cerebral concentration of organic osmolytes that probably reflect compensatory osmoregulatory mechanisms against cell swelling.

Remaining parameters such as GI Bleeding, Coagulopathy and Hepatorenal Syndrome with serum sodium levels <130 mEq/L were found as 53.8 %, 46.1 % and 30.8 % as of higher compared to the other two groups, similarly studied as **DK Reddyet al[15]** have found 32%, 8%, and 28% while compared to **MK Raja et al[12]** found higher as 39%, 58%, 77.7% in GI Bleeding, Coagulopathy and Hepatorenal Syndrome respectively. The pathophysiology of association between HRS and hyponatremia can be explained by increased body fluid resulting from the impairment of solute-free water excretion. This increased risk for HRS may be related to a more severe circulatory dysfunction in patients with hyponatremia compared with patients without hyponatremia. The most common reason for chronic hyponatremia in cirrhosis is impairment in renal solute-free water secretion due to increased antidiuretic hormonesecretion and decreased effective arterial volume. The brain is able to compensate for the increased osmolar pressure (which leads to cerebral oedema) in chronic hyponatremia by extruding intracellular osmolytes, such as potassium, glutamine andmyoinositol, which can take 48 hours for full effect. This adaptive mechanism explains why patients with chronic hyponatremia and serum sodium concentrations above 120mEq/L are often asymptomatic.

**MELD and CP Score:** The present study also showed that the correlation between the mean MELD score and Child Pugh score with the serum sodium levels had shown a strong negative correlation. **OA Khalil et al[13], Kim JH et al[17]** and **DK Reddy et al[15]** found that lower sodium levels were associated with increased MELD score and Child Pugh score. This indicates that lower serum sodium levels were associated with severe disease. Sodium is incorporated in MELD score is proposed by several studies to be superior to MELD score in predicting mortality in patients awaiting liver transplantation.

**Mortality rate:** The present study also shows increased mortality 38.4% among patients with lower sodium levels and no death in patients with normal serum sodium which was similar to **DK Reddy et al[15]** as 20% mortality with serum sodium concentration <130 meq/L.

## CONCLUSION

Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels are associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome. Hyponatremia is also associated with high morbidity and mortality in cirrhotic patients. Hence hyponatremia is a valuable marker that can be used to assess the prognosis in patients with cirrhosis of liver. Incorporation of sodium levels in MELD score is much more useful to assess the prognosis and to refer the patient for liver transplantation.

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