



## **A prospective study on the prevalence of hyponatremia and its prognostic significance in patients with cirrhosis of the liver**

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### **ABSTRACT-**

**BACKGROUND-**We want to study the prevalence of hyponatremia and its prognostic significance in patients with cirrhosis of the liver

**METHODS-**It was a prospective study on the prevalence of hyponatremia and to evaluate the association between hyponatremia and complication in cirrhosis and its prognostic significance, conducted on 100 patients admitted in General Medicine Ward, in ACSR GMC-NELLORE during the period of January 2021-December 2022

**RESULTS-** The prevalence of hyponatremia in this study was 54%, out of the 100 patients of liver cirrhosis 34 (34%) patients had concurrent severe hyponatremia with serum sodium concentrations  $\leq 130$  meq/L. While 20 (20%) patients had mild hyponatremia with serum sodium concentrations between 131-135 meq/L. However, 46(46%) patients had their serum sodium levels more than equal to 136 meq/L. There was a significant association between hyponatremia and hepatic encephalopathy, hepatorenal syndrome. Angeli P et al<sup>1</sup> 17, present study 17.6%, Kim JH et al<sup>2</sup> 17%. There was no significant association between hyponatremia and ascites (p-value - 0.5175). In this study mortality was 12% in patients with hyponatremia.

**KEYWORDS-**Hyponatremia, Cirrhosis, Hepatic encephalopathy

**INTRODUCTION-** Hyponatremia is serum sodium less than 135 meq/L Its homeostasis is vital to the normal physiologic function of cells. A disturbance in body water homeostasis is a common feature of advanced cirrhosis. This is characterized by a higher rate of renal retention of water in relation to sodium due to a reduction in solute-free water clearance. The consequent inability to adjust the amount of water excreted in the urine to the amount of water ingested leads to dilutional hyponatremia. Clinically significant hyponatremia is relatively uncommon and is nonspecific in its presentation; therefore, the physician must consider the diagnosis in patients presenting with vague constitutional symptoms or with an altered level of consciousness. Identifying the etiology and risk factors for hyponatremia will help in reducing its incidence and minimize the complications associated with hyponatremia and improve the overall cost of health care. According to several recent studies; hyponatremia occurring as a result of a reduced solute-free water clearance was a key prognostic factor in patients with liver cirrhosis when hyponatremia was incorporated into the MELD score. There is a lack of Indian data on the clinical spectrum of hyponatremia in cirrhosis and treatment strategies to be adopted in various clinical studies; therefore, we planned to undertake this prospective follow-up study in patients with cirrhosis at our tertiary care center.

**AIMS AND OBJECTIVES** -1. To study the prevalence of hyponatremia in cirrhosis. 2. To evaluate the association between hyponatremia and complication in cirrhosis and its prognostic significance

**MATERIALS AND METHODS SOURCE OF DATA:** The study will be conducted on 100 patients admitted to ACSR GMC NELLORE during the study period from January 2021 to December 2022.

**METHOD OF COLLECTION OF DATA:** Informed consent will be obtained from all patients to be enrolled in the study. The data of the patients were collected in a well-designed proforma. The patients' demographics and the status of the patients at the time of inclusion (inpatient or outpatient) as well as the severity of cirrhosis were assessed according to Child-Pugh score. A total score from 5-6, 7-9, and 10-15 was classified as class A, B, and C respectively. The patients were selected based on clinical examinations, biochemical tests, and ultrasound abdomen. The patients are followed over a period of one year with serum sodium levels measured at regular intervals of 3 months, 6 months, and 1 year.

**INCLUSION CRITERIA:** All patients with cirrhosis of liver

**EXCLUSION CRITERIA:** 1. Patients with cardiac failure 2. Patient on diuretic therapy. 3. Patients with chronic kidney disease 4. Patients on drugs like SSRI, TCA, MAO inhibitors, cytotoxic drugs etc.

**OBSERVATIONS AND RESULTS** -This prospective study included 100 cirrhotic patients out of which 84 (84%) males and 16 (16%) females and the mean age of the patients was 44.89

**TABLE-1: DEMOGRAPHY DETAILS**

SL.No	PARAMETER	N=100
1	Age(years) (Mean + SD)	44.89
2	Sex: (Number) (%)	
	M	84 (84%)
	F	16 (16%)
3	Cause of cirrhosis: (Number)(%) Alcohol	
	HBV :	96(96%)
	HCV:	4(4%)
	Other:	0(0) 0(0)
4	MELD score (Mean + SD)	22.77±8.262
5	Serum sodium : (meq/L) (Mean + SD)	127.9± 11.29
	1) ≤130 meq/L :	34(34%)
	2) 131-135 meq/L :	20(20%)
	3) ≥ 136 meq/L :	46(46%)

The mean age of the patients was 44.89, years (range, 22-70 years) and consisted of 84 (84%) men and 16 (16%) women. Causative factors for liver cirrhosis included alcoholic liver disease (96 cases, 96%), chronic hepatitis B (4 cases 4%). The mean MELD score was 22.77± 8.262 (range, 9-46); and mean serum sodium concentration was 127.9± 11.29 meq/L (range, 106-145 meq/L). Based on the diagnostic criteria for hyponatremia in patients, out of the 100 patients of liver cirrhosis 34 (34%) patients had concurrent severe hyponatremia with serum sodium concentrations ≤130 meq/L. While, 20 (20%) patients had mild hyponatremia with serum sodium concentrations between 131-135 meq/L. However, 46(46%) patients had their serum sodium levels more than equal to the 136 meq/L.

**.Table 2: CHARACTERISTICS OF PATIENTS ACCORDING TO SERUM SODIUM CONCENTRATION**

S.NO	COMPLICATIONS	≤130 meq/L n = 34	131-135 meq/L n = 20	≥136 meq/L n = 46	P value
1	Age(years) (Mean + SD)	45.47+10.28	45.75+11.93	44.09 +9.640	0.7706E
2	Sex: (Number)(%)				
	M	29(85%)	17(85%)	38(83%)	0.9401@
	F	5(15%)	3(15%)	8(17%)	

3	Cause of cirrhosis: (Number)(%)				
	Alcohol:	32(94%)	20(100%)	44(96%)	0.0552@
	HBV :	2(6%)	0(0)	2(4%)	
	HCV:	0(0)	0(0)	0(0)	
	Other:	0(0)	0(0)	0(0)	
4	MELD score (Mean + SD)	25.91+ 8.092	28.00+8.385	18.17 +5.591	< 0.0001£
5	Child-Pugh score	10.5+1.6	9.8+ 1.7	7.8+1.6	<0.0001*
6	Child-Pugh class				
	Class A	1	1	15	<0.0001
	Class B	13	9	23	
	Class C	20	10	8	

@ using Chi Square test; p value < 0.05- statistically significant (95 % CI) £ Using one way ANOVA. P value < 0.05, Significant (@95% CL). \*Using Mean+SD

Patients were classified according to the level of serum sodium, 46(46%) belong to the group of serum sodium concentrations  $\geq 136$  meq/L. While, 34(34%) and 20(20%) patients were belong to serum sodium concentration group of  $\leq 130$  meq/L and 131-135 meq/L respectively. Mean age in these three groups,  $\leq 130$  meq/L, 131-135 meq/L, and  $\geq 136$  meq/L was 45.47+10.28, 45.75+11.93 and 44.09 +9.640 respectively, which were comparable and no statistical difference was found in these three groups (pvalue=0.7706). The frequency of gender and causative factor among these three groups were comparable and no statistical difference was found in this respect (p-value, 0.9401, 0.0552 respectively). To assess the association between serum sodium and Patient characteristics and complications of cirrhosis, the patients were divided into three groups according to serum sodium values. Serum sodium values were not associated with age, sex, or etiology of cirrhosis but were strongly associated with the severity of cirrhosis as assessed via the Child-Pugh class. Low serum sodium had a significantly high Child-Pugh class compared to normal serum sodium. Among 34 patients with serum sodium < 130 meq/l, 20 were in class C Child-Pugh and 13 were in Class B (p=< 0.0001).

In the present study around 85% were males and 15% were females in all three groups and there was no statistically difference between serum sodium concentration and gender (P=0.9401)

In the present study there was no statistically difference between serum sodium concentration and cause of cirrhosis (P=0.0552)

**TABLE 3-CLINICAL PRESENTATION OF PATIENTS AT THE TIME OF ADMISSION**

S.NO	PRESENTATION	N=100 (Number)(%)
1	Abdominal Distension	100(100%)
2	Lower Limb Swelling	99(99%)
3	Jaundice	100(100%)
4	Altered Sensorium	50(50%)
5	Gastrointestinal Bleeding	24(24%)
6	Seizures	1(1%)

All patients (100%) presented to hospital with abdominal distension and jaundice. 99(99%) patients had lower limb swelling at the time of presentation to the hospital. Altered sensorium and gastrointestinal bleeding were present in 50(50%) and 24(24%) of patients respectively. Only one patient with liver cirrhosis was having concurrent seizures at the time of hospital admission.

In the present study commonly patients presented with abdominal distension, lower limb swelling, and jaundice. 50% of patients presented with altered sensorium, 24% of patients had GI bleed, and 1 patient presented with seizures.

**TABLE:4- FREQUENCY OF COMPLICATIONS**

S.NO	COMPLICATIONS	N=100 (Number)(%)
1	Ascites	98(98%)
2	Portal Hypertension	90(90%)
3	Hepatic Encephalopathy	34(34%)
4	GI Bleeding	24(24%)
5	Coagulopathy	9(9%)
6	Hepatorenal Syndrome	9(9%)

Out of the 100 patients of cirrhosis, 98(98%) patients had ascites, 90(90%) portal hypertension, 34(34%) hepatic encephalopathy and GI bleeding in 24(24%) patients. Coagulopathy and hepatorenal syndrome was present in 9(9%) patients each. In the present study ascites was seen in 98%, PH in 90%, hepatic encephalopathy in 34%, gastrointestinal bleeding in 24%, Coagulopathy in 9% and Hepatorenal syndrome in 9% of patients.

**Table:5- FREQUENCY OF COMPLICATIONS BY SERUM SODIUM CONCENTRATION**

S.NO	COMPLICATIONS	≤130 meq/L n = 34	131-135 meq/L n = 20	≥136 meq/L n = 46	P value @
1	Ascites	34(100%)	19(95%)	45(97.8%)	0.0621
2	Portal hypertension	34(100%)	19(95%)	37(80.4%)	0.0111
3	Hepatic encephalopathy	20(59%)	10(50%)	4(8.7%)	< 0.0001
4	GI bleeding	11(32.4%)	4(20%)	9(19.6)	0.6904
5	Coagulopathy	4(11.8%)	2(10%)	3(6.5)	0.7094
6	Hepatorenal syndrome	6(17.6%)	3(15%)	0(0)	0.014

@ using Chi Square test; p value < 0.05- statistically significant (95 % CI)

There was significant difference in three groups of ≤130 meq/L, 131-135 meq/L and ≥136 meq/L with respect to the complications of liver cirrhosis namely portal hypertension, hepatic encephalopathy, hepatorenal syndrome ( p value= 0.0111, < 0.0001, 0.0140 respectively). However no statistical significant difference was found in three groups with respect to ascites, gastrointestinal bleeding and coagulopathy (p value= 0.0621, 0.6904, 0.7094 respectively)

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**TABLE:6- COMPARISON OF COMPLICATIONS ACCORDING TO SERUM SODIUM CONCENTRATION**

S.NO	COMPLICATION	≤130 meq/L n = 34		131-135 meq/L n = 20	
		ODD ratio (95% CI)	P value#	ODD ratio (95% CI)	P value
1	Ascites	2.28 (0.09 to 57.61)	1	0.42 (0.03 to 7.11)	0.5175
2	Portal hypertension	17.48 (1 to 312)	0.0086	4.62 (0.54 to 39.25)	0.2607
3	Hepatic encephalopathy	10.5 (3.08 to 35.8)	< 0.0001	19.5 (4.92 to 77.3)	< 0.0001
4	GI bleeding	1.96 (0.71 to 5.5)	0.2049	1.03 (0.28 to 3.83)	1
6	Coagulopathy	1.9 (0.4 to 9.2)	0.4505	1.6 (0.25 to 10.36)	0.6348
6	Hepatorenal syndrome	15.70 (0.86 to 287.8)	0.0113	18.6 (0.91 to 379.0)	0.0249

# using Fisher's exact test; p value < 0.05- statistically significant (95 % CI)

Patients with a serum sodium ≤130meq/L, as compared with serum sodium ≥136 meq/L had a significantly increased risk for developing complications: 17.48(95% CI=1 to 312, p=0.0086) for portal hypertension, 10.5 (95% CI=3.08 to 35.8, p=< 0.0001) for hepatic encephalopathy and15.70 (95% CI=0.86 to 287.8, p=0.0113) for hepatorenal syndrome. However no statistical difference and increased risk was found for ascites, gastrointestinal bleeding and Coagulopathy (p value=1.000, 0.2049, 0.4505 respectively).

Patients with a serum sodium 131-135 meq/L, as compared with serum sodium ≥136 meq/L had a significantly increased risk for developing complications: 19.5 (95% CI=4.92 to 77.3, p=< 0.0001) for hepatic encephalopathy and 18.6 (95% CI=0.91 to 379.0, p=0.0249) for hepatorenal syndrome. However no statistical difference and increased risk was found for ascites, portal hypertension, gastrointestinal bleeding and coagulopathy (p value=0.5175, 0.2607, 1.0000, 0.6348 respectively).

**TABLE :7- MORTALITY ACCORDING TO SERUM SODIUM CONCENTRATION**

	≤ 130 meq/L n= 34	131-135 meq/L n= 20	≥ 136 meq/L n=46	P value @
Mortality	8 (23.7%)	4 (20 %)	0 (0%)	0.0037

@ using Chi Square test; p value < 0.05- statistically significant (95 % CI)

8 (23.7%) patients died in group of serum sodium levels  $\leq 130$  meq/L, while 4 (20%) patients died in group of serum sodium levels 131-135 meq/L. No patient died in group of serum sodium levels  $\geq 136$  meq/L. Statistically significant difference was found in mortality in three groups ( $p$  value=0.0037).

Mortality was more in patients with low sodium  $< 135$  meq/L compared to normal serum sodium concentration.

**DISCUSSION-** We conducted this prospective study to examine the prevalence of hyponatremia and the association between hyponatremia and the occurrence of major complications in patients with liver cirrhosis. Low serum sodium concentration is an independent predictor of mortality in patients with cirrhosis, but its prevalence and clinical significance are unclear. The prevalence of low serum sodium concentration as defined by a serum sodium concentration sodium  $< 135$  meq/L was associated with severe ascites, as indicated by the high prevalence of refractory ascites, large fluid accumulation rate, frequent use of large-volume paracentesis, impaired renal function, compared with normal serum sodium levels. Moreover, low serum sodium levels were also associated with a greater frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome, but not gastrointestinal bleeding. Patients with serum sodium  $< 130$  mmol/L had the greatest frequency of these complications, but the frequency was also increased in patients with a mild reduction in serum sodium levels (131-135 mmol/L). In conclusion, low serum sodium levels in cirrhosis are associated with severe ascites and a high frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.

Hyponatremia is also a powerful predictor of death in patients with cirrhosis and ascites who are on the waitlist for a liver transplant. In three studies, for example, serum sodium concentrations of less than 135, 126, or 130 meq/L were independent risk factors for death in such patients.

Angeli P et al<sup>1</sup> conducted a multi-center study in overseas countries, 997 patients with liver cirrhosis and concurrent ascites, were assigned to three groups based on serum sodium concentration, in a manner similar to that of the current study. The prevalence of hyponatremia at serum sodium  $\leq 135$  meq/L.

The prevalence of low serum sodium concentration as defined by a serum sodium concentration  $< \text{or} = 135$  mmol/L,  $< \text{or} = 130$  mmol/L,  $< \text{or} = 125$  mmol/L, and  $< \text{or} = 120$  mmol/L was 49.4%, 21.6%, 5.7%, and 1.2%, respectively. The prevalence of low serum sodium levels ( $< 135$  mmol/L) was high in both inpatients and outpatients (57% and 40%, respectively). The existence of serum sodium  $< 135$  mmol/L was associated with severe ascites, as indicated by the high prevalence of refractory ascites, large fluid accumulation rate, frequent use of large-volume paracentesis, and impaired renal function, compared with normal serum sodium levels. Moreover, low serum sodium levels were also associated with a greater frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome, but not gastrointestinal bleeding. Patients with serum sodium  $< 130$  mmol/L had the greatest frequency of these complications, but the frequency was also increased in patients with a mild reduction in serum sodium levels (131-135 mmol/L). In conclusion, low serum sodium levels in cirrhosis are associated with severe ascites and a high frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.

Borroni G et al<sup>3</sup> conducted a study on 156 patients hospitalized with liver cirrhosis, the prevalence of hyponatremia, based on a serum sodium concentration  $\leq 130$  meq/L, was 29.8%, and hyponatremia was significantly correlated with infection and ascites.

Shaikh S et al (2010)<sup>4</sup> conducted a case control study constituted 217 consecutive cirrhotic patients. Hyponatraemia (sodium <130 meq/l.) was present in 58/217(26.7%)patients and 54/217(24.9%)patients had serum sodium from 131-135meq/L while 105/217(48.4%) patients had serum sodium>135meq/L.

In the present study, the results indicate that a large proportion of patients with cirrhosis have abnormal values of serum sodium concentration. In fact, more than one-half (54%) of patients with cirrhosis had values of serum sodium concentration below the normal range (<135meq/L) and one-third (34%) had values<130meq/L. Low serum sodium levels were not associated with age, sex, or etiology of cirrhosis.

Although it is generally believed that the existence of a serum sodium concentration<130meq/L is associated with difficult to treat ascites, few studies have been reported that specifically analyze the relationship between serum sodium levels and responsiveness of ascites to diuretic therapy. Arroyo et al<sup>6</sup>. reported that the presence of serum sodium<130meq/L was associated with lower glomerular filtration rate and solute-free clearance and a poorer response to diuretics compared with patients with serum sodium<130meq/L. Subsequent studies by Bernardi et al<sup>5</sup>. and Angeli et al<sup>1</sup>. showed that patients who do not respond to diuretics have lower serum sodium concentration compared with patients who respond to diuretics.

The results of the current study confirm and extend these observations by showing that patients with serum sodium concentration<130meq/L compared with 24% of patients with serum sodium between 131 and 135 meq/l and 15% of patients had serum sodium levels>135meq/L

Kim JH et al (2009)<sup>2</sup> showed HE was present in 23% of the patients with serum sodium <130 meq/L compared with14% of patients with serum sodium between 131 and 135 meq/l and 24% of patients had serum sodium levels>135meq/L

Shaikh S et al (2010)<sup>4</sup> showed hepatic encephalopathy was present in 26/217 (11.9%) patients, of which 15/58(25.8%) patients were with serum sodium<130meq/L.

In the present study, the frequency of hepatic encephalopathy was associated with serum sodium levels in such a way that patients with serum sodium<130meq/had 20/34 (59%) of hepatic encephalopathy compared to patients with normal serum sodium concentration 4/46 (8.7%). Patients with serum sodium between 131 and 135 meq/l had a higher frequency of encephalopathy 10/20 (50%) compared to patients with serum sodium<130meq/L

TABLE-11: Comparison of Hepatorenal syndrome with the serum sodium

Studies	Frequency of HRS with serum sodium		
	<130meq/L	131-135meq/L	>136meq/L
Present study (n=100)	17.60%	15%	0%
Angeli P et al (n=997) <sup>1</sup>	17%	10%	6%
Kim JH et al (n=188) <sup>2</sup>	3.90%	2.50%	3%

TABLE-12: Association of severity serum sodium with the mortality

SERUM SODIUM	MORTALITY
<130 meq/L	8
131-135 meq/L	4
>136 meq/L	0

## CONCLUSIONS AND SUMMARY

- The prevalence of hyponatremia in this study was 54%. out of the 100 patients of liver cirrhosis 34 (34%) patients had concurrent severe hyponatremia with serum sodium concentrations  $\leq 130$  meq/L. While, 20 (20%) patients had mild hyponatremia with serum sodium concentrations between 131-135 meq/L. However, 46(46%) patients had their serum sodium levels more than equal to the 136 meq/L.
- Severity of hyponatremia was associated high frequency of complications of cirrhosis.
- There was a significant association between hyponatremia and hepatic encephalopathy, and hepatorenal syndrome. Angeli P et al<sup>1</sup> 17% , present study 17.6%, Kim JH et al<sup>2</sup> 17%,
- There was no significant association between hyponatremia and ascites ( p-value - 0.5175)
- In the present study there was no association found between serum sodium and gastrointestinal bleeding and coagulopathy; similar results were shown by Angeli P et al<sup>1</sup> and Shaikh S et al<sup>4</sup>.
- In this study mortality was 12% in patients with hyponatremia.
- Dilutional hyponatremia is frequent in cirrhotic patients and low serum sodium levels in cirrhosis are associated with severe complications of liver cirrhosis like hepatic encephalopathy, hepatorenal syndrome and high morbidity and mortality. Treatment of hyponatremia is important to prevent

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