International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

Original Research Article.

Impact of Serum Sodium with Severity of Complications of Cirrhosis: A Prospective Study in Tertiary Medical Center of Rajasthan

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ABSTRACT

Background/Aim: Hyponatremia is an independent predictor of mortality in patients of cirrhosis, but the prevalence and the impact of the prognostic value of serum sodium levels on complications of cirrhosis are unclear. This study was done with the aim to identify prevalence of hyponatremia and to analyze the relationship between serum sodium levels and severity of ascites and complications of cirrhosis.

Patients and Methods: In this prospective study 191 patients with liver cirrhosis were analyzed for demographic, clinical and biochemical parameters.

Results: The prevalence of low serum sodium concentration as defined by a serum sodium concentration ≤135meq/l, 130meq/l was 12% and 40% respectively. Low serum sodium ≤135meq/l was associated with severe ascites as assessed by frequent need for paracentesis and impaired renal function, compared with normal serum sodium levels. Low serum sodium levels have also shown association with more frequent episodes of hepatic encephalopathy, spontaneous bacterial peritonitis, and hepato renal syndrome, but not gastrointestinal bleeding. These complications were more frequently seen in patients with serum sodium less than 130meq/l but the frequency also increased with mild reduction in serum sodium (131-135meq/l).

Conclusion: Hyponatremia in cirrhotics is associated with severe ascites with repeated paracentesis and increase frequency of hepatic encephalopathy, spontaneous bacterial peritonitis and hepato-renal syndrome.

Key words: Hyponatremia, Cirrhosis, Hepatorenal Syndrome, Paracentasis.

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Article History:

Received: 19-06-2017, **Revised:** 27-07-2017, **Accepted:** 09-08-2017

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2017.3.5.012	

INTRODUCTION

Hyponatremia is a known complication in advanced chronic liver disease and is believed to result due to deranged body water homeostasis.[1-3] In advanced chronic liver disease, reduction in effective arterial blood volume secondary to splanchnic vasodilatation acts as a stimulus for the non-osmotic stimulation of vasopressin release.[4] This causes a reduced solute free water clearance. In addition, a reduced sodium delivery to distal tubule due to reduced glomerular filtration rate acts as an additional factor in the pathogenesis of hyponatermia.[4]

Studies in cirrhotics have proven that the renal ability to excrete free water, as assessed by serum sodium concentration, shows an excellent correlation with survival. Cirrhotics with Hyponatremia have poor survival as compared to patients who have normal serum sodium levels.[5-7] Serum sodium also correlates as a post-transplantation outcome predictor in cirrhosis patient undergoing liver transplantation and hence it has been incorporated in the calculation for model for end stage liver disease score (MELD) to improve the accuracy of this scoring system in organ allocation for liver transplant.[8-11]

However there is still a paucity of knowledge about the prevalence of serum sodium in advanced chronic liver disease and its relationship with development of cirrhotic complications. Therefore the aim of present study was to assess the prevalence of hyponatremia in cirrhotics and to determine the association between serum sodium levels and severity of liver damage.

MATERIALS AND METHODS

We prospectively collected data of 191 patients of chronic liver disease hospitalized from January 2015 to July 2015 in gastroenterology department of SMS hospital, Jaipur. Patients were included according to following criteria 1) Chronic liver disease diagnosed by combination of clinical, biochemical and ultrasonographic findings or histology 2) Presence of ascites determined by Ultrasonography or paracentesis. Data collected was analyzed for various parameters which included demographic features, etiology, severity and duration of cirrhosis (severity assessed using the child pugh score and model for end stage liver disease score). Duration of cirrhosis was estimated in years since

diagnosis. Patients taking diuretic were classified based on type and number of diuretic they were taking. Other parameters which were studied were: spontaneous bacterial peritonitis (SBP), gastrointestinal bleed, hepatic encephalopathy (HE) and hepatorenal syndrome (HRS). Laboratory parameters studied included: complete blood count, prothrombin time/ international normalized ratio, liver function test including serum bilirubin, transaminases, serum alkaline phosphatase, total protein, albumin, globulin, albumin/ globulin ratio, serum creatinine, blood urea, serum sodium, serum potassium. Ascitic fluid analysis was done to rule out spontaneous bacterial peritonitis.

Statistical Analysis

Statistical analysis was performed with the SPSS, trial version 20 for Windows statistical software package (SPSS inc., Chicago, il, USA). The Categorical data were presented as numbers (percent) and 95% CI. To assess any significant association, Chi Square test and Odd's ratio were used. Groups were compared for demographic data, presented as mean and standard deviation and were compared using ANOVA Test and post Hoc Test. Tukey Test was applied to find out the most significant groups among all the groups. Probability P value <0.05 was considered statistically significant.

Table 1: Characteristic of the patient included in the study classified according to serum sodium concentration.

Variables		Serum sodium (meq/l)				P Value
		≤130 (N=77)	131 to135 (N=22)	>135 (N=92)	Total (N=191)	
Age (Years)		43.37±13.14	46.86±14.02	42.96±12.86	43.58±13.09	0.45
Sex	Female	15	4	21	40	P = 0.820
	Male	62	18	71	151	
Duration		1.94±0.809	2.27±1.45	2.07±0.65	2.047±0.84	0.25
Etiology	Alcohol	47	9	54	110	0.23
	Autoimmune	7	1	3	11	0.26
	BCS	1	0	0	1	0.47
	Cryptogenic	9	3	16	28	0.57
	HBV	7	5	14	26	0.21
	HCV	2	2	2	6	0.23
	NASH	4	2	3	9	0.49

NS, not significant

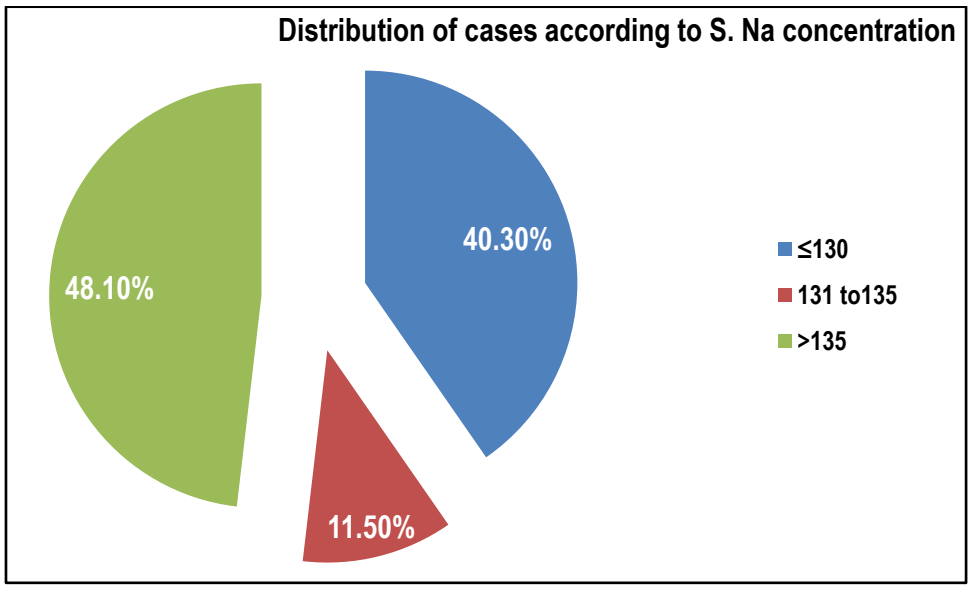

Fig 1: Distribution of cases according to S. Na concentration

RESULTS

A total of 191 patients of chronic liver disease were included in the present study.

Baseline characteristics

Present cohort included 151 (79%) males and 40 (21%) females. The mean age of patients was 43.5±13.09 years. Etiology of cirrhosis in majority of patients was alcohol related 110 (57%), followed by cryptogenic 28 (14%), HBV related 26 (13.6%), autoimmune 11 (5.7%), NASH related 9 (4.7%) and HCV related 6 (3.1%). CTP and MELD score were calculated in all the patients. As this study was conducted on inpatient cohort of a tertiary care centre thus as expected the majority of patients belonged to child class B 53 (27%) and child class C 122 (63%) while 16 (8%) patients belonged to child class A. (Table 1)

Majority of the patients were on diuretics. Most common diuretics used were furosemide and spironolactone. Repeated large volume paracentesis was performed in 85 patients who were non/poorly responsive to diuretics.

Percentage of patients according to serum sodium values is shown in the Figure 1.

More than 50% of the patients (99/191) had serum sodium values below the normal range -135meq/ml. According to serum sodium values patients were grouped in three categories. No relation was found between serum sodium values and age, sex and etiology of cirrhosis (Table 1), however serum sodium values were strongly associated with severity of cirrhosis, assessed by child Pugh class (Table 2) and MELD score. There was a significant relationship between serum sodium and renal function (as assessed by serum creatinine) (Table 2) and severity of ascites (Table 3). Low serum sodium values were associated with repeated use of large volume paracentesis (Table 3) and impaired renal function (Table 2). Mean values of serum creatinine in patients with serum sodium 130meq/l, 131-135meq/l and >135meq/l were 1.82 mg/dl, 1.30meq/l and 1.12meq/l respectively (Table 2).

Analysis was done for relationship between serum sodium and complications of cirrhosis that were present at the time of admission. Decreasing serum sodium values were associated with increased frequency of hepatic encephalopathy, spontaneous bacterial peritonitis, and Hepatorenal syndrome in the present patient population (Table 4). Patients having serum sodium < 130 had greater frequency of these complications. There was a clear cut gradient between the value of serum sodium and incidence of complications (Table 4). The frequency of GI bleed however showed no relation with serum sodium values (figure 2).

Table 2: Characteristics of cases according to biochemical parameters and severity of cirrhosis

Serum Sodium meq/l		B. Urea (mg/dl)	S. Creat (mg/dl)	S. Na (meq/l)	CTP	MELD
▪ Less than 130 (N=77)	Mean	64.87	1.82	127.19	11.73	22.66
	SD	46.94	1.07	3.54	1.91	8.19
▪ 131 to135 (N=22)	Mean	44.36	1.30	133.45	10.18	17.27
	SD	30.59	0.58	1.34	2.15	6.27
▪ More than 135 (N=92)	Mean	34.41	1.12	139.50	9.74	15.43
	SD	19.46	0.31	2.85	2.19	6.77
▪ Total (N=191)	Mean	47.84	1.42	133.84	10.59	18.56
	SD	37.05	0.81	6.52	2.27	8.06
▪ P Value LS		<0.001S	<0.001S	<0.001S	<0.001S	<0.001S

Table 3: Relationship of serum sodium levels with severity of ascites and need for repeated paracentesis.

Variables	Serum Sodium (meq/l)				
	≤130 (N=77)	131 to135 (N=22)	>135 (N=92)	Total (N=191)	P Value
No ascites	3	2	18	22	0.027S
Mild ascites	1	1	2	4	
Moderate to Severe ascites	73	20	72	164	
Repeated paracentisis	60	10	15	85	<0.001S

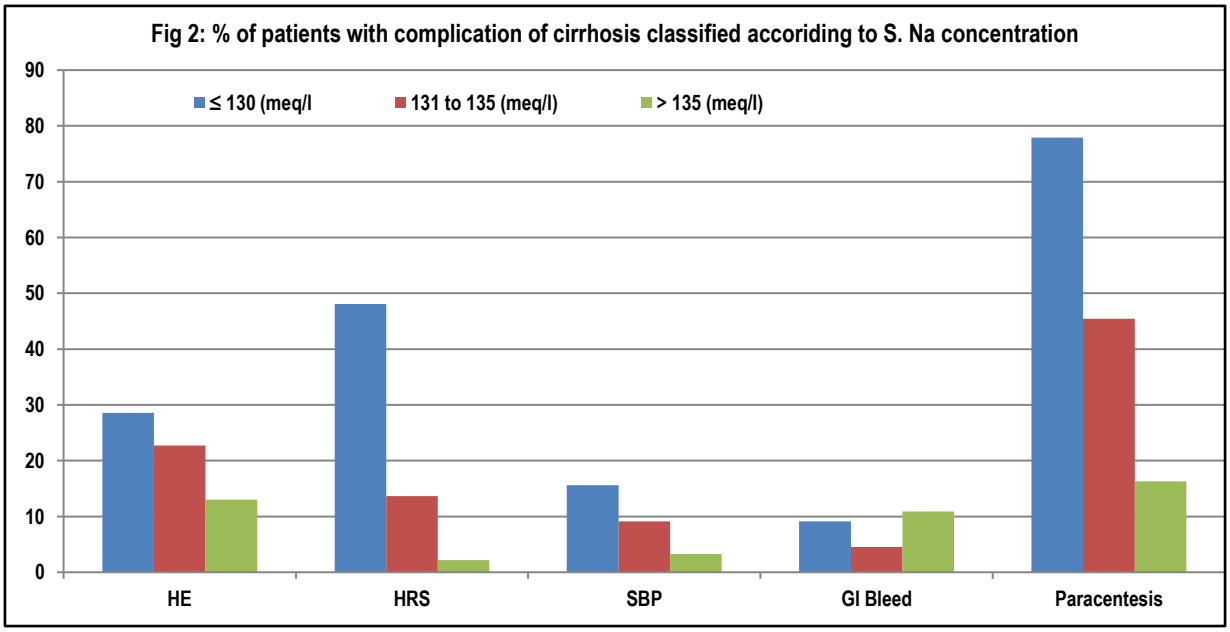

Table 4: Relationship between serum sodium levels and complication of cirrhosis

Variables	Serum Sodium meq/l				P Value
	≤130 N=77	131 to135 N=22	>135 N=92	Total N=191	
HE	22	5	12	39	0.043S
HRS	37	3	2	41	<0.001S
SBP	12	2	3	17	0.02S
GI BLEED	7	1	10	18	0.65NS

DISCUSSION

The current study attempted to study the prevalence of hyponatremia in patients of advanced chronic liver disease and its relationship with the occurrence of various decompensation events. In our cohort almost one half (52 %) of patients with advanced liver disease had values of serum sodium values below normal range (≤135 meq/l). A study from Korea reported the prevalence of hyponatremia at a serum sodium ≤135 mmol/L as 49.4% and that of severe hyponatremia at a serum sodium concentration ≤130 mmol/L was 27.1%.[12]

Low serum sodium has not shown any association with age, sex or etiology of chronic liver disease but was more frequent in patients with advanced parenchymal liver failure.

Previous studies by Bernardi et al and Angeli et al[13,14] showed that patients with low serum sodium were poorly responsive to diuretics in comparison to those who had normal serum sodium levels. In the present study, patients with serum sodium levels <130 meq/l had a higher requirement of large volume paracentesis.

Frequency of hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis was more common with serum sodium <130 meq/l in comparison to those with normal serum sodium. Patients with serum sodium between 131 to135 meq/l had a lower frequency of these complications. Higher occurrence of complication might be the cause for the poor survival in patients with Hyponatremia.[5-10]

Around one third (29%) of the patients with serum sodium < 130meq/l had an episode of HE, while only 22 % patients with serum sodium between 131 meq/l to 135 meq/l suffered from HE. In patients having normal serum sodium above 135 meq/l only 13% patients had an episode of HE (fig 2.).Association between hepatic encephalopathy and low serum sodium may be explained only on the basis of advanced liver parenchymal failure among patients with serum sodium < 130 meq/l which probably reflects compensatory osmoregulatory system against cellular swelling due to a combination of high intracellular glutamine ,as a consequence of hyperammonimia and low extracellular sodium.[15-17] In experimental models of acute liver failure presence of Hyponatremia is associated with larger brain swelling compared with normal serum sodium.[18] Finally in patients with acute liver failure and grade IV encephalopathy the administration of hypertonic saline to increase serum sodium reduces the incidence and severity of intracranial hypertension compared with a control group of patients receiving a standard of care.[19]

However, there is also a possibility that the two events may be path physiologically linked. Studies have shown that low serum sodium in patients with cirrhosis are associated with striking reduction in cerebral concentration of organic osmolyte which probably reflect compensatory osmoregulatory system against cellular swelling due to a combination of high intracellular glutamine ,as a consequence of hyperammonimia and low extracellular sodium.[15-17] In experimental models of acute liver failure presence of Hyponatremia is associated with larger brain swelling compared with normal serum sodium.[18] Finally in patients with acute liver failure and grade IV encephalopathy the administration of hypertonic saline to increase serum sodium reduces the incidence and severity of intracranial hypertension compared with a control group of patients receiving a standard of care.[19]

Hepatorenal syndrome was also strongly associated with low serum sodium. In our cohort (48% in patients with serum sodium less than 130 meq/l compared with 13.6% in patients with serum sodium between 131 meq/l to 135 meq/l and only 2.1 % in patients with normal serum sodium (fig 2, Table 5).This association can be explained by the fact that Hepatorenal syndrome is commonly associated with impaired excretion of solute free water so that majority of patient with Hepatorenal syndrome have low serum sodium.[20,21] It has been shown that Hyponatremia is a major risk factor for the development of Hepatorenal syndrome in patients with ascites.[22]

Our data also shows an existence of relation between spontaneous bacterial peritonitis and low serum sodium. (fig 2, tab.5) Association probably reflects impairment in effective circulating blood volume seen in cirrhotics in the setting of spontaneous bacterial peritonitis and may lead to Hepatorenal syndrome in some patients and others may have only hyponatermia.[23-26]

One limitation of our study was that the results are insufficient to establish a causal link between low serum sodium levels and complications of cirrhosis. They just highlighted the importance of negative impact of hyponatremia on the clinical progression of cirrhosis but did not assess the effect of hyponatremia on the risks for developing complications. Further prospective studies are needed to determine the same.

In conclusion the results of this observational study show that low serum sodium levels are a common occurrence in advanced cirrhosis. In comparison to patients with normal serum sodium, patients with low serum sodium have a more frequent need of repeated paracentesis, more frequency of hepatic encephalopathy, hepatorenal syndrome and spontaneous bacterial peritonitis. These results indicate that close follow up of serum creatinine and serum sodium concentration should be done in cirrhotics throughout the course of a septic insult.

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Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Gaurav Kumar Gupta, Ram Pratap Singh, Dhawal Vyas, Sandeep Nijhawan. Impact of Serum Sodium with Severity of Complications of Cirrhosis: A Prospective Study in Tertiary Medical Center of Rajasthan. Int J Med Res Prof. 2017 Sept; 3(5):56-60. DOI:10.21276/ijmrp.2017.3.5.012