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Original Research Article

Dysnatremia in patients with chronic liver disease: a cross-sectional observational study

Ram Dev Chaudhary*, Kirti Kumari Sah, Ram Prabodh Chaudhary

Department of Medicine, Provincial Hospital, Madhesh province, Janakpurdham, Nepal

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***Correspondence:**
Dr. Ram Dev Chaudhary,
E-mail: doctor_rd05@yahoo.com

ABSTRACT

Background: The clinical significance of serum sodium levels and its association with a higher rate of complications in cirrhosis is debatable. This study was done to study the serum sodium levels in chronic liver disease (CLD) patients and establish its association with the severity of disease in such patients.
Methods: In this cross-sectional study, we included adult patients diagnosed with CLD and assessed their serum electrolytes. The severity of liver disease was assessed using Child Pugh score (CPS) and model for end stage liver disease (MELD). Those with serum sodium levels less than 130 mEq/l were classified as group A, 131 to 135 mEq/l as normal group B and greater or equal to 136 mEq/l as Group C.
Results: In the present study, hepatic encephalopathy ($p<0.01$), hepatorenal syndrome ($p<0.01$) and coagulopathy ($p<0.01$) were found to occur significantly more common among patients from Group A, as compared to those in patients from group B or C. Mean MELD, CPS score and mortality was significantly higher among group A patients.
Conclusions: Patients with lower serum salt levels had a substantially higher MELD score and CPS. Low blood sodium levels were linked to more severe liver disease, greater complications, and increased death. As a result, we urge that serum salt levels be checked on a frequent basis in patients with chronic liver disease.

Keywords: Cirrhosis, Sodium, Hyponatremia, MELD, Prognosis

INTRODUCTION

Chronic liver disorders (CLD) are a major source of morbidity and death globally. Multiple etiological causes contribute to a similar clinicopathological pathophysiology in Chronic liver disorders, albeit progression rates and clinical course may differ.[1] The majority of the rise in CLD mortality has been documented from Asia and Africa's poor and low-middle income (LMIC) nations. Disease burden is changing demographically and epidemiologically in LMIC. India is one of the epicentres of this transformation.[2] Reduced serum sodium concentration is a common finding in patients with cirrhosis, being the most common electrolyte disorder in this setting.[3] Indeed, around 20% of patients had levels less than 130 mmol/l, the current criterion of hyponatremia in cirrhosis. Although hyponatremia can be seen in individuals with early or moderately severe cirrhosis from Child-Pugh classifications A and B, it is more common in people with advanced disease (Child-Pugh class C). The link between hyponatremia and cirrhosis severity is further supported by its close association with the occurrence of complications: the prevalence of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis is significantly higher in patients with serum sodium concentrations of 130 mmol/l than in those with higher levels. In a study conducted in a government medical college in south Kerala, hyponatremia occurred in 57 percenatges of hospitalized patients with cirrhosis.[4] According to recent research, hyponatremia is a significant predictive factor in individuals with chronic liver disease.

Furthermore, the patients with the hyponatremia have worse survival rates than the those without the hyponatremia.[5]

Despite the medical literature supporting the role of blood sodium as a predictive factor in cirrhosis, the clinical relevance of serum sodium levels and whether they are connected with a greater likelihood of particular consequences in cirrhosis remains unknown. Only a few studies have been conducted to examine the relationship between blood sodium levels and the occurrence and severity of liver cirrhosis complications. Thus, the current study was conducted to investigate blood sodium levels in chronic liver disease patients and determine their relationship with the disease severity in the such individuals.

METHODS

Study design and sample size

We conducted an observational cross-sectional study in the department of medicine, Provincial hospital, Madhesh province, Janakpurdham, Nepal from June 2021 till May 2022. In this study, we included patients in the age group of 18 to 65 years, irrespective of gender, diagnosed with chronic liver disease. We also excluded patients aged less than 18 years, with comorbid cardiac failure, with co morbid chronic kidney disease and those taking drugs that alter serum sodium levels. We calculated the sample size using following formulae:

$N=(Z\alpha/2)\ 2*(PQ)/E^2$,

where Zα/2 is Z value at 5% error (1.96), P=taken as 57% (Prasanna et al reported hyponatremia in 57% with liver cirrhosis), Q=1-P and E=allowable error (taken as 10%).[4] The minimum sample size calculated was 94 patients. The study protocol was approved by the Institutional Ethics Committee before commencement and a written informed consent was taken from all patients.

Data collection and data analysis

We acquired demographic information about the patients from their medical records. A history, physical examination, biochemical markers, ultrasonography, and upper gastrointestinal endoscopy were used to identify cirrhosis. Each patient's venous blood was taken and submitted to the institutional laboratory for analysis of serum electrolytes, liver function tests (LFTs), renal parameters, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalised ratio (INR). An automatic biochemical analyzer was used to test the biochemical indicators, while an automated haematology analyzer was used to measure the whole blood cell counts. Complications in the patients included hepatic encephalopathy, varices, hepatorenal syndrome, and infections. In addition, child-Turcotte Pugh score (CPS) and model for end stage liver disease (MELD) score was calculated for all patients.[6]

Those with serum sodium levels less than or equal to 130 meq/l were classified as group A, those with serum sodium levels between 131-135 meq/l as group B and those with serum sodium levels greater than or equal to 136 meq/l as group C. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute number and percentage. Cross tables were generated and chi square test was used for testing of associations. One-way ANOVA was used for comparison of quantitative parameters, along with Bonferroni post-hoc test. A p value of <0.05 is considered statistically significant. All analysis were done using SPSS software, version 24.0.

RESULTS

In the present study, 96 patients were included. It was observed that 28.1% were in group A (≤ 130 mEq/l, n=27), 32.2% were in group B (131 to 135 mEq/l, n=31) and 39.7% were in group C (≥ 136 mEq/l, n=38). The age or gender of the patients was not associated with serum sodium levels (Table 1). All patients had abdominal distension. It was observed that patients from group A had jaundice ($p<0.05$) and altered sensorium ($p<0.001$) significantly more commonly as compared to those from group B and C. Alcohol consumption was reported by 91.6% of the patients. Serum sodium levels was not significantly associated with alcohol consumption. Among all examination findings, icterus ($p<0.05$) and clubbing ($p<0.01$) were found to be significantly more common among patients from group A, as compared to patients from group B or C. Pallor, pedal edema, signs of liver cell failure and organomegaly were not significantly associated with serum sodium levels in our study population. Portal hypertension was observed in 86.4%, hepatic encephalopathy in 25%, hepatorenal syndrome in 23.9%, spontaneous bacterial peritonitis in 5.2% and coagulopathy in 18.7%. Of these, hepatic encephalopathy ($p<0.01$), hepatorenal syndrome ($p<0.01$) and coagulopathy ($p<0.01$) were found to occur significantly more common among patients from group A, as compared to those in patients from group B or C (Table 2). We observed that mean direct bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase were significantly higher among group A patients as compared to those from group B or C respectively. In addition, we observed that mean MELD score was significantly higher among group A patients (17.98±6.74) as compared to those with group B (13.52±5.26) and group C (11.95±4.43). We also observed that mean Child Pugh score was significantly higher among group A patients (9.81±2.17) as compared to those with group B (8.75±1.81) and group C (7.82±1.93). Overall, 10.42% of the patients expired. It was observed that mortality was 25.9 percentages among group A patients, which was significantly higher than that of group B patients (9.68%) or group C patients (0%).

Table 1: Comparison of baseline characteristics between groups based on serum sodium levels.

Variables		Group A (≤ 130 mEq/l, n=27)	Group B (131 to 135 mEq/l, n=31)	Group C (≥ 136 mEq/l, n=38)	Total	P value
Age group (Years)						
25 to 40	N	5	11	11	27	0.42
	%	18.52	35.48	28.95	28.13	
41 to 60	N	18	17	23	58	
	%	66.67	54.84	60.53	60.42	
61 to 80	N	4	3	4	11	
	%	14.81	9.68	10.53	11.46	
Gender						
Female	N	3	4	10	17	0.24
	%	11.11	12.90	26.32	17.71	
Male	N	24	27	28	79	
	%	88.89	87.10	73.68	82.29	
Clinical presentation						
Abd distension	N	27	31	38	96	NA
	%	100	100	100	100	
GI bleed	N	6	7	6	19	0.19
	%	22.22	22.58	15.79	19.79	
Jaundice	N	15	10	8	33	<0.05
	%	55.56	32.26	21.05	34.38	
Alt sensorium	N	16	6	3	25	<0.001
	%	59.26	19.35	7.89	26.04	
Alcohol	N	26	29	33	88	0.85
	%	96.30	93.55	86.84	91.67	
Examination findings						
Pallor	N	6	6	7	19	0.83
	%	22.22	19.35	18.42	19.79	
Icterus	N	20	16	5	41	<0.05
	%	74.07	51.61	13.16	42.71	
Clubbing	N	11	12	3	26	<0.01
	%	40.74	38.71	7.89	27.08	
Pedal edema	N	25	25	29	79	0.77
	%	92.59	80.65	76.32	82.29	
S/o liver cell failure	N	25	30	35	90	0.17
	%	92.59	96.77	92.11	93.75	
Organomegaly	N	3	11	7	21	0.24
	%	11.11	35.48	18.42	21.88	

*analyzed using chi-square test.

Table 2: Comparison of complication rate between groups based on serum sodium levels.

Complications		Group A (≤ 130 mEq/l, n=27)	Group B (131 to 135 mEq/l, n=31)	Group C (≥ 136 mEq/l, n=38)	Total	P value*
Port hypertension	N	24	27	32	83	0.13
	%	88.89	87.10	84.21	86.46	
Hepatic encephalopathy	N	14	6	4	24	<0.01
	%	51.85	19.35	10.53	25	
Hepatorenal syndrome	N	13	5	5	23	< 0.01
	%	48.15	16.13	13.16	23.96	
Spontaneous bacterial peritonitis	N	3	2	0	5	0.45
	%	11.11	6.45	0	5.21	
Coagulopathy	N	11	4	3	18	<0.01
	%	40.74	12.90	7.89	18.75	

*analyzed using chi-square test.

Table 3: Comparison of liver function between groups based on serum sodium levels.

Liver function		Mean	SD	Minimum	Maximum	P value*
Total bilirubin (mg/dl)	Group A (n=37)	3.11	2.49	0.52	9.31	0.07
	Group B (n=39)	2.36	2.14	0.62	12.11	
	Group C (n=44)	2.05	1.72	0.62	7.11	
Direct bilirubin (mg/dl)	Group A (n=37)	2.08	1.81	0.22	6.11	<0.01
	Group B (n=39)	1.42	1.30	0.32	6.51	
	Group C (n=44)	1.27	1.21	0.32	4.41	
Alanine transaminase (U/l)	Group A (n=37)	87.42	85.17	12.12	540.11	<0.01
	Group B (n=39)	53.28	18.55	17.12	96.11	
	Group C (n=44)	47.97	17.97	12.12	82.11	
Aspartate transaminase (U/l)	Group A (n=37)	105.88	96.76	20.12	600.11	<0.01
	Group B (n=39)	64.64	21.79	31.12	149.11	
	Group C (n=44)	57.56	21.14	18.12	130.11	
Alkaline phosphatase (U/l)	Group A (n=37)	142.77	95.06	81.12	624.11	<0.01
	Group B (n=39)	102.82	27.00	70.12	192.11	
	Group C (n=44)	93.13	18.35	62.12	140.11	
Total protein (gm/dl)	Group A (n=37)	6.20	0.92	4.92	7.81	0.71
	Group B (n=39)	6.19	0.74	4.12	8.11	
	Group C (n=44)	6.29	0.94	4.12	8.31	
Albumin (gm/dl)	Group A (n=37)	3.42	0.85	1.82	6.01	0.08
	Group B (n=39)	3.31	0.70	1.92	5.11	
	Group C (n=44)	3.59	0.62	2.52	4.91	

*analyzed using one-way ANOVA and Bonferroni post-hoc test.

Table 4: Comparison of liver cirrhosis severity between groups based on serum sodium levels.

Variables	Mean	SD	Minimum	Maximum	P value*
MELD					
Group A (n=27)	17.98	6.74	6.12	33.04	<0.01
Group B (n=31)	13.52	5.26	8.12	30.04	
Group C (n=38)	11.95	4.43	8.12	25.04	
CPS					
Group A (n=27)	9.81	2.17	6.12	14.04	<0.01
Group B (n=31)	8.75	1.81	6.12	13.04	
Group C (n=38)	7.82	1.93	6.12	15.04	

*analyzed using one-way ANOVA and Bonferroni post-hoc test.

Table 5: Comparison of mortality rate between groups based on serum sodium levels.

Outcome		Group A (≤ 130 mEq/l, n=27)	Group B (131 to 135 mEq/l, n=31)	Group C (≥ 136 mEq/l, n=38)	Total	P value*
Discharged	N	20	28	38	86	<0.001
	%	74.07	90.32	100	89.58	
Expired	N	7	3	0	10	
	%	25.93	9.68	0	10.42	

*analyzed using chi-square test.

DISCUSSION

Hyponatremia affected 60.3% of the individuals in this research. Elkady et al observed that 43.5% had blood sodium levels of 125 mEq/l or less, whereas the rest had serum sodium levels greater than 125 mEq/l.[8] Kim and colleagues discovered that 27.1% of participants had serum sodium of 130 mmol/l, 20.8% had serum sodium of 131 to 135 mmol/l, and 52.1 percent had serum sodium of 136 mmol/l.[9] Umemura et colleagues studied mortality in cirrhotic patients on conventional diuretics and discovered links between blood sodium levels and clinical features.[10]

In their study, 26 of 171 patients (15.2%) had sodium readings below the lower limit of normal range (135 mEq/l), and eight of 171 patients (4.7%) had sodium of 130 mEq/l or less, which is the generally used cut-off number to identify hyponatremia. According to this study, the prevalence of hyponatremia in cirrhotic patients is

likewise low in the Japanese community. This might be due to variances in patient selection, sample size disparities, or ethnic diversity.

Among all physical results, we discovered that icterus and clubbing were substantially more prevalent in Group A patients than in group B or C patients. Ascites and hyponatremia are manifestations of cirrhosis's generalised hemodynamic derangement, which is characterised by low peripheral vascular resistance, reduced effective circulating volume, central antidiuretic hormone overproduction, elevated renin, angiotensin, norepinephrine-reduced glomerular filtration, and marked renal salt and water retention. Hyponatremia is one of the reasons limiting diuretic dosage in ascites therapy and may therefore contribute to ascites becoming resistant. Because refractory ascites has a bad prognosis, effective treatments are required.

Hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were shown to be considerably more prevalent in group A patients than in group B or C patients in the current study. In another study, Elkady et al found that 91% of individuals with blood sodium levels less than 125 mEq/l had hepatic encephalopathy, and 50% had upper gastrointestinal haemorrhage, which was considerably higher than those with serum sodium levels greater than 125 mEq/l. Ascites were shown to be considerably less prevalent in individuals with blood sodium levels of 139 mEq/l, according to Umemura et al (45 vs 65%). Jenq et al found that a substantially larger proportion of individuals with sodium levels less than 135 mEq/l (52/67) developed hepatic encephalopathy than those with sodium levels more than 135 mEq/l (35/59).[11] Serum sodium levels were not substantially linked with esophageal variceal bleeding, peptic ulcer haemorrhage, or the presence of hepatocellular carcinoma. The presence of hypothesised processes involved in poor free-water excretion (e.g., prostaglandins and arterial natriuretic peptide), which is unrelated to gastrointestinal bleeding, might explain this occurrence. Kim et al found ascites in 88% of hyponatremia patients, spontaneous bacterial peritonitis in 33%, hepatic encephalopathy in 43%, and hydrothorax in 23.5% all of which were considerably higher than in patients with normal serum sodium and hypernatremia.

We discovered that mean direct bilirubin, alanine transaminase, aspartate transaminase, and alkaline phosphatase levels were considerably higher in Group A patients than in Group B or C patients. In similar research, Meganathan et colleagues found that ALT, AST, and ALP were not substantially related to serum sodium levels.[12] Elkady et al also found no correlation between ALP, AST, AST, and bilirubin and hyponatremia. Umemura et colleagues discovered that individuals with serum sodium levels of 139 mEq/l had considerably reduced median AST, ALT, GGT, and total bilirubin.

MELD and CPS were found to be considerably higher in group A patients as compared to group B and C patients. Elkady et colleagues also found that individuals with blood sodium 125 mEq/l had a mean MELD score of 18.19±5.3, compared to 16.17±6.2 in patients with serum sodium more than 125 mEq/l. Furthermore, in their study, 61 percent of hyponatermic patients belonged to class C, and the mean CPS was 10.51±2.8, which was substantially higher than patients with blood salt levels greater than 125 mEq/l. In another study, Umemura et colleagues found that patients with MELD values of 139 mEq/l had considerably lower median MELD scores. Jenq et al on the other hand, found no significant relationship between MELD score and blood sodium level. It was 32.9±13.9 for patients with sodium levels less than 135 mEq/l and 29.4±13.6 for patients with sodium levels greater than 135 mEq/l, p=0.158. CPS was considerably higher in individuals with blood sodium levels less than 135 mEq/l (12.4±2.3) than in those with serum sodium levels greater than 135 mEq/l (11.1±2.1). In Kim et al study, mean CPS was substantially higher in hyponatremia patients (10.5±1.6) compared to those with normal blood sodium levels (9.8±1.7) and hypernatremia (8.7±1.6), $p<0.001$.

This study has some drawbacks. First, the individuals were recruited from a single institution, therefore the findings may not be easily extended to other patient groups. Second, serum sodium levels were only measured on the first day of ICU hospitalisation. Serum sodium concentrations measured sequentially (e.g., daily or weekly) may capture the dynamic characteristics of clinical disorders and hence give complete data for mortality risk.

CONCLUSION

In conclusion, individuals with lower serum salt levels had a substantially higher MELD score and CPS. Furthermore, hepatic encephalopathy, hepatorenal syndrome, and coagulopathy were shown to be considerably more prevalent in individuals with blood sodium levels more than 130 mEq/l than in other patients. Our findings show that hyponatremia is common in people with chronic liver disease. Low blood sodium levels were linked to more severe liver disease, greater complications, and increased death. As a result, we urge that serum salt levels be checked on a frequent basis in patients with chronic liver disease. Those suffering from hyponatremia should be prioritised for acute treatment.

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