ORIGINAL ARTICLE

Severity of Hyponatremia and its Influence on Various Complications Seen in Decompensated Chronic Liver Disease

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ABSTRACT

Background: Hyponatremia in cirrhosis has been identified as an independent risk factor for mortality and is common in patients with end-stage liver disease. Only a few studies have been conducted to evaluate the frequency of low serum sodium levels and to examine whether serum sodium levels are indicative of the presence and severity of cirrhotic complications. So we conducted this study.

Aim: To determine frequency and severity of hyponatremia seen in Decompensated chronic liver disease and various complications based on severity of hyponatremia.

Methods: It was descriptive Cross sectional study conducted in the Department of Internal Medicine, jinnah hospital, Lahore from. 1st January 2017 to 30th June 2017. 120 cases of liver cirrhosis presenting with complications were enrolled in the study. Background information like age, sex, severity of hyponatremia, and frequency of different complications observed Child Pugh score etc.

Results: The mean age of p
atients was 44.47±18.14years. There were 91 (75.8%) males and 29 (24.2%) females. There were 84 (70%) patients of hyponatremia, 27 (22.5%) had mild hyponatremia, 38 (31.67%) had moderate hyponatremia while 19 (15.8%) had severe hyponatremia. But 36 (30%) had normal sodium level. Ascites was found in 34 (28.3%) cases, 39 (32.5%) had hepatic encephalopathy, 34 (28.3%) cases had spontaneous bacterial peritonitis, 28 (23.3%) had variceal bleed while 26 (21.7%) had HRS.

Conclusion: Thus the frequency of complications was significantly high in patients with hyponatremia.

Key words: Hyponatremia, decompensated chronic liver disease, ascites, hepatic encephalopathy

INTRODUCTION

Hyponatremia in cirrhosis is a common abnormal finding, and it is prevalent in upto 57% of inpatients with liver cirrhosis and 40% of outpatients.[1] It usually occurs when the disease is at an advanced stage and is associated with complications and increased mortality. Both hypovolemic or hypervolemic hyponatremia can be seen in cirrhosis. The former is indicative of a low concentration of sodium and reduced volume of plasma. The latter is indicative of a significant impairment of the excretion of solute-free water, which results in the abnormal retention of water. The latter very commonly occurs in patients who have cirrhosis and ascites[2]. Dilutional hyponatremia seen in cirrhosis can be attributed to impaired renal sodium handling due to renal hypoperfusion and increased arginine-vasopressin secretion secondary to peripheral arterial vasodilation[3].

Hyponatremia in cirrhosis has been clearly linked with increased mortality and is common in patients with end-stage liver disease.[3, 4] A 2006 survey of 997 cirrhotics showed a prevalence of serum sodium level < 130mmol/L of 21.6%[5]. This patient subgroup also showed higher incidence of hepatic encephalopathy (OR = 3.40; 95% CI: 2.35 4.92), hepatorenal syndrome (OR = 3.45; 95% CI: 2.04-5.82), and spontaneous bacterial peritonitis (OR = 2.36; 95% CI: l.4]-3.93). Refractory ascites and requirement for frequent therapeutic paracentesis was more in patient with serum sodium levels < 135 mmol/L. Hyponatremia is associated with poor outcomes in patients hospitalized with infections. Spontaneous bacterial peritonitis is linked with significant morbidity, including renal failure, and has a high mortality rate[6, 7]. Patients with hyponatremia at diagnosis of spontaneous bacterial peritonitis stand a much greater risk for development of hepatorenal syndrome and death.[6] The incidence of hyponatremia and renal failure in cirrhotic patients admitted for skin and soft tissue infection was higher than in matched cirrhotic controls without infection, and was associated with higher 3-month mortality, compared with patients who had not developed hyponatremia and renal failure (45% vs 19%).[8] The prevalence of dilutional hyponatremia, classified as serum sodium concentrations of <135 mmol/L, <l30 mmol/L and <120 mmol/L were 20.8%, 14.9% and 12.2% respectively; collectively 47.9% as reported by kim et al[9].

To date, only a few studies have been done to evaluate the frequency of low serum sodium levels and to examine whether serum sodium levels correlate with the presence and severity of cirrhotic complications. The close association with the occurrence of complications: the prevalence of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, intractable ascites, and hepatic hydrothorax needs to be investigated. Our aim is to study the frequency of Hyponatremia on occurrence of aforementioned complications?

Operational Definition: Degree of Hyponatremia

Mild Hyponatremia: It was labelled as mild if the patient had serum sodium concentration between l30-l 35mmol/L

Moderate Hyponatremia: It was labelled as moderate if the patient had serum sodium concentration between 120-130 mmol/L(*Serum sodium concentration 136 mmol/L was treated as Normal*)

Severe Hyponatremia: It was labelled as severe if the patient had serum sodium concentration less than 120 mmol/L

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Decompensated chronic liver disease: A patient was labelled as having decompensated chronic liver disease if patient had child class A or B had any of the following complications: Ascites, hepatic encephalopathy, hepatorenal syndrome, esophageal varices along with Abdominal Ultrasound indicating liver cirrhosis or raised serum bilirubin (more than 2.5 times the upper limit of normal) and prolonged prothrombin time (prolonged by more than 3 s)

Complications

Ascites: Patient was labelled as having ascites if he is positive for shifting dullness or fluid thrill along with a confirmatory ultrasonography finding.

Hepatic encephalopathy: The presence of hepatic encephalopathy was diagnosed and graded using West Haven Criteria

Spontaneous Bacterial Peritonitis: For spontaneous bacterial peritonitis diagnosis, the number of polymorphonuclear leucocytes (PMN) from the ascitic fluid obtained by paracentesis, must exceed 250 cells/mm and or positive bacteriological cultures showing single organism.

Variceal Bleed: history of hematemesis along with confirmatory endoscopic evidence for esophageal or gastric varices.

Hepatorenal Syndrome: Patient was labelled as hepatorenal syndrome if there is increase in serum creatinine by more than 0.3mg/dL in less than 48 hours or increase in serum creatinine by more than 50% from a stable baseline reading within 3 months.

MATERIALS AND METHODS

It was a descriptive cross sectional study conducted in the Department of Internal Medicine, Jinnah Hospital, Lahore from 1st January 2017 to 30th June 2017 . To determine the sample size, we assumed a confidence level of 95%, with a precision of 6%. Using a mean prevalence 12.2% hyponatremia (9) in our group of cirrhotic patients on the basis of previous data; the sample size comes out to be 120. Non Probability Consecutive sampling technique was used. Patients aged 15-75 years of both gender diagnosis of cirrhosis confirmed by clinical, biochemical, and ultrasonographic findings were included in the study. Patients using diuretics within a 1-month period before admission with non-viral liver disease were excluded in the study. After approval of synopsis, 120 consecutive cases of liver cirrhosis presenting with complications were offered to enroll in the study. The purpose of the study was explained in detail to all the patients and an informed consent was taken in each case. Ultrasonography, LFTs, Serum electrolytes and other baseline investigations were done to evaluate for hepatic decompensation. The relevant data was collected in a structured proforma containing background information like age, sex, severity of hyponatremia, frequency of different complications observed Child Pugh score etc. All investigations were done in hospital lab and verified by pathologist.

Data was analyzed using SPSS version 21.Mean with standard deviation was calculated for quantitative variable like age and serum sodium levels. In case of qualitative variable like gender, Child-Pugh class, hyponatremia and degree of hyponatremia and different complications seen during liver cirrhosis frequency and percentages were calculated. Data was depicted in tables and graphs. Effect modifier like age, gender, Child-Pugh class and degree of hyponatremia were controlled through stratification. Post stratification, chi square test taking p value ≤0.05 as significant.

RESULTS

The mean age of patients was 44.47±18.14years (Table 1). There were 91 (75.8%) males and 29 (24.2%) females (Fig 1).

The mean Child-Pugh score of patients was 7.78±2.15 (Table 2). In this study, 40 (33.3%) had Child-Pugh class A, 51 (42.5%) had Child-Pugh class B and 29 (24.2%) had Child-Pugh class C (Fig 2). The mean serum sodium level was 129.79±8.69mg/dl (Table 3). There were 84 (70%) patients who had hyponatremia while 36 (30%) had normal sodium level (Fig 3). Out of 84 cases of hyponatremia, 27 (22.5%) had mild hyponatremia, 38 (31.67%) had moderate hyponatremia while 19 (15.8%) had severe hyponatremia. But 36 (30%) had normal sodium level (Fig 4). Ascites was found in 34 (28.3%) cases, 39 (32.5%) had hepatic encephalopathy, 34 (28.3%) cases had spontaneous bacterial peritonitis, 28 (23.3%) had variceal bleed while 26 (21.7%) had HRS (Table 4).

In our study, ascites was present in 32 (38.1%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). hepatic encephalopathy was present in 37 (44.0%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). Spontaneous bacterial peritonitis was present in 34 (40.5%) patients with hyponatremia while in 0 (0.0%) patients without hyponatremia ($p<0.05$). Variceal bleed was present in 26 (31.0%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). HRS was present in 23 (27.4%) patients with hyponatremia while in 3 (8.3%) patients without hyponatremia ($p<0.05$) (Table 5).

Data was stratified for age of patients. In patients of age 15-45years, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$). In patients of age 46-75years, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for HRS ($p>0.05$) (Table 6).

Data was stratified for gender of patients. In male patients, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$). In female patients, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for variceal bleed and HRS ($p>0.05$) (Table 7).

Data was stratified for Child-Pugh class. In patients with Child-Pugh class A, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for variceal bleed and HRS ($p>0.05$). In patients with Child-Pugh class B, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for HRS ($p>0.05$). In patients with Child-Pugh class C, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for hepatic encephalopathy, variceal bleed and HRS ($p>0.05$) (Table 8).

Table 1: Descriptive Statistics of age of patients

Age (years)	n	120
	Mean	44.47
	Standard deviation	18.14
	Minimum	15
	Maximum	75

Fig 1: Distribution of gender of patients

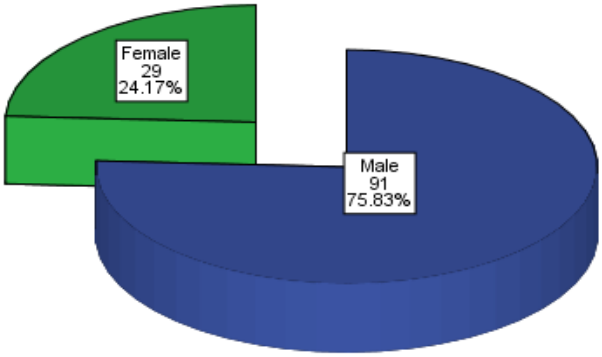

Table 2: Descriptive Statistics of Child-Pugh score

Child-Pugh score	n	120
	Mean	7.78
	Standard deviation	2.15
	Minimum	5
	Maximum	12

Fig 2: Distribution of Child-Pugh class

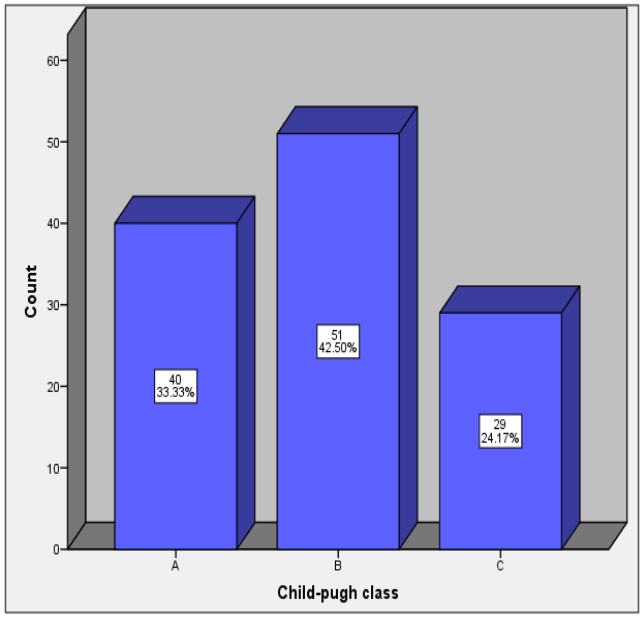

Table 3: Descriptive Statistics of serum sodium level

Serum sodium level (mg/dl)	n	120
	Mean	129.79
	Standard deviation	8.69
	Minimum	115
	Maximum	145

Fig 3: Distribution of hyponatremia

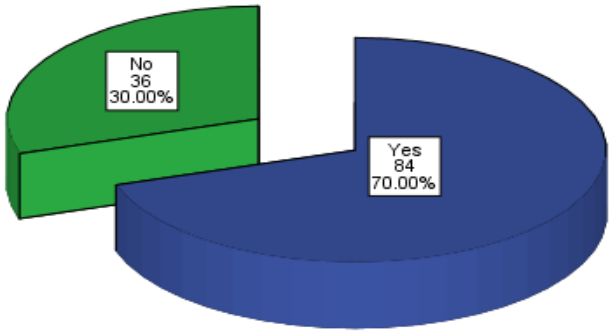

Fig 4: Distribution of degree of hyponatremia

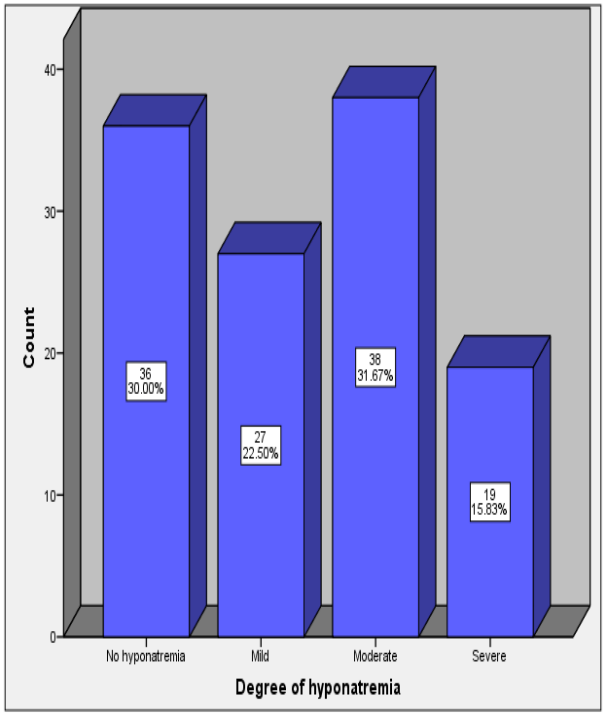

Table 4: Distribution of complications of decompensated chronic liver disease (n=120)

		Frequency	%
Ascites	Yes	34	28.3
	No	86	71.7
Hepatic encephalopathy	Yes	39	32.5
	No	81	67.5
Spontaneous bacterial peritonitis	Yes	34	28.3
	No	86	71.7
Variceal bleed	Yes	28	23.3
	No	92	76.7
HRS	Yes	26	21.7
	No	94	78.3

Table 5: Comparison complications with severity of hyponatremia

		Hyponatremia		Total	p-value
		Yes (n=84)	No (=36)		
Ascites	Yes	32 (38.1%)	2 (5.6%)	34 (28.3%)	0.000
	No	52 (61.9%)	34 (94.4%)	86 (71.7%)	
Hepatic encephalopathy	Yes	37 (44.0%)	2 (5.6%)	39 (32.5%)	0.000
	No	47 (56.0%)	34 (94.4%)	81 (67.5%)	
Spontaneous bacterial peritonitis	Yes	34 (40.5%)	0 (0.0%)	34 (28.3%)	0.000
	No	50 (59.5%)	36 (100%)	86 (71.7%)	
Variceal bleed	Yes	26 (31.0%)	2 (5.6%)	28 (23.3%)	0.003
	No	58 (69.0%)	34 (94.4%)	92 (76.7%)	
HRS	Yes	23 (27.4%)	3 (8.3%)	26 (21.7%)	0.020
	No	61 (72.6%)	33 (91.7%)	94 (78.3%)	

Table 6: Comparison complications with severity of hyponatremia stratified for age

Complications	Age	Hyponatremia		Total	p-value
		Yes	No		
Ascites	15-45	16 (37.2%)	0 (0.0%)	16 (25.8%)	0.002
	46-75	16 (39.0%)	2 (11.8%)	18 (31.0%)	0.041
Hepatic encephalopathy	15-45	19 (44.2%)	0 (0.0%)	19 (30.6%)	0.001
	46-75	18 (43.9%)	2 (11.8%)	20 (34.5%)	0.019
Spontaneous bacterial peritonitis	15-45	11 (25.6%)	0 (0.0%)	11 (17.7%)	0.015
	46-75	23 (56.1%)	0 (0.0%)	23 (39.7%)	0.000
Variceal bleed	15-45	8 (18.6%)	0 (0.0%)	8 (12.9%)	0.044
	46-75	18 (43.9%)	2 (11.8%)	20 (34.5%)	0.019
HRS	15-45	11 (25.6%)	0 (0.0%)	11 (17.7%)	0.015
	46-75	12 (29.3%)	3 (17.6%)	15 (25.9%)	0.358

Table 7: Comparison complications with severity of hyponatremia stratified for gender

Complications	Gender	Hyponatremia		Total	p-value
		Yes	No		
Ascites	Male	23 (35.4%)	1 (3.8%)	24 (26.4%)	0.002
	Female	9 (47.4%)	1 (10.0%)	10 (34.5%)	0.044
Hepatic encephalopathy	Male	29 (44.6%)	2 (7.7%)	31 (34.1%)	0.001
	Female	8 (42.1%)	0 (0.0%)	8 (27.6%)	0.016
Spontaneous bacterial peritonitis	Male	28 (43.1%)	0 (0.0%)	28 (30.8%)	0.000
	Female	6 (31.6%)	0 (0.0%)	6 (20.7%)	0.046
Variceal bleed	Male	21 (32.3%)	1 (3.8%)	22 (24.2%)	0.004
	Female	5 (26.3%)	1 (10.0%)	6 (20.7%)	0.303
HRS	Male	18 (27.7%)	2 (7.7%)	20 (22.0%)	0.037
	Female	5 (26.3%)	1 (10.0%)	6 (20.7%)	0.303

Table 8: Comparison complications with severity of hyponatremia stratified for Child-Pugh class

Complications	Class	Hyponatremia		Total	p-value
		Yes	No		
Ascites	A	13 (50.0%)	1 (7.1%)	14 (35.0%)	0.007
	B	10 (25.6%)	0 (0.0%)	10 (19.6%)	0.050
	C	9 (47.4%)	1 (10.0%)	10 (34.5%)	0.044
Hepatic encephalopathy	A	12 (46.2%)	1 (7.1%)	13 (32.5%)	0.012
	B	18 (46.2%)	0 (0.0%)	18 (35.3%)	0.003
	C	7 (36.8%)	1 (10.0%)	8 (27.6%)	0.124
Spontaneous bacterial peritonitis	A	9 (34.6%)	0 (0.0%)	9 (22.5%)	0.012
	B	19 (48.7%)	0 (0.0%)	19 (37.3%)	0.002
	C	6 (31.6%)	0 (0.0%)	6 (20.7%)	0.046
Variceal bleed	A	5 (19.2%)	1 (7.1%)	6 (15.0%)	0.307
	B	14 (35.9%)	0 (0.0%)	14 (27.5%)	0.015
	C	7 (36.8%)	1 (10.0%)	8 (27.6%)	0.124
HRS	A	9 (34.6%)	1 (7.1%)	10 (25.0%)	0.056
	B	8 (20.5%)	0 (0.0%)	8 (15.7%)	0.088
	C	6 (31.6%)	2 (20.0%)	8 (27.6%)	0.507

DISCUSSION

Chronic liver diseases and its complications are the major health problem, due to big burden of Hepatitis C virus and Hepatitis B virus in the community and it is also the commonest reason of death in Pakistani population. [10, 11] In our study, the mean serum sodium level was 129.79±8.69mg/dl. There were 84 (70%) patients who had hyponatremia while 36 (30%) had normal sodium level. Out of 84 cases of hyponatremia, 27 (22.5%) had mild hyponatremia, 38 (31.67%) had moderate hyponatremia while 19 (15.8%) had severe hyponatremia. But 36 (30%) had normal sodium level.

In our study, ascites was found in 34 (28.3%) cases, 39 (32.5%) had hepatic encephalopathy, 34 (28.3%) cases had spontaneous bacterial peritonitis, 28 (23.3%) had variceal bleed while 26 (21.7%) had HRS. In our study, ascites was present in 32 (38.1%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). hepatic encephalopathy was present in 37 (44.0%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). Spontaneous bacterial peritonitis was present in 34 (40.5%) patients with hyponatremia while in 0 (0.0%) patients without hyponatremia ($p<0.05$). Variceal bleed was present in 26 (31.0%) patients with hyponatremia while in 2 (5.6%) patients without hyponatremia ($p<0.05$). HRS was present in 23 (27.4%) patients with hyponatremia while in 3 (8.3%) patients without hyponatremia ($p<0.05$).

Hyponatremia in cirrhosis has been clearly described as an independent risk factor for mortality and is common in patients with end-stage liver disease.[3, 4]A 2006 survey of 997 cirrhotics showed a prevalence of serum sodium level < 130 mmol/L of 21.6%.[5] This subgroup also showed higher incidence of hepatic encephalopathy (OR = 3.40; 95% CI: 2.35 4.92), hepatorenal syndrome (OR = 3.45; 95% CI: 2.04-5.82), and spontaneous bacterial peritonitis (OR = 2.36; 95% CI: I.4]-3.93). Refractory ascites and requirement for frequent therapeutic paracentesis was more in patient with serum sodium levels < 135 mmol/L. Hyponatremia is associated with poor outcomes in patients hospitalized with infections. Spontaneous bacterial peritonitis is linked with significant morbidity, including renal failure, and has a high mortality rate[6, 7].

Patients with hyponatremia at diagnosis of spontaneous bacterial peritonitis are at much higher risk for development of hepatorenal syndrome and death.[6] The incidence of hyponatremia and renal failure in cirrhotic patients admitted for skin and soft tissue infection has also been shown to be higher than in matched cirrhotic controls without infection, and was associated with higher 3-month mortality, compared with patients who had not developed hyponatremia and renal failure (45% vs 19%).[8] The prevalence of dilutional hyponatremia, classified as serum sodium concentrations of <135 mmol/L, <l30 mmol/L and <120 mmol/L were 20.8%, 14.9% and 12.2% respectively; collectively 47.9% as reported by kim et al[9].

About 30% of patients with CLD usually die due to Portosystemic encephalopathy. The clinical course of patients with CLD is frequently complicated due to increase in the renal function abnormalities and imbalance of electrolytes. [12,13] In another study, hyponatremia was found in 59.46% of cirrhotics, and they showed markedly increased Model for End-Stage Liver Disease score, Model for End-Stage Liver Disease- sodium score, QTc interval, pulmonary vascular resistance, inferior vena cava collapsibility, and decreased Systemic vascular resistance and inferior vena cava diameter. In addition hepatic encephalopathy, ascites, renal failure, infectious complications, and pleural effusion were more commonly seen in hyponatremic cirrhotic patients[1].

In another study, the serum sodium levels of the study subjects had shown that 48% of them had normal sodium levels and 21% had mild hyponatremia and the remaining 31% had severe hyponatremia. Based on the child pugh score of liver cirrhosis class B patients had the mean sodium levels of 133.5 meq/L whereas class C patients sodium levels were 124.8 meq/L and the difference was found to be statistically significant. The correlation between the mean Model for End-Stage Liver Disease score and the serum sodium levels had shown a strong negative correlation between them. It was concluded that a strong association of hyponatremia among patients with liver cirrhosis. Future multicenter surveys are warranted to determine the clinical significance of hyponatremia and identify its association with the severity of possible complications[14].

The mean age of patients was 44.47±18.14years. Data was stratified for age of patients. In patients of age 15-45 years, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$). In patients of age 46-75 years, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for HRS ($p>0.05$). There were 91 (75.8%) males and 29 (24.2%) females. Data was stratified for gender of patients. In male patients, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$). In female patients, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for variceal bleed and HRS ($p>0.05$).

The mean Child-Pugh score of patients was 7.78±2.15. In this study, 40 (33.3%) had Child-Pugh class A, 51 (42.5%) had Child-Pugh class B and 29 (24.2%) had Child-Pugh class C. Data was stratified for Child-Pugh class. In patients with Child-Pugh class A, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for variceal bleed and HRS ($p>0.05$). In patients with Child-Pugh class B, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for HRS ($p>0.05$). In patients with Child-Pugh class C, the difference in patients with or without hyponatremia was significant for all complications ($p<0.05$), except for hepatic encephalopathy, variceal bleed and HRS ($p>0.05$).

CONCLUSION

The frequency of hyponatremia was high in patients with decompensated chronic liver disease. Thus the frequency of complications was significantly high in patients with hyponatremia as compared to patients without

hyponatremia. Now in future, we can implement the results of this study and can implement the screening of patients of decompensated chronic liver disease for serum sodium level and its complications.

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