Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: www.saspublishers.com

OPEN ACCESS

Medicine

A Study of Association of Hyponatremia with Complications in Patients with Liver Cirrhosis

Nagaraja B.S[1*], V.S.Sheshan[2], Umesh K.J[3], Sree Raksha K.N[4]

[1]Professor And Head Of Department, General Medicine, BMCRI, [2]Post Graduate, General Medicine, Sri Siddhartha Medical College, Tumkur, [3,4]Post Graduate, General Medicine, BMCRI, Bangalore Medical College And Research Institute, Fort Road, Bengaluru: 560002.

***Corresponding author:** Nagaraja B.S
| **Received:** 03.06.2019 | **Accepted:** 10.06.2019 | **Published:** 23.06.2019
DOI: 10.36347/sjams.2019.v07i06.013

Abstract **Original Research Article**

Background/Aims*:** Hyponatremia associated with liver cirrhosis is caused by impaired free water clearance.(1) Several studies have shown that hyponatremia is significantly associated with complications of cirrhosis and also correlate with survival in cirrhotic patients. This study aims at studying the association between serum sodium level and the severity of complications in patients with liver cirrhosis. ***Materials and methods: Data of patients with liver cirrhosis was retrospectively reviewed for associated complications. The severity of hyponatremia and its association with severity of complications of 299 patients were analyzed using chi square test and ANOVA. ***Results:*** In our study conducted on 299 patients, the age distribution was between 20 to 85 years and the mean age was 45.7+/-10.94. Male: female ratio - 265:34. 175 patients had hyponatremia. Significant association was found between hyponatremia and ascites (p value-0.019), Severe hyponatremia was associated with the severity of hepatic encephalopathy (p value-0.013), renal dysfunction (p value-0.033) and grade of esophageal varices(p value-0.013). No significant association was found between Child-Pugh score and hyponatremia (p value-0.97). ***Conclusion:*** Results of the study show significant association of hyponatremia with complications of liver cirrhosis such as ascites, hepatic encephalopathy, renal dysfunction and grade of esophageal varices.

Keywords: Hyponatremia; cirrhosis; ascites;encephalopathy; varices;renal dysfunction.

INTRODUCTION

Hyponatremia is a common laboratory abnormality in 57% of the hospitalized and 40% of outpatients with liver cirrhosis[1-2].There are two types of hyponatremia in cirrhotics -hypovolemic and hypervolemic. Hypovolemic hyponatremia occurs as a result of low serum sodium and decreased plasma volume. Hypervolemic hyponatremia is the most common mechanism causing hyponatremia in cirrhotics and occurs due to impaired free water clearance[3-5].

Mechanisms behind dilutional hyponatremia include 1)Renal hypoperfusion-reduced renal handling of sodium. 2)peripheral arterial vasodilation, causing reduced effective blood volume and increased secretion of AVP [6,7].

The relationship between hyponatremia and the severity of complications have been clearly demonstrated in its association with prevalence of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis and other inter-related complications[8-9].

In addition, patients with ascites with hyponatremia tend to have higher incidence of refractory ascites not responding to diuretics and have higher incidence of therapeutic paracentesis[1]. There is an increased risk of mortality in patients with hyponatremia and it is an independent predictor of mortality in patients with end stage liver disease and in those waiting for liver transplantation[10-13].

In fact, very few studies have evaluated the correlation between serum sodium and severity of complications with liver cirrhosis and our study aims to study the association between serum sodium with complications in liver cirrhosis.

AIMS AND OBJECTIVES

To study the association of hyponatremia with complications and their severity in patients with liver cirrhosis.

MATERIALS AND METHODS

A retrospective cross sectional observational study was done in 199 patients with cirrhosis of liver admitted in Bowring and Lady Curzon hospital attached to Bangalore medical college and research institute, during January 2016 to December 2016.

Inclusion criteria

- Patients aged more than 18 years
- Patients with liver cirrhosis as evidenced by clinical, biochemical and ultrasonographic findings.

Exclusion criteria

- Hepatocellular carcinoma
- Patients on diuretics for previous one month and those on antivirals were excluded from the study.

Based on the serum sodium concentration at admission, the patients were divided into three groups: serum sodium <130meq/l, serum sodium between 131-135meq/l and serum sodium >136 meq/l. Complications included ascites, hepatic encephalopathy, renal dysfunction, upper gastrointestinal bleeding and esophageal varices as evidenced by endoscopy. Hepatic encephalopathy and Varices on endoscopy were further classified according to severity as follows:

Hepatic encephalopathy was graded based on West Haven criteria as grades I –IV[14]. Presence of varix as evidenced by endoscopy on current admission was considered and classified by size and shape as small and large esophageal varices[15].

Investigations done included CBC, LFT, RFT, serum electrolytes ,viral markers, PT/INR ,viral markers ,Ultrasonography and endoscopy when indicated. Child-pugh score was calculated for all patients and a total score of 5-6,7-9 and more than 10 were categorized into class A,B and C respectively.

STATISTICAL ANALYSIS

The quantitative data were expressed as mean+/-SD,while categorical data were expressed in percentage. The statistical analysis was done using Chi-square test and ANOVA to find association between variables. All analysis were carried out using the SPSS software. P values of less than 0.05 were considered statistically significant.

RESULTS

199 patients with liver cirrhosis were retrospectively studied for the presence of hyponatremia and the presence of complications associated with liver cirrhosis.

Table-1:Gender distribution

Gender	Frequency	Percent
Females	34	11.4
Males	265	88.6
Total	299	100.0

Table-2: Etiology of cirrhosis in study population

ETIOLOGY	Frequency (%)
ALCOHOL	291 (97.3)
HBsAg	8(2.7)

The mean age of the patients studied 45.7+/-10.94 years.88.6% of the patients were males and 11.4% were females.Etiology- 291 patients had alcohol as etiology and 8 patients had HbSAg positive status.

Table-3: Patient characteristics

	Yes- N(%)	No- N(%)
Hemetemesis	120 (40.1)	179 (59.9)
Malaena	117 (39.1)	182 (60.9)
Ascites	265 (88.6)	34(11.4%)
Hepatic encephalopathy	129(43.1)	170(56.9)
Varices on UGI scopy	189(63.2)	110(36.8)
Renal dysfunction	89(29.8)	210(70.2)

The most common complication that was noted was ascites in 88.6% patients, Upper GI bleed was observed in 79.2% patients, hepatic encephalopathy in 43.1% patients. Varices on endoscopy was seen in 63.2% of the patients and renal dysfunction in 29.8% patients.

Table-4: Distribution of study population based on serum sodium levels.

Sodium	Frequency	Percent
131 to 135	68	22.7
less than 130	107	35.8
More than 136	124	41.5
Total	299	100.0

Total of 58.5% of the patients had serum sodium less than 135 meq/l and 35.8% patients had serum sodium less than 130 meq/l and 41.5% had normal serum sodium levels.

Table-5: Comparison of sodium levels with various complications developed among the study population

Complications(n)	Sodium<130meq/l	Sodium 131-135 meq/l	Sodium >136meq/l	Chi-square	P-value
ASCITES(265)	96	54	115	7.94	0.019*
HEMETEMESIS(120)	38	31	51	1.84	0.39
MALENA (117)	36	27	54	2.37	0.30
RENAL DYSFUNCTION(89)	41	14	34	6.80	0.033*

Table-6: Comparison of serum sodium with grades of hepatic encephalopathy

Sodium levels	HE GRADE					Total
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
less than 130	54	7	7	13	26	107
131 TO 135	37	0	9	6	16	68
More than 136	79	3	19	9	14	124
Total	170	10	35	28	56	299
Chi-square value- 19.43						
p value- 0.013*						

Table-7: Comparison of serum sodium with grade of varices as evidenced on endoscopy

Sodium levels	Upper GI scopy			
	No varices	Small varices	Large Varices	Total
less than 130	40	18	49	107
131 to 135	33	18	17	68
More than 136	37	35	52	124
Total	110	71	118	299

Amongst the various complications studied, significant association was found between hyponatremia and ascites, renal dysfunction, hepatic encephalopathy and esophageal varices as evidenced on endoscopy.

Table-8: Comparison of serum sodium levels with Child-Pugh score

Sodium levels	Childpugh Scores			Total
	A	B	C	
less than 130	5	17	85	107
131 to 135	2	12	54	68
More than 136	5	19	100	124
Total	12	48	239	299
Chi-square value- 0.47				
p value- 0.97				

There was no significant association that was found between hyponatremia and Child-Pugh score in our study.

DISCUSSION

Hyponatremia occurs commonly in hospitalized patients and most patients with liver cirrhosis have dilutional hyponatremia caused by impairment of solute-free water clearance. Hyponatremia resulting from impaired solute free water clearance is usually accompanied by portal hypertension [1]. Very few Indian studies have done till date to study the association of hyponatremia with complications in liver cirrhosis and to predict mortality outcomes.

We observed in our study that the prevalence of hyponatremia (serum sodium <135 meq/l) was 58.5% in patients with liver cirrhosis. Most common etiology was cirrhosis secondary to alcohol consumption in 97.3% patients. Our study showed significant statistical association between hyponatremia and ascites, renal dysfunction, hepatic encephalopathy and esophageal varices as evidenced on endoscopy. Severe hyponatremia was significantly associated with higher grades of hepatic encephalopathy and large varices. No significant association was found between

hyponatremia and Upper GI bleed and Child-Pugh score.

A study by Jong Hoon Kim *et al*. showed that hyponatremia was observed in 47.9% of Patients with liver cirrhosis and significant statistical association was found between hyponatremia and massive ascites, hepatic encephalopathy, hepatic hydrothorax, spontaneous bacterial peritonitis, Child-Pugh and MELD scores [16].

In a review of a previously conducted multicenter study in overseas countries,997 patients with liver cirrhosis and concurrent ascites, the prevalence of hyponatremia at serum sodium below 135meq/l was 49.4%. Complications such as severe ascites, hepatic encephalopathy, impaired renal function, spontaneous bacterial peritonitis and hepatorenal syndrome except GI bleeding occurred with higher probability in cases with severe hyponatremia[1].

In a study conducted by Borroni G *et al*. 156 patients with liver cirrhosis, the prevalence of hyponatremia based on serum sodium <130 mmol/L, was 29.8% and hyponatremia significant correlated with infection and ascites [17]. Arroyo *et al*. also found hyponatraemia < 130 in 30% of cases [18].

In cases in which hyponatremia is concurrently present, however, the increased intracellular concentration of glutamine due to hyperammonemia, along with the adaptation to the hypoosmotic extracellular environment of hyponatremia, increases the severity of hepatic encephalopathy, because organic osmolytes such as myo-inositol become further depleted in the cells [19].

Limitations of our study- Our study was a retrospective study and only analyzed the concurrent presence of complications with sodium levels in a retrospective analysis and did not assess the effect of sodium concentration and the risk of development of complications.

CONCLUSION

In our study conducted on 299 patients,175 (58.5%) patients had hyponatremia. Significant association was found between hyponatremia and ascites (p value-0.019), hepatic encephalopathy (p value-0.013), renal dysfunction (p value-0.033) and esophageal varices (p value-0.013).No significant association was found between Child-Pugh score and hyponatremia (p value-0.97).Thus, hyponatremia can be used as a simple indicator to predict the severity of complications in liver cirrhosis. Further studies are required to analyze the role of hyponatremia in the pathogenesis of these complications.

REFERENCES

1. Angeli P, Wong F, Watson H, Ginès P, Capps Investigators. Hyponatremia in cirrhosis: results of a patient population survey. Hepatology. 2006 Dec;44(6):1535-42.
2. Ginés P, Berl T, Bernardi M, Bichet DG, Hamon G, Jiménez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology. 1998 Sep 1;28(3):851-64.
3. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology. 2004 Oct;40(4):802-10.
4. Fernández-Esparrach G, Sánchez-Fueyo A, Ginès P, Uriz J, Quintó L, Ventura PJ, Cárdenas A, Guevara M, Sort P, Jiménez W, Bataller R. A prognostic model for predicting survival in cirrhosis with ascites. Journal of hepatology. 2001 Jan 1;34(1):46-52.
5. Ripoll C, Bañares R, Rincón D, Catalina MV, Lo Iacono O, Salcedo M, Clemente G, Núñez O, Matilla A, Molinero LM. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD Era. Hepatology. 2005 Oct;42(4):793-801.
6. Gine`s P, Ca´rdenas A, Schrier RW. Liver disease and the kidney. In: Schrier RW, ed. Diseases of the Kidney & Urinary Tract. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006: (3)2179-2205
7. Ginés P, Berl T, Bernardi M, Bichet DG, Hamon G, Jiménez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology. 1998 Sep 1;28(3):851-64.
8. Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, Navasa M, Clària J, Rimola A, Arroyo V, Rodés J. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology. 1993 Jul 1;105(1):229-36.
9. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, Rami L, Monté-Rubio GC, Martín-Llahí M, Arroyo V, Ginès P. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. The American journal of gastroenterology. 2009 Jun;104(6):1382.
10. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology. 2005 Jan;41(1):32-9.
11. Arroyo V, Rodés J, Gutiérrez-Lizárraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. The American journal of digestive diseases. 1976 Mar 1;21(3):249-56.
12. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM.

Hyponatremia and mortality among patients on the liver-transplant waiting list. New England Journal of Medicine. 2008 Sep 4;359(10):1018-26.
13. Londoño MC, Cárdenas A, Guevara M, Quintó L, de las Heras D, Navasa M, Rimola A, Garcia-Valdecasas JC, Arroyo V, Ginès P. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut. 2007 Sep 1;56(9):1283-90.
14. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. The American journal of digestive diseases. 1978 May 1;23(5):398-406.
15. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointestinal endoscopy. 1981 Nov 1;27(4):213-8.
16. Kim JH, Lee JS, Lee SH, Bae WK, Kim NH, Kim KA, Moon YS. The association between the serum sodium level and the severity of complications in liver cirrhosis. The Korean journal of internal medicine. 2009 Jun;24(2):106.
17. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Digestive and Liver Disease. 2000 Oct 1;32(7):605-10.
18. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. The Lancet. 1956 Dec 1;268(6953):1121-5.
19. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. The American journal of digestive diseases. 1978 May 1;23(5):398-406.