



Prevalence of Hyponatremia among patients admitted with Cirrhosis Liver and its Correlation with Hepatic Encephalopathy

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Abstract

Hyponatremia is an electrolyte imbalance encountered in patients with end-stage liver disease. It occurs in about 57% of hospitalized patients with cirrhosis. Hyponatremia in cirrhosis is an independent risk factor for mortality and is common in patients with end-stage liver disease. These patients had a significantly higher incidence of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. Hepatic encephalopathy is worsened by the presence of hyponatremia. Hyponatremia can induce or aggravate HE, leading to disease progression and even death.

Aim: To study the Prevalence of Hyponatremia among Patients admitted with Cirrhosis liver and its correlation with Hepatic Encephalopathy.

Materials and Methods: It is an observational Study of one year duration conducted among 120 patients with cirrhosis admitted in General Medicine and Medical Gastroenterology in a tertiary care centre in south kerala. Data collected and analyzed using SPSS Software.

Conclusions: Among the 120 cases enrolled in the study, majority were males. 36 % of the patients belonged to age group 51 -60 years with mean age 53.28 (SD -9.64). The prevalence of hyponatremia was 59%. There is a positive correlation between hyponatremia and hepatic encephalopathy.(p value 0.001). More patients with severe hyponatremia belonged to Child- Pugh class C. The patients with hyponatremia and hepatic encephalopathy had poor prognosis.

Keywords: Hyponatremia; Cirrhosis, Hepatic encephalopathy, Prevalence.

Introduction

Hyponatremia is an electrolyte imbalance frequently encountered in patients with end-stage liver disease ^[1].

The incidence and severity are variable, occur in about 57% of hospitalized patients with cirrhosis. Hyponatremia is a common complication of advanced cirrhosis related to an

impairment in the renal capacity for eliminating solute-free water, causing a retention of water that is disproportionate to the retention of sodium, and thus leading to a reduction in serum sodium concentration and hypo-osmolality. The main pathogenic factor responsible for hyponatremia is non-osmotic hypersecretion of arginine vasopressin (AVP) or antidiuretic

hormone from the neurohypophysis, related to circulatory dysfunction. An understanding of the pathophysiology of low serum sodium in end-stage liver disease patients is integral to management in both the inpatient and outpatient settings.

Cirrhosis is a condition that is defined histopathologically and has a variety of clinical manifestations and complications, some of which can be life-threatening^[2]. Cirrhosis is the leading causes of death and results in serious complications like ascites, hepatic encephalopathy and variceal hemorrhage. The clinical course of patients with chronic liver disease is complicated by the development of abnormalities in renal function and electrolyte levels and hyponatremia is the most common disorder seen in these patients. Hyponatremia in cirrhosis is defined as a reduction in serum sodium below 130 mmol/L^[5]. Hyponatremia is an independent predictor of poor outcomes in cirrhosis and is associated with refractory ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy^[1,3,4]. Hepatic encephalopathy is worsened by the presence of hyponatremia. Hyponatremia can induce or aggravate HE, leading to disease progression and death. Hyponatremia is associated with increased morbidity and impaired short-term survival after transplantation. In patients with cirrhosis, the existence of hyponatremia is a major risk factor of development of overt Hepatic encephalopathy. Treatment of hyponatremia may be a novel therapeutic approach to preventing HE in cirrhosis. The clinical tool used widely to determine prognosis in patients with alcoholic cirrhosis is the Child-Turcotte-Pugh (CTP) score.

Aims and Objectives

- 1) To find out the prevalence of hyponatremia among patients admitted with cirrhosis
- 2) To identify the correlation between hyponatremia and hepatic encephalopathy

- 3) To study prognosis of patients with hyponatremia and hepatic encephalopathy.

Relevance

Hyponatremia is a common electrolyte abnormality seen in cirrhosis patients.

It is a risk factor for HE. There is a positive correlation between hyponatremia and hepatic encephalopathy. Hence early recognition of hyponatremia and early correction can prevent hepatic encephalopathy and hence can decrease mortality in cirrhosis patients.

Materials and Methods

This is an observational study among 120 cirrhotic patients admitted in General medical and Medical Gastroenterology wards in a tertiary care centre in South Kerala from March 2015 to February 2016. All Patients admitted with Cirrhosis of any etiology were included in the study. Written consent was obtained from all patients participating in the study. All patients satisfying inclusion criteria are evaluated as per the proforma designed for the study. All patients undergone detailed clinical examination with particular reference to Serum Electrolytes. Serum sodium is done to identify hyponatremia. USG Abdomen is done for all patients. EEG is done for patients with hepatic encephalopathy.

Study Variables

Name, Age, Sex, IP No, H/O present illness, Co-morbidities, General and Systemic examination, Clinical features, Blood investigations like LFT, Serum Sodium, PT, INR, EEG and USG Abdomen.

Inclusion Criteria

- 1) All Patients admitted with Cirrhosis.

Exclusion Criteria

- 1) Patients not willing to take part in the study.
- 2) Patients on diuretics for non hepatic causes
- 3) Patients admitted with complications other than encephalopathy
- 4) Patients known to have other causes of encephalopathy.

HE was diagnosed after excluding infections, metabolic problems, intracranial vascular events, history of CLD and precipitating factors. The demographic profile of patient was noted and severity of liver disease was assessed according to Child Pugh score.

Patients were divided into three groups according to serum sodium concentration as follows

Sodium level <130 meq/L- Significant hyponatremia

Sodium level between 131 - 135 meq/L - Mild hyponatremia Sodium level >135 meq/L - Normal Sodium.

Statistical Analysis

Data was entered into Excel sheet and analysis by using SPSS version 16. All numerical variables was compared using independent samples t test or ANOVA. Categorical variables was compared using Chi square test.

P - value less than 0.05 was considered significant.

Observations

Fig 1 : Gender distribution in cirrhosis patients

Incidence of cirrhosis is higher among men than among women.

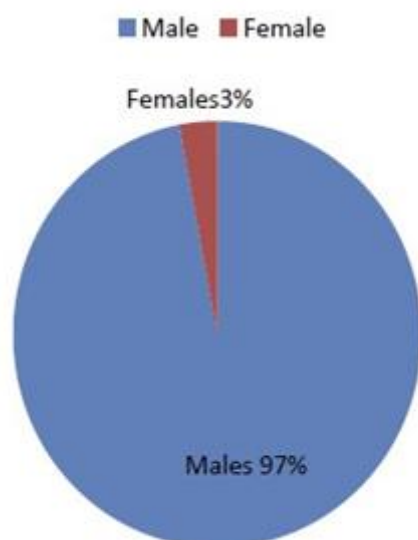


Fig 2 : Age distribution

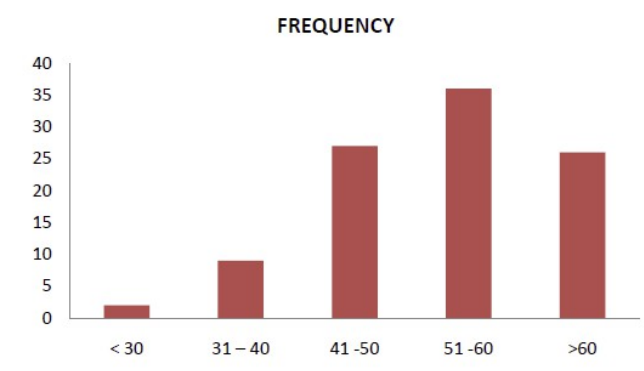


Fig 3 : Prevalance of Hyponatremia

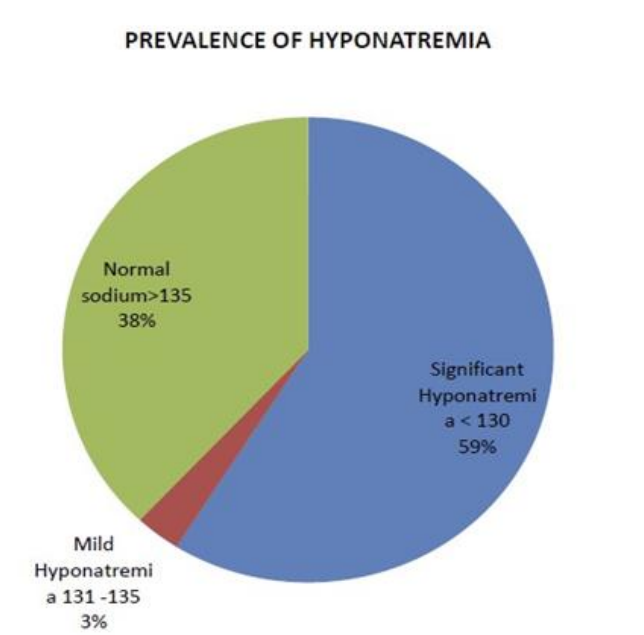


Fig 4: Hepatic Encephalopathy Hepatic encephalopathy is seen in 59 % (71 cases)of patients with cirrhosis

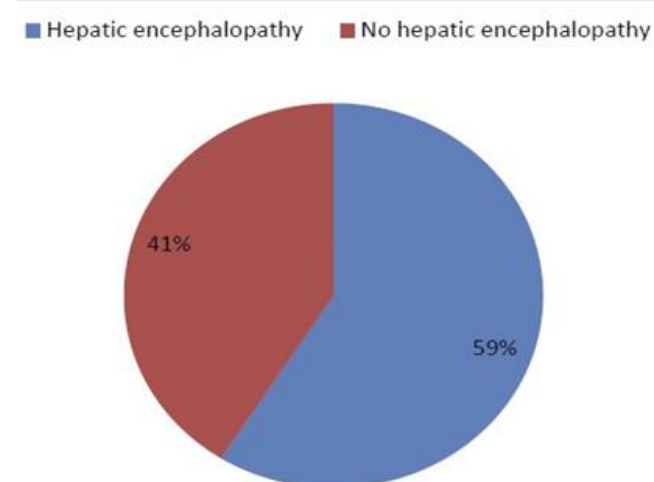
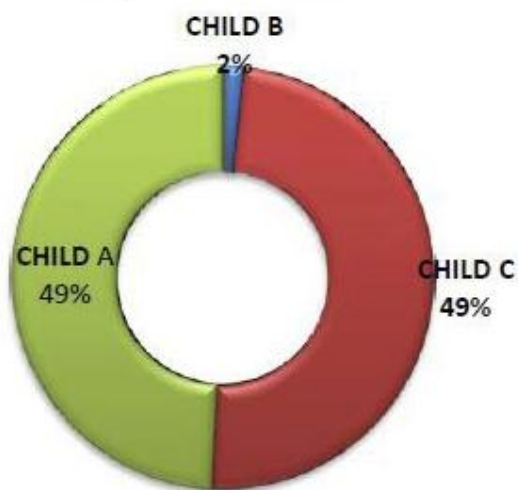
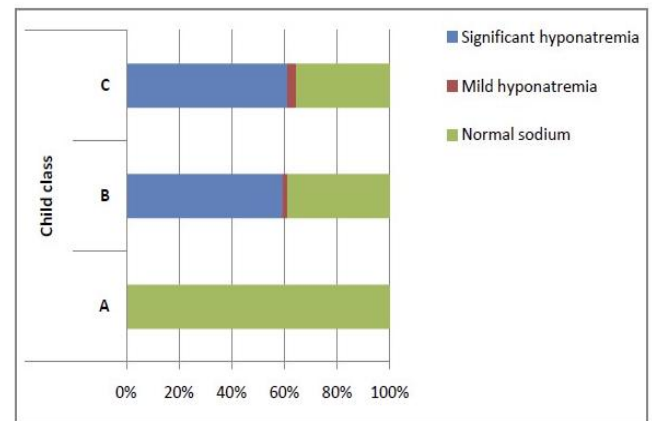


Table 1 : Hyponatremia and severity of liver disease

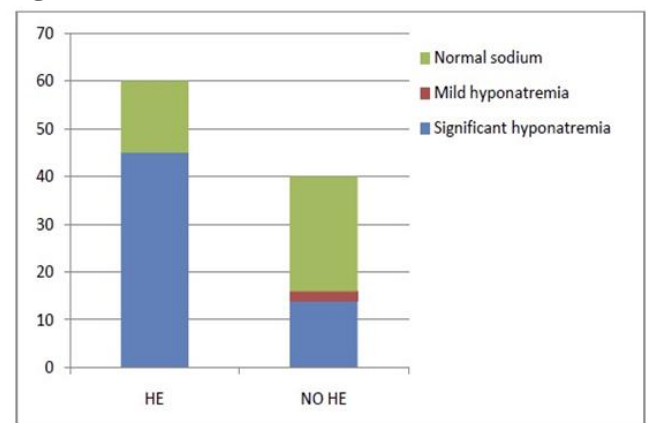
Sodium level	Child class			Total	p value
	A	B	C		
Significant hyponatremia	0	35	36	71	0.441
Mild hyponatremia	0	1	2	3	
Normal sodium	2	23	21	46	
Total	2	59	59	120	

Fig 5**Severity of liver disease****Table 2 :** Correlation between Hyponatremia and Severity of liver disease

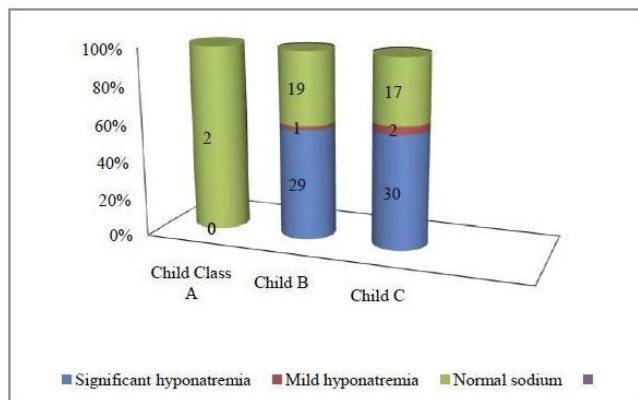
Sodium level	Child class			Total
	A	B	C	
Significant hyponatremia	0	35	36	71
Mild hyponatremia	0	1	2	3
Normal sodium	2	23	21	46
Total	2	59	59	120

Fig 6**Table 3:** Correlation between hyponatremia and hepatic encephalopathy

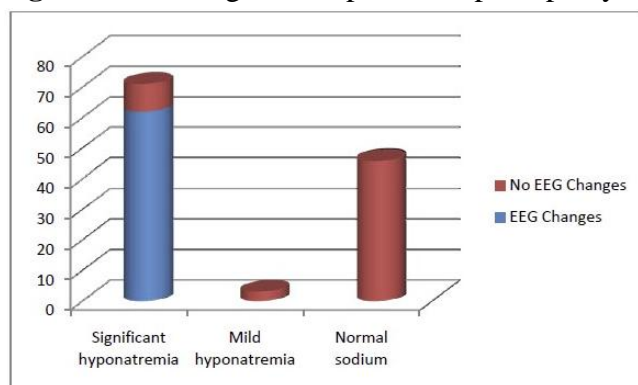
	HE%	No HE %	Total
Significant hyponatremia	45	14	59
Mild hyponatremia	0	2	2
Normal sodium	15	24	39

Fig 7**Table 4 :** Correlation between Hyponatremia and Child class

Sodium level	Child class		
	A	B	C
Significant hyponatremia	0	35 (29 %)	36 (30 %)
Mild hyponatremia	0	1 (1 %)	2 (2 %)
Normal sodium	2 (2 %)	23 (19 %)	21 (17 %)
Total	2 (2 %)	59 (49 %)	59 (49 %)

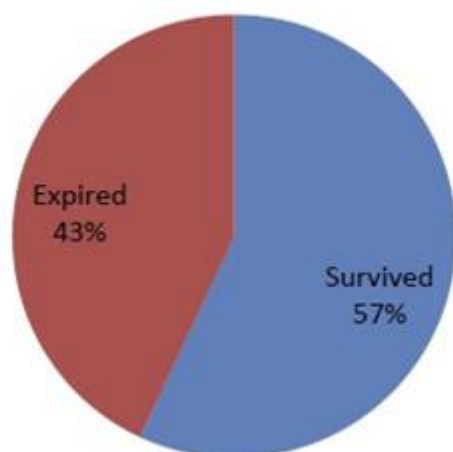
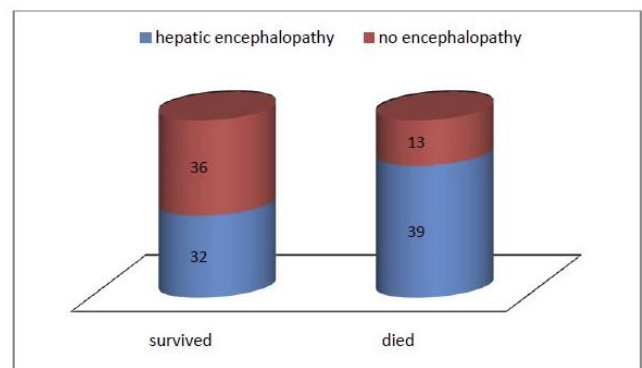
Fig 8**Table 5-** Correlation between hyponatremia and hepatic encephalopathy

	Hepatic encephalopathy	No hepatic encephalopathy	Total	p value
Significant Hyponatremia	55	16	71	0.001
Mild Hyponatremia	1	2	3	
Normal Sodium	15	31	46	
Total	71	49	120	

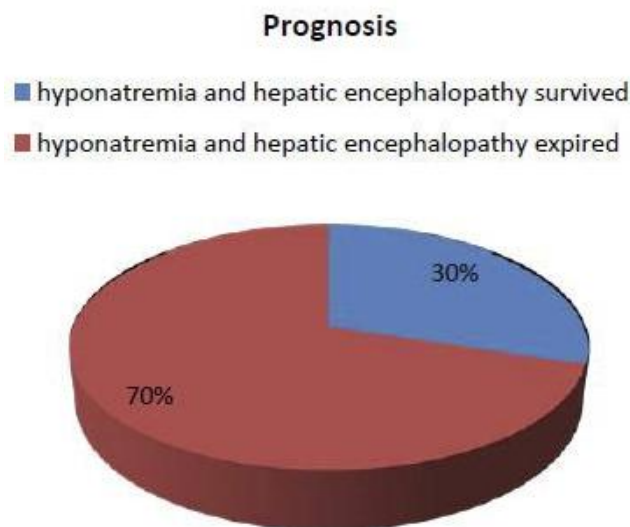
Fig 9 : EEG changes in Hepatic encephalopathy**Table 6 :** Effect of hepatic encephalopathy on survival

	Count	outcome		Total
		1	2	
hepaticencephalopathy	1	32	39	71
	2	36	13	49
Total		68	52	120

Chi square=9.522 df=1 p=0.000

Fig 10: Correlation between Hyponatremia, Hepatic encephalopathy and Survival**Outcome in cirrhosis patients****Fig 11 :** Effect of hepatic encephalopathy on survival**Table 7:** Correlation between hyponatremia, hepatic encephalopathy and Survival

	Number	Percentage
Patients with hyponatremia and hepatic encephalopathy survived	16	30%
Patients with hyponatremia and hepatic encephalopathy expired	39	70%
Total	55	100%

Fig 12: Correlation between hyponatremia, hepatic encephalopathy and Survival**Table 8** Statistical Correlation between hyponatremia and hepatic encephalopathy

Correlations			
		Severity	Encephalopathy
severity	Pearson Correlation	1	-.443**
	Sig. (2-tailed)		.000
	N	120	120
encephalopathy	Pearson Correlation	-.443**	1
	Sig. (2-tailed)	.000	
	N	120	120

** . Correlation is significant at the 0.01 level (2-tailed).

55 out of 71 cases with hepatic encephalopathy had significant hyponatremia compared to only 16 out of 49 without hepatic encephalopathy ($p=0.000$, significant). Those proportion of patients with hyponatremia was more in those with hepatic encephalopathy than in those without (55/71 vs 16/49, $p=0.000$).

Table 9: Severity of hyponatremia- hepatic encephalopathy Crosstabulation

		hepaticencephalopathy		Total
Count		1	2	
severity	1	15	31	46
	2	1	2	3
	3	55	16	71
Total		71	49	120

Chi square=24 df=1 $p=0.000$

Table 10: Statistical correlation between hyponatremia and child class

Correlations			
		severity	child_pugh
severity	Pearson Correlation	1	.116
	Sig. (2-tailed)		.208
	N	120	120
child_pugh	Pearson Correlation	.116	1
	Sig. (2-tailed)	.208	
	N	120	120

Mortality in patients with hepatic encephalopathy 55% (39 cases) of patients with hepatic encephalopathy expired.

Table 11: Outcome in patients with hepatic encephalopathy

	Percentage	Number
Patients with hepatic encephalopathy survived	32	45%
Patients with hepatic encephalopathy expired	39	55 %

Table 12: Effect of hepatic encephalopathy on survival

	Survived	Expired	Total	p value
Hepatic encephalopathy	32	39	71	0.000
No hepatic encephalopathy	36	13	49	
Total	69	51	120	

Out of those who died, 39/52 cases had hepatic encephalopathy compared to 32/68 in those who were cured. ($p=0.000$)

Discussion

Hyponatraemia an electrolyte imbalance found in patients with end-stage liver disease, can induce or aggravate HE, leading to disease progression and death. This study evaluated the prevalence of hyponatremia and association between hyponatremia and occurrence of major

complications like hepatic encephalopathy and outcome in cirrhosis patients.

This was an observational study done in 120 Cirrhosis patients. All patients above 18 years with established CLD of any etiology were included in the study. CLD was confirmed by clinical, biochemical and ultrasonographic findings.

Age Distribution

Out of 120 patients analysed, 36 % of cases(44 cases) belonged to the age group 51 - 60 years. 26 % of cases (31 cases) were of age greater than 60 years. Mean age is 53.28 ± 9.64 .

Gender Distribution

Out of 120 patients, 97% cases (117 cases) were males and 3% cases (3 cases) were females. This is in accordance with the fact that men are 2-fold more likely to die from CLD than women according to an analysis by the National Center for Health Statistics reported in 2005. In a study 67% patients were males. As per Muhammad Omar Qureshi et al ^[9] Out of 202 patients studied, 90 (44.6%) were males and 112 (55.4%) females. The greater incidence in males in this study may be due to the increased risk factor - alcoholism.

Prevalence of Alcoholics

75 % of cases (90 cases) were alcoholics

Duration of Cirrhosis

60 % of cases (50 cases) have cirrhosis of duration < 2 years.

Liver Function Abnormalities

1. Serum Bilirubin is elevated in 76 % of cases (91 cases).
2. Serum Albumin: Hypoalbuminemia was present in 44% (53 cases)of cases with cirrhosis.

Serum Sodium

In our study, 59% cases (71 cases) had significant hyponatremia that is S. Sodium < 130 meq/L and 3 % (3 cases) had mild hyponatremia.(Serum Sodium between 130 - 135 meq /L.and 38 % of cases (46 cases) had Serum Sodium > 135 meq/L. Ali Akbar et al ^[10]study reported 72% prevalence for hyponatremia in patients with liver cirrhosis, of which 27.8% had mild, 41.7% had

moderate and 30.6 had severe hyponatremia. Angeli P et al ^[1]had shown 50.6% mild, 27.8% moderate and 21.6% severe hyponatremia in cirrhotic patients. As per Muhammad Omar Qureshi et al^[9] more than one half (57.9%) of patients had values of serum sodium concentration < 135 meq/l and 30.7% had values <130 meq/l. Borroni et al.^[8] reported hyponatraemia, serum sodium < 130 meq/L in 30% of cases.

Our study shows an increased prevalence of hyponatremia .The prevalence of hyponatremia < 130 meq/L is 59 % (71 cases). 62 % cases (74 cases) had serum sodium < 135 meq/L and 59% cases (71 cases) had serum sodium < 130 meq/L. The frequency of Serum sodium < 135 meq/L is in accordance with study by Muhammad Omar Qureshi et al^[9] more than one half (57.9%) of patients had values of serum sodium concentration below the normal range (< 135 meq/l).

Hepatic Encephalopathy

Hepatic encephalopathy was seen in 59 % (71 cases) with cirrhosis. In Muhammad Omar Qureshi et al^[9] study, the prevalence of HE was greater (34.15%) as compared to other national and international studies. The patients with serum sodium <130 meq/l had a significantly greater frequency (64%) of HE. Ali Akbar et al.^[10] showed that Hepatic encephalopathy was observed in 40% patients. Guevara M et al^[7] reported 28 of the 61 patients developed 57 episodes of overt HE during follow-up This patient subgroup had a higher incidence of hepatic encephalopathy 95% cases. In this study, the prevalence of HE was greater (59 %) as compared to other national and international studies. The patients with serum sodium <130 meq/l had a significantly greater frequency (59 %) of HE. Patients with significant hyponatremia had higher incidence of HE.

Correlation between Hyponatremia and Hepatic Encephalopathy

Regarding Child's class, 2 % cases (2 cases) were in class A,49 % cases (59 cases) in class B, and 49% cases (59 cases) were in class C. More patients with severe hyponatremia belonged to

Child class C. This is in accordance with Muhammad Omar Qureshi et al^[9] who reported out of 202 patients, 16 (7.9%) were in class A, 85 (42.1%) in class B, and 101 (50%) in class C. More patients with severe hyponatremia belonged to Child class C. Low serum sodium levels were more frequent in patients with severe liver failure (Child- Pugh class C) irrespective of age and gender of the patient. The results proved that severe hyponatremia is associated with increased severity of HE. In previous studies, there is correlation between hyponatremia and HE, but this is even more highlighted in this study. There is a Correlation between Hyponatremia and Severity of liver disease in this study that more patients with severe hyponatremia belonged to Child class C.

EEG Changes in Hepatic Encephalopathy

In the present study, 52 % cases (62 cases) cases with hepatic encephalopathy had EEG changes.

Prognosis

Out of 120 cases. 52 cases (43 % of cases) expired during the study period. Higher frequency of complications and poor survival is reported for patients with low serum sodium concentration. In our study, out of the 71 cases (59 % of cases) with significant hyponatremia, 39 cases (55 %) expired.(p value is 0.003). There is a positive correlation between hyponatremia and hepatic encephalopathy and survival. According to Bustamante et al^[6], the survival probability was 42% at 1 year of followup and 23% at 3 years. According to D'Amico et al^[11], the median survival of patients with cirrhosis decreases from 8 years to approximately 2 years. The development of HE has been associated with shortened survival among patients with end-stage liver disease.

Summary and Conclusions

The present study was undertaken to find out the prevalence of hyponatremia in Cirrhosis patients and its correlation with hepatic encephalopathy. 120 patients were included in the study.

The findings obtained in the study is as follows.

- 1) Majority of the patients belonged to age group between 51 - 60 years. Mean age is 53.28
- 2) Majority of the patients are males. Incidence of cirrhosis is higher among men than among women
- 3) Most of the patients with cirrhosis are alcoholics.
- 4) Prevalence of hyponatremia with serum sodium < 130 meq/L was 59%.
- 5) Patients with significant hyponatremia had higher incidence of Hepatic encephalopathy.
- 6) Patients with severe hyponatremia belonged to Child Pugh Class C
- 7) EEG changes was found in 52 % cases of hepatic encephalopathy.
- 8) There is a positive correlation between hyponatremia and hepatic encephalopathy.
- 9) Patients with hyponatremia and hepatic encephalopathy had a bad prognosis

Hyponatremia is the most common electrolyte abnormality seen in cirrhosis patients and severe hyponatremia is associated with increased severity of HE. Higher frequency of complications and poor survival is reported for patients with low serum sodium concentration. The existence of serum sodium concentration <135 meq/L was associated with greater frequency of hepatic encephalopathy. It was also noticed that more severe the hyponatremia, greater will be the grade of hepatic encephalopathy. The results suggest that serum sodium levels should be closely monitored in patients experiencing these complications. Treatment of hyponatremia is important to prevent fatal hepatic encephalopathy related complications.

Limitations of Study

- 1) Sample size is small. Only a small group of patients could be studied
- 2) Grading of hepatic encephalopathy was not done.

- 3) The study did not assess the effect of serum sodium concentration on the risk for developing complications but simply examined the concurrent presence of complications and sodium levels in a retrospective analysis.

References

1. Angeli P, Wong F, Watson H, et al. CAPPS Investigators. Hyponatremia in cirrhosis: Results of a patient population survey. *Hepatology*. 2006;44:1535-42
2. Harrison, Tinsley Randolph et al. *Harrison's Principles Of Internal Medicine*. 19th ed. New York: McGraw Hill Education, 2015. Print.
3. Ahluwalia V, Wade JB, Thacker L, et al. Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. *J Hepatol*. 2013;59:467-73
4. Biggins SW, Rodriguez HJ, Bacchetti P, et al. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology*. 2005;41:32-39.
5. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53:397-417.
6. Bustamante J, Rimola A, Ventura PJ, et al: Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol* 1999; 30:890-5.
7. Guevara M, Baccaro ME, Torre A, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with timedependent analysis. *Am J Gastroenterol*. 2009;104: 1382-89.
8. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatremia for the hospital outcome of cirrhotic patients. *Dig Liver Dis* 2000; 32:605-10.
9. Qureshi MO, Khokhar N, Saleem A, Niazi TK. Correlation of hyponatremia with hepatic encephalopathy and severity of liver disease. *J Coll Physicians Surg Pak*. 2014;24(2):135-137.
10. Akbar, A., Jaffery, M.H., Memon, M.A., Arwani, S., Memon, H.N.A. and Shah, S.Z.A., 2015. LIVER CIRRHOSIS; FREQUENCY AND SEVERITY OF HYPONATREMIA IN PATIENTS. *Professional Medical Journal*, 22(4).
11. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of hepatology*. 2006 Jan 1;44(1):217-31.

Abbreviations

CLD: Chronic Liver Disease
HE: Hepatic Encephalopathy