Journal of Muhammad Medical College
Website: jmmc.mmc.edu.pk

Original Article

Correlation of serum sodium with severity of hepatic encephalopathy in liver cirrhosis patients presenting at Dr. Ruth K.M. Pfau Civil Hospital Karachi.

Darshan Kumar [1,*], S. Muhammad Kashif[2], Gul Anum[3], Saima[4], Madiha Mehmmood[5], Rashid Qadeer[6].

1: Associate Professor, Department Medical Unit -1 Dr. Ruth K.M. Pfau Civil Hospital Dow University Health Sciences Karachi.

2: Assistant Professor, Department Medical Unit -5 Dr. Ruth K.M. Pfau Civil Hospital. Dow University Health Sciences Karachi.

3: Medical Officer. Dr. Ruth K.M. Pfau Civil Hospital, Dow University Health Sciences Karachi.

4: Medical Officer. Department Medical Unit -5, Dr. Ruth K.M. Pfau Civil Hospital. Dow University Health Sciences Karachi.

5: Consultant Department Medical Unit -5 Dr. Ruth K.M. Pfau Civil Hospital Dow University Health Sciences Karachi.

6: Professor & Controller of examination. Department Medical Unit -5 Dr. Ruth K.M. Pfau Civil Hospital. Dow University Health Sciences Karachi.

***=corresponding author**
darshan.kumar@duhs.edu.pk.

Abstract:

Introduction: Cirrhotic patients suddenly or insidiously develop hepatic encephalopathy. Approximately three-fourth of the patients usually die within 3 years of onset of their first episode of hepatic encephalopathy. Hyponatremia, a multifactorial phenomenon in cirrhotic patients may lead to cerebral edema and astrocytes swelling.

Objective: To determine the correlation of serum sodium with severity of hepatic encephalopathy in liver cirrhosis patients presenting at tertiary care hospital, Karachi.

Methodology: This prospective cross-sectional study conducted at Department of Medicine, Civil Hospital, Karachi between October 31, 2019 till April 4,2020. Data collected from 138 patients after taking written consent; presented as was as mean, standard deviation, frequency and percentages. Effect modifiers were controlled through stratification to see the effect of these on the outcome variable taking p-value of ≤0.05 as significant.

Results: Among 138 patients 92 (66.7%) were male and 46 (33.3%) were female. Mean age, duration of symptoms, height, weight and serum sodium in our study was 51.14±4.49 years, 12±7.21 hours, 161±6.78 cm, 85.2±8.54 kg and 132.7±6.32 mEq/L. Out of 136 patients, 28 (20.3%), 35 (25.4%), 54 (39.1%) and 21 (15.2%) patients belonged to sodium quartile 1, 2, 3 and 4; while 21 (15.2%), 41 (29.7%), 28 (20.3%) and 48 (34.8%) belonged to hepatic encephalopathy severity grade 1, 2, 3 and 4. Hepatic encephalopathy severity showed correlation with rising sodium levels.

Conclusion: Hyponatremia was found with increased frequency in patients with cirrhosis of liver having a correlation with frequency and severity of hepatic encephalopathy.

Key words: Encephalopathy, Liver Cirrhosis, Hyponatremia.

Introduction:

Cirrhosis of liver carries high morbidity and mortality in developing countries. Cirrhosis is the abnormal scarring of the normal liver tissue leading to the fibrosis caused by liver disease and it is not a single disease entity, rather it can be further divided into distinct clinical prognostic stages, with 1-year mortality ranging from 1% to 57% depending upon the stage[1]. Liver cirrhosis develops over months to years caused by the disorders in which normal liver tissue damages over the course of clinical illness subsequently developing tissue fibrosis and nodule formation. This process started with the failure of detoxification of harmful substances which progressed to start systemic pro-inflammatory state further hastening disease progression[2]. Hepatic encephalopathy (HE) is a clinical disorder in which patients develop abnormal neurological dysfunction secondary to the portosystemic venous shunting which may be insidious or acute in on set. HE is also considered as a strong prognosticator of death as three-fourth of the patients usually die within 3 years of onset of their first episode of hepatic encephalopathy[3]. Patients presented with this clinical condition have a variety of neurological changes ranging from subtle psychological abnormalities to profound coma[4]. Till date, the most accepted and widely used HE grading method is the West Haven Criteria (WHC) (on scale from 0 to 4) with greater score indicating more severe impaired motor function and impaired neuromotor function[5]. The nitrogenous substances that are derived from the gut detrimentally affect the brain function and lead to HE. This access of nitrogenous compounds to systemic circulation is result of compromised hepatic function or raised portal pressure leading to portal-systemic shunting. These compounds upon reaching the brain tissue create alteration in the neurotransmission process ultimately affecting consciousness and behavior[6]. In advance stage of cirrhosis, the body water homeostasis gets impaired; resulting in increased retention of salt and water in correlation to the sodium content secondary to the reduced solute-free water clearance[7]. Consequently, this process started with the dysregulation of the amount of water excreted in urine to the amount of water being taken which subsequently results in the development of dilutional hyponatremia[8]. Hyponatremia which develops secondary to ongoing cirrhosis is defined as[9] serum sodium level of less than 130 mEq/L. The factors causing hyponatremia in relation to cirrhosis is because of hypovolemia which may either develop secondary to the loss of extracellular fluid either because of the diuretics use or expansion of extracellular fluid volume secondary to the renal inability to excrete solute-free water in proportion to the amount of free water ingested[10]. Hyponatremia in cirrhotic patients may present as mild cognitive dysfunction, seizures, coma and death depending upon the severity of hyponatremia[11]. Patients with cirrhosis and subsequent hyponatremia experience poor quality of life due to water restriction[12]. Hyponatremia has been found to be an independent risk factor for impaired quality of life and HE in cirrhotic patients[13]. Number of studies have been reported that the severity of hyponatremia and as cites is a major determinant of severity of disease and prognosis in cirrhosis[14]. Hyponatremia in cirrhosis is a long-term process which may cause osmotic hit to cerebral edema and astrocytes swelling in addition to the astrocyte dysfunction characterized by raised intracellular glutamine concentration from ammonia metabolism leading to the development hepatic encephalopathy[15].

Objective:

To determine the correlation of serum sodium with severity of hepatic encephalopathy in liver cirrhosis patients presenting at tertiary care hospital, Karachi.

Methodology:

This cross-sectional study conducted at the Department of Medicine, Civil Hospital, Karachi between 31 October 2019 to 30 April 2020, after approval from College of Physicians and Surgeons Pakistan and Ethical Research Committee of the Institution. The sample size was calculated using correlation coefficient of r= -0.3, 95% power of test and 5% significance level using the WHO software. After taking the written and informed consent, 138 liver cirrhosis patients presenting with hepatic encephalopathy within 24 hours were enrolled via non-probability consecutive sampling technique. Patients included in the study consist of both male and female having an age range between 30 to 70 years.

Demographic information, brief history and duration of illness was noted. The physical examination of each patient was carried out that include height in meters and body weight to the nearest kilogram using a weighing machine. The study population was grouped into various BMI categories according to WHO international

classification. The findings of quantitative and qualitative variables (age, gender, hypertension, smoking status, T2DM, hypertension, family monthly income status, occupational status and duration of symptoms) were noted in the Performa`.

The patients were examined by the researcher using classification for the severity of hepatic encephalopathy using grades of West Haven classification. At the time of admission, for the measurement of serum sodium, 5 cc blood sample (i.e.,5ml blood) from peripheral vein was drawn by researcher himself. Sample of each patient, after labelling, was sent to hospital laboratory to get standardize result. The result so obtained were categorized into quartiles. SPSS-16used for statistical analysis. The categorical variables were presented as frequencies and percentages. The numerical variables were expressed as mean and standard deviation. Spearman rank correlation test was calculated to identify relationship between sodium quartiles and severity of hepatic encephalopathy, p-value of ≤ 0.05 was considered as significant. Effect modifiers, age, gender, diabetes, hypertension and smoking was controlled through stratification. After stratification, Spearman rank correlation test was calculated to identify relationship between sodium quartiles and severity of hepatic encephalopathy, p-value of ≤ 0.05 was considered as significant.

Results:

For 138 enrolled patients, age ranges between 38 to 70 years, with a mean age of 51.14 ± 4.49 years. The mean duration of symptoms, height, weight, and serum sodium were 12 ±7.21 hours, 161 ±6.78 cm, 85.2 ±8.54 kg and 132.7 ±6.32 mEq/ L, respectively; as shown in table 1.

Male outnumber female patients (66.7%:33.3%). Among 138 patients with HE, 21 (15.2%), 41 (29.7%), 28 (20.3%) and 48 (34.8%) had a place with hepatic encephalopathy severity grade 1, 2, 3 and 4 respectively. Comorbidities in these patients were type 2 diabetes in 56 (40.6%), hypertension in 101 (73.2%) and majority (104,75.4%) were smokers. Stratification for sodium quartile for the severity of hepatic encephalopathy showed that 00 (00%), 14 (50%), 00 (00%), and 14 (50%) patients in sodium quartile 1, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively; whereas 07 (20%), 21 (60%), 00 (00%), and 07 (20%) patients who were in sodium quartile 2, had 1, 2, 3, and 4 hepatic encephalopathy grade respectively. While 14 (25.9%), 06 (11.1%), 14 (25.9%) and 20 (37%) patients who were in sodium quartile 3, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. Finally, 00 (00%), 00 (00%), 14 (66.7%) and 07 (33.3%)patients who were in sodium quartile 4, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. p-value was 0.11 (r 0.133). Data presented in table 2**.**

Patients with diabetes mellitus type II were categorized according to the severity of hepatic encephalopathy, with 00 (00 %), 04 (36.4 %), 00 (00%), and 07 (63.6%) in sodium quartile 1 ; 03 (23.1%), 08 (61.5%), 00 (00%), and 02 (15.4%) in the sodium quartile 2; 04 (16.7%), 02 (8.3%), 07 (29.2%) and 11 (45.8%) in patients who were in sodium quartile 3, and finally, 00 (00%), 00 (00%), 04 (50%) and 04 (50%) in patients who were in sodium quartile 4, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. The p-value was found to be 0.001 (r 0.0001). However, patients who did not have diabetes mellitus type II, 00 (00%), 10 (58.8%), 00 (00%) and 07 (41.2%) patients who were in sodium quartile 1, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. Whereas 04 (18.2%), 13 (59.1%), 00 (00%) and 05 (22.7%) patients who were in sodium quartile 2, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. Moreover, 10 (33.3%), 04 (13.3%), 07 (23.3%) and 09 (30%) patients who were in sodium quartile 3, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. Finally, 00 (00%), 00 (00%), 10 (76.9%) and 03 (23.1%) patients who were in sodium quartile 4, had 1, 2, 3 and 4 hepatic encephalopathy grade respectively. p-value was 0.001 (r 0.0001).

Discussion:

Cirrhosis stands among the leading causes of mortality resulting in life threatening complications such as ascites, hepatic encephalopathy and variceal hemorrhage[15]. The clinical course of chronic liver disease (CLD) is usually complicated by the development of abnormal renal function and hyponatremia which is the most common electrolyte abnormality observed in these patients[16]. Recent advances clearly observed that hyponatremia is the poor prognostic factor in patients with CLD and patients presenting with hyponatremia had poor survival as compared to those patients not having hyponatremia[17]. In a study from Pakistan, it has been shown that approximately 51.6% of

the patients with cirrhosis had serum sodium level below 135 mEq/L and 26.7% of the patients had values less than 130 mEq/L. Our study included a total of 138 diagnosed hepatic encephalopathy in liver cirrhosis patients. Mean age, duration of symptoms, height, weight and sodium in our study was 51.14±4.49 years, 12±7.21 hours, 161±6.78 cm, 85.2±8.54 kg and 132.7±6.32 mEq/L. 92 (66.7%) and 46 (33.3%) were male and female. Out of 138 patients with hepatic encephalopathy, 28 (20.3%), 35 (25.4%), 54 (39.1%) and 21 (15.2%) belonged to sodium quartile 1, 2, 3 and 4 and 21 (15.2%), 41 (29.7%), 28 (20.3%) and 48 (34.8%) belonged to hepatic encephalopathy severity grade 1, 2, 3 and 4 Hepatic encephalopathy severity showed correlation with rising sodium levels. A study done by Afridi et al[18] on 130 patients; out of which 76 (58.5%) were male while 54 (41.5%) were female, mean age was 55.52 ±10.144 years; hyponatremia was reported in 48 (36.9%) patients. When severity of hyponatremia was assessed, it was found that mild hyponatremia was present in 12 (9.2%), moderate in 28 (21.5%) and severe in 8 (6.2%) patients. Approximately 88 (67.7%) patients in total were found to be in state of hepatic encephalopathy out of which grade I was present in 27 (20.8%), grade II in 31 (23.8 %), grade III in 16 (12.3 %), and grade IV in 14 (10.8%) patients while 48 patients were reported with hyponatremia where 42 were suffering from hepatic encephalopathy (r = 0.32, p value <0.001)[18]. Another study in this regard was carried out on 202 patients diagnosed as hepatic encephalopathy. When serum sodium levels were analyzed, 62 (30.7%) patients showed sodium levels less than 130 mEq/l[19]. In a Korean study, the prevalence of hyponatremia was 47.9% in CLD patients and 21.1% patients showed severe hyponatremic levels (less than 130meq/l). The study also concluded that the severity of hyponatremia was found to be corresponded with higher risk for development of ascites, HE and other complications of cirrhosis when compared with patients showing serum sodium levels less hyponatremic that is 136meq/l[19]. Kim et al [20]reported that 23% of the cirrhotic patients who developed HE and majority of them were those having hyponatremia. On the other hand, the severity of hyponatremia was in direct proportion to the severity of grade of HE (p-0.001) in a study done by Shaikh et al[21]. Furthermore, one of the complications of cirrhosis other than HE, development of ascites also showed increased frequency in those patients having hyponatremia as compared to the patients showing normal serum sodium levels[22]. Recent literature suggests that the neurological dysfunction which develops as a result of hyponatremia is based on a fact that hyponatremia causes low grade cerebral edema resulting in increased osmotic pressure on astrocytes[23]. Nevertheless, there also may develop a significant decrease in the levels of organic osmolytes which include myo-inositol, choline, glutamine and taurine[24]. Both the phenomena are highly dependent upon severity of hyponatremia and acute fall in serum sodium concentration. Studies also support the relation of low levels of myo-inositol with developing HE[25]. Also, these findings were analogous to the existence of elevated ammonia levels in CLD patients. Arshad et al[26] conducted a study in which 62% patients were male and 38% were female. Five percent of patients had severity of grade I, 39% patients had severity of grade II, 48% patients had severity of grade III and 8% patients had severity of grade IV. This study was intended to find the correlation of severity of hepatic encephalopathy with serum sodium levels, and finally concluded that patients with severity of grade IV had serum sodium levels in the range of 120-125 mEq/L as compare to the grade I patients showing serum sodium in the range of 131-133 mEq/L[25].

Conclusion:

Serum sodium concentration less than 135 mEq/L found to be strongly associated severity of hepatic encephalopathy, more severe is the hyponatremia, worse is hepatic encephalopathy. Therefore, it is wise to monitor serum sodium levels as closely as possible in patients with cirrhosis of liver if cirrhosis related complications are to be deter.

Ethical permission: Dow University of Health Sciences Karachi / CPSP.

Conflict of Interest: There is no conflict of interest.

Funding: None.

Variable	MEAN	±SD	Min-Max
Age (YEARS)	51.14	±4.49	38-70
Height (CM)	161	±6.78	148-168
Weight (KG)	85.2	±8.54	68-115
Duration of symptoms (hours)	12	±7.21	06-24
SODIUM (mEq/L)	132.71	±6.32	115-142

Table 1: Profile of the patient with hepatic encephalopathy

	Grade 1	Grade 2	Grade 3	Grade 4	Total
QUARTILE 1	0	14	0	14	28
	0.0%	50.0%	0.0%	50.0%	100.0%
QUARTILE 2	7	21	0	7	35
	20.0%	60.0%	0.0%	20.0%	100.0%
QUARTILE 3	14	6	14	20	54
	25.9%	11.1%	25.9%	37.0%	100.0%
QUARTILE 4	0	0	14	7	21
	0.0%	0.0%	66.7%	33.3%	100.0%
Total (n)	21	41	28	48	138
Total (%)	15.2%	29.7%	20.3%	34.8%	100.0%
p value	0.117 (r = 0.133)				

Table 2: Distribution of sodium quartile and grade of hepatic encephalopathy

References:

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014 May 17;383(9930):1749-61. doi: 10.1016/S0140-6736(14)60121-5.
2. Pinzani M, Rosselli M, Zuckermann M. Liver cirrhosis. Best Pract Res Clin Gastroenterol. 2011 Apr;25 (2):281-90. doi: 10.1016/j.bpg.2011.02.009.
3. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodés J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999 May;30(5):890-5. doi: 10.1016/s0168-8278(99)80144-5.
4. Munoz SJ. Hepatic encephalopathy. Med Clin North Am. 2008 Jul;92(4):795-812, viii. doi: 10.1016/j.mcna.2008.03.009.
5. Hassanein, T.I., Hilsabeck, R.C. & Perry, W. Introduction to the Hepatic Encephalopathy Scoring Algorithm (HESA). Dig Dis Sci; 2008: 53, 529–538.
6. Aki Abe, Kazuaki Inoue, Takeshi Tanaka, Junko Kato, Naoki Kajiyama, etal. Quantitation of hepatitis B virus genomic DNA by real-time detection PCR. Journal of clinical microbiology 1999: 37(9)2899-903. doi:10.1128/JCM.37.9.2899-2903.1999
7. Hecker R, Sherlock S. Electrolyte and circulatory changes in terminal liver failure. Lancet. 1956 Dec 1;271(6953):1121-5. doi: 10.1016/s0140-6736(56)90149-0.
8. Arroyo, V., Rodés, J., Gutiérrez-Lizárraga, M.A. *et al.* Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Digest Dis Sci. 1976; 21, 249–256. doi.org/10.1007/BF01095898
9. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006 Jul;119(7 Suppl 1):S30-5. doi: 10.1016/j.amjmed.2006.05.005. PMID: 16843082.
10. Ginès, Pere, and Mónica Guevara. "Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management." Hepatology (Baltimore, Md.) 2008. 48 (3): 1002-10. doi:10.1002/hep.22418
11. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013 Oct;126(10 Suppl 1):S1-42. doi: 10.1016/j.amjmed.2013.07.006. PMID: 24074529.
12. John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol. 2015 Mar 21;21(11):3197-205. doi: 10.3748/wjg.v21.i11.3197.
13. Wunsch E, Naprawa G, Koziarska D, Milkiewicz M, Nowacki P, Milkiewicz P. Serum natremia affects health-related quality of life in patients with liver cirrhosis: a prospective, single centre study. Ann Hepatol. 2013;12(3):448-455.
14. Salerno F, Merli M, Riggio O, et al. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. *Hepatology*. 2004;40(3):629-635. doi:10.1002/hep.20364
15. Frederick RT. Current concepts in the pathophysiology and management of hepatic encephalopathy. Gastroenterol Hepatol (N Y). 2011;7(4):222-233.
16. Vilstrup, Hendrik et al. Hepatic encephalopathy in

chronic liver disease. Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver." Hepatology (Baltimore, Md.). 2014: 60(2) 715-35. doi:10.1002/hep.27210

17. Yoon J, Ahn SH, Lee YJ, Kim CM. Hyponatremia as an independent prognostic factor in patients with terminal cancer. Support Care Cancer. 2015 Jun;23(6):1735-40. doi: 10.1007/s00520-014-2522-7.
18. Afridi MAR, Ali Z, Muhammad R, Asghar M, Afridi MF, Alam AB, Alam I. Hyponatremia and its correlation with hepatic encephalopathy in patients with cirrhosis liver. J Postgrad Med Inst 2017; 31 (3): 243-6.
19. 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 Feb;24(2):135-7.
20. Kim JH, Lee JS, Lee SH, et al. The association between the serum sodium level and the severity of complications in liver cirrhosis. Korean J Intern Med. 2009;24(2):106-112. doi:10.3904/kjim.2009.24.2.106
21. Shaikh S, Mal G, Khalid S, Baloch GH, Akbar Y. Frequency of hyponatraemia and its influence on liver cirrhosis-related complications. J Pak Med Assoc. 2010 Feb;60(2):116-20.
22. 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. doi: 10.1002/hep.21412.
23. Sterns RH. Treatment of Severe Hyponatremia. Clin J Am Soc Nephrol. 2018 Apr 6;13(4):641-649. doi: 10.2215/CJN.10440917. Epub 2018 Jan 2.
24. Córdoba, J., Gottstein, J. and Blei, A.T. Glutamine, *myo*-inositol, and organic brain osmolytes after portocaval anastomosis in the rat: Implications for ammonia-induced brain edema. Hepatology, 1996; 24(4): 919-923. doi.org/10.1002/hep.510240427
25. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol. 2009;104(6):1382-9. doi: 10.1038/ajg.2009.293.
26. Arshad, M., Zeb, S., Tauseef, M, Ullah, N. Correlation of Serum Sodium with Severity of Hepatic Encephalopathy. Journal of Gandhara Medical and Dental Science, 2016: *3*(01), 3-10. doi.org/10.37762/jgmds.3-01.41 .