Original Article

Hyponatremia as a Predicting **Factor of Mortality in Chronic Liver Disease**

Hyponatremia in **Chronic Liver** Disease

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ABSTRACT

Objective: To determine the worth of hyponatremia as a predicting factor of poor prognosis and mortality in chronic liver disease.

Study Design: Cross Sectional Study

Place and Duration of Study: This study was conducted at the Department of General Medicine, Primary and Secondary Healthcare DHQ Hospital Narowal from January 2017 to January 2018.

Materials and Methods: A total 192 patients were included in our study. All the patients who were suffering from chronic kidney disease, congestive cardiac failure, already using diuretic drugs and conivaptan/tolvaptan, and on dialysis were excluded from our study. The continuous data including age, MELD score, MELD -Na score, albumin, creatinine, alanine transaminase, aspartate transaminase, gamma glutamyltransferase, total bilirubin level, serum chloride, platelet count, international normalized ratio were analyzed by applying Student T test. All the nominal data including male percentage, etiology of the end stage liver disease and complications of cirrhosis were compared by applying Pearson Chi-square test. SPSS v.23 software used and a P value of <0.05 was considered significant.

Results: Serum levels of alanine and aspartate transaminases (ALT & AST), gamma glutamyltransferase (GGT), total bilirubin and international normalized ratio (INR) was significantly low in the patients with serum sodium levels of ≥139mEq/L (p-value 0.014, <0.001, <0.001, 0.001 and 0.018, respectively) but serum chloride was significantly higher (<0.001) in this group.

Conclusion: This study concludes that the concentration of sodium in the serum < 139 mEa/L combined with MELD- Na score more than 12 can be the extrapolative indicators of poor prognosis and mortality in the patients having chronic liver disease. This can be used to identify the threat of poor outcomes and adequate treatment can be given to improve the serum sodium levels and in turn, improve the prognosis.

Key Words: Hyponatremia, chronic liver disease, poor prognosis.

Citation of articles: Idrees M< Joiya MA, Hameed SP. Hyponatremia as a Predicting Factor of Mortality in Chronic Liver Disease. Med Forum 2018;29(4):20-23.

INTRODUCTION

Chronic liver disease is a prolonged disease course consisting of various simultaneous processes of progressive liver parenchyma destruction and regeneration¹, which eventually leads to fibrosis and cirrhosis². The minimum time period to tag the liver disease as chronic is six months. There are numerous causes for this pathology which include chronic hepatitis B and hepatitis C virus infection, nonalcoholic fatty liver disease, alcoholic hepatitis, cryptogenic autoimmune hepatitis, hepatitis, hemochromatosis, Wilson's disease, primary biliary cirrhosis, and drug induced hepatitis 3-8. The factors pre-disposing to the developing chronic liver disease are obesity, poor hygiene, body fluids exchange with

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Accepted: March, 2018

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Received: January, 2018;

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the infected persons, sharing of the infected needles and syringes, unprotected sex with infected person or multiple sex partners, toxic work environment, metabolic syndromes and excessive consumption⁹. Different predisposing factors are related with different etiological type of chronic liver disease. Chronic liver disease is very long process and takes many years to present its manifestation. The outcome of chronic liver disease is cirrhosis which ultimately results in portal hypertension, hypoalbuminemia, ascites, hypersplenism with or without splenomegaly, esophageal varices, hepatorenal syndrome, hepatic encephalopathy and hepatocellular carcinoma. Liver function tests, ultrasound abdomen and liver biopsy are different modalities used for the definite diagnosis. Hyponatremia often results due to the dysfunction of the water homeostasis of the body. Due to hypoalbuminemia and increased arginine vasopressin, there is excessive water shift into the third space and loss from the kidneys. In turn, kidneys try to replace the lost water via the renin-angiotensin-aldosterone mechanism. The increase in water reabsorption in the collecting tubules of the kidney in response to the overactivation of renin-angiotensin-aldosterone system leads to dilutional hyponatremia.

(140- Na)

In chronic liver disease, there is impaired synthesis of clotting proteins, bilirubin and liver enzymes such as alanine transaminase, aspartate transaminase and γ -glutamyltransferase 10,11 . Altered levels of these components in the serum are somehow related with the risk of morbidity and mortality. The levels of derangements of these components also change according to the serum sodium concentration. Serum electrolyte imbalance is concomitant with poor prognosis. Similarly, when there is altered serum sodium level in the patients having chronic liver disease, there is different pattern of metabolic derangements which can be used to analyze the link of various sodium levels with the level of morbidity and mortality.

Some studies have shown that there is association of hyponatremia with poor prognosis in patients having liver cirrhosis, in Europe and United States of America. There is deficiency of regional data about the clinical significance of serum sodium levels in the chronic liver disease patients and the correlation of serum sodium levels with mortality. This study is directed to evaluate the risk of poor outcomes in patients having low serum sodium levels and the chronic liver disease and the relationship between clinical characteristics and serum sodium concentration.

MATERIALS AND METHODS

Protocol approval for our cross sectional study was obtained from the ethical committee of DHQ Hospital, Narowal. A sample of one hundred and ninety two patients, who had any form of chronic liver disease and were treated from January 2017 to January 2018, was selected consecutively. Sample size was calculated using study by Umemura T et al.¹² as reference. Data was collected by the researcher himself, on a preformed performa, in the general medicine department of the hospital. The study was performed from January 10, 2017 to January 10, 2018.

Written consent was acquired from all the patients who were involved in the study. The patients were diagnosed of chronic liver disease on history, clinical laboratory investigations. examination and Demographic data was noted. Etiology of the chronic liver disease was found by laboratory investigations. Serum levels of sodium, creatinine, albumin, alanine transaminase, aspartate transaminase, glutamyltransferase, total bilirubin level and chloride; and international normalized ratio (INR) along with platelet count were ordered for laboratory testing. Model for End-stage Liver Disease (MELD) score and MELD-Na score were acquired for every patient. All the data was obtained before the start of the treatment, especially diuretics medication. MELD score and MELD-Na score were calculated as using the following formulas:

MELD = $11.2 \times \log (INR) + 3.78 \times \log (Total Bilirubin) + 9.57 \times \log (Creatinine) + 6.43$ MELD -Na = MELD+ $(140 - Na) - 0.025 \times MELD \times$

Complications of cirrhosis including foot edema, ascites, esophageal varices, spontaneous bacterial peritonitis and hepatic encephalopathy were also included in the clinical information. Ultrasonography and computed tomography were the modalities used to confirm the presence of ascites. Hepatitis B and hepatitis C viral infections were confirmed by the viral markers i.e. hepatitis B viral surface antigen and antihepatitis C viral antibody along with polymerase chain reaction (PCR) for hepatitis C RNA (when antihepatitis C virus antibody was positive). Serological testing and tissue biopsy of liver for microscopic examination were performed to look for the cases of primary biliary cirrhosis and autoimmune hepatitis. Conventional methods were used to diagnose the cases of non-alcoholic fatty liver disease. All the patients who were suffering from chronic kidney disease, congestive cardiac failure, already using diuretic drugs and conivaptan/tolvaptan, and on dialysis were excluded from our study.

All the continuous data including age, MELD score, MELD-Na score, albumin, creatinine, alanine transaminase. aspartate transaminase. gamma glutamyltransferase, total bilirubin levels, serum chloride, platelet count, international normalized ratio were analyzed by applying Mann-Whitney U-test. All the nominal data including male percentage, etiology of end stage liver disease and complications of the cirrhosis were compared by applying Pearson Chisquare test. SPSS v.23 software used and a value of less than or equal to 0.05 for p was considered significant, statistically.

RESULTS

Total of 192 patients were haphazardly allocated into two groups on the basis of serum sodium levels. Both the groups were compared and were not much different in terms of age and male percentage. In the whole group, MELD score and MELD-Na score was 10 and 12 (Table I), respectively. MELD and MELD-Na score was significantly higher in the patients having serum sodium levels <139mEq/L (p<0.001for both). The frequency of different etiologies of cirrhosis such as hepatitis B, primary biliary cirrhosis, non-alcoholic fatty liver disease, autoimmune hepatitis and cryptogenic hepatitis, was similar in both the groups (p>0.05), but the prevalence of hepatitis C significantly higher in the patients having serum sodium levels <139mEq/L (p=0.007) (Table 2). Symptoms associated with chronic liver disease were seen more frequently in the patients with serum sodium levels <139mEq/L. Leg edema was present in 85.3% and 83.1% (p=0.679); esophageal varices in 61.5% and 37.3% (p=0.001);

ascites in 56.9% and 30.1% (p<0.001); hepatic encephalopathy in 23.9% and 20.5% (p=0.579); and spontaneous bacterial peritonitis in 28.4% and 12% (p=0.006) of the patients with serum sodium levels <139mEg/L and with serum sodium levels ≥139mEg/L, respectively (Table 3). Serum albumin concentrations, serum creatinine and platelet count was not significantly different in both the groups (p-value 0.410, 0.885 and 0.718, respectively). Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), y-Glutamyltransferase (GGT), total bilirubin and international normalized ratio (INR) was significantly low in the patients with serum sodium levels of ≥ 139 mEq/L (p-value 0.014, < 0.001, < 0.001, 0.001 and 0.018, respectively) but serum chloride was significantly higher (<0.001) in this group. (Table-4)

Table No.1: Baseline Features at Admission Rendering To Serum Sodium Levels

Variable	Whole-	Na<	Na	Р-
	Group	139mEq/L	≥139mEq/L	value
	(n =192)	(n =109)	(n = 83)	
Age	63 (59-86)	64 (59-68)	63 (59-68)	0.923
(years)				
Male	114(59.4)	64 (58.7)	50 (60.2)	0.831
MELD	10 (9-12)	11 (9-13)	9 (8-11)	< 0.001
Score				
MELD-Na	12 (9-17)	16	8 (7-10)	< 0.001
Score		(12.5-19)		

Table No.2: Type of Chronic Liver Disease

Disease Type	Whole-	Na<	Na	P -
	Group	139mEq/L	≥139mEq/L	value
	(n =192)	(n =109)	(n = 83)	
Hepatitis C	90(33.3)	45 (41.3)	19 (22.9)	0.007
Hepatitis B	77(19.8)	20 (18.3)	18 (21.7)	0.565
NAFLD	7(13.5)	15 (13.8)	11 (13.3)	0.919
Primary	3(12.5)	12 (11)	12 (14.5)	0.474
Biliary				
Cirrhosis				
Autoimmune	5(12.5)	11 (10.1)	13 (15.7)	0.248
Hepatitis				
Cryptogenic	10(8.3)	6 (5.5)	10 (12)	0.104
Hepatitis				

Table No.3: Complications of Cirrhosis

Complication	Whole-	Na<139	Na ≥139	P -
Type	Group	mEq/L	mEq/L	value
	(n =192)	(n =109)	(n = 83)	
Leg Edema	162(84.4)	93 (85.3)	69 (83.1)	0.679
Esophageal	98(51)	67 (61.5)	31 (37.3)	0.001
Varices				
Ascites	87(45.3)	62 (56.9)	25 (30.1)	< 0.0
				01
Hepatic	43(22.4)	26 (23.9)	17 (20.5)	0.579
Encepha-				
lopathy				
Spontaneous	41(21.4)	31 (28.4)	10 (12)	0.006
Bacterial				
Peritonitis				

After the univariate analysis of the factors predictive of mortality i.e. low serum albumin, low serum sodium and chloride concentrations, low platelet count, high aspartate aminotransferase, alanine aminotransferase, γ -glutamyltransferase, bilirubin, and high MELD and MELD-Na scores, showed a significantly positive predictive worth of these factors (p<0.05).

Table No.4: Hematological Findings

Blood Tests	Whole-	Na< 139	Na ≥139	P -value
Reports	Group	mEq/L	mEq/L	
	(n = 192)	(n = 109)	(n = 83)	
Albumin	3.3	3. 2	3 .5	0.410
(g/dl)	(2.7-3.8)	(2.6-3.9)	(2.8-3.8)	
Creatinine	0.8	0.8	0.8	0.885
(mg/dl)	(0.6-1.1)	(0.6-1)	(0.6-1.1)	
Alanine	48	48	42	0.014
Transaminases	(35-55)	(39-55)	(26-55)	
(IU/L)				
Aspartate	56	60	51	< 0.001
Transaminases	(45-70)	(46-87)	(44-63)	
(IU/L)				
γ-Glutamyl-	50.5	56	44	< 0.001
transferase	(39-63)	(45-69)	(37-57)	
(IU/L)				
Total Bilirubin	1.51	1.51	1.50	0.001
(mg/dl)	(1.2-2.2)	(1.3-2.3)	(1-2.2)	
Chloride	103	97	105	< 0.001
(mEq/L)	(95-108)	(93-105)	(97-112)	
Platelets	10.3	10.3	10.5	0.718
$(\times 10^{3}/\mu L)$	(8-12)	(8-12)	(8-12)	
International -	1.23	1.25	1.22	0.018
Normalized -	(1.14-	(1.12-1.42)	(1.14-1.40)	
Ratio	1.40)			

Data is mentioned as number (percentage) and median (first and third interquartile); MELD= Model for end-stage liver disease; NAFLD=non-alcoholic fatty liver disease.

DISCUSSION

In our study, we observed that there was a significant derangement of the liver enzymes, total bilirubin level and international normalized ratio in the patients having chronic liver who had serum sodium levels below 139mEq/L. The complications of chronic liver disease were also more prevalent in this group. In our cohort, the median value of MELD-Na score was 12. The patients with low sodium levels had MELD-Na score above 12. Lower sodium levels combined with MELD-Na score of more than 12 was associated with the increased possibility of poor outcomes and mortality in the patients with chronic liver disease.

Umemura T. et al.¹² performed a study on Japanese population and found out that MELD-Na score >10.5 and serum Na <139mEq/L was predictive of poor prognosis as well as higher mortality in the patients who has developed liver cirrhosis. Biggins SW et al.¹³, after doing research on serum sodium levels in patients with chronic liver disease and incorporated sodium into the Model for End-stage Liver Disease (MELD). They

established MELD-Na model to predict the prognosis in the patients who were on the waiting list for the liver transplant surgery. Kogiso T. et al.¹⁴ witnessed that tolvaptan improved the prognosis and reduced mortality in the in the patient with cirrhosis by improving the serum sodium levels and bringing it within the normal range. In the patients who had developed liver cirrhosis and hyponatremia, normalized serum levels of sodium after one week of treatment with tolvaptan can be a predictive of better outcome and increased survival.

Two studies were conducted, one in England¹⁵ and other in Korea¹⁶. According to both of them, a combination of Model for End-stage Liver Disease (MELD) score and serum sodium levels can be used to assign the priority to the liver transplant candidates. This can, in turn, result in improved and prolonged survival in patients of chronic liver disease and liver failure. Nishikawa H, et al.17 directed a study on hepatocellular carcinoma patients and deduced that baseline sodium levels had a predictive significance about the prognosis in hepatocellular carcinoma patients complicated with cirrhosis. Low serum sodium level was related with high Child-Pugh score and advanced stage of hepatocellular carcinoma. In a study conducted by Maruyama H. et al¹⁸ in 2015, it was observed that the serum level of sodium prior to the treatment is a significant predicting factor for good and bad prognosis in the class A and B patients of the Child-Pugh score who had undergone endoscopic sclerotherapy for treatment of esophageal varices.

CONCLUSION

This study concludes that the concentration of sodium in the serum less than 139 mEq/L and MELD-Na score of above 12 can be the predictive indicators of poor prognosis and mortality in the patients having chronic liver disease. This can be used to identify the threat of poor outcomes and adequate treatment can be given to improve the serum sodium levels and in turn, improve the prognosis.

Author's Contribution:

Concept & Design of Study: Muhammad Idrees
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Data Analysis: Shehzadi Pulwasha
Revisiting Critically: Mohammad Awais Joiya
Final Approval of version: Muhammad Idrees

Conflict of Interest: The study has no conflict of interest to declare by any author.

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