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The Association between Serum Sodium Level, Incidence and Severity of Complications in Liver Cirrhosis

Running title: *Association between serum sodium level and complications in liver cirrhosis*

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Abstract: ***Introduction: Sodium (Na) is one of the essential elements in the body. It is important for the functioning of cells and transport of water and minerals across cell membranes. Hyponatremia is one of the most common electrolytic disturbances in Decompensated liver cirrhosis. Several studies have reported that lower serum Na levels were associated with increased complications and mortality leading to incorporation of Na in the MELD - Na score. Aim: To evaluate the association between serum Na level and severity of complications in liver cirrhosis. Methods: A total of 275 patients who presented to our institute with cirrhosis of liver with over a period of 18months were analyzed. At admission, all selected patients were examined and clinical findings noted and laboratory investigations were done. Baseline MELD - Na score was calculated. Based on serum Na value, subjects were divided into three groups: Group - 1 (Na level <120mEq/L), group - 2 (Na level 120 - 125mEq/L) and group - 3 (126 - ≤ 130mEq/L) and were assessed for 90 - day mortality rates. The areas under the receiving - operator characteristic curve (AUROC) were calculated for mortality. Results: Mean age was 42.87±5.58 years; 247 were males (89.8%) and 28 were females (10.2%). Based serum Na level, 13 patients were classified into group - 1 (4.7%), 38 patients into group - 2 (13.8%), and 224 patients into group - 3 (81.5%). Four patients had MELD - Na score ≤9 (1.5%), 13 had MELD - Na score 10 to ≤19 (4.7%), 154 had MELD - Na score 20 to ≤29 (56%), 97 had MELD - Na score 30 to ≤39 (35.3) and 7 had MELD - Na score ≥40 (2.5). The AUROC for predicting 90 - day mortality was 0.770 and 0.990 for serum Na level and MELD - Na scores, respectively. Conclusion: Serum Na level can be taken as simple indicator for predicting 90 - day mortality and complication in patients with liver cirrhosis, but is not superior to MELD - Na.***

Keywords: hyponatremia, serum sodium, MELD - Na, cirrhosis.

1. Introduction

Sodium is one of the essential elements in the body. It is important for the functioning of cells and transport of water and minerals across cell membranes. Decompensated chronic liver disease (DCLD) is associated with disturbance in water homeostasis leading to dyselectrolytemia. [1 - 7]

Hyponatremia defined as serum Na level <135mEq/L, but in cirrhosis of liver patients ≤130mEq/L is considered as hyponatremia. A study from Europe showed 21.6% of patients with cirrhosis had Na <130mEq/L, 5.7% had <125mEq/L and 1.2% had <120mEq/L. [8]

Several studies have reported that lower serum Na levels were associated with increased complications and mortality leading to incorporation of Na in the MELD - score. [6, 8] However, the relationship between the degree of dilutional hyponatremia and development of cirrhotic complications is little known. The aim of this study is to evaluate the association between the serum Na level and severity of complications in liver cirrhosis.

Pathogenesis

In general true hyponatremia is of three types: hypovolemic hyponatremia, hypervolemic hyponatremia and euvolemic hyponatremia. Cirrhotic patients predominantly (90%) have hypervolemic hyponatremia. [9]

Portal hypertension leads to opening of porto - systemic shunts thereby increasing intestinal permeability. This further leads to endotoxemia and release of nitric oxide and prostaglandins, causing splanchnic and systemic vasodilatation, resulting in hypotension.

To compensate, Renin - angiotensin - aldosterone system is activated along with release of non osmotic Arginine vasopressin. This results in Na retention, renal vasoconstriction, solute - free water retention and ultimately dilutional hyponatremia. [10]

2. Materials and Methods

This is a single - center prospective study involving 275 patients presenting with cirrhosis of liver, meeting the inclusion criteria during period of 2021 - 2022. This study

was approved by institutional ethics committee (No: 09042022).
All patients, >18 years of age diagnosed with cirrhosis of liver and serum Na level ≤130mEq/L were included in the study after obtaining written and informed consent.

Patients with age <18years, pregnancy, hepatocellular carcinoma, any other malignancy, history of diuretic use in past 60days and chronic kidney disease were excluded from this study.

All the patients were managed in the emergency room with adequate resuscitation. At admission, all selected patients were examined and clinical findings noted and laboratory investigations were done. Baseline CTP and MELD - Na scores were calculated. Patients were followed up for 90 - days and the mortality noted.

The CTP score was calculated using bilirubin, albumin, INR, grade of ascites and encephalopathy. CTP class was A if the score was 5–6, B if the score was 7–9 and C if the score was ≥10. The MELD score was calculated as: 0.957×loge (creatinine mg/dl) +0.378×log (bilirubin mg/dl) +1.1 20×loge (INR) +0.643. MELD - Na was calculated through the formula MELD - Na = MELD+1.32× (137 - Na) −0.033×MELD× (137 - Na).

Based on serum Na value, subjects were divided into three groups: Group - 1 (Na level <120mEq/L), group - 2 (Na level 120 - 125mEq/L) and group - 3 (126 - ≤ 130mEq/L) and were assessed for 90 - day mortality rates. The areas under the receiving - operator characteristic curve (AUROC) were calculated for this purpose.

Microsoft Excel was used for data feeding and analysis was done by SPSS program version - 22. The results are given in the text as mean and SD for quantitative variables and percentages for qualitative variables. A comparison between the chosen variables and 90 - day mortality was performed.

To compare Mean and SD for quantitative variables between groups, the Student's t - test (unpaired) and to compare proportion/percentages between groups, the chi - square test was used. Multivariate logistic regression using the stepwise selection method was performed starting from the variables with $p < 0.01$ in the univariate analysis. ROC curve analyses were performed to determine the value of MELD - Na and serum Na level in predicting the 90 - day mortality. AUROCs with 95% confidence intervals were calculated and compared. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value with 95% confidence intervals were reported at the best cut - off value. $p<0.05$ was considered statistically significant.

3. Results

A total of 275 patients who presented with cirrhosis of liver with hyponatremia to our institution were analyzed in this study. There were 247 males (89.8%) and 28 females (10.2%). Mean patient age was 42.87±5.58 years. Ethanol was the most common cause seen in 222 patients (80.7%). Other etiologies included hepatitis - B virus (HBV) (6.2%), hepatitis - C virus (HCV) (1.8%), non - alcoholic fatty liver disease (NAFLD) (2.5%), cryptogenic (2.2%), ethanol+HBV (3.6%), ethanol+HCV (1.5), 1 case of Wilson's disease, 1 case of autoimmune hepatitis, 2 cases of buddchiari syndrome (Figure - 1).

The mean baseline variables of the patients are shown in Table - 1.

Eighty one patients were CTP class - B (29.5%), 185 were CTP class - C (70.5%) and no one belonged to CTP class - A (table - 2, 3). Four patients had MELD - Na score ≤9 (1.5%), 13 had MELD - Na score 10 to ≤19 (4.7%), 154 had MELD - Na score 20 to ≤29 (56%), 97 had MELD - Na score 30 to ≤39 (35.3) and 7 had MELD - Na score ≥40 (2.5) (table - 4, 5). Using the serum Na level, 13 patients were classified into group - 1 (4.7%), 38 patients into group - 2 (13.8%), and 224 patients into group - 3 (81.5%) (table - 6). Out of 275 patients, 63 expired (22.9) (table - 7).

In group - 1, thirteen patients had ascites (100%), 13 patients had hepatic encephalopathy (HE) (100%), 12 patients had hepato - renal syndrome (HRS) (92.3%), 8 patients had upper gastro - intestinal (UGI) bleed (61.5%), 4 had spontaneous bacterial peritonitis (SBP) (30.8%). In group - 2 ascites was seen in 38 (100%), HE in 22 patients (57.9%), HRS in 22 patients (57.9%), UGI bleed in 17 patients (44.7%), SBP in 4 patients (10.5%). In group - 3, ascites was seen in 224 (100%), HE in 119 patients (53.1%), HRS in 85 patients (39.9%), UGI bleed in 77 patients (34.4%) and SBP in 21 patients (9.4%) (table - 8).

For predicting mortality, the AUROC was 0.770 for Na and 0.990 for MELD - Na (figure - 3, 4).

4. Discussion

Various studies have established that lower serum Na levels were associated with ascites which required frequent large volume paracentesis. In present study also, all the patients had ascites.

Jenq et al. [11] found that hyponatremia exacerbates astrocyte swelling due to differences in osmolality between the intracellular and the extracellular compartments, so when a patient has cirrhosis, hyponatremia is associated with an increased incidence of HE. Also, the hypotonicity of the extracellular fluid due to hyponatremia favors the osmotic effect of glutamine, enhancing cell swelling and cerebral edema induced by hyperammonemia. Thus, hyponatremia potentiates the neurological effects of altered ammonia metabolism in end - stage liver disease. [12] Guevara et al. [13] concluded that dilutional hyponatremia is correlated directly with the incidence of HE and is predictive of its subsequent development. In present study, percentage of patients with HE increased with increasing severity of hyponatremia ($p=0.001$).

Study by Angeli P et al. [8] found renal failure to be more common in patients with hyponatremia with ascites. In that study, 40.5% patients with serum Na level <130 had HRS - AKI. Study by Planas R et al. [14] and Gin`es A et al. [15] found the probability of developing HRS in ascites is

anywhere between 11% - 40%, and hyponatremia is an independent risk factor for renal failure in patients with ascites. In our study, 43.3% of patients had HRS, which is similar to above studies. Also, as the serum Na level decreased, percentage of patients with HRS increased, more in group - 1 than in group - 2 and 3 (*p=0.001*).

Ascites, hyponatremia and renal dysfunction are interrelated and are a reflection of progressive splanchnic vasodilatation and compensatory mechanisms. Their relationship is not linear. Additional stresses such as SBP, infections and GI hemorrhage and medications including diuretic could further precipitate or worsen renal function. [16]

Angeli P et al. [8] and Jong Hoon Kim et al. [17] found no association between GI bleeding and serum sodium levels. The present study also reflected the same.

Angeli P et al. [8] found that low serum Na level was associated with increased frequency of SBP. Jong Hoon Kim et al. [17] reported that 33.3% of patients with serum Na levels ≤130mEq/L had SBP. In our study 30.8% patients in group - 1 had SBP compared with 10.5% and 9.4% patients had in group - 2 and 3 respectively. Even though SBP is more common in hyponatremia, present study showed no correlation with severity of hyponatremia and SBP (*p=0.051*).

Jong Hoon Kim et al. [17] found that lower serum Na levels were associated with increased MELD - Na score and CTP - scores. Present study also showed similar results (*p - value 0.018* and *0.001* respectively).

As serum Na level decreases, mortality has increased.79.6%, 28.9% and 18.8% patients expired in group - 1, 2 and 3 respectively (Figure - 2) (*p=0.001*).

Serum Na level and MELD - Na level were found to have negative correlation (pearson correlation: - 0.436) indicating that as serum Na level decreases as MELD - Na value increases.

For predicting mortality, the AUROC was 0.770 for serum Na level and 0.990 for MELD - Na (Figure - 3, 4). Serum Na ≤127mEq/L can predict mortality with sensitivity and specificity of 85.71% and 56.60%. MELD - Na >34 can predict mortality with sensitivity and specificity of 96.83% and 95.28%.

Compared to serum Na level, MELD - Na was found to be a better predictor of mortality probably because it also includes creatinine, bilirubin, albumin and INR which reflect severity of underlying liver disease. Also, serum Na levels may be influenced by many factors along with liver disease.

Limitations of this study are that it is a single - centre study, serum Na level and other variable values were taken only at admission. Patients with hyponatremia were taken in to study, however results were not compared with patients with normal serum Na level.

5. Conclusion

Serum Na level can be taken as simple indicator for predicting 90 - day mortality and complication in patients with liver cirrhosis, but is not superior to MELD - Na. Further large prospective studies are needed to compare its utility in assessing complications in cirrhotics.

References

[1] Epstein M. Derangements of renal water handling in liver disease. Gastroenterology.1985; 89: 1415 - 1425.
[2] Arroyo V, Claria J, Salo J, Jime´nez W. Antidiuretic hormone and the pathogenesis of water retention in cirrhosis with ascites. Semin Liver Dis.1994; 14: 44 - 58.
[3] Gine`s P, Abraham W, Schrier RW. Vasopressin in pathophysiological states. SeminNephrol.1994; 14: 384 - 397.
[4] Hecker R, SherlockS. Electrolyte and circulatory changes in terminal liver failure. Lancet.1956; 271: 1121 - 1125.
[5] ShearL, Hall P W 3rd, Gabuzda G J. Renal failure in patients with cirrhosis of the liver. II. Factors influencing maximal urinary flow rate. Am J Med.1965; 39: 199 - 209.
[6] Arroyo V, Rodes J, Gutierrez - Lizarraga MA. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Dig Dis Sci.1976; 21: 249 - 256.
[7] Gine`s P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, etal. Hyponatremia in cirrhosis: from pathogenesis to treatment. HEPATOLOGY.1998; 8: 851 - 864.
[8] Angeli P, WongF, Watson H, et al. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology 2006; 44: 1535–42.
[9] Bashar Attar. Approach to Hyponatremia in Cirrhosis. Clin Liver Dis (Hoboken).2019 Apr 30; 13 (4): 98 - 101. doi: 10.1002/cld.790.
[10] Savio John, Paul J Thuluvath, et al. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol.2015 Mar 21; 21 (11): 3197 - 205. doi: 10.3748/wjg. v21. i11.3197.
[11] Jenq CC, Tsai MH, Tian YC et al., “Serum sodium predicts prognosis in critically ill cirrhotic patients”. J. Clin Gastroenterology.2010; 44 (3): 220 - 6, doi: 10.1097/MCG.0b013e3181aabbcd, PMid: 19636261.
[12] Bernardi M, Ricci CS, Santi L. Hyponatremia in Patients with Cirrhosis of the Liver. J. Clin. Med.2015, 4, 85 - 101. doi: 10.3390/jcm4010085, PMid: 26237020, PMCid: PMC4470241.
[13] Guevara, M.; Baccaro, M. E.; Torre, A.; Gomez - Anson, B.; Rios, J.; Torres, F.; Rami, L.; Monte - Tubio, G. C.; Martin - Llahi, M.; Arroyo, V.; 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, 1382 - 9. doi: 10.1038/ajg.2009.293, PMid: 19455124.
[14] Planas R, Montoliu S, Ballest´e B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol.2006; 4 (11): 1385-1394.

[15] Gin`es A, Escorsell A, Gin`es P, et al. Incidence, predictive factors and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology.1993; 105: 229–36.
[16] Joseph J Alukal, Savio John, Paul J Thuluvath. Hyponatremia in Cirrhosis: An Update. Am J Gastroenterol.2020 Nov; 115 (11): 1775 - 1785.
[17] Jong Hoon Kim, June Sung Lee, Seuk Hyun Lee, Won Ki Bae, Nam - Hoon Kim, Kyung - Ah Kim, and Young - Soo Moon. The Association Between the Serum Sodium Level and the Severity of Complications in Liver Cirrhosis. Korean J Intern Med. Jun 2009; 24 (2): 106–112.

Tables

Table 1: The mean baseline variables of the patients

Variable	Mean±SD
Age	42.87±5.58
Bilirubin	5.89±4.73
Albumin	2.51±0.51
Sodium	126.65±3.11
INR	2.10±0.58
Creatinine	1.6±0.82
CTP score	11.77±2.41
MLED Na score	27.99±7.40

Table 2: Patients classification based on CTP class

CTP class	Frequency	Percent
A	0	0
B	81	29.5%
C	194	70.5%
TOTAL	275	100%

Table 3: Number of different CTP class patients in three groups

CTP class	Group - 1	Group - 2	Group - 2
A	0 (0%)	0 (0%)	0 (0%)
B	0 (0%)	4 (10.5%)	77 (34.4%)
C	13 (100%)	34 (89.5%)	147 (65.6%)
TOTAL	13	38	224

Table 4: Patients classification based on MELD - Na score

MELD score	Frequency	Percent
≤ 9	4	1.5%
10 to ≤19	13	4.7%
20 to ≤29	154	56%
30 to ≤39	97	35.3%
≥ 40	7	2.5%
Total	275	100%

Table 5: Different MELD - Na score patients in three groups

MELD score	Group - 1	Group - 2	Group - 2
≤ 9	0 (0%)	0 (0%)	4 (1.8%)
10 to ≤19	0 (0%)	2 (5.3%)	11 (4.9%)
20 to ≤29	1 (7.7%)	21 (55.3%)	132 (58.9%)
30 to ≤39	11 (84.6%)	14 (36.8%)	72 (32.1%)
≥ 40	1 (7.7%)	1 (2.6%)	5 (2.2%)
Total	13	38	224

Table 6: Number of patients in three groups based on serum Na level

Na level	Frequency	Percent
Group - 1	13	4.7%
Group - 2	38	13.8%
Group - 3	224	81.5%
Total	275	100%

Table 7: Patients classification based on survival

	Frequency	Percent
Survived	212	77.1%
Expired	63	22.9%
Total	275	100%

Table 8: Frequency of cirrhosis related complications in three groups

Variable	Group - 1	Group - 2	Group - 3
Ascities	13 (100%)	38 (100%)	224 (100%)
HE	13 (100%)	22 (57.9%)	119 (53.1%)
HRS	12 (92.3%)	22 (57.9)	85 (39.9%)
UGI bleed	8 (61.5%)	17 (44.7%)	77 (34.4%)
SBP	4 (30.8%)	4 (10.5%)	21 (9.4%)

Figures

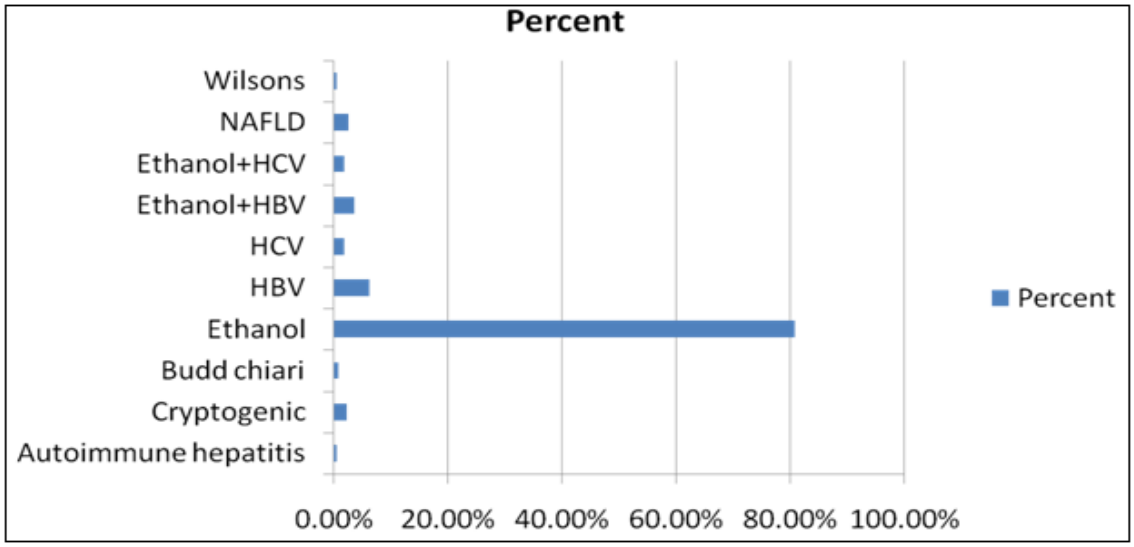

Figure 1: Etiology of cirrhosis

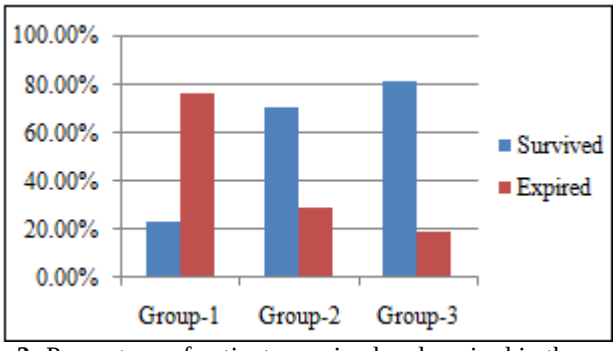

Figure 2: Percentage of patients survived and expired in three groups

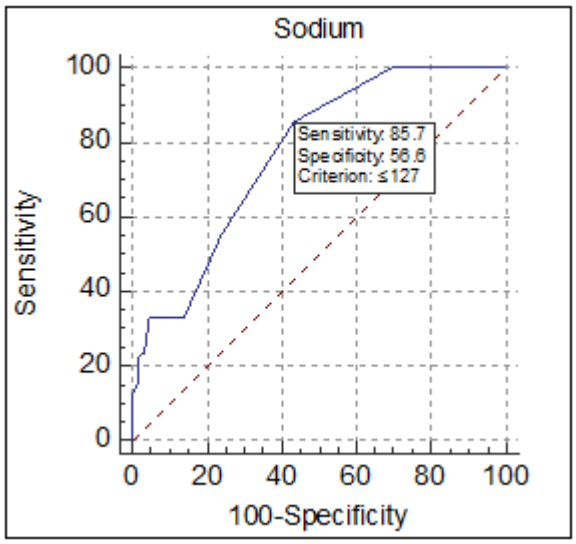

Figure 3: AUROC curve of serum Na

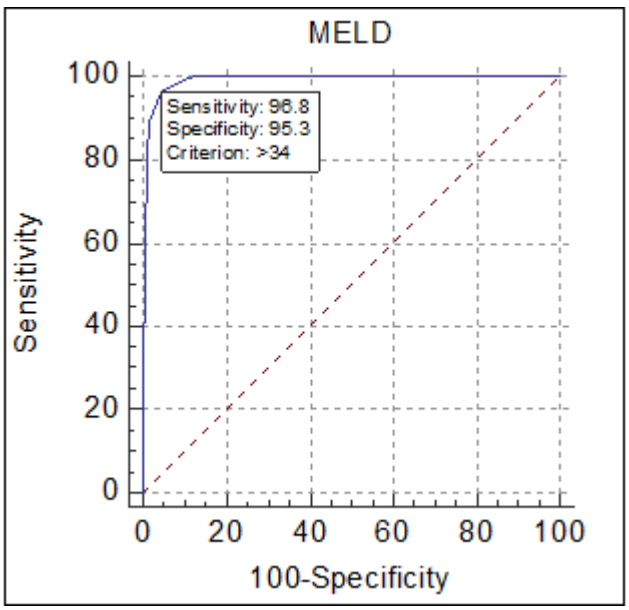

Figure 4: AUROC curve of MELD - Na.