Hyponatremia in Decompensated Chronic Liver Disease, A Marker of Poor Prognosis

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1. Abstract

1.1. Background: Hypovolemic hyponatremia is seen in nearly half of the patients with cirrhosis. There is a scarcity of data correlating hyponatremia with either liver/renal function markers or mortality in patients with decompensated cirrhosis. Our study aimed to identify relationship of hyponatremia with renal and hepatic function in decompensated cirrhosis as well as its role as indicator of prognosis.

1.2. Materials and Methods: Patients diagnosed with decompensated cirrhosis were administered a pilot-tested questionnaire to determine epidemiological characteristics, etiology of cirrhosis, features of decompensation, laboratory investigations and other associations. It was followed by severity assessment of liver disease via calculation of MELD and MELD-Na score. Patients were divided into 2 groups based on serum sodium above or below 136 mEq/L. Data analysis was performed using multivariate COX regression analysis, Chi-square, log rank, and independent t-test.

1.3. Results: Our study enrolled 197 individuals with decompensated cirrhosis. Patients in group A with Na concentration <136 mEq/L (129.17±5.78) showed statistically significant low serum chloride and albumin, elevated liver enzymes, prothrombin time/INR, serum potassium, total bilirubin and creatinine as opposed to patients in group B who had Na concentrations ≥ 136 mEq/L (140.56±4.09). Incidence of one-year mortality (27.9 % vs 6.3 %, p<0.001), MELD score (p=0.001) and MELD-Na score (p<0.001) were significantly higher in group A as compared to group B.

1.4. Conclusion: Hyponatremia was found to be a major poor prognostic marker indicating decreased survival in conjunction with its association with both poor liver and renal function profile.

2. Introduction

Cirrhosis is the end stage of chronic liver disease which gives rise to a multitude of life-threatening and severely morbid complications such as esophageal varices, upper gastrointestinal bleeding, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, etc. [1] Because of high prevalence of Hepatitis B and Hepatitis C, cirrhosis is one of the most common liver diseases in Pakistan and accounts for a high morbidity and mortality. [2, 3] Model for End Stage Liver Disease (MELD) and Child Pugh Scoring system are used to determine the severity and prognosis of chronic liver disease and stratify patients in terms of management plan. These scoring systems use multiple laboratory parameters such as serum albumin, serum creatinine, prothrombin time, and serum albumin as well as clinical parameters such as ascites and hepatic encephalopathy to produce a score which then classify patients according to the severity of their liver disease [4-8].

Electrolyte imbalances are one of the major and well documented consequences of chronic liver disease that develop as a result of third space shifting of body water, decreased effective circulatory volume, poor kidney perfusion, excessive secretion of vasopressin and its altered metabolism, secondary hyperaldosteronism as well as use of diuretics and aldosterone receptor antagonists [9-13].
Although many studies have studied the relationship of cirrhosis with various electrolyte imbalances, however there is a scarcity of data correlating disturbances in serum sodium concentration with mortality in patients with decompensated hepatic cirrhosis in terms of survival rates and prognosis of these patients. Our study aims to identify alterations of serum sodium levels in patients with decompensated cirrhosis as indicator of prognosis, mortality and overall survival in terms of MELD and Child Pugh Classification. This will help identify and stratify patients with decompensated cirrhosis in terms of treatment plan and need for aggressive medical care that will help improve their survival and quality of life.

3. Objective
To find out the association between severity of chronic liver disease and hyponatremia in patients with decompensated cirrhosis in terms of survival rate, mortality as well as liver and renal function profile.

4. Materials and Methodology
4.1. Study Setting
This Prospective Cohort study was conducted in Karachi during the period of January 2018 to May 2019. The study enrolled 217 patients admitted in five different Medical Wards at Civil Hospital Karachi.

All the patients with the diagnosis of decompensated cirrhosis based on ultrasonographic findings were enrolled. Patients were labeled to have cirrhosis if at least two of the following ultrasonographic findings were present: liver changes (nodularity, irregularity, increased echogenicity, atrophy or segmental hypertrophy), portal vein of more than 13mm, spleen size of more than 11cm and presence of ascites. In our study we defined “decompensated cirrhosis” as presence of or history of: ascites, esophageal varices, variceal bleeding or hepatic encephalopathy. The presence of any one of these findings classified patients as having decompensated cirrhosis.

All those patients with a history of Diabetes Mellitus, Hypertension, Ischemic heart disease, Cerebrovascular disorder, Renal failure, Hyperlipidemia, Acute pancreatitis, Sepsis, BMI>30 and those using oral contraceptives, lipid lowering drugs and anticoagulants were excluded from this study.

At the time of admission, the patients were administered a pilot-tested questionnaire. The questionnaire was divided into three parts. The first part comprised of the epidemiological characteristics which included Age and Gender. The second part involved etiology, ultrasonographic findings, features of decompensation, associated illnesses, and any drug usage. The last part of the questionnaire included laboratory investigations. Intravenous non-fasting sample of patients were drawn after informed consent. These samples were sent to Hospital laboratory for serum electrolytes, total bilirubin, Creatinine and INR (International Normalized Ratio).

Severity Assessment of Liver Damage: For grading the severity, Model of End Stage Liver Disease (MELD) and Child Pugh Classification were used.

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For MELD score calculation below mentioned equation was used:
MELD = 9.6 × log [creatinine (mg/dL)] + 3.8 × log [bilirubin(mg/dL)] + 11.2 × log (INR) + 6.43

Patients will be divided into four groups based on their individual score:
I. Group 1: score of less than or equal to 10
II. Group 2: score of 11-18,
III. Group 3: score of 19-24 and
IV. Group 4: score of more than 25.

MELD-Na were further calculated by using equation = MELD + (140 − Na) − 0.025 × MELD × (140 − Na) as it adds the serum Na to the overall calculation and provide a more accurate prediction of morality. All patients were followed for one year to determine the relationship of serum Na levels and MELD score with actual mortality.

The patients were divided into two groups, a (Na < 136 mEq/L) and B (Na ≥ 136 mEq/L) according to the median value of Na in our sample which was 136 mEq/L.

4.2. Laboratory Analysis
Electrolytes, Liver function tests (LFTs), blood urea nitrogen (BUN) and creatinine (Cr) were determined using Roche Cobas c501 chemistry analyzer (Roche Diagnostics). The coagulation profile was calculated by blood coagulation analyzer, SYSMEX CA-1500.

4.3. Statistical Analysis
The data was tested for normality by Shapiro-Wilk test. All the continuous variables were expressed as mean+ standard deviation (SD) or as median (interquartile range) while categorical variables were expressed in terms of frequency (percentages). Independent t-test or Mann-Whitney U-tests were applied to compared continuous variables while Chi-square or Fisher’s exact test were used to compared categorical variables. Survival curves were generated by means of the Kaplan-Meier analysis and differences between groups were determined by the log-rank test. All variables which had a p<0.25 in univariate analysis were included in Multivariate COX regression analysis. The forward stepwise likelihood ratio method was used to identify the independent predictors of mortality. All tests were two-tailed and a p-value of less than 0.05 was considered significant. Data was analyzed using SPSS Statistics, version 17.0 (IBM SPSS Inc., Chicago, IL).

5. Results
The average age of the population was 50.30±14.39 while more than half (n=103, 52.3%) of the patients were females. Mean MELD and MELD-Na scores were 16.66±8.06 and 18.86±9.03, respectively. During the follow-up period of 12 months, 31 (15.7%) patients died due to hepatic-related causes. The etiology of cirrhosis was hepatitis C in 69.5% (n=137) of patients, hepatitis B in 11.2% (n=22) of patients, alcoholic liver disease in 1.0% (n=2) of patients and hemochromatosis in 0.5% (n=1) of patients. Almost 17% (n=34)
of patients had cirrhosis of unknown etiology. Major presenting complaint were abdominal distension (n=96, 48.7%), encephalopathy (n=83, 42.1%), esophageal varices (n=78, 39.6%), abdominal pain (n=71, 36.0%), altered level of consciousness (ALOC) (n=68, 34.5%), fever (n=48, 24.4%) and melena (n=40, 20.3%) (Table 1).

Detailed comparison of the baseline characteristics, clinical features and biochemical markers of the groups are shown in table 1. On comparison between Group A (Na<136 mEq/L, n =86) and Group B (Na >136 mEq/L, n=111), except for the presence of positive Hepatitis C serology, there was no significant difference in presenting complaints while complications were significantly higher in group A as compared to group B (p=0.025).

Among biochemical markers serum Na (p<0.001), serum Chloride (p<0.001) and albumin levels (p<0.001) were significantly higher in group B as compared to group A. However, alanine transaminase (ALT) (p=0.001), alkaline phosphatase (ALP) (p=0.015), total bilirubin (p=0.002) and creatinine (Cr) (p=0.003) levels were significantly higher in group A as compared to group B. Incidence of mortality at one-year follow-up (27.9 % vs 6.3 %, p<0.001), MELD score (p=0.001) and MELD-Na score (p<0.001) were also significantly higher in group A as compared to group B.

A total of 73 (37.1%) patients had Na levels of less than normal lower limit i.e 135 mEq/L and 41 (20.8%) of patients had Na levels of 130 mEq/L or less (Figure 1).

![Bar chart showing distribution of serum sodium concentration values in patients with decompensated liver cirrhosis.](https://jjgastrohepto.org/)

**Figure 1:** Bar chart showing distribution of serum sodium concentration values in patients with decompensated liver cirrhosis.

**Table 1:** Comparison of baseline characteristics between the two groups, A (Na<137 mEq/L) and B (Na > 137 mEq/L).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall sample (n=197)</th>
<th>Na&lt;136 mEq/L (n=86) (Group A)</th>
<th>Na ≥ 136 mEq/L (n=111) (Group B)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.30±14.39</td>
<td>50.93±14.92</td>
<td>49.82±14.01</td>
<td>0.592</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.572</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>94 (47.7)</td>
<td>43 (50.0)</td>
<td>51 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>103 (52.3)</td>
<td>43 (50.0)</td>
<td>60 (54.1)</td>
<td></td>
</tr>
<tr>
<td>Etiology of cirrhosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>137 (69.5)</td>
<td>67 (77.9)</td>
<td>70 (63.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>22 (11.2)</td>
<td>7 (8.1)</td>
<td>15 (13.5)</td>
<td>0.235</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1 (0.5)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>0.437</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>2 (1.0)</td>
<td>1 (1.2)</td>
<td>1 (0.9)</td>
<td>0.684</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>34 (17.3)</td>
<td>10 (11.6)</td>
<td>24 (21.6)</td>
<td>0.066</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>71 (36.0)</td>
<td>29 (33.7)</td>
<td>42 (37.8)</td>
<td>0.551</td>
</tr>
<tr>
<td>ALOC, n (%)</td>
<td>68 (34.5)</td>
<td>29 (33.7)</td>
<td>39 (35.1)</td>
<td>0.836</td>
</tr>
<tr>
<td>Abdominal distension, n (%)</td>
<td>96 (48.7)</td>
<td>45 (52.3)</td>
<td>51 (45.9)</td>
<td>0.374</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Score 1</td>
<td>Score 2</td>
<td>Score 3</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>ALOC*</td>
<td>3.79</td>
<td>1.781-8.077</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Albumin, +1g/dL</td>
<td>0.344</td>
<td>0.133-0.889</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>MELD</td>
<td>1.079</td>
<td>1.035-1.125</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Na&lt;137 (mEq/L)*</td>
<td>3.836</td>
<td>1.615-9.114</td>
<td>&lt;0.002</td>
<td></td>
</tr>
</tbody>
</table>

**5.1. Survival Analysis**

Kaplan-Meier survival curve showed that the mortality rate was significantly higher in patients with Na <136 mEq/L than those with Na >136 mEq/L (27.9% [24/86] vs 6.3% [7/111]) (log-rank test, p value <0.001) (Figure 2A). Similarly, the survival rates in patients with MELD-Na score of >18.75 had greater risk of mortality than those with MELD-Na score of <18.75 (28.3% [28/99] vs 3.1 % [3/98]) (log-rank test, p value <0.001) (Figure 2B).

**5.2. Multivariate Analysis**

ALOC (HR 3.8, 95% CI 1.8-8.1, p<0.001), MELD score (HR 1.1, 95% CI 1.0-1.1, p=0.001), Na<137 mEq/L (HR 3.8, 95% CI 1.6-9.1, p=0.002) were independent predictors of mortality. Increasing level of albumin had protective effects and it reduce mortality rates by almost 70% (HR 0.3, 95% CI 0.1-0.9, p=0.03) (Table 2).
6. Discussion

This study represents the only investigation reported from Pakistan which evaluates the correlation of hyponatremia with prognosis, mortality and survival rate in patients with decompensated cirrhosis. The results indicate that a large proportion of patients with cirrhosis have values of serum sodium concentration below the normal range. In fact, close to half (43.4%) of patients with cirrhosis in our study had Na concentration ≥ 136 mEq/L, a figure that is similar to previously conducted studies. Kim et al. found that the prevalence of hyponatremia in their cohort of cirrhotic patients was 47.9%. [14] Similarly, another observational cohort study reported the prevalence...
of hyponatremia to be 44.1% in cirrhotic patients admitted to a tertiary center in Slovakia. [15] Our study demonstrated no significant association of low serum sodium levels with age, gender and etiology of cirrhosis, except that Hepatitis C etiology was found to be significantly higher in hyponatremic group A patient (Na<136 mEq/L) as compared to group B (Na > 136 mEq/L) (p=0.025). Moreover, Hepatitis C was found to be the most common cause of cirrhosis among our study population (69.5%). This is in conjunction with another study conducted in Pakistan which also reported chronic hepatitis C as the most common etiology of cirrhosis (71.6%). [16] In Pakistan, decompensated chronic liver disease results in 68% of the ward admissions, 92% of ER patients overall causing 78.2% deaths. [17] Through our study and previous literature, it can be established that such rampant incidence of cirrhosis in Pakistan is due to the high prevalence of hepatitis C which is preventable by standard community health services [18].

The principal finding of this study was that hyponatremia is a major poor prognostic marker as indicated by significantly higher incidence of 1-year mortality and significantly lower survival rate in group A as compared to group B. Lower survival rates among hyponatremic patients have been corroborated by several authors. Boin et al reported that nononatremic patients displayed 1, 5, and 10-year survivals of 65.2%, 50.3%, and 42.0%, respectively; while hyponatremic subjects had 44.4%, 34.3%, and 28.6%, for the same periods. [19] Furthermore, a study conducted by Planas R et al demonstrated that for cirrhotic patients, the 1-year probability of survival after developing hyponatremia was only 25.6%. [20] Survival rates are negatively impacted in hyponatremia by major complications of hepatorenal syndrome, infectious complications, and neurologic disorders. An investigation conducted in Taiwan confirms these observations by demonstrating that cirrhotic patients with hypernatremia have a significantly higher incidence of ascites, renal failure, sepsis, hepatic encephalopathy, and in-hospital mortality. In the same study, it was also established that hyponatremia increases the risk of these complications by 4.5, 3.7, 2.0, 2.3, and 2.1 times, respectively [21]. In addition to that, hyponatremia has also been recognized as an independent predictive factor of the impaired health related quality of life in cirrhotic patients owing to the requirement for strict fluid restriction in such individuals [22].

Another major finding of our study was the association of hyponatremia with increased severity of liver disease as evidenced by the statistically significant negative correlation of serum sodium concentration with MELD score and MELD-Na score. In a study conducted in Egypt, a similar relationship was found between serum sodium level and the two scoring systems: Child-Pugh score (r = -0.690, p<0.001) and MELD score (r = 0.586, p<0.001). [23] In the multivariate analysis of our study, MELD score and serum sodium concentration were found to be independent predictors of mortality. A previously conducted study, which looked at data from 6769 patients registered with the Organ Procurement and Transplantation Network in 2005 and 2006, also highlighted the significant association of both the MELD score and the serum sodium concentration with mortality (HR for death, 1.21 per MELD point and 1.05 per 1-unit decrease in the serum sodium concentration for values between 125 and 140 mmol/L; P < .001 for both variables). [14] These findings are in good agreement with the findings of other studies which established both serum sodium levels and MELD scores as predictors of mortality in patients with advanced cirrhosis. [24, 25] Thus, these outcomes may point towards the incorporation of serum sodium level in the severity and prognosis assessment of cirrhosis. The MELD score has been criticized for its limited prognostic accuracy for certain subgroups including patients with cirrhosis, complicated by ascites and hyponatremia. Consequently, some investigators have advocated for the usage of MELD-Na (the MELD with the incorporation of serum sodium) model for more accurate survival prediction before creating priority lists for liver transplantation. [26] In addition to MELD-Na, two other sodium incorporated prognosticators, the I MELD (the integrated MELD) and the MESO index (the MELD to sodium index), have been assessed by investigators and have shown positive results in predicting the prognosis of patients with decompensated cirrhosis for short and intermediate periods [27].

Other findings of our study include laboratory data and biochemical markers demonstrating poor liver and renal function profile associated with hyponatremia. Patients in group A with Na concentration <136 mEq/L showed statistically significant low serum chloride and albumin and significantly elevated liver enzymes, prothrombin time (PT), International Normalized Ratio (INR), total bilirubin and creatinine as opposed to patients in group B who had Na concentrations ≥ 136 mEq/L. Similar laboratory parameters were observed in a prospective study conducted in 2015 in which the hyponatremic cohort had significantly greater serum creatinine, total bilirubin, PT, and INR, while serum albumin was significantly reduced. [24] Therefore, as per this data, hyponatremia is a marker of liver and renal dysfunction and corresponds with escalated chances of variceal bleeding which is also a risk factor for developing hepatic encephalopathy. [24] However, ultrasonographic changes and specific complications of decompensated cirrhosis; portal hypertension (portal vein size ≥ 13 mm and splenic size ≥ 11 cm), ascites, hepatic encephalopathy, variceal bleeding and jaundice did not alter much with change in serum sodium levels. The presence of dilutional hyponatremia is also associated with severe ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. [28] In one study, the serum sodium level before the onset of spontaneous bacterial peritonitis (SBP) was an independent predictor of renal impairment failure triggered by SBP in cirrhotic patients. [29] It has also been suggested that serum sodium is an earlier and more sensitive test than serum creatinine to detect circulatory dysfunction resulting in renal failure and/or death [22].

Our study demonstrated serum albumin levels as a survival marker for cirrhosis and our multivariate analysis showed that higher levels of albumin can independently lessen mortality rates by approx-

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imately 70%. A recently conducted randomized trial reported that long-term albumin administration to patients with decompensated cirrhosis improves survival with a 38% reduction in the mortality hazard ratio (0.62 [95% CI 0.40–0.95]) compared with standard medical treatment alone. [30] In another randomized trial, patients who received intravenous albumin had a higher rate of hyponatremia resolution, independent of renal function and baseline sodium levels, which was in turn associated with a better 30-day survival. [31] These protective benefits of albumin may derive from a combination of its oncotic and non-oncotic properties, and might be a result of albumin mitigating effective hypovolaemia which is a major pathogenic factor for ascites formation. [32] However, further studies are warranted to determine the albumin concentration threshold which might possibly be needed to achieve the therapeutic effects, as well as to determine the cost effectiveness of this intervention as albumin supplementation is an expensive treatment, particularly for low income countries.

Hyponatremia presents as an ominous complication in patients of decompensated cirrhosis and is associated with increased morbidity and mortality. The experimental results of this study verify that a finding of serum sodium concentration < 136 mEq/L in cirrhotic patients should be considered an indicator of negative outcome. Therefore, coordinated efforts need to be made to ensure early detection and management of this electrolyte imbalance with an aim to successfully channel these patients to liver transplantation. The approach to liver transplantation is to prioritize the allocation of liver grafts on the basis of the estimated risk of death for a patient on the waiting list. [14] Considering that both serum sodium levels and MELD score are independent predictors of mortality, other models such as MELD-Na might provide better calibration and may subsequently reduce mortality among patients on the waiting list. Thus, more research needs to be done to thoroughly investigate the predictability of alternate scoring systems for preoperative mortality, as well as for post-operative mortality. The treatment of hyponatremia also remains a challenge and there is a dire need to further examine the safety profile and long-term benefits of current and newly developed oral agents for the management of hyponatremia in cirrhosis.

Our study should be analyzed in light of certain limitations. First, our sample size was drawn from one urban tertiary care setting; therefore, the findings may not be generalized for other patient populations. Second, time trends were not taken into consideration as the laboratory data was obtained only when the patients were admitted. Factors such as volume status and the use or nonuse of diuretics may alter serum sodium concentrations; hence a sequential measurement of serum sodium concentrations might provide a more complete picture for mortality risk. Nonetheless, published data and common clinical observations indicate that hyponatremia in patients with cirrhosis is difficult to alter. [14] Third, more than 80% of our patient population comprised of hepatitis B and C patients. Therefore, this study might not be directly extrapolated to populations with predominantly non-viral etiologies of cirrhosis, such as alcoholic liver disease.

7. Conclusion

Hyponatremia is one of the major poor prognostic markers indicating decreased survival because of its association with both poor liver function profile manifested by low serum albumin levels, raised prothrombin time and International Normalized Ratio (INR), raised liver enzymes levels and raised serum total bilirubin as well as worsening kidney function status marked by alterations in other electrolytes and rising serum creatinine levels overall theoretically raising chances of developing and/or worsening already existing complications of decompensated chronic liver disease. Therefore, patients with decompensated chronic liver disease who present with hyponatremia should be marked as candidates that require intensive care, aggressive management and careful monitoring which may increase their survival rate.

References


