Impact of hyponatremia on frequency of complications in patients with decompensated liver cirrhosis

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Abstract

Introduction: Hyponatremia is common in cirrhosis. The relationship between hyponatremia and severity of cirrhosis is evidenced by its close association with the occurrence of complications, the prevalence of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, rectorary ascites, and hepatic hydrothorax. The aim of this study was assess the impact of hyponatremia on the occurrence of both liver-related complications and the hemodynamic cardiovascular dysfunction.

Methods: This prospective study was conducted in 2015 on 74 patients with liver cirrhosis. The patients were from the Gastroenterology and Hepatology Department of Theodor Bilharz Research Institute in Giza, Egypt. The patients were divided into three groups according to their serum level of sodium. Group 1 included 30 patients with serum sodium >135 meq/L, group 2 included 24 patients with serum sodium between135 and 125 meq/L, and group 3 included 20 patients with serum sodium <125 meq/L. For each of the patients, we conducted a clinical examination, laboratory investigations, chest X-ray, ECG, abdominal sonar, and echocardiography.

Results: Hyponatremia was found in 59.46% of our cirrhotic patients, and they showed significantly increased Model for End-Stage Liver Disease (MELD) score, MELD-Na score, QTc interval, Pulmonary vascular resistance (PVR) and inferior vena cava (IVC) collapsibility, and decreased SVR and IVC diameter. Also hepatic encephalopathy, ascites, renal failure, infectious complications, and pleural effusion were significantly more common in hyponatremic cirrhotic patients.

Conclusion: In cirrhosis, hyponatremia is more common in severe cardiovascular dysfunction and associated with increased risk of hepatic encephalopathy, ascites, illness severity scores, renal failure, infectious complications, and pleural effusion. We recommend selective oral administration of vasopressin V2-receptor antagonist, tolvaptan, which acts to increase the excretion of free water, thereby resolving hypervolemic hyponatremia and may have the potential to improve outcomes in these patients.

Keywords: liver cirrhosis, hyponatremia, ascites, hepatorenal syndrome, hepatic encephalopathy

1. Introduction

Hyponatremia in cirrhosis is a common abnormal finding, and it is reported in approximately 57% of hospitalized patients with liver cirrhosis and in 40% of outpatients with liver cirrhosis (1). It has been suggested that the prevalence of serum sodium concentrations less than 135 meq/L in patients with cirrhosis and ascites is 49.4% (2).

Generally, two types of hyponatremia occur in patients with cirrhosis, i.e., hypovolemic and hypervolemic hyponatremia. The former is indicative of a low concentration of sodium and reduced volume of plasma. The latter is indicative of a significant impairment of the excretion of solute-free water, which results in the abnormal retention of water. The latter very commonly occurs in patients who have cirrhosis and ascites (3). The main mechanisms that result in dilutional hyponatremia are 1) renal hypoperfusion, which reduces the kidneys’ ability to handle sodium

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and 2) peripheral arterial vasodilation, which causes reduced effective volemia and increased secretion of arginine-vasopressin (4). Increased production of nitric oxide (NO) leads to arterial vasodilation (5) and enhances the biological effects of arginine vasopressin (AVP), which plays a pivotal role in renal handling of sodium and water in cirrhosis (6). The systemic hemodynamic status of cirrhosis unloads the high-pressure baroreceptors, which results in the nonosmotic stimulation of AVP that is mediated by the baroreceptors (4). The kidneys and the liver metabolize AVP (7), and patients with cirrhosis are likely to have reduced liver clearance. Patients with cirrhosis excrete less urine, depending on the severity of the cirrhosis. In fact, patients with refractory ascites and hepatorenal syndrome exhibit the lowest levels of urine excretion (8). Evidence of the relationship between hyponatremia and the severity of cirrhosis is clearly demonstrated in its close association with the prevalence of hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, the occurrence of interrelated complications (9) and hepatic hydrothorax. In addition, patients with ascites who also have hyponatremia do not respond as well to diuretics, generally have a higher incidence of refractory ascites, and require more frequent therapeutic paracentesis (10). There is apparently an increase in the risk of mortality by about 12% for each unit of decrease in the concentration of sodium in the serum in the range of 120 to 135 meq/L (11). Patients with hyponatremia have greater three-month mortality than patients without hyponatremia (12), and they also have been found to have a higher risk of early death before transplantation, independent of the severity of their cirrhosis as assessed by the Model for End-Stage Liver Disease (MELD) scores (13). Also, hyponatremia was found to be a risk factor for increased morbidity and mortality after liver transplantation (12, 14). The term “cirrhotic cardiomyopathy” was introduced to describe impaired contractile responsiveness to stress, diastolic dysfunction, and electrophysiological abnormalities in the absence of known cardiac disease (15). An impaired cardiac ventricular response to physiological or pharmacological stress may be present despite the increase in baseline cardiac output (16-18). Diastolic dysfunction (E/A ratio <1) may contribute to the pathogenesis of fluid retention in these patients (19, 20) and may precede systolic dysfunction in cirrhosis (21, 22). Prolonged QT intervals on the electrocardiogram have been documented in cirrhosis, with a prevalence that exceeds 60% in patients with advanced disease, and they have been related with the severity of liver disease (23). It is difficult to assess intravascular volume in patients with cirrhosis, even with the use of invasive monitoring (24). Other potential techniques that could help assess the status of the volume include the use of ultrasound to measure the diameter and collapsibility of the inferior vena cava and echocardiographic assessment of the right atrial and ventricular volumes (25). Our aim was to study the impact of hyponatremia on occurrence of both liver-related complications and hemodynamic cardiovascular dysfunction.

2. Material and Methods

2.1. Patients

This was a prospective human study conducted in 2015 in which adult patients with post-viral cirrhosis and ascites were recruited from the Gastroenterology and Hepatology Department at Theodor Bilharz Research Institute. The study was approved by the Research Ethics Committee of Theodor Bilharz Research Institute. Informed consent was obtained from all patients in the study. Seventy-four patients that had been diagnosed with cirrhosis of the liver based on clinical, biochemical, and morphological criteria were included in the study. They were divided into three groups according to their serum level of sodium. Group 1 included 30 patients with serum sodium >135 meq/L, group 2 included 24 patients with serum sodium between 135 and 125 meq/L, and group 3 included 20 patients with serum sodium levels <125 meq/L.

2.2. Exclusion criteria

Subjects with non-viral liver diseases, such as autoimmune hepatitis, alcohol consumption, liver masses, any malignancy, heart disease, pulmonary disease, diabetes mellitus, hypertension (blood pressure >140/89 mmHg), hyperlipidemia, and pregnancy were excluded. No patient was taking beta blocker, diuretics, or albumin. They were enrolled in the study when they were admitted to the hospital, and blood samples were taken before any medication was administered.

2.3. Methods

A thorough history was taken for all of the patients, and each patient was subjected to a physical examination and blood sampling for liver function tests, renal function tests, serum electrolytes, HBs antigen, and anti HCV antibody. Twelve lead surface resting ECGs were done for all patients. The QT interval duration was calculated manually from the beginning of the q wave to the end of the T wave in all 12 leads. The maximal duration of the QT interval was measured among these 12 leads. QT intervals were corrected in accordance with the rate using the BAZET formula, i.e., QTc = QT / √RR. QTc >440 ms was considered prolonged (23, 26). Chest X-rays were done to
evaluate lung parenchyma and pleural effusion. A trained investigator who was part of the study team but who was blinded to all clinical and laboratory data performed abdominal ultrasound scanning for all participants using a Toshiba Nemo 30 scanner that was equipped with a 3.5-MHz linear transducer. We used the results of laboratory tests, which included hepatitis C virus antibodies, low albumin concentrations in the serum, high INR, and low platelet count, as well as abdominal ultrasonographic findings, to diagnose cirrhosis of the liver caused by the post-hepatitis C virus. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (27) by a blinded member of the study team. The measurements were made using a high resolution (ALT 5000 HDI) Toshiba Nemo 30 scanner that was equipped with a 2.5-MHz transducer. The same scanner was used to conduct two-dimensional echocardiography and Doppler ultrasound studies. Using the M-mode, we made separate measurements of the thicknesses of the interventricular septum (IVS) and the left ventricle posterior wall (PWT) during the diastole and the systole, and we determined the diameters of the left ventricle end-diastolic (LVED) and the left ventricle end-systolic (LVES). The parasternal long axis view at the end of the systole was used to determine the size of the left atrium. The Teichholz formula was used to measure the ejection fraction of the left ventricle (EF%) from the M-mode dimensions (28).

We obtained pulsed Doppler spectral recordings in the apical four-chamber view from a sample volume that was positioned at the tips of the mitral leaflets. We used the transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles to measure the velocities of peaks E and A. An E/A ratio <1 was used to define impaired relaxation (29). The time-velocity integral (TVILVOT) of the outflow from the left ventricle (LV) was obtained by placing a pulsed-wave sample volume in the LV outflow tract when imaged from the apical five-chamber view. Continuous wave Doppler was used to determine peak mitral regurgitant velocity (MRV) in meters per second. We obtained multiple echocardiographic views and used the highest velocity that was obtained. Systemic vascular resistance was calculated as \( SVR = MRV/TVILVOT \) (30). The right ventricular (RV) outflow time-velocity integral, \( TVI_{RVOT} \) (cm), was obtained by placing a 1- to 2-mm pulsed wave Doppler sample volume in the proximal right ventricular outflow tract when imaged from the parasternal short-axis view. The sample volume was placed so that the closing click, but not the opening click, of the pulmonary valve was visualized. Continuous-wave Doppler was used to determine the peak TRV (m/sec). The highest velocity obtained from multiple views was used. For patients with \( TRV/TVI_{RVOT} < 0.275 \), Pulmonary vascular resistance (PVR) is likely > 6 WU (31). Vena cava sonography was performed in the supine position with two-dimensional, guided M-mode echocardiography, using a 3.5-Mhz ultrasound probe. From a subxiphoidal long axis view, the diameters were measured immediately in end-expiration (32). Most studies agree that the measurement should be distal to the junction with the right atrium and within 3 cm of that point (33-35). Then, the inspiratory and expiratory diameters of the inferior vena cava (IVC) can be measured on the M-mode image, at the smallest and largest locations, respectively. In patients with decreased intravascular volume, the diameter of the IVC will be decreased and the percentage collapse will be greater than 50%. With complete collapse, the IVC may become difficult to visualize. Volume overload patients with increased intravascular volume will have a large IVC diameter and minimal collapse on inspiration. In severe cases, there may not be any notable respiratory variation seen in M-mode (36).

2.4. Statistical Analysis
Statistical analyses were conducted using the statistical package for Social Sciences for Windows version 20.0 (SPSS-IBM). Descriptive statistics for each variable were determined. Results for continuous variables were demonstrated as Mean ± SE, and were analyzed using Kruskal-Wallis, and Friedman's ANOVA. Also, Comparisons between groups were made using Fisher's exact and chi-squared tests for categorical variables; two-sided p-values equal to or less than 0.05 were considered to be statistically significant.

2.5. Research ethics
The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and it was approved by the local hospital’s Ethics Committee for human investigations.

3. Results
Table 1 shows the demographic and basic clinical data of the three groups. Hyponatremia was found in 59.46% of the patients. No statistically significant difference was found between the three groups with respect to age and gender. There was a significant decrease in the diastolic BP and increase in the pulse rate and temperature in group 3 compared to groups 1 and 2. The same was true of group 2 compared to group 1. There was a significant decrease in the systolic BP in groups 2 and 3 compared to group 1. There was a significant increase in the respiratory rate in group 3 compared to group 1. Electrocardiographic data showed a statistically significant increase in heart rate and
QTc in group 3 compared to groups 1 and 2 and in group 2 compared to group 1. The laboratory data showed a significant increase in serum creatinine, total bilirubin, PT, and INR in the patients in group 3 compared to groups 1 and 2; the same was true for the patients in group 2 compared to group 1. There were significant decreases in Na and PC in the patients in group 3 compared to groups 1 and 2; the same was true for the patients in group 2 compared to group 1. There was a significant increase in direct bilirubin and decreases in serum albumin and Hb in the patients in group 3 compared to group 1; the same was true for the patients in group 2 compared to group 1. There were significant increases in BUN and WBCs in the patients in group 3 compared to group 1; the same was true for the patients group 3 compared to group 2 (Table 2).

Table 1. Demographic and electrocardiographic data of the patients

| Variables                  | Group 1          | Group 2          | Group 3          |
|----------------------------|------------------|------------------|------------------|
| Age                        | 46.29 ± 1.30     | 45.33 ± 2.01     | 47.67 ± 1.89     |
| Gender                     | Ratio of Males/Females 2/1 | 1/1             | 1/1              |
|                            | Males 16 (66.6%)  | Males 12 (60%)   | Males 12 (60%)   |
|                            | Females 8 (33.4%) | Females 8 (40%)  | Females 8 (40%)  |
| Pulse, beats/min           | 98 ± 1.09        | 104 ± 2.45b      | 116 ± 4.03bb,cc  |
| Systolic blood pressure, mmHg | 102 ± 1.46      | 92 ± 2.04bb      | 88 ± 3.57bb      |
| Diastolic blood pressure, mmHg | 72 ± 1.09       | 68 ± 1.63bb      | 58 ± 2.68aa      |
| Temperature, °C            | 36.9 ± 0.13      | 37.3 ± 0.16bb    | 38.1 ± 0.31bb,cc |
| Respiratory rate, breaths/min | 17 ± 0.91        | 19 ± 1.22        | 22 ± 1.79bb      |
| Heart rate, beats/min      | 94 ± 1.64        | 106 ± 2.24bb     | 117 ± 3.13aa     |
| Corrected Tc, msec         | 452.53 ± 3.34    | 478.35 ± 2.49bb  | 492.53 ± 5.85bb,cc |

aa: p<0.01 versus group 1 and 2, b: p<0.05 & bb: p<0.01 versus group 1, c: p<0.05 versus group 2

Table 2. Laboratory data for the three groups of patients

| Variables                  | Group 1          | Group 2          | Group 3          |
|----------------------------|------------------|------------------|------------------|
| BUN                        | 19.81 ± 2.25     | 24.92 ± 0.69bb   | 48.83 ± 4.98aa   |
| Creatinine                 | 0.90 ± 0.04      | 1.15 ± 0.10bb    | 1.62 ± 0.07aa    |
| Na                         | 137.83 ± 0.33    | 130.41 ± 0.54bb  | 121.83 ± 0.11aa  |
| K                          | 4.68 ± 0.13      | 4.65 ± 0.14      | 4.87 ± 0.21      |
| ALT                        | 44.17 ± 14.26    | 35.33 ± 8.09     | 53.50 ± 4.17c    |
| AST                        | 54.92 ± 4.75     | 66.52 ± 18.09    | 71.50 ± 4.72b    |
| Tbil                       | 1.77 ± 0.23      | 3.42 ± 0.25bb    | 4.70 ± 0.30aa    |
| Dbil                       | 0.62 ± 0.09      | 1.77 ± 0.91bb    | 2.08 ± 0.13aa    |
| Alb                        | 2.80 ± 0.11      | 2.44 ± 0.14a     | 2.17 ± 0.07bb    |
| WBCs                       | 6.49 ± 0.19      | 5.68 ± 0.56      | 9.63 ± 1.45b,cc  |
| HB                         | 11.00 ± 0.17     | 10.46 ± 0.25b    | 10.30 ± 0.31b    |
| PLT                        | 138.58 ± 9.34    | 120.02 ± 12.21   | 89.40 ± 12.25b   |
| PT                         | 15.65 ± 0.54     | 19.92 ± 0.96bb   | 29.65 ± 1.06bb   |
| PC                         | 62.54 ± 2.136    | 44.89 ± 3.55bb   | 21.00 ± 2.53aa   |
| INR                        | 1.44 ± 0.34d     | 1.72 ± 0.11bb    | 2.53 ± 0.18aa    |

aa: p<0.01 versus group 1 and 2, b: p<0.05 & bb: p<0.01 versus group 1, c: p<0.05 & cc: p<0.01 versus group 2

There was significant increase in the number of patients who had encephalopathy, renal injury, SBP, GIT bleeding, degree of ascites, anemia, and pleural effusion in group 3 compared to group 1. Also, there was a significant increase in patients with GIT bleeding in group 2 compared to group 1, and there was a significant increase in
patients with degree of ascites and pleural effusion in the patients in group 3 compared to group 2 (Table 3). The abdominal ultrasound data shown in Table 4 indicated that there was a significant decrease in liver span in group 3 compared to groups 1 and 2. Also, there were significant increases in portal vein and spleen diameters in group 3 compared to group 1 and in group 2 compared to group 1. The MELD and MELD-Na scores increased significantly in group 3 compared to groups 1 and 2 and in group 2 compared to group 1. There was significant decrease in EDD in the patients in group 2 compared to group 1, and there was a significant increase in EDD in the patients in group 3 compared to group 2. There was significant increase in LA diameters in the patients in group 3 compared to groups 1 and 2. There was a significant decrease in the E/A ratio in the patients in groups 2 and 3 compared to group 1, meaning that there was diastolic dysfunction in the patients in groups 2 and 3 (Table 5). There was a significant decrease in SVR in the patients in group 3 compared to groups 1 and 2, as well as in the patients of group 2 compared to group 1. There was a significant increase in PVR in the patients in group 3 compared to groups 1 and 2. There was a significant decrease in IVC diameter and increase in IVC collapsibility in the patients in group 2 and 3 compared to group 1 (Table 6).

Table 3. Frequency of cirrhosis-related complications in the groups of patients

| Variables       | Group 1 | Group 2 | Group 3 |
|-----------------|---------|---------|---------|
| Encephalopathy  | 3 (10%) | 6 (25%) | 8 (40%)<sup>bb</sup> |
| Renal Injury    | 1 (3.3%)| 3 (2.5%)| 6 (30%)<sup>bb</sup> |
| SBP             | 2 (6.6%)| 6 (25%) | 8 (40%)<sup>bb</sup> |
| GIT Bleeding    | 3 (10%) | 8 (33.3%)<sup>b</sup> | 12 (60%)<sup>bb</sup> |
| Tense Ascites   | 10 (33.3%)| 12 (50%)| 18 (90%)<sup>aa</sup> |
| Anemia          | 2 (6.6%)| 4 (17%) | 8 (40%)<sup>bb</sup> |
| Pleural effusion| 6 (20%) | 8 (33.3%)| 14 (70%)<sup>bb,c</sup> |

<sup>a</sup>: p<0.01 versus group 1 and 2; <sup>b</sup>: p<0.05 & <sup>bb</sup>: p<0.01 versus group 1; <sup>c</sup>: p<0.05 versus group 2

Table 4. Abdominal ultrasound data and severity of liver cirrhosis for the three groups of patients

| Variables          | Group 1 (Mean ± SE) | Group 2 (Mean ± SE) | Group 3 (Mean ± SE) |
|--------------------|---------------------|---------------------|---------------------|
| Liver, cm          | 12.38 ± 0.51        | 12.38 ± 0.35        | 11.00 ± 0.01<sup>ccc</sup> |
| PV, mm             | 13.00 ± 1.61        | 14.52 ± 0.97<sup>bb</sup> | 15.20 ± 1.92<sup>bb</sup> |
| Spleen, cm         | 11.8 ± 0.9          | 14.8 ± 1.8<sup>bb</sup> | 15.3 ± 2.2<sup>bb</sup> |
| MELD score         | 13.37 ± 3.20        | 18.70 ± 8.50<sup>bb</sup> | 27.47 ± 4.67<sup>aa</sup> |
| MELD-Na score      | 14.87 ± 2.81        | 24.00 ± 9.56<sup>bb</sup> | 32.40 ± 6.64<sup>aa</sup> |

<sup>a</sup>: p<0.05 & <sup>a</sup>: p<0.01versus group 1 & 2; <sup>b</sup>: p<0.05 & <sup>bb</sup>: p<0.01 versus group 1; <sup>c</sup>: p<0.01 versus group 2

Table 5. Echocardiographic data of the groups of patients

| Variables | Group 1 (Mean ± SE) | Group 2 (Mean ± SE) | Group 3 (Mean ± SE) |
|-----------|---------------------|---------------------|---------------------|
| IVS       | 1.04 ± 0.23         | 1.00 ± 0.04         | 1.05±0.04           |
| PW        | 1.03 ± 0.02         | 1.03±0.02           | 1.03±0.04           |
| LVM       | 198.14 ± 10.29      | 184.77±10.61        | 224.59±9.03         |
| EDD       | 5.13 ± 0.12         | 4.93±0.13<sup>b</sup> | 5.53±0.14<sup>cc</sup> |
| ESD       | 3.23 ± 0.09         | 3.05±0.12           | 3.43±0.12           |
| EF        | 0.67 ± 0.01         | 0.67±0.02           | 0.68±0.01           |
| LA        | 37.96 ± 0.93        | 37.83±1.06          | 41.67±0.44<sup>aa</sup> |
| AO        | 29.24 ± 0.79        | 30.84±0.66          | 30.17±0.49          |
| E/A       | 1.13 ± 0.04         | 0.92±0.03<sup>bb</sup> | 0.91±0.02<sup>aa</sup> |

<sup>a</sup>: p<0.01 versus group1&2; <sup>b</sup>:p<0.05 & <sup>bb</sup>:p<0.01 versus group 1; <sup>c</sup>: p<0.01 versus group 2.
4. Discussion

Reduced concentration of serum sodium is a very common electrolyte disorder in patients who have cirrhosis (1). In our study, the prevalence of hyponatremia in decompensated liver cirrhosis (serum sodium ≤ 135 meq/L) was 59.46%. Angeli and his colleagues found that serum sodium levels of ≤ 135 meq/L occurred in 49.4% in their cirrhotic patients (2). Also, Kim et al. found that the prevalence of hyponatremia (serum sodium ≤ 135 meq/L) in people with cirrhosis of the liver was 47.9% (37). In our study, we found that hyponatremia was associated with increased severity of liver disease as indicated by increased MELD scores, MELD-Na scores, portal vein diameters, spleen sizes, and decreased liver span. These findings were in good agreement with the findings of other studies in which it was found that both serum sodium levels and MELD scores could be used to predict mortality in patients with advanced cirrhosis (11, 37-40). Combining the serum sodium level with the MELD score (MELD-Na score) was shown to be more accurate in predicting mortality than the MELD score alone. This was particularly true in patients with lower overall MELD scores (38-40). In our study on cirrhotic patients, hyponatremia was associated with decreased systolic and diastolic blood pressure and decreased systemic vascular resistance and with increased heart rate, QTc interval, LV end-diastolic diameter, LA diameter, and pulmonary vascular resistance. Patients with hyponatremia had diastolic dysfunction. Also, the diameter of the inferior vena cava was decreased in hyponatremia, while its collapsibility was increased. Hemodynamic studies in cirrhotic patients frequently show the expansion and redistribution of volume of circulating, resulting in relative splanchnic hypervolemia and effective central hypovolemia (41, 42). The combination of decreased systemic vascular resistance and central hypovolemia leads to a hyperdynamic circulatory state that is unique to patients with ESLD (5). This hemodynamic state results in increased pulmonary and systemic flows at baseline with high-normal or elevated right ventricular (RV), pulmonary artery, and left-atrial (LA) pressures (16, 17, 43). Also, Iwakiri and Groszmann conducted a study in which it was found that the hallmarks of this state of hyperdynamic circulation were increases in heart rate (HR), cardiac output (CO), and left ventricular ejection fraction (LVEF) and decreases in systemic vascular resistance (SVR), mean arterial pressure (MAP), and blood vessel contraction (5). Gaduputi et al. observed a statistically significant inverse correlation between SVR and the severity of liver disease severity only in patients with low levels of sodium (44). Goitein, Valeriano, and their colleagues found that diastolic dysfunction (mitral E/A ratio ≤ 1) is present in 50-70% of patients with ESLD and that it became more evident as the disease progressed (MELD ≥ 20) (45, 46). In a recent study, Garg et al. indicated that patients who have ESLD have time-velocity integrals (TVIs) of the right ventricular and left ventricular outflows that are upper normal to elevated, which are indicative of the high-flow state. Also, they have left atrial (LA) dilation, hyperdynamic left ventricular (LV) function, and mild elevation of the pressures in the pulmonary arteries. The transmital Doppler inflow and annular velocity in a patient with ESLD showed abnormal mitral inflow and annular tissue velocities, consistent with diastolic dysfunction (47). Pozzi et al. (48) and Abd-El-Aziz et al. (49) found that the size of the LA was significantly larger in cirrhotic patients than in controls, but the sizes of their LVs were similar. In contrast, Finucci et al. (19) found significantly increased left atrial volumes, LV end diastolic volumes, and stroke volumes in cirrhotic patients compared to controls. Mild LVH is a common finding in cirrhotic cardiomyopathy (19, 48, 49). In a recent study, Venkateshwarlu et al. found that the changes in the ECGs of patients with cirrhosis of the liver indicated that 44% of them had long QTc intervals. Also, the LAD and LVED were above normal limits in all of the patients in the study group. The mass of the LV was greater than the normal limit in 66% of the patients. All of the patients in the study had MELD criteria scores greater than 40, which showed a significant correlation with cardiac structural and functional abnormalities (50). Mandell, Sun, and their colleagues found that the prolongation of QTc in cirrhotic patients is due to changes in myocardial repolarization and can lead to ventricular arrhythmias, perhaps due to changes in the permeability of the cell plasma membrane (51, 52). Another recent study conducted by Moaref et al. showed a positive correlation between QTc prolongation as an electrocardiographic finding and LVED in echocardiography of cirrhotic patients. This may

Table 6. Specific echocardiographic data of the groups of patients

| Variables         | Group 1 (Mean ± SE) | Group 2 (Mean ± SE) | Group 3 (Mean ± SE) |
|-------------------|---------------------|---------------------|---------------------|
| SVR               | 0.22 ± 0.01         | 0.14±0.01<sup>bb</sup> | 0.09±0.01<sup>bb</sup> |
| PVR               | 0.26 ± 0.01         | 0.26±0.001          | 0.30±0.01<sup>bb, c</sup> |
| IVC diameter, mm  | 16.4 ± 0.22         | 10.3±0.43<sup>bb</sup> | 11.3±0.69<sup>bb</sup> |
| IVC collapsibility, % | 51.2 ± 0.42       | 83.2±1.70<sup>bb</sup> | 77.5±1.03<sup>bb</sup> |

<sup>a</sup> p<0.01 versus group 1 & 2, <sup>b</sup> p<0.01 versus group 1, <sup>c</sup> p<0.05 versus group 2
indicate a direct relationship between electrophysiological problems and the severity of the volume overload in cirrhotic patients (53). Our study was consistent with the guidelines from the American Society of Echocardiography that support the general use of IVC size and collapsibility for the assessment of volume status (33, 54).

In our study, hyponatremia was associated with increased incidence of hepatic encephalopathy in patients with decompensated liver cirrhosis. Jenq and his colleague 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 hepatic encephalopathy (55). By favoring astrocyte swelling, hyponatremia becomes a major risk for the development of this complication, particularly if there are diuretic treatments, bacterial infections, or transjugular intrahepatic porto-systemic shunts. 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 (4). Guevara et al. concluded that dilutional hyponatremia is correlated directly with the incidence of hepatic encephalopathy and is predictive of its subsequent development (2, 56). In our study, cirrhotic patients with hyponatremia had increased incidence of fever and spontaneous bacterial peritonitis (SBP). The results of our study agreed with those of other studies in that hyponatremia was found to be an indicator of poor outcomes for patients who are hospitalized with infections. Spontaneous bacterial peritonitis (SBP) often is associated with significant morbidity, including renal failure, and it has a high mortality rate in published series (57, 58). Patients with hyponatremia and SBP are at much higher risk for the development of hepatorenal syndrome and death (57). In our study, we found that hyponatremia is associated with increased risk of complications (encephalopathy, renal injury, SBP, GIT bleeding, degree of ascites, anemia, and pleural effusion) in patients with decompensated cirrhosis. This was in accordance with the study of Priyank and his colleagues, who found that patients with serum sodium levels ≤135 meq/L had a greater frequency of ascites, illness severity scores, hepatic encephalopathy, sepsis, renal failure, and in-hospital mortality (59). Other studies have shown that hyponatremia is associated with difficult-to-control ascites (2, 10) and greater frequency of neurologic disorders, renal failure, and infectious complications (12, 60, 61). In our study, hyponatremia was associated with gastrointestinal bleeding and anemia. This was in good agreement with Figueiredo’s study, which indicated that increased blood flow in the splanchnic bed exacerbates the portal hypertension and consequently increases the incidence of esophageal varices, variceal bleeding, and ascites (62). Angeli and his colleagues found that concurrent complications, such as severe ascites, impaired renal function, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome (except for gastrointestinal bleeding), occurred with a higher probability in cases of severe hyponatremia (serum sodium ≤130 meq/L) (2). We found that hyponatremia in liver cirrhosis was associated with increased incidence of plural effusion (hepatic hydrothorax). Another study showed that hepatic hydrothorax occurs in approximately 6–10% of patients with advanced cirrhosis (63). This is more common with the concomitant presence of ascites (64). The selective oral vasopressin V2-receptor antagonist, tolvaptan, significantly increased the serum sodium levels of patients with hyponatremia, supporting the efficacy of this drug in ESLD with refractory ascites and hyponatremia (65). The limitations of our study were its small sample size and the lack of randomization. However, the group of patients that we studied was homogeneous because we only included patients who had viral causes for cirrhosis of the liver.

5. Conclusions
Hyponatremia is a common finding in patients with decompensated liver cirrhosis that assumes an adverse prognostic meaning as it indicates an advanced disease with severe cardiovascular dysfunction. It is associated with increased risk of hepatic encephalopathy, refractory ascites, illness severity scores, renal failure, infectious complications, and pleural effusion. Selective oral vasopressin V2-receptor antagonist tolvaptan acts to increase free water excretion, which helps to resolve hypervolemic hyponatremia and may have the potential to improve outcomes in these patients.

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Conflict of Interest:
There is no conflict of interest to be declared.
Authors' contributions:
All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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