Association of Cirrhosis and Cardiomyopathy

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ABSTRACT

Introduction: We investigated association of pro-BNP, troponin-I, electrocardiography (ECG) and echocardiography (ECHO) during diagnosis and identification of cirrhotic cardiomyopathy in cirrhotic patients.

Materials and methods: Patients were divided into three groups as; compensated cirrhotic patients (group 1, n = 30), decompensated cirrhotic (group 2, n = 30) and control group (group 3, n = 30). ECHO, and ECG were performed, and troponin-I and levels of pro-BNP were analyzed.

Results: Average age of group 1 was 46.36 ± 16 years (range 19–86), 60% were female; group 2 was 57.03 ± 13.54 years (range 22–89), 56% female; and group 3 was 49.13 ± 9.95 years (range 18–80), 56% female. A significant increase in QTC was detected in compensated cirrhotic patients compared to the control group (p < 0.05). Pro-BNP levels were significantly higher (p < 0.05) in the compensated cirrhotic group compared to the control group. The levels of pro-BNP were also significantly higher in the decompensated cirrhotic group compared compensated cirrhosis group and control group (p < 0.001).

Conclusion: The increase of pro-BNP levels with severity of the disease in cirrhotic patients and the prolongation of QTc interval supports an association between these factors with cardiomyopathy.

Keywords: Cardiomyopathy, Cirrhosis, Pro-BNP, Troponin-I, QT prolongation.

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INTRODUCTION

The increase of the cardiac output in patients with cirrhosis was first defined more than 50 years ago. In the subsequent studies, a combination of cardiac dysfunction consisting of reduction in cardiac contractility, systolic and diastolic dysfunction and electrophysiological abnormalities has been shown. This syndrome was named as cirrhotic cardiomyopathy. Three major diagnostic criteria have been proposed in the pathogenesis of cirrhotic cardiomyopathy; structural and functional ventricular abnormalities, pharmacological, abnormal ventricular response to physiological and surgical stress and cardiac electrical abnormalities.1,2

Systolic dysfunction has been shown to play a role in the development of renal failure in advanced stages of the disease. Diastolic dysfunction reflects the delay in the left ventricular filling and has been partially linked to ventricular hypertrophy, subendocardial edema, and disruption of collagen structure. The prolonged QT interval present in about half of cirrhotic patients can be normalized by beta-blockers.1,3 In a study conducted in 40 patients with cirrhosis, it has been shown that left ventricular hypertrophy and diastolic dysfunction is diminished following liver transplantation, as well as it was reported that systolic response and exercise capacity during stress was normalized. This improvement after liver transplantation confirms the notion that cardiomyopathy may have a cirrhotic origin.4

Unexpected deaths due to heart failure are reported following the liver transplantation, shunt operations, and TIPS applications. Preload of the heart increases significantly with this procedure and is likely to aggravate the probably present but asymptomatic diastolic dysfunction and developing pulmonary edema.5,6

Although all this evidence brought on the concept of cirrhotic cardiomyopathy syndrome, there is a paucity of information about markers of cirrhotic cardiomyopathy.

In this study, we explored an association pro-BNP, troponin-I, ECG and ECHO in the diagnosis and identification of cirrhotic cardiomyopathy.

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MATERIALS AND METHODS

Study Design and Patients

The study was conducted from July 2012 to December 2012, including 60 patients with liver cirrhosis followed up in the outpatient or inpatient clinic of internal medicine and gastroenterology and 30 healthy control group. Patients were divided into three groups; compensated cirrhotic patients (group 1, n = 30), decompensated cirrhotic (group 2, n = 30) and control group (group 3, n = 30). Written consent from the patients and ethics committee permission of our hospital in accordance with the specifications outlined in the Helsinki declaration was obtained.

Patient Inclusion Criteria

Patients diagnosed with cirrhosis of the liver by liver biopsy, clinical, laboratory and imaging studies were enrolled in the study as patient group and patients whose cirrhosis was excluded by means of these findings as a control group. The presence of encephalopathy and ascites was taken into account as findings of decompensating cirrhosis.7

Patient Exclusion Criteria

Patient diagnosed with acute coronary syndrome, ischemic heart disease, rheumatic heart disease, who received chemotherapy or
radiotherapy due to solid malignant tumors and patients with the chronic obstructive pulmonary disease were excluded.

**Evaluation of Patients**
A detailed history of the patients included in the study consisting of sex, age, hypertension, diabetes, ischemic heart disease, rheumatic heart disease, chronic obstructive pulmonary disease, and chronic renal failure was obtained. Use of medications and disease age were recorded. The physical examination of patients and healthy volunteers was performed. Esophagogastroduodenoscopy, splenomegaly through physical examination or ultrasound and acid were documented as evidence of portal hypertension.9

Classification of cirrhosis was made according to the etiology, functional and clinical stage. The severity of liver disease was assessed by the child-pugh scoring method and MELD score. In the child-pugh scoring; for 5–6 score child-pugh A, 7–9 score child-pugh B, and 10–15 score child-pugh C were taken into account.9

**Evaluation of Blood Samples**
A total of 5 mL venous blood samples was taken from everyone in the study group. Then the serum samples from which troponin and pro-BNP levels will be obtained were centrifuged for 10 minutes at a 1500 rpm/minute. All serum samples obtained after labeled were stored in a freezer at −80°C in the laboratory chemistry until the analysis day.

**Laboratory Tests and Measurements**
Patients and control group serum pro-BNP, and troponin-I levels were measured with (Siemens advice Centaur XP device, Germany) chemiluminescence measurement methods using commercial Siemens kits. Serum pro-BNP levels were expressed as pg/mL, and troponin levels as ng/mL.

**Echocardiography Review**
Echocardiography (ECHO) evaluation was performed in the left lateral decubitus position using Vivid brand (Vivid S6 General Electric, Horten, Norway) 3 MHz transducer and images were obtained from the parasternal long axis, short axis and apical two and four spaces. Studies were conducted in accordance with the recommendations of the American Society of ECHO. The left ventricle, atrium, aortic diameters, and septal and posterior wall thickness were recorded from the parasternal long axis. Diastolic and end-systolic volumes were obtained from the apical four-chamber, and ejection fraction was calculated using the modified Simpson method.2

**Electrocardiography**
**QT Analysis**
They were read by researchers blinded to electrocardiographic ECG timing and grouping. At least seven derivations in the ECG were measured. QT and RR interval in each ECG were calculated in accordance with standard measurements by taking the average of at least three cycles measured from each lead. QT interval was corrected according to the heart rate using the Bazett’s formula (QTc = QT/RR1/2), and the corrected QT (QTc) was calculated.10 The QTcd (QTc/RR1/2) interval from the maximum QTc was calculated by subtracting the minimum QTc interval from the maximum QTc.11,12

**Statistics**
Statistical analysis was performed using the statistical package for social sciences 16.0 (SPSS Inc, Chicago, IL, USA) statistical package program. The descriptive statistical data of the study results were expressed as the mean ± standard deviation for parametric data and minimum, maximum and median for nonparametric data. Data were analyzed with the Kolmogorov-Smirnov test to confirm the normal distribution. Pearson’s Chi-square test was used for intergroup comparisons in categorical variables. One-way analysis of variance (ANOVA) was used for data showing the parametric distribution and Bonferroni for post hoc analysis. Kruskal–Wallis was used for nonparametric data, and the Mann–Whitney U test was used for determining the difference-forming groups. A p <0.05 was considered statistically significant. Categorical data were expressed as number (n) and percentage (%).

**Results**
A total of 90 subjects consisting of 60 patients with liver cirrhosis (30 compensated and 30 decompensated) and 30 controls were included in the study. Patients were divided into three groups; compensated cirrhotic patients (group 1, n = 30), decompensated cirrhosis (group 2, n = 30) and control group (group 3, n = 30). The average age of group 1 was 46.36 ± 16 years (range 19–86), 60% were female, group 2 was 57.03 ± 13.54 years (range 22–80), 56% were female, and group 3 was 49.13 ± 0.95 years (range 18–80), 56% were female. No statistically significant difference was found between groups in term of age and gender distribution (p >0.5).

The demographic and laboratory characteristics of patients participating in the study are shown in Table 1. According to the Child-Turcotte-Pugh scoring system, 53.3% of patients were child A, 38.3% child B and 8.3% child C. The MELD score of 86.7% of patients was <15 and 13.3% was >15. The number of patients with child B and C stage was high in decompensated cirrhosis group. Smoking incidence was found higher in a total cirrhotic group compared to the control group. The number of people using alcohol was similar between groups.

A statistically significant difference between groups was found in terms of hematocrit, platelets, aspartate aminotransferase (AST), total bilirubin, prothrombin time, QTc, LVDD, pro-BNP levels (p <0.05). There was not a statistically significant difference between all three groups in terms of E/A and troponin-I levels (p >0.5) (Table 1).

AST and bilirubin levels were significantly higher in the compensated and decompensated patients compared to the control group (p <0.001). Albumin was found significantly lower in the compensated and decompensated cirrhosis groups (p <0.05) and both groups of patients compared to the control group (p <0.001). No significant difference was found between patients and control group and between both patients group in terms of pro-BNP levels (p >0.05). While a difference was detected between compensated and decompensated cirrhosis groups, no difference was observed between the patient and control group in terms of LVDD (p <0.05). Although within normal limits a significant increase of QTc was found in compensated cirrhotic patients compared to the control group (p <0.05), no difference was observed between both patients groups and between compensated cirrhosis and control group. While pro-BNP levels were found significantly higher in a compensated cirrhotic group compared to control group and lower compared to decompensated cirrhotic group (p <0.05), in the decompensated cirrhotic group, was significantly higher compared to the compensated cirrhotic and control group (p <0.001) (Table 2).

**Discussion**
Prolonged QTc has been shown in cirrhotic patients. It was suggested that this finding may be due to the changes in channel
activity of the cardiomyocytes.\textsuperscript{13-15} QT indexes are altered in cirrhotic patients and have a potential diagnostic predictive value.\textsuperscript{16} In our study, although within normal limits, a statistically significant prolongation of QTc interval was shown in patients with compensated cirrhosis compared to the control group. The lack of overcoming of the pathological limits of QTc was thought to be due to the patients’ good functional capacity and cardiomyopathy not being yet developed.

In the study conducted by Moller et al.,\textsuperscript{1,3} has been shown that with the increase of liver disease severity according to Child-Pugh score, BNP and pro-BNP levels also increased, cardiac hypertrophy reduced and local ventricular fibrosis occurred. Henriksen et al.\textsuperscript{17} hypothesized that beta blockers, diuretics, angiotensin-converting enzyme inhibitors frequently reduce the BNP concentrations. Decompensated cirrhotic patients in our patient population were generally using diuretics. Pro-BNP levels in these patients were significantly higher suggesting that the level might have been higher in these patients. This study clearly showed that pro-BNP levels rise as the disease progresses supporting the present literature and added new evidence in the literature on this subject. On the other hand, the fact that pro-BNP might be an indicator of cirrhotic cardiomyopathy; suggests that can be used as a marker of prognosis in these patients due to its correlation with the disease severity. For practical use, further research is needed to enable the detection of the “cutoff” value.

In the literature, there are studies showing that varying degrees of diastolic dysfunction is present in all patients with liver disease.\textsuperscript{18,19} It has been shown that E/A, mitral E-wave deceleration time (EDT), is volumetric contraction time (ICT) and left atria diameter to deteriorate in patients with liver cirrhosis.\textsuperscript{20} In our study, significant LVDD was found in compensated cirrhosis group. The

### Table 1: Demographic distribution of groups

| Group 1 (n 30) | Group 2 (n 30) | Group 3 (n 30) | p       |
|---------------|---------------|---------------|---------|
| Age (year)    | 46.36 ± 16    | 57.03 ± 13.54 | 49.13 ± 0.95 | 0.588   |
| Sex: M/F      | 12/18         | 13/17         | 13/17   | 0.512   |
| Hb (g/dL)     | 13.98 ± 2.63  | 12.53 ± 1.82  | 14.55 ± 1.38 | 0.010   |
| Hematocrit (%)| 42.86 ± 6.74  | 38.71 ± 4.34  | 44 ± 3.69 | p < 0.001 |
| Leucocyte (K/µL) | 6.45 ± 3.32  | 7.78 ± 5.21  | 7.79 ± 2.18 | 0.315   |
| Platelet (K/µL) | 126.39 ± 59.53 | 127.14 ± 98.1 | 275.06 ± 67.34 | p < 0.001 |
| Glucose (mg/dL) | 117.36 ± 46.99 | 119.66 ± 51.47 | 99.96 ± 18.61 | 0.221   |
| Urea (mg/dL)  | 34.6 ± 31.84  | 42.67 ± 28.88 | 31.23 ± 7.65 | 0.198   |
| Creatinin (mg/dL) | 0.85 ± 0.87  | 0.79 ± 0.21  | 0.72 ± 0.1  | 0.080   |
| Albumin (mg/dL) | 3.48 ± 0.49  | 3.01 ± 0.67  | 4.18 ± 1.69 | 0.079   |
| AST (U/dL)    | 56.3 ± 43.92  | 48.56 ± 36.38 | 27.76 ± 19.86 | p < 0.001 |
| ALT (U/dL)    | 49.55 ± 44.16 | 33.9 ± 22.88 | 29.13 ± 16.98 | p < 0.001 |
| T.Bil (mg/dL) | 1.42 ± 1.04   | 2.06 ± 1.04   | 0.63 ± 0.23  | p < 0.001 |
| PT (sec)      | 16.3 ± 2.84   | 17.26 ± 4.08  | 12.53 ± 0.89 | p < 0.001 |
| QTc (sec)     | 32.51 ± 16.58 | 50.33 ± 28.33 | 20.75 ± 8.76 | p < 0.05  |
| LVDD (cm)     | 2.70-145-30   | 4-323-9       | 18.80-166-71.50 | p < 0.001 |
| E/A           | 0.97 ± 0.35   | 1.03 ± 0.49   | 1 ± 0.35    | 0.037    |
| Troponin (ng/L) | 0.0 ± 0.02   | 0.01 ± 0.03   | 0.0 ± 0.0   | 0.081    |
| Pro-BNP (pg/mL) | 7.10 ± 8.45  | 29.85 ± 46.35 | 1.61 ± 2.07 | p < 0.001 |

(M, male; F, female; Hb, hemoglobin; g/dL, gram/deciliter; mg/dL: milligram; U/dL, unit/deciliter; T.Bil, total bilirubin; PT, prothrombin time; sec, second)

### Table 2: Comparison of p value of the parameters between groups

| Group 1 vs group 2 (p) | Group 1 vs group 3 (p) | Group 2 vs group 3 (p) |
|------------------------|------------------------|------------------------|
| Troponin (ng/L)        | 0.179                  | 0.638                  | 0.054                  |
| LVDD (cm)              | <0.05                  | 0.069                  | 0.797                  |
| QTc (sec)              | 0.430                  | <0.05                  | 0.069                  |
| Pro-BNP (pg/mL)        | <0.05                  | <0.05                  | <0.001                 |
| AST (U/dL)             | 0.705                  | <0.001                 | <0.001                 |
| ALT (U/dL)             | 0.193                  | <0.05                  | 0.460                  |
| T.Bil. (mg/dL)         | 0.052                  | <0.001                 | <0.001                 |
| Albumin (mg/dL)        | <0.05                  | <0.001                 | <0.001                 |

T.Bil, total bilirubin
reason behind the lack of significant LVDD in the decompensated cirrhosis group, lack of significant differences between patients and controls in terms of E/A may be limited in the number of patient groups. On the other hand, cirrhotic cardiomyopathy, unlike other complications of cirrhosis, may progress without showing symptoms and obvious signs in echocardiographic measurements due to low vascular resistance and decrease in cardiac afterload.

As a result, although the lack of a significant difference between groups in terms of troponin-I, LVDD and E/A rates do not support cirrhotic cardiomyopathy, the correlated increase of pro-BNP levels with disease severity and prolongation of QTc interval in the ECG does support it. Pro-BNP independently of echocardiographic measurements carries a diagnostic and prognostic significance in terms of determining the status of the compensation, cardiac dysfunction and parallelly the severity of liver disease in cirrhotic patients. There is a need for comprehensive prospective studies including larger and longer follow-up of the diagnosed patient population to evaluate the echocardiographic, histopathologic, ECG and various biomarkers and determining the “cutoff” values of the existing ones in the identification of cirrhotic cardiomyopathy.

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