

Brain Natriuretic Peptide in Liver Cirrhosis and Fatty Liver: Correlation with Cardiac Performance

Amna Metwaly¹, Ashraf Abdel khalik¹, Fatma Mohammad Nasr¹, Amal Ismail Sabry¹, Mohamed Fathy Gouda²,
Mona Hassan³

¹ Intensive Care Department, Theodor Bilharz Research Institute, Giza, Egypt

² Gastroenterology and Hepatology Department, Theodor Bilharz Research Institute, Giza, Egypt

³ Clinical Chemistry Department, Theodor Bilharz Research Institute, Giza, Egypt

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Abstract

Objective: The aims of the present study were to assess the serum BNP level in patients with post hepatitis C liver cirrhosis and patients with fatty liver and to determine the correlation between BNP and the severity of liver disease and cardiac performance.

Methods: The study was conducted on 140 subjects subdivided into 3 groups: group 1 included 60 patients having post hepatitis C virus (HCV) liver cirrhosis; group 2 included 60 patients with nonalcoholic fatty liver disease (NAFLD); and group 3 included 20 healthy volunteers serving as a control group. All patients and volunteers were subjected to full physical examinations, laboratory evaluation of hemoglobin percent, liver and renal function tests, serum electrolytes, cholesterol, triglyceride, HBs antigen, HCV antibody and serum BNP levels, ECG, abdominal ultrasonography, and echocardiography.

Results: There was a significant increase in the BNP level in cirrhotic patients compared to the other two groups ($p = 0.000$), and it was correlated with the severity of liver disease assigned as Child's classification ($p = 0.000$). Also, there was a significant increase in the BNP level in cirrhotic patients with decompensation components compared to those without decompensation components ($p = 0.000$), history of hepatic encephalopathy ($p = 0.000$), history of variceal bleeding ($p = 0.000$), history of spontaneous bacterial peritonitis ($p = 0.000$), presence of ascites ($p = 0.000$) and portal vein diameter > 11 mm in abdominal ultrasound ($p = 0.000$), and prolonged QTc interval in ECG ($p = 0.011$). There was a significant increase in serum BNP in patients with cirrhosis with the following echocardiographic findings: IVST > 11 mm, PWT > 11 mm, LA diameter > 40 mm, EF% $< 54\%$, and E/A ratio < 1 compared to those without these echocardiographic findings ($p = 0.000$).

Conclusion: BNP level increases in post hepatitis C cirrhotic patients and tends to decrease in fatty liver disease patients, and it is correlated with both the severity of liver disease and the morpho-functional cardiac changes. Given the ever-increasing prevalence of liver cirrhosis and fatty liver disease worldwide, it is important to understand the benefits and limitations of BNP as a heart failure biomarker in hepatic patients, where the relationship between BNP level and myocardial function is complex and is altered by the liver disease.

Keywords: brain natriuretic peptide (BNP), post hepatitis C virus liver cirrhosis, fatty liver, echocardiography

1. Introduction*1.1. Background and study logic*

Brain natriuretic peptide (BNP) is a cardiac neurohormone that is secreted from the ventricles in response to increased diastolic pressure or volume (1). When cirrhosis is present, the BNP concentrations may be higher (2). Several studies have shown elevated BNP levels are related to the severity of cirrhosis, myocardial hypertrophy, myocardial dysfunction, and QT prolongation (3, 4). Increased BNP concentrations in people who have liver cirrhosis may be due to the hyperdynamic state and cirrhotic cardiomyopathy. Pimenta et al. (2) observed that BNP level in cirrhosis reflects the cardiac systolic function and is an independent predictor of medium-term survival in

Corresponding author:

Fatma Mohammad Nasr, Intensive Care Department, Theodor Bilharz Research Institute, Giza, Egypt.

Tel: +20.1003542204, E-mail: fatma_elwakeel@live.com

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advanced cirrhosis. Padillo's study showed that increased baseline BNP concentrations, along with high Child and MELD scores, may be regarded as the critical cardiac dysfunction parameter in cirrhotic patients (5). Radvan et al. found a significant correlation between B-type natriuretic peptide in plasma and the severity of liver disease in cirrhotic patients. High plasma BNP appears to be a good negative prognostic factor of death from cirrhosis (6). Serum BNP levels were correlated positively with the Child score, the grade of esophageal varices, a history of spontaneous bacterial peritonitis, and the presence of ascites and collateral circulation. BNP levels that exceeded the median value were associated with an increased prevalence of death within 12 months after discharge (7). The association of metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) is so strong that the latter is considered as the hepatic manifestation of MetS (8, 9). Steatosis is associated with an increased prevalence and incidence of cardiovascular disease (10, 11), and several investigators have examined the association of NAFLD with subclinical cardiovascular disease CVD, e.g., carotid artery intima-media thickness or clinical CVD (12). Higher natriuretic peptide levels were characterized by decreased visceral and liver fat and increased lower body fat irrespective of age, gender, race, and obesity status. This suggested that there might be a link between the heart and adipose tissue distribution that is mediated through natriuretic peptides (13). A study of 608 Japanese patients with type 2 diabetes indicated that there was an inverse relationship between BNP and body mass index (BMI), with a more robust inverse association between BNP and visceral fat compared with other measures of adiposity (14). Also, in the Framingham Heart Study, inverse associations between BNP and visceral fat were similarly described based on a multivariable adjusted analysis, which included BMI, with no independent association seen with abdominal subcutaneous fat (15).

1.2. Objective

The general objective of this study was to evaluate serum BNP levels in two groups of chronic liver disease patients (post hepatitis C virus liver cirrhosis and fatty liver). The specific objective was to find its correlation with the severity of liver disease and cardiac performance.

2. Material and Methods

2.1. Setting and patients

The present study was conducted on 140 subjects from Theodor Bilharz Research Institute Hospital, selected to represent 3 groups:

- 1) Group 1: Included 60 patients having post hepatitis C virus liver cirrhosis, which was diagnosed based on the results of laboratory tests (hepatitis C virus antibody, low serum concentrations of albumin, high INR and low platelet count) and abdominal ultrasonographic findings (irregularity of the liver's surface). The stage of cirrhosis was classified according to the Child-Pugh classification, which reflects the severity of the disease.
- 2) Group 2: Included 60 patients with NAFLD, which was diagnosed by a characteristic liver echo pattern (diffuse hyperechogenicity of liver compared with right kidney) and negative hepatitis markers. Grading of diffuse hepatic steatosis on ultrasound was used to evaluate the extent of fatty changes in the liver, grade I: increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity; grade II: increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm; and grade III: increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of the diaphragm (16).
- 3) Group 3: Included 20 healthy volunteers, who were age and gender matched with the study groups, to serve as a control group with normal liver ultrasonography, normal liver function tests, and negative hepatitis markers.

2.2. Exclusion criteria

Subjects with histories of heart disease, diabetes mellitus, obesity (BMI > 25), hypertension (blood pressure > 140/90 mmHg), dyslipidemia, acute or chronic kidney disease, any malignancy, pregnancy, anemia with hemoglobin less 10 gm%, taking any medication with adverse effects on the liver or cardiovascular system, or alcohol consumption were excluded.

2.3. Methods

All patients and normal volunteers underwent:

- 1) Thorough histories and physical examinations
- 2) Blood sampling for serum electrolytes, cholesterol, triglyceride, HBs antigen and HCV antibody and liver and renal function tests

- 3) Immunoassay for detection of BNP: Circulating BNP was determined by commercially available ELISA. The BNP ELISA kit allows in vitro quantitative determination of BNP concentrations in serum
- 4) Resting ECGs with 12 leads. The duration of the QT interval was calculated manually. The QT intervals were corrected in accordance with the rate using the BAZET formula, i.e., $QTc = QT / \sqrt{RR}$. $QTc > 440$ ms was considered prolonged (17, 18)
- 5) Abdominal ultrasound scanning using a Toshiba Memo 30 scanner equipped with a 3.5 MHz linear transducer
- 6) Echo-Doppler study: All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (19). M-mode, two-dimensional echocardiography, and Doppler ultrasound studies were conducted using a high resolution Toshiba Memo 30 scanner. Using the M-mode, measurements of interventricular septum (IVS) and left ventricle posterior wall (PWT) thicknesses were conducted and the diameters of the left ventricle end-diastolic (LVED) and end systolic (LVES) were determined. The left ventricular mass was calculated according to Devereux and associates' convention, i.e., $LVM (gm) = 1.04 \times \{ (LVED + IVST + PWT)^3 - LVED^3 \} \times 0.8 + 0.6$ (20). The diameter of the left atrium was determined from the parasternal long axis view at the end systole. The left ventricular ejection fraction (EF%) was measured from M-mode dimensions using the Teichholz formula (21). The velocity of the mitral inflow early, rapid-filling wave (E), the peak velocity of the late-filling wave due to atrial contraction (A), and the E/A ratio also were measured.

2.4. Research ethics

The Ethics Committee of TBRI approved the study, and it was conducted in accordance with the Helsinki Declaration (1975). All participants gave written informed consent. The study was conducted in 2014 and 2015.

2.5. Statistical Analysis

Statistical analysis was performed using SPSS version 17. Data were expressed as the mean \pm standard deviation (SD) for numerical variables. $p \leq 0.05$ was considered to be statistically significant, and $p \leq 0.01$ was considered to be statistically highly significant.

3. Results

The demographic data of the patients with liver cirrhosis, those with steatosis, and that of the controls indicated that the mean ages were 43.67 ± 9.46 , 44.87 ± 7.4 , and 44.8 ± 8.5 years, respectively. In group 1, 40 were males (66.67%), and 20 were females (33.33%). In group 2, 45 were males (75%), and 15 were females (25%). In group 3, 15 were males (75%), and 5 were females (25%). The laboratory data showed a statistically significant increase in serum sodium, alanine aminotransferase, total bilirubin, direct bilirubin, and serum albumin in patients with liver cirrhosis group and fatty liver group compared to the controls. Also, there was a statistically significant increase in serum potassium, aspartate aminotransferase, and brain natriuretic peptide in the patients with liver cirrhosis compared to the controls. There were statistically significant increases in serum sodium, serum potassium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, and brain natriuretic peptide in patients with liver cirrhosis compared to those in the fatty liver group (Table 1). The electrocardiography data showed a statistically significant increase in corrected QT interval (QTc) in patients with liver cirrhosis and in the fatty liver group compared to the controls and also in patients in the liver cirrhosis group compared to the fatty liver group (Table 2). The echocardiographic data showed a statistically significant increase in the diameters of the left atrium and the aorta, as well as increases in the interventricular septum thickness (IVST), posterior wall thickness (PWT), end-systolic diameter (ESD), and left ventricular mass (LVM), in addition to a statistically-significant decrease in E/A in patients with liver cirrhosis and fatty liver compared to the controls. Also, there was a statistically significant increase in end-diastolic diameter (EDD) and decrease in ejection fraction (EF) in patients with fatty livers compared to the controls. Also, there was a statistically significant increase in posterior wall thickness (PWT) in patients with fatty livers compared to patients with liver cirrhosis (Table 2). There was a statistically significant increase in serum brain natriuretic peptide (BNP) in the group of patients with cirrhosis compared to the controls. There was a statistically significant increase in serum BNP in Child class B patients compared to Child class A patients. Also, there was a statistically significant increase in serum BNP in Child class C patients compared to Child class B patients (Table 3).

Table 1. Laboratory data of the patients and control group

Variables	Liver cirrhosis	Fatty liver	Control	p_1 value	p_2 value	p_3 value
Na, mEq/L	131.3 ± 4.8	138 ± 3.1	141.0 ± 2.5	0.000	0.000	0.000
K, mEq/L	4.7 ± 0.6	4.0 ± 0.4	4.0 ± 0.3	0.000	0.169	0.000
Creat, mg/dL	1.10.5	0.9 ± 0.3	1.0 ± 0.2	0.603	0.169	0.009
BUN, mg/dL	23.5 ± 17.3	26.2 ± 5.9	24.1 ± 10.4	0.883	0.259	0.251
ALT, U/L	31.8 ± 33.8	16.7 ± 3.3	13.5 ± 2.0	0.015	0.000	0.000
AST, U/L	65.9 ± 88.8	14.4 ± 5.1	13.3 ± 4.2	0.0009	0.377	0.000
T bil, mg/dL	3.4 ± 4.3	0.9 ± 0.2	0.5 ± 0.1	0.003	0.000	0.000
D bil, mg/dL	1.8 ± 2.7	0.2 ± 0.0	0.1 ± 0.0	0.006	0.000	0.000
Alb, g/dL	2.5 ± 0.7	3.8 ± 0.6	4.2 ± 0.1	0.000	0.004	0.000
BNP, pg/mL	165.0 ± 12.4	31.0 ± 8.4	33.8 ± 7.2	0.000	0.185	0.000

p_1 value: significance between liver cirrhosis and control group, p_2 value: significance between fatty liver and control group, p_3 value: significance between liver cirrhosis and fatty liver group, Na: serum sodium, K: serum potassium, Creat: creatinine, BUN: blood urea nitrogen, ALT: alanine aminotransferase, AST: aspartate aminotransferase, T bil.: Total bilirubin, D bil.: Direct bilirubin, BNP: brain natriuretic peptide

Table 2. Electrocardiography and echocardiographic data of the patients and control group

Variables	Liver cirrhosis	fatty liver	Control	p_1 value	p_2 value	p_3 value
QTc, msec	478.35 ± 29.2	422.43 ± 26.7	393.24 ± 9.6	0.000	0.000	0.000
LA, mm	38.3 ± 5.2	39.5 ± 6.5	34.6 ± 3.2	0.003	0.001	0.258
AO, mm	30.3 ± 3.2	30.7 ± 3.0	28.4 ± 2.5	0.014	0.002	0.466
IVST, cm	1.0 ± 0.2	1.04 ± 0.3	0.9 ± 0.1	0.035	0.044	0.391
PWT, cm	1.0 ± 0.1	1.06 ± 0.2	0.9 ± 0.1	0.000	0.001	0.039
EDD, cm	4.8 ± 0.8	4.9 ± 0.9	4.5 ± 0.5	0.073	0.035	0.467
ESD, cm	3.0 ± 0.7	3.1 ± 0.5	2.7 ± 0.5	0.040	0.000	0.284
EF, %	66.6 ± 8.7	65.7 ± 7.9	70.7 ± 6.9	0.056	0.012	0.549
LVM, gm	183.0 ± 52.1	192.4 ± 32.8	136.8 ± 29.2	0.000	0.000	0.239
E/A	0.82 ± 0.16	0.81 ± 0.13	1.21 ± 0.36	0.000	0.000	0.687

p_1 value: significance between liver cirrhosis and control groups, p_2 value: significance between fatty liver and control groups, p_3 value: significance between liver cirrhosis and fatty liver groups, QTc: Corrected QT interval, LA: left atrium diameter, Ao: aortic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness, EDD: end diastolic dimension, ESD: end systolic dimension, EF: ejection fraction, LVM: left ventricular mass, E/A: ratio of early rapid filling wave velocity of mitral inflow to peak velocity of the late filling wave due to atrial contraction

Table 3. BNP concentrations in patients with cirrhosis as related to their Child-Pugh classification

Group (n)	BNP level	p-value
Controls (20)	33.8 ± 7.2	
Cirrhosis (60)	165.0 ± 12.4	0.000
Child class A (6)	91.4 ± 9.6	
Child class B (24)	156.6 ± 14.8	0.000
Child class C (30)	221.2 ± 21.7	0.000

BNP = brain natriuretic peptide; $p < 0.000$: cirrhosis group (total) compared to control group; $p=0.000$: child class B group compared to child class A group; $p=0.000$: child class C group compared to child class B group.

There was a statistically significant increase in serum brain natriuretic peptide (BNP) in patients with cirrhosis with decompensation components (history of hepatic encephalopathy, history of variceal bleeding, history of spontaneous bacterial peritonitis, presence of ascites and portal vein diameter > 11 mm in abdominal ultrasound and prolonged QTc interval in ECG) compared to patients without these decompensation components (Table 4). There was a statistically significant increase in serum brain natriuretic peptide (BNP) in patients with cirrhosis with the following echocardiographic findings: IVST > 11 mm, PWT > 11 mm, LA diameter > 40 mm, EF% < 54%, E/A ratio < 1 compared to patients without these echocardiographic findings (Table 5). There was a statistically insignificant decrease in serum brain natriuretic peptide (BNP) in patients with steatosis compared to the controls. There was a

statistically insignificant decrease in serum BNP in grade II patients compared to grade I patients. Also, there was a statistically insignificant decrease in serum BNP in grade III patients compared to grade II patients (Table 6). There was a statistically significant increase in serum brain natriuretic peptide (BNP) in patients with steatosis with the following echocardiographic findings: IVST > 11 mm, PWT > 11 mm, LA diameter > 40 mm, EF% < 54%, and E/A ratio < 1 compared to patients without these echocardiographic findings (Table 7).

Table 4. BNP levels according to cirrhosis decompensation component

Component	BNP levels				
	n	Present, %	n	Absent	p-value
History of hepatic encephalopathy	50	167.1 ± 16.3	10	106.1 ± 8.0	0.000
History of variceal bleeding history	15	198.1 ± 14.3	45	137.1 ± 5.2	0.000
History of spontaneous bacterial peritonitis	20	169.3 ± 12.7	40	126.2 ± 7.3	0.000
Ascites	55	184.2 ± 13.2	5	125.4 ± 12.1	0.000
Portal vein diameter > 11 mm	55	155.7 ± 8.4	5	110.9 ± 8.8	0.000
Corrected QT interval > 440 ms	10	484.37 ± 10.5	50	462.17 ± 26.2	0.011

BNP = brain natriuretic peptide

Table 5. BNP levels according to echocardiographic findings in patients with liver cirrhosis

Component	BNP levels				
	n	Present, %	n	Absent	p-value
IVST > 11 mm	12	155.8 ± 9.3	48	102.9 ± 5.3	0.000
PWT > 11 mm	11	154.2 ± 6.4	49	97.9 ± 8.8	0.000
LA diameter > 40 mm	18	157.4 ± 7.5	42	94.9 ± 7.4	0.000
EF% < 54%	4	158.7 ± 8.4	56	123.9 ± 3.7	0.000
E/A ratio < 1	19	168.7 ± 8.6	41	93.2 ± 3.4	0.000

BNP = brain natriuretic peptide, IVST: interventricular septum thickness, PWT: posterior wall thickness, LA: left atrium dimension, EF: ejection fraction, E/A: ratio of early rapid filling wave velocity of mitral inflow to peak velocity of the late filling wave due to atrial contraction.

Table 6. BNP concentrations in patients with steatosis as related to their ultrasound grading

Group	n	BNP level	p-value
Controls	20	33.8 ± 7.2	
Steatosis (total)	60	31.0 ± 8.4	0.185
Grade I	15	32.4 ± 9.6	
Grade II	35	28.6 ± 9.8	0.212
Grade III	10	24.2 ± 7.7	0.198

BNP = brain natriuretic peptide, P < 0.185: steatosis group (total) compared to control group; p=0.212: Grade II steatosis group compared to Grade I steatosis group; P = 0.198: Grade III steatosis group compared to Grade II steatosis group.

Table 7. BNP levels according to echocardiographic findings in patients with steatosis

Component	BNP levels				
	n	Present, %	n	Absent	p-value
IVST > 11 mm	14	35.8 ± 9.3	46	22.9 ± 5.3	0.000
PWT > 11 mm	12	34.2 ± 6.4	48	27.9 ± 8.8	0.023
LA diameter > 40 mm	19	37.4 ± 7.5	41	24.9 ± 7.4	0.000
EF% < 54%	6	38.7 ± 8.4	54	23.9 ± 3.7	0.000
E/A ratio < 1	29	39.3 ± 8.6	31	23.2 ± 3.4	0.000

BNP = brain natriuretic peptide, IVST: interventricular septum thickness, PWT: posterior wall thickness, LA: left atrium diameter, EF: ejection fraction, E/A: ratio of early rapid filling wave velocity of mitral inflow to peak velocity of the late filling wave due to atrial contraction.

4. Discussion

In our study, there was a statistically significant increase in serum BNP in patients with liver cirrhosis compared to fatty liver patients and the control group. Our study agrees with the studies of El Nakeeb et al. and Henriksen et al., who found a statistically significant higher level of circulating BNP concentration in patients with liver cirrhosis compared to the controls (4, 22). We found that serum BNP was significantly higher in Child class B patients compared to Child class A patients and in Child class C patients compared to Child class B patients. In agreement with our study, Henriksen et al. (4) found statistically significant higher BNP concentrations in patients with advanced grade of liver cirrhosis. Also, this was in agreement with Yilmaz et al. (23), who evaluated the relationship of increased serum BNP levels with the grade of liver cirrhosis and found a significant, positive correlation between BNP levels and higher grades of Child Pugh score, indicating that the BNP levels were related to severity of liver cirrhosis. Also, Shi et al showed that serum BNP levels were increased significantly in patients with cirrhosis compared to the controls; BNP concentrations were positively related to the severity of cirrhosis according to the Child-Pugh classification and the decompensation component of cirrhosis (7). Radvan et al. (6) reported a significant correlation between serum BNP levels and MELD scores. Our results showed a statistically significant increase in serum BNP in patients with cirrhosis with decompensation components, i.e., history of hepatic encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis, ascites, portal vein diameter > 11 mm in abdominal ultrasound, and a prolonged QTc interval in ECG. This is in agreement with the findings of Krishnan et al. who concluded that the increased BNP concentrations in liver cirrhosis were associated with the decompensation components of cirrhosis, such as hepatic encephalopathy, esophageal varices, and ascites (24). Also, Henriksen et al. found that the concentration of circulating BNP was related to Child score and to arterial oxygen tension, heart rate, and QT interval (4). According to the results of the study of Yilmaz et al., the existence of ascites, collateral circulation, and esophageal varices were related to increased BNP levels (23). These findings were confirmed by the study of Shi et al., who found that the existence of ascites, collateral circulation, a history of spontaneous bacterial peritonitis, and esophageal varices were related to increased BNP levels. These findings indicated that BNP also might be a prediction tool to follow the clinical progress of patients with cirrhosis (7). In our study, there was a statistically significant increase in serum BNP in patients with cirrhosis with the following echocardiographic findings: interventricular septum thickness (IVT) > 11 mm, posterior wall thickness (PWT) > 11 mm, left atrium LA diameter > 40 mm, ejection fraction (EF) % < 54%, and E/A ratio < 1 compared to the patients without these echocardiographic findings. Several studies have found that the increased serum BNP levels are correlated with the severity and functional capacity of chronic heart failure (1), and BNP increases in both systolic and diastolic dysfunction, but the increase is more pronounced when both are present (25, 26). In another study, BNP level was increased in correlation with the thickness of the ventricular walls, diastolic dysfunction, stress-induced systolic dysfunction, hyperdynamic circulation, and structural cardiac changes in patients with liver cirrhosis (27). Yilmaz et al. found significantly higher serum BNP levels in patients with a left ventricle posterior wall thickness \geq 11 mm compared to patients with a wall thickness < 11 mm (23). BNP may be related to large atrial volumes. Myocardocyte stretching is one of the main factors that stimulate the production of natriuretic hormones (1). BNP levels could be a marker of cardiovascular diastolic dysfunction in patients with end-stage liver disease (1, 3). Pimenta et al., in their study that included patients with decompensated cirrhosis, observed that BNP levels in cirrhosis reflect cardiac systolic function (2). These data suggest that BNP is a marker of cardiac subclinical dysfunction participating to liver decompensation. BNP levels are significantly associated to increased left atrial volumes and to signs of cardiac diastolic dysfunction, which characterize morpho-functional changes usually found in end-stage liver disease (28). Our study indicated that there were statistically significant increases in IVST, PWT, and LVM in the fatty liver group compared to the control group. These findings were similar to those of Goland et al., who found increased thickness of the interventricular septum, posterior wall, and larger left ventricular mass (LVM) and LV mass/height in the NAFLD group compared to the controls (29). We found significant increases in end diastolic diameter (EDD) and end systolic diameter (ESD) in the fatty liver group compared to the controls. Ramachandran et al. concluded that the increased echocardiographic left ventricular internal dimensions (EDD or ESD) are a risk factor for the development of congestive heart failure (30). Our study was inconsistent with the study of Fotbolcu et al., who found that patients with NAFLD have impaired LV systolic function, even in the absence of morbid obesity, hypertension, or diabetes (31). In our study, we found increased left atrium (LA) diameters and decreased E/A ratios (diastolic dysfunction) in patients who had fatty liver disease compared to the controls. Similar findings were reported by Serban et al. (32), who found a higher frequency of diastolic dysfunction in patients that had NAFLD compared to those without NAFLD. Bonapace et al. reported that, in patients that had NAFLD, even if the LV morphology and systolic function were preserved, early features of LV diastolic dysfunction may be detected (33). Also, inconsistent with our study, Aparci et al. (34) found significantly enlarged left atrial diameter and volume in patients with liver steatosis. In our study, we found a statistically insignificant

decrease in BNP level in patients with liver steatosis compared to the controls. There was a statistically insignificant decrease in serum BNP in grade II steatosis patients compared to grade I patients and in grade III patients compared to grade II patients. We also found a statistically significant increase in serum BNP in patients with steatosis with the following echocardiographic findings: IVST > 11 mm, PWT > 11 mm, LA diameter > 40 mm, EF% < 54%, and E/A ratio < 1 compared to those without these echocardiographic findings. In many studies, fatty liver is considered a part of visceral fat (35-37). Cheng et al. (15) found an inverse relationship between BNP levels and visceral adipose mass. The reason decreased BNP levels in our fatty liver patients did not reach significance may be that we excluded obese and overweight patients from our study, and it also may be due to the presence of cardiac morpho-functional changes in some of our patients that increased their BNP levels, thereby counteracting the effect of visceral adiposity. In a study of 1873 community-based individuals, Cheng et al. (15) found an inverse relationship between BNP levels and visceral adipose mass. Also, in a Japanese study performed on 608 patients with type 2 diabetes, an inverse relationship between BNP and BMI was demonstrated with a more robust inverse association between BNP and visceral fat compared with other measures of adiposity (14). In the Framingham Heart Study, the inverse associations between BNP and visceral fat were described in a multi-variable, adjusted analysis that included BMI, and no independent association was observed with subcutaneous abdominal fat (15). Higher natriuretic peptide levels were associated independently with a favorable adiposity profile, which is characterized by decreased visceral and liver fat and increased lower body fat. Such a profile suggests that there might be a link between the heart and the distribution of adipose tissue that is mediated by natriuretic peptides (13). Although overweight and obese heart failure (HF) patients have relatively lower BNP levels, these levels still are predictive of worse symptoms, impaired hemodynamics, and higher mortality irrespective of the BMI level (38). Researchers have demonstrated a consistent inverse relationship between obesity (i.e., BMI \geq 30) and circulating BNP levels. In a study of 3,389 subjects without HF from the original Framingham Heart Study offspring cohort, Wang et al. (39) were the first to describe the inverse relationship between obesity and BNP levels. They adjusted the results of multi-variable regression analysis for echocardiographic variables, such as left atrial size left ventricular mass. The mean levels of BNP in plasma were 21.4, 15.5, and 12.7 pg/mL in lean (BMI < 25), overweight (BMI of 25-29.9), and obese (BMI \geq 30), respectively. In the Dallas Heart Study, multi-variable regression models were adjusted for age, gender, ethnicity, left ventricular mass, hypertension, and end diastolic volume, and the results showed that higher BMI values were associated with lower levels of serum BNP ($p < 0.001$) (40). Also, decreased BNP levels were observed in obese patients who had stable or acute CHF (41, 42).

5. Conclusions

BNP level increases in cirrhotic patients, and they are correlated with both the severity of liver cirrhosis and the morpho-functional cardiac changes. BNP level tends to be lower in fatty liver patients than in normal subjects, and they are insignificantly correlated with the severity of their fatty liver disease. Cardiac morphofunctional changes that occur in fatty liver disease patients alter their BNP levels. Given the ever-increasing prevalence of liver cirrhosis and fatty liver disease worldwide, it is important to understand the benefits and limitations of BNP as a heart failure biomarker in hepatic patients, where the relationship between BNP level and myocardial function is complex and is altered by the liver disease.

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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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