The heart matters when the liver shatters! Cirrhotic cardiomyopathy: frequency, comparison, and correlation with severity of disease

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Abstract

Introduction: Cirrhotic cardiomyopathy is a visor complication among patients with cirrhosis of the liver, manifesting during stress, exertion, transjuglar intrahepatic portosystemic shunt (TIPS), or liver transplantation. Cirrhotic cardiomyopathy is reported to be most common cause of post transplant mortality after rejection of 7% to 21%.

Aim: To determine the frequency of cirrhotic cardiomyopathy and was further designed to compare parameters of cardiac dysfunction in patients with or without cirrhotic cardiomyopathy.

Material and methods: All confirmed cases of cirrhosis with various aetiologies were enrolled. Resting ejection fraction (EF) was determined in all patients. Patients were grouped with resting EF < 55% (suspected cardiomyopathy) or > 55% (without cardiomyopathy). Stress echocardiography with dobutamine infusion in both groups yielded an increase of less than 10% in left ventricular (LV) EF at peak dobutamine infusion confirming systolic dysfunction. The diastolic dysfunction (E/A ratio), electrocardiographic parameter (prolong QT interval), and cardiac biomarker (NT-proBNP) were also determined in both the groups to confirm cirrhotic cardiomyopathy.

Results: Among 89 patients with cirrhosis, 35 (39.32%) had cirrhotic cardiomyopathy. All components of cirrhotic cardiomyopathy, like systolic dysfunction, diastolic dysfunction, prolong QT interval, and cardiac biomarkers, were found to be statistically significant (p = 0.001) when compared with patients without cardiomyopathy. Cirrhotic cardiomyopathy parameters were positively correlated with advancing liver disease.

Conclusions: Cirrhotic cardiomyopathy is a frequent but unmasked complication in cirrhosis of the liver. All components of cardiac dysfunction, such as systolic, diastolic, and electrocardiographic changes, are present in patients with cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is positively correlated to severity of liver disease.

Introduction

Hyperdynamic circulatory response in cirrhosis of the liver was described more than half a century ago, where impaired thiamine metabolism or endogenous vasodilators were implicated for increased cardiac output [1]. Earlier studies revealed circulatory and cardiac dysfunction among cirrhotics predominantly due to peripheral vasodilatation [2]. There is now considerable substantiation that hyperdynamic syndrome in cirrhosis of the liver is because of deranged liver function and portal hypertension [3, 4]. In cirrhosis of the liver, circulating blood volume is redistributed to splanchnic circulation, resulting in significant hypovolaemia, which consequently activates the sympathetic nervous system [5]. This additionally aggravates the hyperdynamic circulation and thus cardiac strain.

The term "cirrhotic cardiomyopathy" emerged on the basis of experimental and clinical studies denoting impaired myocardial contractility as well as electrophysiological abnormalities in cirrhosis [6]. Cirrhotic cardiomyopathy is defined as chronic cardiac dysfunction, characterised by blunted contractile responsiveness to stress, altered diastolic relaxation, with electrophysiological abnormalities (QT interval prolongation) in the absence of any other cardiac disease [7].

The exact prevalence of cirrhotic cardiomyopathy is unknown; recent studies have shown its frequency to be 3% to 23.4% [8, 9]. Therefore, the natural history of the disease is not well known. The condition remains asymptomatic and well tolerated for months to years. The response to treatment and prognosis of cirrhotic cardiomyopathy is vague. Cirrhotic cardiomyopathy is unmasked (ventricular insufficiency) when complications like upper GI haemorrhage and SBP cause haemodynamic changes in peripheral and splanchnic circulation. Cirrhotic cardiomyopathy has been reportedly the most common cause of post transplant mortality after rejection with 7% to 21% mortality [10].

The diastolic dysfunction in cirrhotic cardiomyopathy can be assessed with Doppler echocardiography (decreased E/A ratio, delayed relaxation time) [11]. Masked cardiac systolic dysfunction in cirrhotics can be assessed by dobutamine stress echocardiography [11]. Electrophysiological abnormalities (prolongation of the QT interval) and serum cardiac biomarkers like proBNP are important diagnostic parameters for cirrhotic cardiomyopathy [12, 13].

Pakistan has a high burden of liver cirrhosis with advance disease Child Turcott Pugh (CTP) stage B and C [14, 15]. Patients with cirrhosis of the liver have a higher rate of complications and an overall increased mortality. Upper gastrointestinal haemorrhage, spontaneous bacterial infection, and repeated paracentesis in cases of refractory ascites are important inciting events in these patients for unmasking cardiac dysfunction (cirrhotic cardiomyopathy). The published data on cirrhotic cardiomyopathy in Pakistan is mostly based on either the systolic dysfunction or ECG parameters in cirrhotic patients [16, 17]. This particular study accentuate on current consensus defining criteria of cirrhotic cardiomyopathy as proposed by world congress of Gastroenterology (Montreal proposal) [13] where systolic, diastolic, electrocardiographic and serum cardiac biomarker all were determined.

Aim

The objectives of the study were: 1) to determine the frequency of cirrhotic cardiomyopathy and to compare parameters of cardiac dysfunction in patients with and without cirrhotic cardiomyopathy; 2) relate the severity of liver cirrhosis with parameters of cirrhotic cardiomyopathy.

Material and methods

Institutional Ethics Committee approval was sought before commencing the study. It was a hospital based, prospective, analytical study performed on patients with the diagnosis of cirrhosis of the liver in a medical unit of the civil hospital in Karachi from July 2014 to September 2014. All confirmed cases of cirrhosis with age > 18 years with various aetiologies were included except alcoholic cirrhosis and haemochromatosis because these two conditions can have dilated cardiomyopathy as a consistent feature. Patients with known hypertension, cardiac, endocrine, and renal disease were excluded. Patients with recent haemorrhage within 1–2 months, haemoglobin < 7 g/dl, serum creatinine > 1.5 mg/dl, and using drugs that might prolong QT interval were also excluded.

Study protocol

Cirrhosis of the liver

Cirrhosis of the liver was diagnosed on clinical, biochemical, radiological (trans-abdominal ultrasound or computerised tomography had to demonstrate a small shrunken liver with or without splenomegaly and intra-abdominal varices), and histopathological grounds, wherever required [15]. Severity of cirrhosis was determined in accordance to CTP stages CTP-A, CTP-B, and CTP-C.

Cirrhotic cardiomyopathy

As there are no definitive criteria for diagnosis of cirrhotic cardiomyopathy it was diagnosed in accordance with the Montreal proposal at the World Congress of Gastroenterology consensus definition [13]. According to this study, cirrhotic cardiomyopathy was confirmed on the following:

Systolic dysfunction

Resting ejection fraction (EF < 55%), blunted increase in cardiac output with dobutamine stress echocardiography, where blunted response is defined as < 10% increase in resting EF [18].

Diastolic dysfunction

Diastolic dysfunction is labelled through echocardiographic estimation of ventricular relaxation: atrial contraction (E/A ratio), diastolic dysfunction is graded according to E/A ratio (E/A ratio < 1.0, may be reversed to > 2 in case of severe diastolic dysfunction) [19]. Deceleration time (DT) and intra ventricular relaxation time (IVRT) as other parameters for diastolic dysfunction were also determined. Diastolic dysfunction was labelled when DT > 200 ms and IVRT > 80 ms [13].

Supportive criteria

Cardiac biomarker, NT pro basic natriuretic peptide (NT-proBNP level > 144 pg/ml) and corrected prolonged QT interval (QT_C > 440 ms) on ECG were two supportive criteria used in this study to confirm cirrhotic cardiomyopathy.

N Terminal prohormone brain natriuretic hormone (NT-proBNP)

The increased pro-BNP level, determined via Elecsys NT-proBNP assay (Roche diagnostics, Mannheim, Germany). The cut-off level for cirrhotic cardiomyopathy was > 144 pg/ml [20].

Corrected QT interval (QT_c interval)

QT_C Interval was calculated through online QT_C calculator [21] where Bazetts formula $QT_C = QT/\sqrt{RR}$ was used for correction. QT_C interval ≥ 440 ms is considered abnormal QT_C.

Resting EF was determined in all cirrhotic patients. Patients with resting EF < 55% were suspected of having cirrhotic cardiomyopathy whereas patients with resting EF > 55% were considered otherwise. Stress echocardiography was carried out in both groups, and rise in resting EF of not more than 10% confirmed cardiomyopathy. The other group, with resting EF rise > 10% after stress echocardiography, was labelled as without cirrhotic cardiomyopathy. The diastolic dysfunctions (E/A ratio), electrocardiographic parameter (prolong QT interval), and cardiac biomarker (NT-proBNP) were also determined in both the groups. These parameters further confirm cirrhotic cardiomyopathy.

Resting echocardiography

Three-dimensional colour Doppler echocardiography was done in all patients with cirrhosis in accordance with the protocol of the American Society of Echocardiography [22]. The resting ejection fraction and E/A ratio were estimated. Diastolic dysfunction was graded in accordance with the E/A ratio.

Stress echocardiography

All patients underwent stress echocardiogram with graded dobutamine infusion starting at 5 µg/kg/min increasing at 3-minute intervals to a maximum of 40 µg/kg/min, in accordance with guidelines for stress echocardiography given by the American Society of Echocardiography [23], and ejection fraction was estimated at peak infusion. The blunted systolic response was labelled if the increase in resting EF was < 10%.

Statistical analysis

The data of the study were entered into Statistical Packages for the Social Sciences (SPSS) version 15.0 (SPSS Inc, Chicago, IL, USA) for statistical analysis. For continuous variables the means and standard deviations were calculated, while percentages and proportions were used for discrete variables. For comparing parametric and non-parametric data of patients the Student *t* test and χ^2 test were applied where *p*-values < 0.05 were considered as statistically significant.

Results

Out of total 89 patients of cirrhosis 35 (39.32%) patients had cirrhotic cardiomyopathy while 59.55% had no evidence of cardiomyopathy. Overall mean age of patients with cirrhosis was 51.49 ±12.42 years. Patients with cirrhotic cardiomyopathy had a mean age of 53.71 ±8.95 years while patients without cirrhotic cardiomyopathy had a mean age of 49.57 ±14.09 years. Most of the patients with cirrhosis were male 50 (56.17%) while 39 (43.82%) were females. The further gender distribution in both groups with and without cirrhotic cardiomyopathy is given in Table I.

The most common cause of cirrhosis was chronic hepatitis C in 53 (59.55%) patients and hepatitis B in 31 (34.83%) patients, followed by autoimmune in three patients (3.37%), and Wilson disease in 2 (2.24%) patients. The distribution of causes of cirrhosis in both the groups with and without cardiomyopathy is given in Table I. Most of the patients in this study had advanced liver diseases, with 43 (48.31%) patients in CTP-B and 29 (32.58%) patients in CTP-C category. The severity of liver disease CTP stages in both cardiomyopathy and without cardiomyopathy group are also highlighted in Table I.

Systolic dysfunction

Out of 89 patients of liver cirrhosis 35 (39.32%) had resting EF (%) < 55 while in 54 (59.55%) it was > 55. The mean resting EF of each group according to CTP stage of liver disease is highlighted in Table II. Resting EF when compared in each group remained statistically insignificant. Stress EF was determined in both groups in accordance with CTP staging of cirrhosis. In patients with suspected cardiomyopathy resting EF < 55 was increased after dobutamine infusion (stress EF) to 57.95 ±0.31% in CTP-A, 57.04 ±0.40% in CTP-B, and 55.78 ±0.56% in CTP-C. The stress EF failed to rise > 10% from their resting value in this group, which confirms systolic dysfunction. In patients without suspected cardiomyopathy, where resting EF was > 55% after dobutamine infusion, EF was increased to 62.46 ±0.51% in CTP-A, 60.55 ±0.49% in CTP-B, and 57.17 ±0.77% in CTP-C. The stress EF increased to > 10% from their resting value ruled out underlying systolic dysfunction in these patients. Stress EF values in the cirrhotic cardiomyopathy group, when compared with the non-cirrhotic group in accordance with severity of liver diseases, have a statistically significant *p*-value of 0.001, as shown in Table II.

Table I. Demographic profile of patients with and without cirrhotic cardiomyopathy

Variables	Total (n = 89)	Patients with cirrhotic cardiomyopathy (n = 35)	Patients without cirrhotic cardiomyopathy (n = 54)	P-value
Age	51.22 ±12.49	53.71 ±8.95	49.57 ±14.09	
Gender:				
Male	50 (56.17%)	19 (54.28%)	31 (57.40%)	0.77
Female	39 (43.82%)	16 (45.71%)	23 (42.59%)	0.77
Aetiology:				
HCV	53 (59.55%)	20 (37.73%)	33 (62.26%)	0.82
HBV	31 (34.83%)	12 (38.70%)	19 (61.29%)	0.1
Autoimmune	3 (3.37%)	2 (66.66%)	1 (33.33%)	0.55
Wilsons	2 (2.24%)	1 (50%)	1 (50%)	1.00
Severity of cirrhosis:				
CTP-A	17 (19.10%)	4 (11.42%)	13 (24.07%)	0.17
CTP-B	29 (32.58%)	11 (31.42%)	18 (33.33%)	1.00
CTP-C	43 (48.31%)	20 (57.14%)	23 (49.59%)	0.04

Diastolic dysfunction

The diastolic dysfunction E/A ratios were determined on echocardiography in patients with and without cardiomyopathy. In patients with cardiomyopathy, diastolic dysfunction E/A ratio in accordance to severity of liver disease was 0.915 ±0.02 in CTP-A, 0.87 ±0.03 in CTP-B, and 1.775 ±0.25 in CTP-C. Diastolic dysfunction increases with severity of liver disease. In patients without cardiomyopathy the E/A ratios were 1.24 ±0.01 in CTP-A, 1.29 ±0.01 in CTP-B, and 1.32 ±0.21 in CTP-C. Diastolic dysfunction was compared in both groups in accordance with severity of liver diseases and had a statistically significant p-value of 0.001, as shown in Table II. In patients with cardiomyopathy, diastolic dysfunction deceleration times (DT) in accordance with severity of liver disease were 226.84 ±11.72 ms CTP-A, 76.755 ±14.95 ms in CTP-B, and 70.23 ±4.54 ms in CTP-C. Diastolic dysfunction DT increases with severity of liver disease. In patients without cardiomyopathy DT were 169.21 ±26.27 ms in CTP-A, 85.57 ±3.80 ms in CTP-B, and 135.80 ±17.94 ms in CTP-C. Diastolic dysfunction DT, compared in both groups in accordance with severity of liver diseases, has a statistically significant p-value, as shown in Table II. In patients with cardiomyopathy, diastolic dysfunction intra ventricular relaxation times (IVRT) in accordance with severity of liver disease were 114.87 ±9.59 ms in CTP-A, 90.99 ±3.68 ms in CTP-B, and 84.75 ±5.63 ms in CTP-C. Diastolic dysfunction intra ventricular relaxation time (IVRT) increases with severity of liver disease. In patients without cardiomyopathy IVRT were 85.85 ±13.17 ms in CTP-A, 85.57 ±3.80 ms in CTP-B, and 76.25 ±10.01 ms in CTP-C. Diastolic dysfunction IVRT was compared in both groups in accordance with severity of liver diseases and was shown to have a statistically significant p-value, as shown in Table II.

Electrocardiographic changes

The corrected QT interval (QT_c) was determined through ECG in patients with cardiomyopathy and without cardiomyopathy. In patients with cardiomyopathy, corrected QT intervals in accordance with severity of liver disease were 482.17 ±1.639 ms in CTP-A, 530.09 ±1.92 ms in CTP-B, and 590.75 ±1.86 ms in CTP-C. The prolongation of QT interval increases with severity of liver disease. In patients without cardiomyopathy corrected QT intervals were 400.23 ±0.66 ms in CTP-A, 416.11 ±0.50 ms in CTP-B, and 435.66 ±1.07 ms in CTP-C. QT_c interval was compared in both groups in accordance with severity of liver diseases and was shown to have a statistically significant p-value of 0.001, as shown in Table II.

NT pro brain natriuretic peptide (NT-proBNP)

The cardiac biomarker NT-proBNP level was determined in patients with cardiomyopathy and without cardiomyopathy. In patients with cardiomyopathy, NT-proBNP level in accordance with severity of liver dis-

Table II. Comparison of cardiac dysfunctions in patients with and without cirrhotic cardiomyopathy

Parameters of cirrhotic cardiomyopathy	Patients with resting EF < 55% (suspected cirrhotic cardiomyopathy) *n* = 35		Patients with resting EF > 55% (suspected without cirrhotic cardiomyopathy) *n* = 54		*P*-value
Systolic:					
Resting EF %:					
CTP-A	4 (11.42%)	54.55 ±0.58	13 (24.07%)	55.33 ±0.88	0.65
CTP-B	11 (31.42%)	53.72 ±0.26	18 (33.33%)	55.93 ±0.44	0.16
CTP-C	20 (57.14%)	53.33 ±0.67	23 (49.59%)	56.31 ±0.36	0.91
Stress EF (> 10% increase after dobutamine infusion):					
CTP-A	4 (11.42%)	57.95 ±0.31	13 (24.07%)	62.46 ±0.51	< 0.001
CTP-B	11 (31.42%)	57.04 ±0.40	18 (33.33%)	60.55 ±0.49	< 0.001
CTP-C	20 (57.14%)	55.78 ±0.56	23 (49.59%)	57.17 ±0.77	< 0.001
Diastolic:					
E/A ratio:					
CTP-A	4 (11.42%)	0.915 ±0.02	13 (24.07%)	1.24 ±0.01	< 0.001
CTP-B	11 (31.42%)	0.87 ±0.03	18 (33.33%)	1.29 ±0.01	< 0.001
CTP-C	20 (57.14%)	1.775 ±0.25	23 (49.59%)	1.32 ±0.21	< 0.001
Deceleration time:					
CTP-A	4 (11.42%)	226.84 ±11.72	13 (24.07%)	169.21 ±26.27	< 0.001
CTP-B	11 (31.42%)	76.755 ±14.95	18 (33.33%)	85.57 ±3.80	0.023
CTP-C	20 (57.14%)	70.23 ±4.54	23 (49.59%)	135.80 ±17.94	< 0.001
Isovolumetric relaxation time (IVNRT):					
CTP-A	4 (11.42%)	114.87 ±9.59	13 (24.07%)	85.85 ±13.17	0.001
CTP-B	11 (31.42%)	90.99 ±3.68	18 (33.33%)	85.57 ±3.80	< 0.001
CTP-C	20 (57.14%)	84.75 ±5.63	23 (49.59%)	76.25 ±10.01	0.003
ECG changes QT_c interval:					
CTP-A	4 (11.42%)	482.17 ±1.639	13 (24.07%)	400.23 ±0.66	< 0.001
CTP-B	11 (31.42%)	530.09 ±1.92	18 (33.33%)	416.11 ±0.50	< 0.001
CTP-C	20 (57.14%)	590.75 ±1.86	23 (49.59%)	435.66 ±1.07	< 0.001
NT-proBNP level [pg/ml]:					
CTP-A	4 (11.42%)	151.5 ±4.50	13 (24.07%)	103.23 ±3.65	< 0.001
CTP-B	11 (31.42%)	1781.0 ±4.30	18 (33.33%)	118.27 ±2.63	< 0.001
CTP-C	20 (57.14%)	188.36 ±6.15	23 (49.59%)	136.08 ±3.14	< 0.001

ease was 151.5 ±4.50 pg/ml in CTP-A, 1781.0 ±4.30 pg/ml in CTP-B, and 188.36 ±6.15 pg/ml in CTP-C. The NT-proBNP level increases with severity of liver disease. In patients without cardiomyopathy NT-proBNP level was 103.23 ±3.65 pg/ml in CTP-A, 118.27 ±2.63 pg/ml in CTP-B, and 136.08 ±3.14 pg/ml in CTP-C. NT-proBNP levels were compared in both groups in accordance with severity of liver diseases and were shown to have a statistically significant *p*-value of 0.001, as shown in Table II.

Table III. Correlation of parameters of cirrhotic cardiomyopathy with severity of liver cirrhosis

Parameters of cirrhotic cardiomyopathy	Severity of liver disease in accordance to Child-Pugh staging						χ^2/ANOVA statistic	*P*-value
	CTP-A		CTP-B		CTP-C			
	n	%	*n*	%	*n*	%		
Increase in 10% EF after stress echocardiography:								
Yes	13	40.6	18	56.2	1	3.1		
No	4	7.0	11	19.3	42	73.7	41.825	< 0.001
Diastolic dysfunction E/A ratio:								
< 1	4	25.0	11	68.8	1	6.2		
> 1	13	17.8	18	24.7	42	57.5	15.330	< 0.001
Corrected QT interval [ms]:								
< 440	13	27.1	19	39.6	16	33.3		
> 440	4	9.8	10	24.4	27	69.5	9.882	0.007
Ejection fraction at rest (%)	54.38 ±0.81		53.85 ±0.39		53.32 ±0.53		23.994	< 0.001
Ejection fraction after stress echocardiography (%)	61.45 ±2.06		59.22 ±1.79		56.52 ±0.97		71.326	< 0.001
NT-proBNP level [pg/ml]	114.59 ±21.43		134.83 ±21.79		160.56 ±26.85		24.397	< 0.001

CTP – Child-Turcotte-Pugh, EF – ejection fraction, NT-proBNP – N terminal pro brain natriuretic peptide.

Association between various parameters of cardiomyopathy with severity of liver disease

The association between various parameters of cardiomyopathy with severity of liver disease was determined in all patients. All parameters, including resting EF, stress EF, increase in > 10% EF after pharmacologic stimuli, and cardiac biomarker (NT-proBNP), showed significant association with severity of liver disease except corrected QT interval, as shown in Table III.

Comparison of cardiac dysfunction

Various components of cardiac dysfunction in cirrhotic cardiomyopathy were compared with patients without cardiomyopathy. Resting EF in the group with cardiomyopathy and without cardiomyopathy remained statistically insignificant ($p = 0.255$), as shown in Table IV. Increase in resting EF > 10% after stress was found to be statistically significant in patients with cardiomyopathy when compared with patients without cardiomyopathy ($p \leq 0.001$), as depicted in Table IV. Diastolic dysfunction E/A ratio was found to be statistically significant in the cardiomyopathy group when compared to patients in the group without cardiomyopathy ($p \leq 0.001$), as shown in Table IV. Prolongation of QTc interval was found to be significant in the cardiomyopathy group when compared to patients in the group without cardiomyopathy ($p \leq 0.001$), as illustrated in Table IV. Elevation of cardiac biomarker NT-proBNP was found to be statistically significant in the cardiomyopathy group when compared to patients in the group without cardiomyopathy ($p \leq 0.001$), as shown in Table IV.

Discussion

Most patients with cirrhosis are complicated by ascites, volume overload, and signs of hyperdynamic circulation. They have normal resting echocardiographic parameters, but abnormal cardiac responses during stress, exertion, TIPS, or liver transplantation, consistent with cirrhotic cardiomyopathy [24]. In this study the frequency of cirrhotic cardiomyopathy was 39.32%. An earlier local study [25] showed a slightly higher frequency (44%) of cirrhotic cardiomyopathy in comparison to our study. The higher frequency of cirrhotic cardiomyopathy in the above-mentioned study is possibly due to its small sample size. In an the above-mentioned study cirrhotic cardiomyopathy was not confirmed on stress echocardiography. Recent studies [8, 9] showed the frequency of cirrhotic cardiomyopathy ranging from 3–23%, which is slightly lower than seen in this study.

The most common cause of cirrhosis found was chronic hepatitis C and hepatitis B. The frequency of chronic viral hepatitis correlates to their prevalence in Pakistan and Asia, where 60–70% of cirrhotics are

Table IV. Comparison of cardiac parameters in patients with and without cardiomyopathy

Parameters	Cirrhotic cardiomyopathy				χ^2/*t*-test statistic	*P*-value
	Yes		No			
	Frequency	Percentage	Frequency	Percentage		
Child-Pugh staging:						
Child Pugh A	4	23.5	13	76.5	2.732	0.255
Child Pugh B	11	37.9	18	62.1		
Child Pugh C	20	46.5	23	53.5		
Increase in 10% EF after stress echocardiography:						
Yes	0	0	32	100.0	32.38	< 0.001
No	35	61.4	22	38.6		
E/A ratio:						
< 1	15	93.8	1	6.2	24.21	< 0.001
> 1	20	27.4	53	72.6		
Corrected QT interval [ms]:						
< 440	1	2.1	47	97.9	60.56	< 0.001
> 440	34	82.9	7	17.1		
Ejection fraction at rest (%)	53.59 ±0.68		53.76 ±0.6871		–1.161	0.249
NT-proBNP	176.03 ±15.82		122.24 ±13.65		17.04	< 0.001

anti-HCV positive [26–29]. The high prevalence of chronic hepatitis C is further endorsed by recent studies that have shown that 50% cases of hepatocellular carcinoma in Pakistan are anti-HCV positive [30]. Pakistan is in the intermediate HBV prevalence area with a carrier rate of 3–4% [31], also emphasising that HBV is an important cause of cirrhosis of the liver [32]. The majority of the patients in this study had advanced cirrhosis of the liver: 43 (48.31%) patients in CTP-B and 29 (32.58%) patients in CTP-C the category, which is similar to former studies [32–34]. An earlier study [33] contrasted to our study and showed less advanced chronic liver disease (CTP-C – 15% and CTP-B – 35%). More severe disease in this study as compared to western studies is probably due to an ineffective health care system, lack of education, poverty, and false beliefs about the disease.

Systolic dysfunction was discovered to be an important component of the cirrhotic cardiomyopathy of this study. Resting EF < 55% was present in 39.32% of patients, while 59.55% patients had EF > 55%. On stress echocardiography patients with < 55% EF (suspected cardiomyopathy) failed to show an increase > 10% in resting EF, which confirms systolic dysfunction. Patients with resting EF > 55% showed an increase of > 10% in their resting EF on stress echocardiography, which ruled out systolic dysfunction in this group. An earlier local study of cirrhotics showed systolic dysfunction of 33.8% in their patients, although systolic dysfunction was not confirmed on stress echocardiography, but it was assessed just on the basis of resting EF (< 55% or > 55%) [25].

A recent study on Korean patients with cirrhosis of the liver showed 25.5% systolic dysfunction on stress echocardiography [35]. The above-mentioned study used the same criteria for systolic dysfunction on stress echocardiography as in this study. Systolic dysfunction tends to increase with severity of liver disease (in accordance to Child-Pugh staging) in this study. An earlier study also demonstrated worsening of systolic functions with increasing severity of liver disease [25]. Recent clinical and experimental studies are also congruent with this study and show the correlation between the extent of cirrhotic cardiomyopathy and the severity of liver disease [36, 37].

Diastolic dysfunction is considered to be present in almost all patients with cirrhotic cardiomyopathy; it may be diagnosed with simple echocardiographic diastolic dysfunction indices such as the E/A ratio even

at rest. The E/A ratio has been proposed recently as a predictive marker for survival after TIPS [38, 39]. In this study diastolic dysfunction (based on E/A ratio) was found in patients with cirrhotic cardiomyopathy and remains statistically significant when compared with patients without cirrhotic cardiomyopathy ($p < 0.001$). Diastolic dysfunction increases with severity of liver disease in this study. A previous local study also showed diastolic dysfunction in patients with cirrhotic cardiomyopathy and gave a positive correlation between the cirrhotic cardiomyopathy with severity of liver disease [25]. Valeriano *et al.* also showed diastolic dysfunction within patients having cirrhotic cardiomyopathy when compared with healthy controls [40].

The limitation of the above study is its comparison with healthy controls not within the subgroups of cirrhosis itself. Although some diastolic alterations may precede systolic disturbances, both types of dysfunction may develop simultaneously in cirrhotic patients. Diastolic dysfunction has also been reported in non-cirrhotic portal hypertension and in patients with ascites but without cardiac hypertrophy [40]. Diastolic dysfunctions may improve after paracentesis and albumin infusion [41]. In this study other parameters of diastolic dysfunction, like DT and IVRT, were also determined and were found to be impaired in patients with cirrhotic cardiomyopathy. Earlier studies have also shown impaired DT and IVRT in patients with cirrhotic cardiomyopathy, which is congruent with this study [42, 43].

Independent to the cause of cirrhosis, multiple electrical abnormalities (QT-interval abnormalities, electrical and mechanical dyssynchrony, and chronotropic incompetence) have been recognised, which is related to autonomic dysfunction. Patients with cirrhosis have prolongation of the QT interval (> 0.44 s) even with mild increments in portal pressure [44]. It has been suggested that both delayed repolarisation of cardiomyocytes (K^+ channel abnormalities) and sympathoadrenergic hyperactivity may contribute to QT-interval prolongation [45]. QT interval was prolonged in this study in patients with cirrhotic cardiomyopathy. Prolongation of QT interval was found to be statistically significant ($p = 0.001$) when compared to patients without cardiomyopathy.

An earlier local study [25] also showed prolongation of QT interval in patients with cirrhotic cardiomyopathy. In this study prolongation of QT interval was correlated with severity of liver disease as maximum prolongation was noted in CTP-C. Genovesi *et al.* [46] in their study also found prolongation of QT interval in cirrhosis of the liver and having positive correlation with severity of cirrhosis, as in this study. However, the above study also showed a significant relationship between prolonged QT interval and hepatic venous pressure gradient. Previous studies were also in agreement with this study because they have shown prolongation of QT interval and its correlation with severity of liver disease [47–49].

Recently, considerable attention has been paid to the cardiac biomarkers: BNP and its pro-hormone NT-proBNP, which are released by heart ventricles in response to massive stretching of muscle cells, or to mild cardiac damage [50, 51]. Furthermore, recent studies showed that elevated serum levels of NT-proBNP are found in patients with cirrhosis of viral aetiology [52, 53]. The relation of NT-proBNP with the severity of liver disease and cardiac dysfunction made it a useful marker for cirrhotic cardiomyopathy [54].

In this study NT-proBNP level was elevated in patients with cardiomyopathy, and, when compared with patients without cirrhotic cardiomyopathy, was found to be statistically significant ($p = 0.001$). NT-proBNP level had a positive correlation with severity of liver disease. An earlier local study also showed increased levels of NT-proBNP in cirrhotic cardiomyopathy with positive correlation with severity of liver disease [25]. Cavaşi *et al.* have also shown the positive correlation of NT-proBNP with advancing stage of cirrhosis, which is congruent to this study [55]. A study by Radvan *et al.* reported a significant correlation between serum BNP levels and MELD scores [56]. Kim *et al.* in their study have shown that elevated BNP in patients with end-stage liver disease may reflect increased pulmonary arterial pressure, and predicts post-transplant mortality [57]. In conclusion, serum BNP level is correlated significantly with the stage of cirrhosis, hepatocellular failure, and portal hypertension. Therefore, serum BNP level can be used as a valuable parameter in predicting the prognosis of, and monitoring the response to, therapy in cirrhotic cardiomyopathy.

Conclusions

Cirrhotic cardiomyopathy is a frequent but hidden complication in patients with cirrhosis of the liver. All components of cardiac dysfunction like systolic, diastolic, and electrocardiographic changes are present in patients with cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy has a positive correlation with severity of liver disease**.**

Conflict of interest

The authors declare no conflict of interest.

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