*Original Article*

# Frequency of cirrhotic cardiomyopathy in patients with cirrhosis of liver: A tertiary care hospital experience

*Samiullah Shaikh[1], Mukhtiar Abro[2], Iftikhar Qazi[3], Akbar Yousfani[4]*

**ABSTRACT**

***Objective:*** To determine the frequency of cirrhotic cardiomyopathy in patients with liver cirrhosis.

***Methodology:*** This Descriptive case series study was conducted in Medical Department of Liaquat University Hospital Jamshoro / Hyderabad from 3rd January 2009 to 16th June 2009.This study included 74 consecutive cases of cirrhosis of liver of either sex above 14 years of age. Firstly, resting ECG was done in all the patients. QTc values were calculated from lead II. QTc interval of >0.44 sec were considered as prolonged. Systolic dysfunction was assessed by ejection fraction (value of >55% was considered as increased). Diastolic dysfunction manifested by reduced E/A ratio (<1 was considered as decreased). Thirdly, all patients had determination of proBNP levels. The presence of cirrhotic cardiomyopathy was confirmed by abnormal ECG or echocardiography, along with proBNP abnormalities. Statistical package for social sciences (SPSS™) version 16 was used for data processing purpose. Means ±Standard Deviation of age and pro BNP levels were calculated. Frequency and percentage were computed for cirrhotic cardiomyopathy in cirrhosis patients.

***Results:*** A total of 74 patients were selected for this study, out of which 41 (55.41%) were male and 33 (44.59%) were female. The mean age was 46.2 years (± 10.8 SD). Out of 74 patients 9 (12.2%) belonged to child Pugh A, 29(39.2%) to child-Pugh B and 36(48.6%) in child-Pugh C. Elevated pro BNP was present in 42(56.8%) cases, E/A ratio < 1 in 15 (20.3%) cases, prolong QT interval (>0.44sec) in 16 (21.6%), Ejection fraction (EF) > 0. 55 was present in 25 (33.8%) patients. Cirrhotic cardiomyopathy was present in 33(44.6%) cases. A strong relation was found between cardiomyopathy and severity of cirrhosis of liver (p=0.001), pr0-Bnp levels (p=0.003), QTc > 44 sec (0.004), Ejection fraction > 55% (0.004) and E/A ratio < 1 (p=0.005).

***Conclusion:*** Cirrhotic cardiomyopathy was present in a sizeable proportion of cirrhotic patients, more so in the later stages of cirrhosis of liver.

**KEY WORDS:** Cirrhosis, Cardiomyopathy, ECG, Echocardiography, proBNP.

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Correspondence:

Dr. Samiullah Shaikh,
H.No:55, Green Homes,
Qasimabad, Hyderabad, Pakistan.
E-mail: shaikhsamiullah@yahoo.com
samiullahshkh7@gmail.com

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## INTRODUCTION

Cirrhotic cardiomyopathy is a pathological condition defined as "a chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalitie in the absence of known cardiac disease".[1] Liver cirrhosis is associated with several cardiovascular disturbances. Patients with cirrhosis

of liver have normal systolic function at rest. As the cirrhosis advances a hyperdynamic circulation characterized by tachycardia, high ejection fraction, and increased cardiac output develops. This systolic dysfunction is unmasked when the patient is put under physical or pharmacological stress.[2] In bacterial infection such as spontaneous bacterial peritonitis where a high cardiac output is required, systolic incompetence becomes evident.[3] The evidence of inability to mount a sufficient cardiac output is further strengthened when patient develops hepato-renal syndrome as a result of reduced cardiac output.[4] The cardiac systolic function is suppressed by negative inotropic cytokines such as TNF-a and interleukin-1b produced by infection leading to the development of Hepato-renal syndrome.[5]

It has also been observed that Diminished health-related quality of life (HRQoL) and fatigue have been reported in patients with cirrhosis. The presence of cirrhotic cardiomyopathy and the attendant poor cardiac response to physical stress may affect HRQoL and contribute to fatigue in these patients.[6] NT-proBNP also plays important role in development of cardiac dysfunction in patients with cirrhosis of liver. One of the study concluded that plasma NT-proBNP levels were high in cirrhotic patients and are likely to be related to the severity of disease. Advanced cirrhosis is associated with advanced cardiac dysfunction, and NT-proBNP levels have predictive value for concomitant cardiac dysfunction and cirrhosis progression.[6] In addition to increased plasma level of NT proBNP echocardiographic abnormalities were also noticed in cirrhotic patients.[7] Garcia-Tsao G. studied morphological echocardiographic parameters in a heterogeneous group of 60 cirrhotic without cardiovascular or pulmonary disease. Enlarged left ventricle (20% of cases) associated with enlarged atrium (15% of cases), enlarged right ventricle (23.3% of cases), left ventricular hypertrophy (10% of cases) and signs of pulmonary hypertension (6.7% of cases) were the most common changes encountered. These were assumed to be due to the hemodynamic changes described in cirrhosis and were related to the decompensation of the liver function and not to the etiology of liver disease, hepatic activity without decompensation, or age.[8]

The objective of the above study was to determine the frequency of cirrhotic cardiomyopathy in patients with liver cirrhosis visiting a tertiary care teaching hospital.

## METHODOLOGY

This descriptive case series study included 74 consecutive patients admitted in Medical department Liaquat University Hospital Jamshoro and Hyderabad from 3rd January 2009 to 16th June 2009. The patients were admitted from outdoor or causality departments. Confirmed cases of cirrhosis (by clinical, biochemical, radiological and prior biopsy as described earlier) of either sex above 14 years of age were selected. Patients with prior history of myocardial infarction, valvular heart disease, conduction abnormalities, cardiac failure, hypertension, electrolyte imbalance H/O drug intake such as calcium channel blockers, antiarrhythmics and digoxin were excluded.

All patients fulfilling above criteria were selected for study. Informed consent was obtained from all patients (or next of kin in case patient was unconscious). Patient's biodata regarding age, gender, weight, grade of cirrhosis were entered in a proforma. Blood test for liver functions test, prothrombin time, Protein profile, ultrasound of abdomen was done from Liaquat University Hospital Laboratory.

Cirrhosis was labeled on the basis of: [9]

a. Clinical (reduced liver span <8 cm on clinical exam with ascites and splenomegaly)
b. Biochemical (prolonged prothrombin time >12 seconds and reduced level of serum albumin <3.5 g/dl)
c. Radiological (increased liver echo pattern, shrunken liver <8cm in mid-clavicle line, portal vein diameter >1.3 cm and spleen size >13 cm longitudinally) and confirmed on biopsy (presence of widespread fibrosis, obliteration of central vein and regenerating nodules).

Firstly, resting ECG was done (in Medical Unit by certified ECG technician who has at least 5 year experience of taking ECGs) in all the patients.

***ECG abnormalities:***

a. QTc: QTc values was calculated in all patients by following formula

$$QTc = \frac{QT}{\sqrt{RR}}$$

The value of QTc of > 0.44 sec was considered as prolonged[10]

b. Heart Rate: was calculated via following formula

HR = RR / 1500

Presence of both prolonged QTc and heart rate >100[10] was labeled as 'abnormal ECG' and 'positive cardiomyopathy'. Secondly, echocardiographic examination was done (by a consultant cardiologist who had at least 10-year experience of

echocardiography and who did not knew the primary diagnosis of cirrhosis at Echocardiography room), which included two dimension echo and color flow Doppler study. Systolic dysfunction was assessed ejection fraction (value of >55% was considered as increased).[11] Diastolic dysfunction manifested by reduced mitral E/A ratio (<1 was considered as decreased).[12]

Pro B type Natriuretic Peptide (pro BNP): The increased pro-BNP level, determined via Elecsys NT-proBNP assay (Roche diagnostics, Mannheim–Germany), was labeled as 'positive cardiomyopathy'. The cut-off level for males was e"93-pg/ml and the cut-off level for females was e"144-pg/ml.[13]

Cirrhotic cardiomyopathy: cirrhotic cardiomyopathy was diagnosed if evidence of either systolic or diastolic dysfunction, together with supporting criteria such as electrophysiological abnormalities or abnormal serum markers was present.[14]

***Statistical procedure:*** Continuous variables such as age and QTc interval (sec), pro-BNP and E/A ratio was expressed as mean with standard deviation. Categorical variables such as sex, Child-Pugh Class, Elevated pro BNP Increased, E/A ratio, prolong QT interval, Ejection fraction (EF), presence or absence of cirrhotic cardiomyopathy were expressed as frequency and percentage. Chi-square test was applied for comparing categorical variables such as Child-Pugh Class, pro BNP, E/A ratio less than 1 or equal to or more than 1, QT interval less than 0.44 Sec or equal to or more than 0.44sec and Ejection fraction (EF) less than 55% or equal to or more than 55% with cirrhotic cardiomyopathy. A p-value < 0.05 was considered as statistically significant. All calculations were done using SPSS version 16 (Chicago, IL, USA).

## RESULTS

A total of 74 patients were selected for this study, out of which 41 (55.41%) were male and 33 (44.59%) were female. The mean age was 46.2 years (± 10.8 SD), QTc interval 0. 3778 ± 0.05 sec, pro-BNP 182.97 ±45.31 and E/A ratio 0.976±0.0637. Out of 74 patients 9 (12.2%) belonged to child Pugh A, 29(39.2%) to child-Pugh B and 36(48.6%) in child-Pugh C. Elevated pro BNP was present in 42(56.8%) cases, E/A ratio less than 1 in 15 (20.3%) cases, prolong QT interval (>0.44sec) in 16 (21.6%), Ejection fraction (EF) > 0. 55 was present in 25 (33.8%) patients. On the basis of mentioned criteria cirrhotic cardiomyopathy was present in 33 (44.6%) cases. Table-I shows the baseline characteristics of patients studied. A strong relation was found between cardiomyopathy and severity of cirrhosis of liver (p=0.001), pr0-Bnp levels (p=0.003), QTc equal to or more than 44 sec (p=0.004), Ejection fraction equal to or more than 55% (p=0.004) and E/A ratio less than 1 (p=0.005) as shown in Table-II.

## DISCUSSION

In this study presence of cirrhotic cardiomyopathy was directly proportional with the severity of cirrhosis associated with electrophysiological, echocardiographic and biochemical changes. Bernardi M et al observed that frequency of cirrhotic cardiomyopathy increased from 25% in child-Pugh

Table-I: Baseline Characteristics of Patients.

| *Continuous Variables* | *Mean* | *±SD* |
|---|---|---|
| Age(years) | 46.2 | 10.8 |
| QTc interval (normal 0.30 to0.44sec) | 0. 3778 | 0.05 sec |
| pro-BNP (pg/mL) (normal males: <93pg/ml, females: <143 pg/ml) | 182.97 | 45.31 |
| E/A ratio (normal <1) | 0.976 | 0.0637 |
| *Categorical Variables* | *Frequency* | *Percentage* |
| *Gender* | | |
| Male | 41 | 55.41 |
| Female | 33 | 44.59 |
| Child-Pugh Class | | |
| Class A | 09 | 12.2 |
| Class B | 29 | 39.2 |
| Class C | 36 | 48.6 |
| pro BNP | | |
| Increased | 42 | 56.8 |
| Normal | 32 | 43.2 |
| E/A ratio | | |
| < 1 | 15 | 20.3 |
| >1 | 59 | 79.7 |
| QT interval | | |
| >0.44sec | 16 | 21.6 |
| < 0.44 Sec | 58 | 78.4 |
| Ejection fraction (EF) | | |
| >55% | 25 | 33.8 |
| < 55 % | 49 | 66.2 |
| cirrhotic cardiomyopathy | | |
| present | 33 | 44.6 |
| Absent | 41 | 55.4 |

Table-II: Relationship between Cirrhotic cardiomyopathy and severity of cirrhosis of liver, pr0 BNP levels, QTc, Ejection fraction & E/A ratio.

| *Variables* | *P-Value* |
|---|---|
| Severity of cirrhosis | 0.021 |
| pr0-Bnp levels | 0.003 |
| QTc >44 sec | 0.004 |
| Ejection fraction >55% | 0.004 |
| E/A ratio | 0.005 |

class A to 51% in class B and up to 60% in child-Pugh class C associated with prolong QT-intervel.[15] Yildiz R also observed a proportional increase in the frequency of cirrhotic cardiomyopathy according to the severity of cirrhosis of liver with increase in pro-BNP.[16] The agreed components of this disorder include three phenomena: electrophysiological changes, echocardiographic abnormalities and the fluctuation of levels of Natriuretic peptides.[17] This study focused on these three components.

The electrophysiological abnormalities included prolonged repolarization, which manifests itself in the form of prolonged QT interval.[18] In this study 21.62% of the patients had prolonged QTc interval. This finding is very much identical with prior study done on electrophysiological abnormalities by Zuberi et al in 2006.[19] That study showed QTc interval prolongation in 19.2% of cirrhotic patients. However Wong [in 2009] disputes such values and reports QTc interval abnormalities at a staggering 45% in cirrhotic subjects and further elaborates that QT prolongation is present in only 5% of the general population which is a significant finding. This means that the patients who have QT interval prolongation are much more susceptible to polymorphic ventricular tachyarrhythmias than normal controls.[20]

The echocardiographic abnormalities present in these patients were classified into two types: systolic dysfunction and diastolic dysfunction.[16] In this study two dimensional echo with color flow Doppler ultrasound technique (via the transthoracic approach) was utilized to evaluate for these abnormalities.

Systolic dysfunction was presumed to be present when ejection fraction was >55% at rest. Classically other studies like Baik et al[21] focused on stress inducing environments during echocardiography, whereas this study focused on echo abnormalities at rest (because stressing these patients require highly controlled environments which were not feasible in the setup at which the author practices medicine).

Diastolic dysfunction was represented by reversed E/A ratio. In this study 6.76% patients exhibited these abnormalities. Pozi et al[22] suggested that around 50% of patients had E/A ratio reversal at rest, especially when they had ascites in addition to cirrhosis. Moller and Henriksen suggest that if ascites is drained then significant improvement is witnessed in E/A ratio, which doesn't convert to that of a normal person but improves significantly.[23] A similar Indian study further emphasized that diastolic dysfunction was present in majority of patients suffering from cirrhosis.[24] The most significant abnormality noted in this (author's) study was that huge proportion of patients showed elevated levels of proBNP (56.8%). As majority of study subjects were having decompensated cirrhosis [Child Class B and C] and the mean proBNP in Child Class A cirrhosis was 241, whereas in Child Class B and C cirrhosis it was 585. The same finding is reported by Henriksen et al that the patients who had ascites had much higher average levels of proBNP than those cirrhotic who were ascites free.[23] There used to be a misconception that these elevated levels of proBNP represented some twisted form of alcoholic cardiomyopathy and that terming it cirrhotic cardiomyopathy was a gross misnomer. To evaluate this issue further Woo JJ found [25] that the levels of proBNP rose markedly in patients with Child Pugh Turcot class C than Child Pugh Turcot classes A, B. However, the importance of proBNP in detection and diagnosis of cirrhotic cardiomyopathy is still not fully clarified yet.

## CONCLUSIONS

This study demonstrates that cirrhotic cardiomyopathy is a common occurrence. There is a direct relationship of cirrhotic cardiomyopathy with the severity of liver disease whereas electrophysiological, echocardiographic and biochemical changes provide base for the condition.

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### *Authors Contribution:*

***Samiullah Shaikh*** conceived, designed and did statistical analysis & editing of manuscript.
***Samiullah Shaikh, Mukhtiar Abro, Iftikhar Qazi and Akbar Yousfani*** did data collection and manuscript writing. ***Mukhtiar Abro*** did review and final approval of manuscript.

Authors:

1. Samiullah Shaikh, FCPS,
   Assistant Professor,
2. Mukhtiar Abro,
   Postgraduate Student (FCPS II),
3. Iftikhar Qazi,
   Postgraduate Student (FCPS II),
4. Akbar Yousfani, MD,
   Assistant Professor,

1-4: Department of Medicine,
Liaquat University of Medical & Health Sciences,
Jamshoro, Hyderabad, Pakistan.