

# Echocardiographic study of left ventricular structure and functions in patients with chronic liver disease and its correlation to disease severity

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## ABSTRACT

**Background:** The concept of cirrhotic cardiomyopathy includes impaired cardiac contractility, decreased beta-adrenergic receptor function, abnormal beta-adrenergic post-receptor function, defective excitation-contraction coupling, and cardiac conduction abnormalities. The aim of our study is to assess the cardiac dysfunctions in patients of cirrhosis of liver, irrespective of etiology, and establish correlation between severity of disease and incidence of cardiomyopathy.

**Methods:** This was a cross-sectional, observational study of patients with CLD without any known cardiac disease attending the medical outpatient and inpatient department of the tertiary care center. Selected patients after informed consent were investigated further along with M-mode and Doppler echocardiographic studies to determine the cardiac structure and systolic and diastolic cardiac functions.

**Results:** A total of 60 subjects were enrolled for the study. Maximum cases of this study, that is, 70% patients were in the age group of 40–60 years with the mean age of  $51.82 \pm 6.48$  years and male: female ratio of 3.1:1. Prolongation of QTc is observed in 35% of the study group. Diastolic dysfunction (E/A <1.0) was found in 43.33% of cases, varying from 60% in model for end-stage liver disease Group III to 41.6% in Group I and 39.5% in Group II, showing a positive correlation between severity of cirrhosis and E/A ratio. The left ventricular mass index in subject showed its proportional increase in relation to degree of severity of cirrhosis.

**Conclusion:** We demonstrated an increase in cardiac dysfunction, especially diastolic in the subjects and its significant associations with the severity of disease.

**Key words:** Cardiomyopathy, chronic liver disease, cirrhotic cardiomyopathy, CLD, diastolic dysfunctions

## INTRODUCTION

Chronic liver disease is a common disease in India as well as in western country mostly caused by alcoholism, viral hepatitis, and malnutrition. The clinical picture of patients with cirrhosis is dominated by the classical complications such as ascites, bleeding from esophageal varices, portal hypertension, and encephalopathy.<sup>[1]</sup> Liver cirrhosis is a systemic disease with widespread functional consequences affecting almost any other organ including the cardiovascular system. Cardiovascular abnormalities also have been reported by several investigators. Cirrhotic cardiomyopathy is the term used to describe a collection of characters expressive of abnormal heart structure and function in patients with cirrhosis.<sup>[2]</sup> Many studies indicated that some level of diastolic dysfunction exists in most patients with cirrhosis.

Cirrhotic patients have hyperdynamic circulation with decreased peripheral vascular resistance, increased cardiac output and stroke volume, and low systemic arterial pressure. The level of circulating vasoactive substances which are not inactivated

by the liver is increased such as vasoactive intestinal peptide, glucagon, and tumor necrosis factor- $\alpha$ , prostacyclin, nitric oxide, endothelin-1, and endothelin-3. These circulatory changes in cirrhosis are responsible for diastolic dysfunctions.<sup>[3]</sup> Most studies on the impact of CLD on cardiac structure and function have emanated from developed countries.

The aim of our study is to assess cardiac dysfunctions in patients of cirrhosis of liver, irrespective of etiology, and establish correlation between severity of disease and incidence of cardiomyopathy.

## MATERIALS AND METHODS

It is a cross-sectional and observational study done on 60 patients admitted to two tertiary care centers, Rajendra Institute of Medical Sciences, Ranchi and Indira Gandhi Institute of Medical Sciences, Patna. Patients were selected from outpatient department and inpatient department of medicine of the hospital as per inclusion and exclusion criteria after informed consent.

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### Inclusion Criteria

The following criteria are included in the study:

1. Age group >18 years and
2. Patients with clinical features, laboratory tests, and imaging suggestive liver cirrhosis.

### Exclusion Criteria

The following criteria are excluded from the study:

1. Patients suspected of liver malignancy.
2. Patients of ischemic heart disease, valvular heart disease, conduction defects, cardiac arrhythmias, and congenital heart disease.
3. Known cases of diabetes and hypertension.
4. Patient with hepatic encephalopathy.
5. Patients having congenital corrected QT (QTc) interval prolongation.

After inclusion in the study, patients were subjected to following minimum investigations:

1. Complete blood count.
2. Serum bilirubin/ALT/aspartate transaminase.
3. Prothrombin time (PT) with international normalized ratio (INR).
4. Blood urea nitrogen/serum creatinine/serum electrolytes.
5. Ultrasonography.
6. 12-lead electrocardiogram was done to calculate QT interval manually and QT<sub>c</sub> using Bazett's formula as  $QT_c = QT \text{ INTERVAL} / \sqrt{T \text{ INTERVAL}}$ . Prolonged QT interval was defined as value > 440 ms (0.44 s).
7. 2D Echo was done by Philips HD (7× E) with adult probe and was used to assess cardiac anomaly with special reference to the left atrial diameters, left ventricle end diastolic volume, I.V. septal thickness, and left ventricular posterior wall thickness and to assess E/A ratio where E stands for early maximum left ventricular filling velocity and A for late diastolic left ventricle filling velocity; the left ventricle systolic function was calculated using ejection fraction (EF%) and diastolic function was assessed by E/A and if ratio was <1, it was taken as diastolic dysfunction. The left ventricular mass was calculated by ASE-cube formula:

$$L\text{t. ventricle mass (g)} = 0.8 \{1.04 [([left ventricle end diastolic diameter [LVEDd] + IVSd + PWs]^3 - LVEDd^3)] + 0.6$$

[LVEDd = (mm), Pwd = for posterior left ventricular wall thickness at end diastole (mm), IVSd = for septal wall thickness at end diastole (mm), 1.04 = specific gravity of the myocardium (g/cm<sup>3</sup>).]

Normal left ventricular mass in males is <170 g, and in females, it is <160 g.

Patients grading for cirrhosis was done by model for end-stage liver disease (MELD) criteria as follows:

$$MELD = 3.78 [\text{Ln Serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57 [\text{Ln serum creatinine (mg/dL)}] + 6.43$$

MELD Scoring:

- Stage I - MELD Score < 9.
- Stage II - MELD Score 10–19.
- Stage III - MELD Score >20.

### Statistical Analysis

All data generated were entered into a standard pro forma. Continuous variables were summarized as mean and standard deviation while nominal/categorical variables as proportions (%). ANOVA was used for analysis of continuous variables, whereas Chi-square test was used for nominal/categorical variables. *P* < 0.05 was taken as statistically significant. Microsoft Word and Excel were used to generate graphs, tables, and derivation.

The study was approved by institutional scientific and ethics committee.

### RESULTS AND OBSERVATIONS

In our study, most of the patients, that is, 70% (42/60) were in the age group of 40–60 years, followed by 16.6% (10/60) in 60–80 years and 13.33% (8/60) were in 18–40 years of age with the mean age of 51.82 ± 6.48 years. 38 of 60 were males (63.33%) and 12 (36.67%) were females [Figure 1].

Categorization of the patient according to the MELD classification shown in Figure 2 where around 64% (38/60) of cases belong to MELD Group II followed by 20% in Group I and 16% in Group III.

### Biochemical Profile

Mean serum bilirubin in MELD Group I was 1.41 ± 0.13 mg/dl, 2.62 ± 0.40 mg/dL in MELD Group II, and 6.86 ± 1.87 mg/dl in

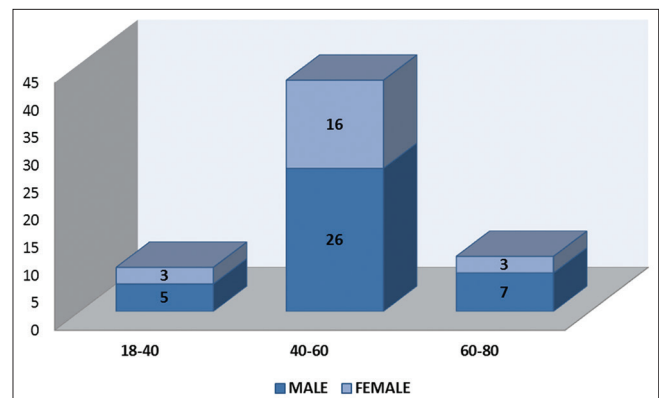


Figure 1: Composite distribution of age and sex in study group

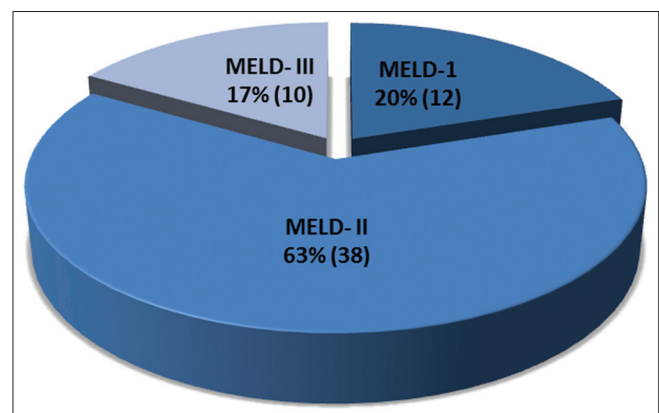


Figure 2: Distribution of patient among model for end-stage liver disease groups

**Table 1: Comparison of S. bilirubin and S. creatinine in MELD groups**

MELD group	Number of cases	Mean S. bilirubin±SD	Mean S. creatinine±SD	Significance (ANOVA)
I	12	1.41±0.13	0.92±0.14	P < 0.001
II	38	2.62±0.40	1.38±0.18	
III	10	6.86±1.87	1.86±0.28	

SD: Standard deviation, MELD: Model for end-stage liver disease

**TABLE 2: Mean QTc interval value among MELD group**

MELD group	Number of cases	Mean±SD (QTc interval)	Significance
I	12	418.68±14.61	P value < 0.001
II	38	434.21±10.30	
III	10	454.61±12.64	

SD: Standard deviation, MELD: Model for end-stage liver disease

MELD Group III. Hence, bilirubin level is increasing with increase in MELD grading of the disease.

Mean serum creatinine level in MELD Group I was  $0.92 \pm 0.14$  mg/dL, in MELD Group II, it is  $1.38 \pm 0.18$  mg/dL, and in MELD Group III, it is  $1.86 \pm 0.28$  mg/dL. Both parameters in different groups showed a significant difference in each MELD group ( $P < 0.05$ ) [Table 1].

In the entire study group, the PT was prolonged with a mean value of  $27.04 \pm 2.05$  along with INR ( $2.18 \pm 0.53$ ) being raised in almost all patients except two patients in MELD Group I.

### Cardiac Parameters

Prolongation of QTc is observed in 35% (21/60) of cases. It is 60% (6/10) in Group III, 34.2% (13/38) in Group II, and 16.66% (2/12) in Group I of MELD score, suggesting thereby that there is a positive correlation between degree of cirrhosis and prevalence of prolonged QTc. The findings of mean QTc interval MELD Group III ( $454.61 \pm 21.65$  ms) were significantly higher ( $P < 0.05$ ) in comparison to mean QTc interval in MELD Group I ( $418.68 \pm 14.61$  s) and MELD Group II ( $434.21 \pm 10.30$  ms) [Table 2].

Diastolic dysfunction (E/A < 1.0) was found in 43.33% (26/60) of patients in the present study, varying from 60% (6/10) in MELD Group III to 41.6% (5/12) in MELD Group I and 39.5% (15/38) in MELD Group II showing a positive correlation between severity of cirrhosis and E/A ratio which is a hallmark of ventricular dysfunction ( $P < 0.05$ ) [Table 3].

Mean left atrial diameter in MELD Group II ( $37.12 \pm 3.60$  mm) and Group III ( $38.11 \pm 3.12$  mm) was higher than MELD Group I ( $33.18 \pm 1.18$ ).

Mean left ventricular end diastolic diameter was  $48.26 \pm 5.56$  mm in MELD Group I,  $50.52 \pm 3.82$  mm in MELD Group II, and  $53.34 \pm 4.12$  mm in MELD Group III depicting that higher is the degree of MELD score, poor is the left ventricular diastolic function ( $P < 0.05$ ).

Similar significant association of interventricular septal wall thickness with disease severity was observed. Their higher values were present in MELD Group III ( $9.46 \pm 2.14$  mm) than in MELD Group I ( $8.27 \pm 1.10$  mm) and MELD Group II ( $8.76 \pm 1.81$  mm).

## DISCUSSION

Diastolic dysfunction is a complex process that arises from numerous interrelated contributing factors such as pressure variations in the ventricle, cardiac preload and afterload, and ventricular relaxation and compliance. The increased circulating blood volume found in patient with cirrhosis, led to a high cardiac preload, and decreased peripheral vascular resistance with low cardiac afterload. The alteration in the diastolic function is likely due to an impaired ventricular relaxation.<sup>[4]</sup>

Maximum cases of this study, that is, 70% patients were in the age group of 40–60 years with the mean age of  $51.82 \pm 6.48$  years and male: female ratio of 3.1:1. Genovesi showed in their study that most of the patients were >45 years of age (86.1%), with the majority being in the 45–60 years age group which is very similar to our study.<sup>[5]</sup> Sidmal *et al.* and Patil *et al.* also showed similar age group and sex distribution in their study done on patient with cirrhosis.<sup>[1,6]</sup>

In this study, prolongation of QTc is observed in 35% of study group. QTc prolongation was seen in 38.33% patients of cirrhosis studied by Patil *et al.*<sup>[6]</sup> Similarly, Kosar *et al.* demonstrated QTc prolongation in 32% in study population.<sup>[7]</sup> All these study showed the frequency of prolonged QTc similar to our study. Furthermore, Li *et al.* demonstrated QTc prolongation in a similar study in 46.93% of patients which is slightly higher than our study.<sup>[8]</sup>

Diastolic dysfunctions (E/A < 1.0) were noted in 48.33% of patients by Patil *et al.*, varying from 70% in MELD Group III and 50% (10/20) in MELD Group I which is comparable to our study.<sup>[6]</sup> Similar study conducted by Achechar and Gonzalez-Tallon, in 2011, showed that 50% of cirrhotic patients had left ventricular diastolic dysfunction.<sup>[9]</sup> The prevalence of diastolic dysfunction was 51% in a study conducted by Salari, in 2013.<sup>[10]</sup>

The left ventricular mass index as calculated by the left ventricular mass/body surface area ( $m^2$ ), and it was  $81.320 \pm 14.48$  g/ $m^2$  in MELD Group I and  $118.40 \pm 14.78$  g/ $m^2$  in MELD Group III, therefore, showing a proportional increase in the left ventricular mass index in relation to degree of severity of cirrhosis. Patil *et al.* showed significant correlation between the left ventricular mass index and disease severity in their study and their results are comparable to results in our study<sup>[5]</sup>. Similar results were also demonstrated in the study by Silvestre *et al.*<sup>[11]</sup>

In a study performed by Fu-Rong Sun *et al.*, in 2011, of 82 patients, MELD score was positively correlated with enlarged left atrial diameter, increased interventricular septum thickness (IVST). This association between enlarged left atrial diameter and IVST with disease severity (MELD score) was also significant in our study.<sup>[12]</sup>

**Table 3: Diastolic dysfunction among study group**

MELD group	Total number of cases	Cases with E/A<1.0
I	12	5
II	38	15
III	10	6
Total	60	26

MELD: Model for end-stage liver disease

## CONCLUSION

Cardiac dysfunction is a common complication of advanced cirrhosis that can make a variety of disturbances including diastolic dysfunction. Duration of disease, increased age, and severity of cirrhosis can increase the severity of diastolic dysfunction. Due to high prevalence of diastolic dysfunction in cirrhotic patients and risk of decompensation following invasive procedures, it could be suggested that all patients would be screened routinely by echocardiography before invasive procedures.<sup>[13]</sup>

Early detection of systolic/diastolic myocardial dysfunction by 2D Echo and appropriate early treatment of this cirrhosis will delay the onset of cardiac dysfunction associated with the disease. A high alerting social awareness programed to promote alcoholic withdrawal and nutritional supplementary drive to overcome hepatic assault will minimize cirrhosis and thereby decreasing the incidence of cardiomyopathy and national burden on economy of nation.

In our study, diastolic and other cardiac dysfunctions are significantly associated with severity of disease.

However, there are currently no specific guidelines for the diagnosis and treatment of cardiovascular disease in this patient population. Thus, new prospective studies are needed to identify more specific criteria and standardized procedure for cardiovascular assessment and treatment of cardiac dysfunction in patients with liver cirrhosis.

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