

Original Research Article

Study of cardiac manifestations in patients with chronic liver disease

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ABSTRACT

Background: Chronic liver disease is a common cause of mortality and morbidity worldwide. This has pathological effects on various systems in the body including cardiovascular system which usually is unnoticed. In majority of cases of chronic liver disease, cardiovascular complications develop as a subclinical condition which manifests only during stressful situations. Hence early detection of cirrhotic cardiomyopathy by echocardiography and 2D-ECHO studies in all patients of chronic liver disease helps in reducing the morbidity and mortality.

Methods: 100 cases of chronic liver disease were included in the study. Data was collected through a prepared proforma. All patients were subjected to cardiac evaluation by ECG and Echocardiography. Serum pro-BNP levels were done for selected patients. Severity of the liver disease was assessed by using Child-Pugh score. Cardiac abnormalities were noted and correlated with the severity of the liver disease.

Results: Out of 100 patients studied, 83% were males. 80% of the patients had history of alcoholism. 59% of the patients had abnormal ECG finding. 40% of them had QT prolongation and was related to the severity of liver disease. 60% of the total patients studied had positive pro-BNP values in patients with significant cardiac dysfunction. 46% of the patients had normal echocardiographic finding; most common abnormal finding was diastolic dysfunction (43%) and positively correlated with severity of liver disease.

Conclusions: In chronic liver disease patient's QT prolongation is the most common ECG abnormality. Most common Echocardiographic finding was diastolic dysfunction which had strong correlation with the severity of the liver disease.

Keywords: Chronic liver disease, Diastolic dysfunction, Pro-BNP, QT prolongation

INTRODUCTION

Chronic liver disease is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis.¹ The causes of cirrhosis are multiple and include congenital, metabolic, inflammatory, and toxic liver diseases.² The most common causes of cirrhosis are chronic alcoholism, chronic hepatitis B and C, biliary diseases and hemochromatosis.³ Regardless of the cause of cirrhosis, the pathologic features consist of the development of fibrosis to the point that there is

architectural distortion with the formation of regenerative nodules.⁴ Patients with cirrhosis are at increased risk of numerous complications and have a decreased life expectancy due to its pathological effects on various systems in the body including cardiovascular system which usually is unnoticed.⁵ The prevalence is reported to be between 40 to 50% in cirrhotic patients independent of liver disease aetiology.⁶

During the course of cirrhosis, there is a progressive deterioration of cardiac function manifested by the disappearance of the hyperdynamic circulation due to a failure in heart function and decreased cardiac output.⁷

Cirrhotic cardiomyopathy is a cardiac condition observed in patients with cirrhosis regardless of the etiologies, and characterized by impaired contractile responsiveness to stress stimuli, and/or impaired diastolic relaxation, and electrophysiological abnormalities with prolonged QT interval, in the absence of other known cardiac disease.⁸⁻¹² This is due to deterioration in inotropic and chronotropic function which takes place in parallel with a diastolic dysfunction and cardiac hypertrophy. In majority of cases of chronic liver disease, cardiovascular complications develop as a subclinical condition which manifests only during stressful situations like TIPS and liver transplantations, which have a poor outcome.¹³

As many as 50% of cirrhotic patients undergoing liver transplantation show signs of cardiac dysfunction, and 7% to 21% of deaths after orthotopic liver transplantation result from overt heart failure.¹⁴ Hence early detection of cirrhotic cardiomyopathy by Echocardiography (ECG) and 2D-ECHO studies in all the patients of chronic liver disease help in reducing the morbidity and mortality.¹⁵

METHODS

This was a cross sectional study conducted on 100 cases in Victoria Hospital and Bowring and Lady Curzon Hospital, Bangalore from November 2015 to May 2017. Patients with Ultrasonographic evidence of chronic liver disease/cirrhosis and admitted or treated as outpatient in Department of Medicine of Bowring and Lady Curzon Hospital and Victoria Hospital, BMCRI, Bangalore were selected for the study.

The sample size is calculated with the following formula:

$$N = \frac{(Z\alpha^2 2 pq)}{d^2}$$

$Z\alpha^2$ at 95% confidence interval = 1.96
 $p = 0.615$, $1-p = q = 0.385$, $d = 0.10$

With 10% absolute precision (α) at 95% confidence interval, sample size (N) is 91. Expecting 10% nonresponse; the final sample size of 100 was taken for the study.

Inclusion criteria

- Patients above the age of 18 years
- Patients with evidence of chronic liver disease of any etiology
- Patients who have given informed written consent for the study

Exclusion criteria

- Patients with prior history suggestive of heart diseases-congenital, ischemic heart diseases, congestive cardiac failure

- Patients with comorbid diseases which can affect on heart like diabetes and hypertension.

Selected patients were thoroughly examined for the signs of liver cell failure and hepatic encephalopathy. Blood pressure measurement and thorough cardiovascular system examination was done. All patients were subjected to laboratory investigations like complete blood profile, liver function tests, renal function tests, PT/INR, aPTT, viral markers like HBsAg, and HCV. pro BNP was done for selected cases. Patients were also subjected to Ultrasound abdomen, ECG and 2D echocardiography. Further the patients were assessed using Child Pugh scoring.

Statistical methods

Descriptive and inferential statistical analysis had been carried out in the present study. Results on continuous measurements were presented on Mean \pm SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5 % level of significance. The following assumptions on data were made,

Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, and cases of the samples should be independent. Analysis of variance (ANOVA) had been used to find the significance of study parameters between three or more groups of patients. Chi-square/ Fisher Exact test had been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher exact test used when cell samples are very small.

Significant figures

- ±Suggestive significance (P value: $0.05 < P < 0.10$)
- * Moderately significant (P value: $0.01 < P \leq 0.05$)
- ** Strongly significant (P value: $P \leq 0.01$)

Statistical software

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel had been used to generate graphs, tables etc.

RESULTS

In this study, 100 patients with chronic liver disease were subjected to cardiac evaluation the correlation with severity of liver disease had been studied. Majority of the patients were in the age group of 41-50 years (88%), with a mean age of 47.22 ± 11.43 years. The study had male dominance which comprised 83% of all total study subjects, 17% of the subjects were females. Majority of the males were in the age group of 41-50 years (33.73%),

whereas the females were in the age group of 31-40 years (58.8%).

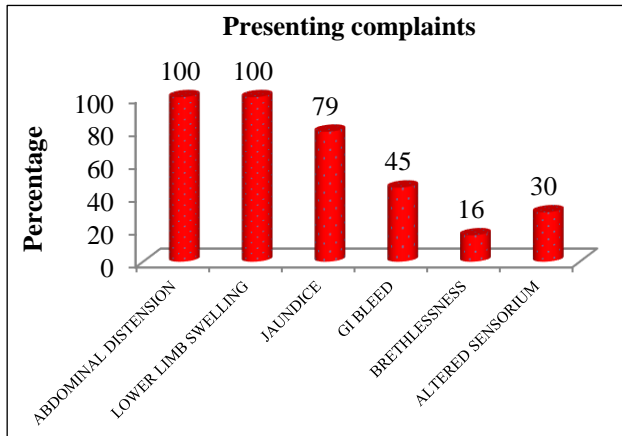


Figure 1: Presenting complaints of patients in our study.

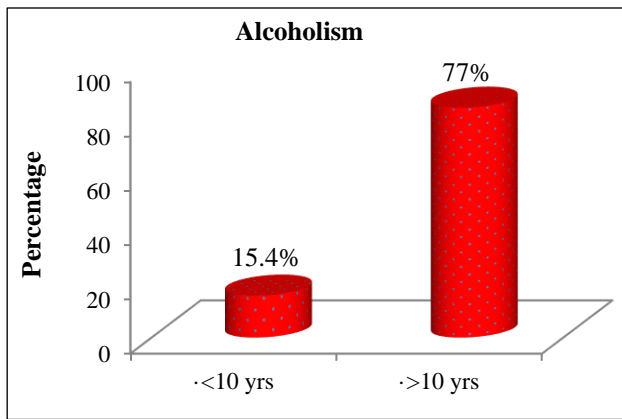


Figure 2: Duration of alcoholism in years.

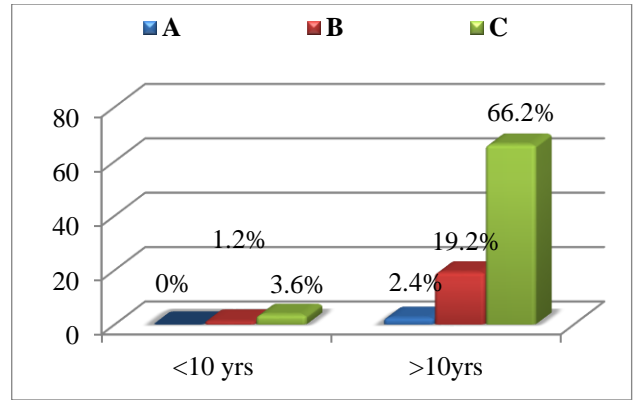


Figure 3: Child Pugh Scoring in male.

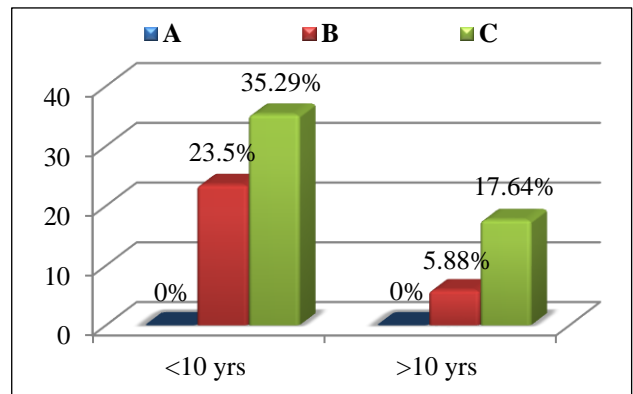


Figure 4: Child Pugh score in females.

Most common presenting complaints of the patients studied were abdominal distension (100%) and lower limb swelling (100%). 79% of the patients had Jaundice, 45% had GI bleeding, 30% of them had altered sensorium, and 16% had breathlessness. (Figure 1).

Table 1: Alcoholism distribution of patients.

Alcoholism	No. of patients (n=100)		%	p value
	Male(n=83)	Female(n=17)		
No	6(7.22)	3(17.64)	9.0	
Yes	77(92.77)	14(82.35)	91.0	
<10 years	3(3.89)	11(78.5)	14.0	
>10 years	74(96.1)	3(21.4)	77.0	<0.00001

Chi-square-119.2, df=2

Table 2: Duration of alcoholism and severity of liver disease.

Duration of alcoholism	Child Pugh Scoring						%
	Male(n=83)			Female(n=17)			
	A	B	C	A	B	C	
< 10 years	0(0%)	1(1.2%)	3(3.6%)	0(0%)	4(23.5%)	6(35.29%)	14%
> 10 years	2(2.4%)	16(19.2%)	55(66.2%)	0(0%)	1(5.88%)	3(17.64%)	77%
Total	2(2.4%)	17(20.4%)	58(69.87%)	0(0%)	5(29.41%)	9(52.94%)	91%

Chi-square=0.126, P value=0.9390, df=2

In this study, 80% of the patients had history of alcoholism as the cause for chronic liver disease, 5% had HBsAg positivity and 1 patient had HCV infection. 11% patients had combined history and 3% of the patients had unknown etiology for chronic liver disease.

Table 3: Pro BNP distribution in patients with chronic liver disease.

Pro BNP (pg/ml)	No. of patients	%
Positive	6	60.0
Negative	4	40.0
Total	10	100.0

Table 4: Correlation of Pro-BNP with severity of liver disease.

Pro-BNP	Child Pugh Scoring			p value
	Child A	Child B	Child C	
Positive	0(0%)	1(10%)	5(50%)	0.0000001
Negative	2(20%)	1(10%)	1(10%)	

Chi square=44.44, df=2, p value=0.0000001

Table 5: Correlation of Pro-BNP with diastolic dysfunction.

Pro-BNP	Diastolic dysfunction
Positive	100%
Negative	50%

Majority of the females (78%) had history of short duration of alcoholism of <10years, whereas 96.1% of males had duration of alcoholism >10 years. (Table 1)

In this study 71% of the patients were in Child Pugh C. 26% patients were child B and 3% were in child A. 35.29% of the females developed severe liver disease (Child C) within 10 years of alcoholism, whereas most of the males (66.2%) developed severe liver disease (Child C) after 10years of alcoholism. (Table 2).

Table 8: Correlation of severity of liver disease and Echocardiographic manifestations.

Echocardiographic findings	Child Pugh Scoring			Percentage
	A	B	C	
Normal	3(100%)	16(61.53%)	27(38.02%)	46%
Diastolic Dysfunction	0(0%)	9(34.61%)	34(47.88%)	42%
Systolic and Diastolic Dysfunction	0(0%)	0(0%)	8(11.26%)	8%
Pulmonary HTN	0(0%)	1(3.84%)	1(1.40%)	2%
Dilated cardiomyopathy	0(0%)	0(0%)	1(1.40%)	1%
Total	3(100%)	26(100%)	71(100%)	100%

Chi square test, df=4, p=0.001

Out of 100 patients, 34% had QT prolongation. 42.2% of them were in Child Pugh C, 15.38% were in Child Pugh B.

Table 6: Echocardiographic manifestations in chronic liver disease.

ECG	No. of patients (n=100)	%
Normal	41	41.0
Abnormal	59	59.0
RBBB	5	5.0
Sinus tachycardia	20	20.0
QT Prolongation	34	34.0

6 patients of the total 10 patients studied had positive pro-BNP values, majority of the patients with positive pro-BNP values were in Child Pugh class C. All the patients those who had positive pro BNP values had diastolic dysfunction in 2D ECHO studies. (Table 3, Table 4, Table 5)

Out of total 100 patients studied, 59% of them had abnormal ECG findings. QT prolongation was the most common abnormal finding, found in 34% of the total patients. 20% of the patients had sinus tachycardia and 5% of the patients had RBBB (Table 6).

Table 7: Echocardiographic manifestations in chronic liver disease.

2D ECHO manifestations	Total number of patients	Percentage	p value
Normal	46	46%	0.001
Diastolic dysfunction	43	43%	
Systolic and Diastolic dysfunction	8	8%	
Pulmonary HTN	2	2%	
Dilated cardiomyopathy	1	1%	

Chi-square test, df=4, p=0.001

In this study 46% of the patients had a normal echocardiographic finding. The most common abnormal finding was diastolic dysfunction which was found in

43% of the patients. 8% of the patients had systolic and diastolic dysfunction. Pulmonary hypertension was found in 2% of the total patients studied. 1% had dilated cardiomyopathy. (Table 7)

On comparing the duration of alcohol consumption and cardiac dysfunction, author found that 39% of the patients developed diastolic dysfunction following more than 10 years of alcohol consumption whereas only 3% of the patients with diastolic dysfunction had history of alcohol consumption within 10 years.

All of 42% of the chronic liver disease patients had diastolic dysfunction on echocardiography, and 47.88% of them were in Child Pugh C, hence there is a significant correlation between diastolic dysfunction and severity of liver disease (Table 8).

In this study 42% of the chronic liver disease patients had diastolic dysfunction on echocardiography, and 47.88% of them were in Child Pugh C, Hence there is a significant correlation between diastolic dysfunction and severity of liver disease. 8% of the patients had both systolic and diastolic dysfunction.

DISCUSSION

Patients with cirrhosis are at increased risk of numerous complications and have a decreased life expectancy due to its pathological effects on various systems in the body including cardiovascular system which usually is unnoticed.⁵ The prevalence is reported to be between 40 to 50% in cirrhotic patients independent of liver disease aetiology.⁶

Cirrhotic cardiomyopathy is a cardiac condition observed in patients with cirrhosis regardless of the etiologies, and characterized by impaired contractile responsiveness to stress stimuli, and/or impaired diastolic relaxation, and electrophysiological abnormalities with prolonged QT interval, in the absence of other known cardiac disease.⁸⁻¹²

Various types of molecular biomarkers have been studied as markers of LV dysfunction in patients with cirrhosis. Mainly, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) measurements are related to several indexes of systolic and diastolic functions. Cirrhotic patients have demonstrated significantly elevated serum levels of BNP and NT-pro-BNP. These correlate with parameters of cirrhosis severity, abnormal cardiac structure and function.¹⁶ In this study, various cardiac manifestations were identified in chronic liver disease patients irrespective of the etiology and are correlated with the severity of liver disease.

Age distribution

In the present study, mean age of the patients studied was 47.2 years. The highest incidence was found in 41-50

years (33%). In Barbosa M et al, study – Mean age was 54.6 years. In Puneekar, et al, - Majority of cases belong to age group Of 40-49 years.

Sex distribution

Out of 100 patients 83% were males and 17% were females. In Barbosa M et al, study out of 26 patients studied 22 were male (84.6%) and 4 patients (15.4%) were females. In Puneekar, et al, out of 100 cases 72% were male and 28% were females. This study also showed male predominance as other studies.

Etiology of chronic liver disease studied

Most common etiology in this study was Alcohol intake-found in 80% of the patients. Other causes were – viral infections like HBsAg (5%), HCV (3%), and combined causes (11%). In Barbosa M et al, study – Most common etiology was alcohol intake (77%), viral infections (11%) and mixed (11%). In Puneekar, et al, Incidence of alcohol related cirrhosis of liver was found to be present in 57% cases' followed by chronic hepatitis B 20% and others (Cryptogenic, Wilson disease, etc) 18%. This study also showed that alcohol intake is most common and predominant etiology as other studies.

Child Pugh scoring

Out of 100 patients, Majority of the patients (71%) were Child Pugh C. Child Pugh A was the least common (3%). In Barbosa M et al, study Majority were in Child Pugh A (65.4%) and least were in Child Pugh C (3.8%).

In Puneekar, et al, Among the cirrhotics, 43 patients (43%) were in Child Pugh class A, 45 Patients (45%) were in severity class B, 12 patients (12%) were in severity Class C. This study differed from other study because in other studies small sample sizes were taken. Studies with large sample size on this topic are yet to be undertaken.

Pro-BNP levels

In this study out of 100 patients, randomly 10 patients were selected for pro-BNP level estimation. Out of 10 patients 6 patients had significantly positive values (60%); 83% of them were in Child Pugh C and all the patients with positive pro-BNP values had diastolic dysfunction in echocardiography. Since only 10 patients were subjected for pro-BNP estimation, statistical correlation with severity of liver disease could not be done. In Barbosa M et al, study 30.8% of the patients had significantly elevated pro-BNP values, and this did not correlate with severity of liver disease.

This study differed from other study because in this study pro-BNP estimation was done only for selected cases; hence studies with large sample size on this topic are needed.

Electrocardiographic manifestations

The 59% of patients had abnormal ECG findings; QT prolongation was the most common abnormal finding, found in 41% of the patients. And it is significantly correlated with severity of liver disease.

Patients with QT interval prolongation had a statistically significant higher rate of gastro esophageal varices with upper GI bleeding comparing with those without QT interval prolongation.

In Barbosa M et al, study Prolongation of the QTc interval was found in 77% of the patients. No correlation was found between severity of liver disease and QT prolongation, but there was a statistically significant relation between upper GI bleeding and QT prolongation (95.0% vs 50.0%, P = 0.028).

Echocardiographic manifestations

A 42% of the chronic liver disease patients had diastolic dysfunction, 8% of the patients had both systolic and diastolic dysfunction in Echocardiography, and 47.88% of them were in Child Pugh C. Hence there was a significant correlation between diastolic dysfunction and severity of liver disease. 2% of the patients had pulmonary hypertension and 1% had dilated cardiomyopathy.

In Barbosa M et al, study 30.8% patients had diastolic dysfunction, whereas 61.5% had both systolic and diastolic dysfunction. Echocardiographic manifestations were unrelated to the etiology and severity of the liver disease.

In Punekar, et al, out of 100 cases incidence of diastolic dysfunction was found to be more in 32% of cases, pericardial effusion was noted in 22%. Incidence of pulmonary arterial hypertension was 6% and incidence of systolic dysfunction was found in 6%.

Limitations of the study small sample size (100), Special investigation (serum pro-BNP levels) was done only in selected patients. Hence this could not be used for the statistical correlation with severity of liver disease. Alcohol itself has a direct effect on heart, hence the cardiac manifestations in chronic liver disease patients secondary to the direct effect of alcohol cannot be ruled out.

CONCLUSION

Diastolic dysfunction is the most common abnormal cardiac manifestation in patients with chronic liver disease. There is no relationship between the development of cardiac dysfunction and the etiology of chronic liver disease. There is a significant correlation between the severity of chronic liver disease and development of cardiac dysfunction. QT prolongation is

the most common ECG finding in chronic liver disease patients and it is related to the severity of the liver disease. Serum pro-BNP levels were significantly elevated in patients with cirrhosis and it is related with the severity of liver disease. There is significant relationship between upper GI bleeding and QT prolongation.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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