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Cardiac Dysfunction in Patients with Liver Cirrhosis

Niyanta Karki,[1] Sudhamshu KC,[1] Dilip Sharma,[1] Bikash Jaishi,[1] Sandip Khadka[1]

[1]Department of Medicine, Liver Unit, Bir hospital, Kathmandu, Nepal.

ABSTRACT

Background: The clinical picture in cirrhosis is dominated by the classical complications such as ascites, bleeding varices, portal hypertension and encephalopathy. Cardiac dysfunction in patients with cirrhosis, which contributes significantly to the morbidity and, mortality though prevalent, is less studied and not widely recognized entity since it is largely asymptomatic at rest, with overt heart failure seen mainly during pharmacological stress, transjugular intrahepatic portosystemic shunt, liver transplantation.

Methods: It is a cross sectional study done on patients admitted in wards or attending to outpatient department of Liver unit, Bir Hospital, between May 2015 to May 2016. Diagnosis of cirrhosis was based on clinical examination, lab parameters, ultrasound examination, endoscopy and/or liver biopsy. Cirrhotic patients after assessing the exclusion criteria were recruited for the study. Child Pugh and model for end stage liver disease scores were calculated to assess the liver function. Cardiac function was evaluated by resting pulse, mean arterial pressure, electrocardiography, and 2 dimensional echocardiography.

Results: Diastolic dysfunction was seen in 61.9%(48) and was more common in alcoholic group (63.2%Vs 58.6%). Systolic dysfunction was seen in 6.6% of alcoholic patients only. 51.4% had cirrhotic cardiomyopathy according to the criteria (proposed by World congress of gastroenterology in 2005). Prolonged QTc of >0.44 seconds was noted in 79%, mainly in child pugh C, with model for end stage liver disease score >10.

Conclusions: Cardiac dysfunction is prevalent with sizeable number of patients with cirrhosis especially in the form of diastolic dysfunction independent of etiology. QTc prolongation might be an early indicator of cardiac dysfunction and is directly correlated with child pugh and model for end stage liver disease scores.

Keywords: Chronic liver disease; cardiac dysfunction; MELD score; QTc.

INTRODUCTION

The hyperdynamic circulation that is characterized by increased cardiac output and heart rate, and decreased systemic vascular resistance (SVR) with low arterial blood pressure arises as a complication of portal hypertension[1] seen in patients with liver cirrhosis is the main cause leading to cardiac hypertrophy and cardiomyocyte edema.[2] Cardiac dysfunction in cirrhosis is often undetected and widely unrecognized since it remains asymptomatic at rest and convert into overt heart failure when there is physiological and pharmacological stress which can lead to significant morbidity and mortality. Cardiac evaluation which directly influences the prognosis of patients with cirrhosis remains ignored and we aimed to see the prevalence of cardiac dysfunction in cirrhotic patients.

METHODS

It is a hospital based cross sectional study of the patients coming to liver OPD or admitted in the liver ward of National Academy of Medical Sciences, Bir Hospital, Nepal. The cirrhotic patients with or without ascites were enrolled in the study. The study period was from May 2015 to May 2016. All the cirrhotic patients with or without the history of ascites were evaluated for the study. Diagnosis of cirrhosis was based on clinical grounds -stigmata of chronic liver diseases, esophageal/gastric/ectopic varices, impaired liver function tests and ultrasonography of abdomen (coarse parenchyma with features of portal hypertension). Evidence of cardiovascular disease (ischemic Heart Disease, rheumatic heart disease, congenital heart disease, arrhythmias). Hypertension, diabetes mellitus, thyroid

Correspondence: **Dr Niyanta Karki, Department of Medicine, Liver Unit, Bir hospital, Kathmandu, Nepal. Email: niyakb@gmail.com, Phone: +9779841220848.**

disorder, Severe anemia (<6 gm/dl) which can cause hyperdynamic circulation and ultimately to stiffening of the left ventricle and lead to diastolic dysfunction were excluded from the study. Routine blood investigations were done in all patients. Child pugh and model for end stage liver disease (MELD) scores were calculated to assess the liver function. Resting pulse and blood pressure were recorded with calculation of mean arterial pressure. Cardiac function was evaluated by electrocardiography and conventional 2D echocardiography in all patients. ECHO was done by cardiologist with >10 years experience. EF < 50% was considered as systolic dysfunction and normal EF with E/A ratio < 1 was considered as diastolic dysfunction. The presence of cardiac dysfunction in cirrhotic patients in any form either systolic or diastolic dysfunction was only aimed for this study. Thus, grade of diastolic dysfunction was not assessed. QT interval was measured and corrected by applying Bazzet's formula. QTc interval of more than 0.44 seconds was considered to be prolonged and was correlated with type of cardiac dysfunction and severity of liver dysfunction. Sample size was calculated by using N= (Za2) (P) (Q)/d2 where, N=required sample size, Za=Variate corresponding to desired reliability level (1.96 for 95% reliability), P=Estimated proportion in the population, Q=100-P (if P is in % i, e 40%), d=Maximum tolerable error=10% of P. Since prevalence of cardiac dysfunction is estimated to be 40% in cirrhotic patients, the minimum sample size required for this study was calculated to be 92.196. So, 105 patients were made available for the final analysis despite of normal ECG to assess the systolic or diastolic dysfunction. Chi square test and student T-test were used to compare the results of various numerical parameters among the studied patients. ANOVA test was used to see the association of parameters with Child Pugh and MELD scores. Logistic regression analysis (Pearson correlation coefficient) was performed for determining the degree of association between different parameters. All values were expressed as mean ± SD, a 95% confidence interval was taken and P values of <0.05 was considered to be statistically significant.

RESULTS

One hundred and twenty five consecutive patients were enrolled for the study. After applying the exclusion criteria, 105 patients made available for the study and were subjected for the evaluation of cardiac function by different means like electrocardiography, 2D echocardiography.

The age of the patient enrolled in the study was from 24 years - 82 years with mean age being 48.29 years. 70.5% were male and 29.5% were female with M: F ratio of 2.38:1. Total patients were divided into three sub groups on the basis of their age (<40 years, 40-60 years and more than >60 years. Maximum 54.3% fell in age group 40-60 years.

Predominant cause of cirrhosis among the recruited patients was alcohol being 72.4% followed by chronic hepatitis B, cryptogenic, chronic hepatitis B with alcohol being 6.7% each, chronic hepatitis C with alcohol, chronic Budd chiari syndrome being 2.85% each and chronic hepatitis C, choledochal cyst being 1% each.

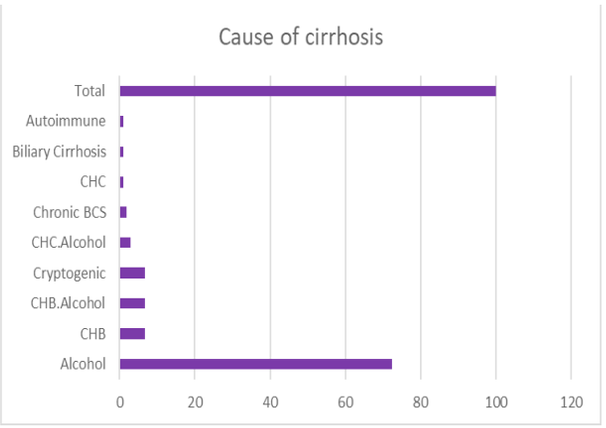

Figure 1.Causes of cirrhosis.

Echocardiographic findings were normal in 33.3%. Systolic dysfunction was seen in 4.8% of patients and diastolic dysfunction was seen in 61.9% of cases (Figure 2).

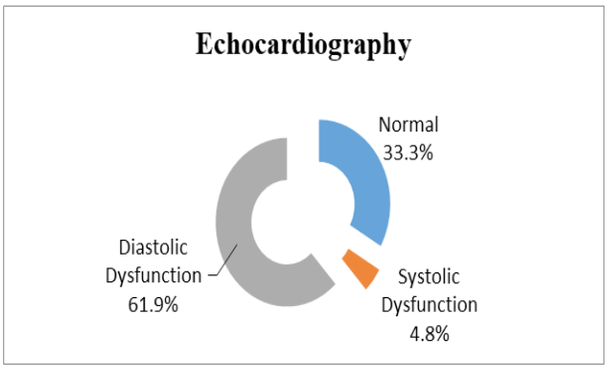

Figure 2. Echocardiographic findings in cirrhosis.

According to the etiology, two groups (one alcoholic and another nonalcoholic) were subdivided and evaluated for cardiac function. Diastolic dysfunction was prevalent in both alcoholic and non-alcoholic group being 63.2% and 58.6% respectively with slightly predominant in the alcoholic group. 6.6% had systolic dysfunction and 30.3% had normal echocardiography showing that cardiac dysfunction more common in alcoholic group with

Table 1.Echocardiographic findings according to etiology.

Etiology	Echocardiography				
	Normal	Systolic Dysfunction	Diastolic Dysfunction	Total	P
Alcoholic	23 (30.3%)	5(6.6%)	48 (63.2%)	76 (100.0%)	0.307
Non alcoholic	12 (41.4%)	0(0%)	17 (58.6%)	29 (100.0%)	
Total	35 (33.3%)	5(4.8%)	65 (61.9%)	105 (100.0%)	

predominant diastolic dysfunction though the P value was not significant. (Table 1)

Cirrhotic cardiomyopathy was seen in 51.4 % according to the criteria (proposed by WCGE in 2005[3] and 44.8% had no cirrhotic cardiomyopathy. 3.8% had dilated cardiomyopathy (Figure3)

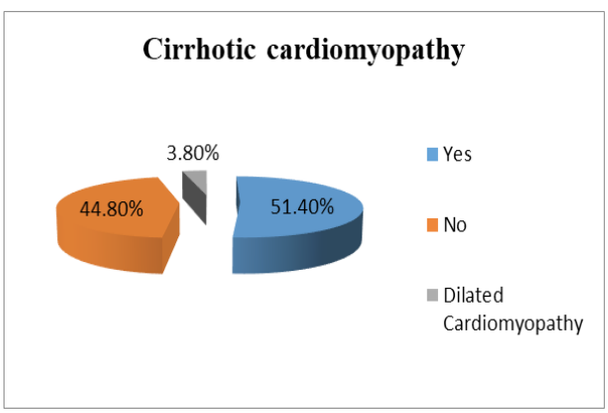

Figure 3. Cirrhotic cardiomyopathy.

Among other cardiac findings, 9.5% had isolated dilated chamber, 4.8% had regurgitant lesions, 2.9% had dilatated chambers and regurgitant leisons , 0.95% had pericardial effusion.

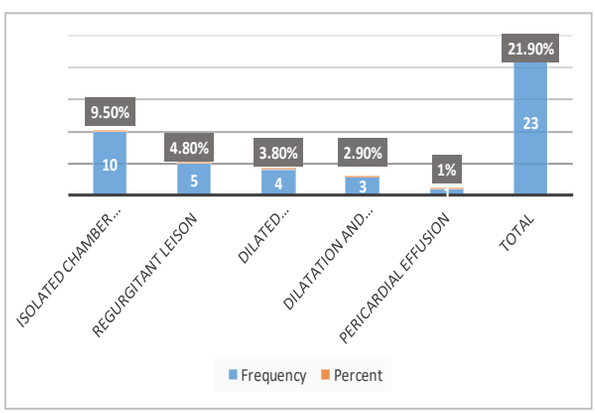

Figure 4. Cardiac findings other than cirrhotic cardiomyopathy.

Resting pulse and BP were assessed in both alcoholic and non-alcoholic group. Resting pulse in alcoholic cirrhosis group ranged from 60-128 beats per minute (BPM) with mean 83.90 BPM whereas resting pulse in non-alcoholic cirrhosis group ranged from 68-88 BPM with mean 78 BPM. Mean MAP in alcoholic cirrhosis group was 86.32 and in non-alcoholic cirrhosis group, it was 81.25mmHg. Both resting pulse and MAP were higher in alcoholic cirrhosis group (Table 2).

Table 2. Comparision of pulse and MAP as per etiology of cirrhosis (Alcoholic Vs Non-alcoholic).

Type of cirrhosis	RP range	Mean RP	MAP range	Mean MAP
Alcoholic cirrhosis	60-128	83.90	65-112	86.32
Nonalcoholic cirrhosis	68-88	78	65-97.5	81.25
P value	0.02		0.632	

QT interval was measured in electrocardiogram and corrected by applying Bazzet's formula. Prolonged QTc of >0.44 seconds was noted in 83 i.e 79% of total patients and <0.44 seconds was seen in 22 i.e 21% of total patients. (Figure 3). QTc was prolonged in 79.04% of total patients. QTc was prolonged mostly in patients with MELD score >10, in group 10-20 about 80.95% 0f total 63 patients and in group >20, about 80.55% of 36 patients. (Table 3) So, more the MELD score, more chance of QTc interval to be prolonged. Likewise, among Child pugh A, B and C, QTc <0.44 secs were seen in 36.4%, 17% and 16.7% respectively and QTc >0.44 secs were seen in 83.3% maximum in child pugh C followed by 83% in Child pugh B and 63.6% in Child pugh A.

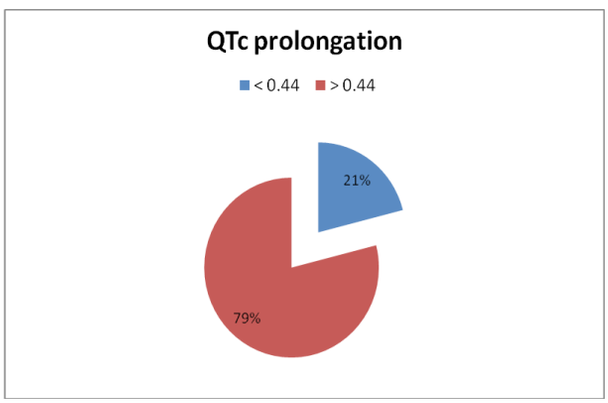

Figure 5. QTc interval in cirrhotic patients.

Table 3: MELD score and QTc interval

MELD score	QTc(<0.44 secs)	QTc(>0.44 secs)	Total	P value
<10	3 (50%)	3 (50%)	6 (100%)	0.264
10-20	12 (19.04%)	51(80.95%)	63 (100%)	
>20	7 (19.44%)	29(80.55%)	36 (100%)	
	22 (20.95%)	83(79.04%)	105 (100%)	

DISSCUSSION

Prominent cardiac dysfunction was the diastolic dysfunction being 63.2% slightly higher in alcoholic group than nonalcoholic group which is similar to the study done by Dadhich S et al which showed that cirrhotic patients with or without ascites has both morphological and functional cardiac dysfunction, left ventricular diastolic dysfunction being 70% and systolic dysfunction is preserved in the absence of renal failure and refractory ascites.[4] In preexistent left ventricular diastolic function, when the left atrial (LA) pressure and/or LV end-diastolic pressure increases, the velocity of the *E* wave increases and that of the *A* wave decreases, which is called 'pseudonormalization' (PN) and is seen with various LV myocardial disorders like Myocardial infarction, structural heart disease.[5] In cirrhosis, myocardial dysfunction was associated with the progression of liver disease. Systolic dysfunction, however, is mostly latent. Reduction in myocardial function becomes overt under conditions of pharmacological or physical stress. Accordingly, clinical symptoms of systolic heart failure may evolve after liver transplantation or a Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement.[6] In contrast to systolic impairment, diastolic dysfunction is a prominent feature of cirrhotic cardiomyopathy like in our study, diastolic dysfunction being 63.2% and systolic dysfunction only 6.6%. The underlying mechanism of diastolic dysfunction in cirrhosis is likely due to the increased myocardial wall stiffness caused by myocardial hypertrophy, fibrosis and sub-endothelial edema, and subsequently resulting in high filling pressures of the left ventricle and atrium. Comparison of the incidence of left ventricular diastolic dysfunction with no prior history of cardiovascular disease to that of the patients with hepatic cirrhosis caused by alcohol abuse was carried out by Brotanek, J. et al which confirmed that the incidence of left ventricular diastolic dysfunction in patients with alcohol-related liver cirrhosis, classified as Child-Pugh grade A and B, was significantly higher than in the controls without any prior liver disease which is also similar to our study.[7] There is limited data regarding the actual prevalence of cirrhotic cardiomyopathy due to the fact that the disease usually remains silent with near normal cardiac function unless the patients are exposed to stress.[8] In most studies thus far performed in cirrhosis, diagnosis of LVDD has been based on E/A ratio<1 using two-dimensional (2D) Doppler echocardiography. However, the E/A ratio is strongly dependent on pre-load.[9] TDI is superior to conventional 2D doppler echocardiography for diagnosing and grading of LVDD. The categorization of patients in three groups according to diastolic function has prognostic relevance. Patients without LVDD had the longest and those with grade 2 LVDD the shortest probability of survival.[10] It has been estimated that as many as 50 % of patients undergoing liver transplantation developed some signs of cardiac dysfunction and about 7–21 % of patients died from heart failure in the post liver transplantation period.[11] The prevalence of cirrhotic cardiomypathy is also similar to our study. A study by Scarlatescu E et al found that QTc interval is frequently prolonged in patients with cirrhosis regardless of etiology of the disease and sex of the patients and which correlates well with the severity of the liver disease.[12] In the study done by Bhatti et al, QTc interval was prolonged in 24.7% of cirrhotic patients with significant increase in frequency with worsening of Child Pugh Grade, thereby indicating an association between QTc prolongation and the severity of cirrhosis[13] consistent with the findings of our study. The age of the patient enrolled in this study ranged from 24 years - 82 years with mean age being 48.29 years. 46.3% fell in 40 – 60 years of age group and maximum. 54.3% fell in age group 40-60 years. The youngest age having cirrhosis in our study was 24 years and the cause was chronic hepatitis B infection. Most of the patients sought consultation once they decompensated. The time period to develop cirrhosis is mainly 10-20 years whatsoever is the underlying cause with rate of decompensation being 5-7%/year depending upon the cause.[14] Considering this time period, age below < 40 years are less likely to decompensate. > 60 years' age group was less because patient at least once hospital visit with features of decompensation in between age 40-60 years. Kowalski et al in their study concluded that patients with end-stage liver disease manifest a hyperdynamic circulation characterized by a decrease in the systemic vascular resistance and arterial pressure, and an increase in the heart rate and cardiac output which include warm skin, spider angioma, palmer erythema, and bounding pulse. These findings were then confirmed in multiple experimental models of portal hypertension and in patients with cirrhosis. Initially it was thought that these changes were a manifestation of latent alcoholic cardiomyopathy, however future studies confirmed the same circulatory dysregulation in cirrhotic patients with

different underlying diseases.[15] In our study also, resting pulse, MAP and QTc were higher in the alcoholic cirrhotic group. Pericardial effusions are reported in up to 63% of patients with end stage of liver disease in the study done by Cheung TK et al, but are typically small in size and hemodynamically well tolerated. [16] In our study, pericardial effusion was minimal being only 0.95%. Since we had not enrolled the patients with end stage liver diseases only, it can be linked to the study population of cirrhotic patients of any stages with significant number being in child pugh A without ascites and peripheral oedema.

To our best of knowledge, this is first ever study in this field from our country. Cardiac dysfunction is neglected in LC and is often asymptomatic. However, it can predict the prognosis and asses the treatment plan. The limited number is the weakness of this study. We have not assessed the grade of diastolic dysfunction in this study that would have added the strength. Our aim was to find out the prevalence of types of cardiac dysfunction only. Based on our findings, we recommend that the cardiac assessment should be an integral part in the management of liver cirrhosis patients.

CONCLUSIONS

Cardiac dysfunction especially diastolic dysfunction is prevalent among males especially in alcoholic group. Systolic dysfunction was seen in only a very few number of cases especially in alcoholic cirrhotic group with ascites and hepatorenal syndrome. In the absence of ascites, systolic dysfunction was not seen. Cirrhotic cardiomyopathy was seen in more than half of the patients which has one of the core component of QTc prolongation. QTc prolongation correlated with liver dysfunction and was more prevalent in CTP-C and MELD score of >10. Resting pulse and MAP which are the indicators of hyperdynamic circulation and QTc interval were slightly higher in alcoholic cirrhotic group than other etiology. Cardiac dysfunction though being a common entity is the most neglected part of clinical evaluation. So, assessment of cardiac function should be done in all patients with cirrhosis.

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