DOI: 10.34172/mejdd.2021.228

Factors Predicting Cardiac Dysfunction in Patients with Liver Cirrhosis

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Received: 01 Sep. 2020
Accepted: 19 Mar. 2021

ABSTRACT

BACKGROUND

Left ventricular diastolic dysfunction (LVDD) is the earliest cardiac dysfunction noted in patients with liver cirrhosis, which increases the morbidity and mortality in such patients. There are sparse studies from India evaluating the predictive factors of LVDD in patients with cirrhosis. Hence we undertook this prospective study with an aim to evaluate the factors predicting the development of LVDD in liver cirrhosis.

METHODS

104 patients with cirrhosis were enrolled in this prospective study. A detailed cardiac evaluation was done by 2 D echocardiography with tissue Doppler imaging by an experienced senior cardiologist. The severity of liver disease was defined by Model For End-Stage Liver Disease (MELD) and Child-Pugh score.

RESULTS

The prevalence of LVDD was 46% in our study. Multivariate logistic regression analysis revealed that serum albumin, MELD score, and presence of ascites (OR = 0.1, 95%CI 0.03-0.3, $p < 0.001$; Or = 1.12, 95%CI 1.03-1.22, $p < 0.001$; OR = 4.19, 95%CI 1.38-12.65, $p < 0.01$, respectively) were independent predictors of LVDD in patients with cirrhosis. Diastolic dysfunction was unrelated to age, sex, and etiology of cirrhosis. The patients with cirrhosis and LVDD had significantly higher child Pugh score, MELD score, and lower serum albumin than patients without LVDD. The echocardiographic parameters like E/e' ratio, Deceleration time (DT), and Left atrial volume index (LAVI) were significantly different in cirrhotic patients with higher MELD and child Pugh score than lower.

CONCLUSION

The present study showed a significant correlation of diastolic dysfunction with the severity of the liver disease. Low serum albumin, high MELD score, and presence of ascites significantly predict the development of LVDD in patients with cirrhosis.

KEYWORDS:
Diastolic dysfunction; MELD, Child-Pugh score, Ascites, Cirrhosis of liver

Please cite this paper as:
Behera M K, Narayan J, Sahu M K, Behera S K, Singh A, Mishra D, Agarwal S, Uthansingh K. Factors Predicting Cardiac Dysfunction in Patients with Liver Cirrhosis. *Middle East J Dig Dis* 2021;**13**:216-222. doi: 10.34172/mejdd.2021.228.

INTRODUCTION

Liver cirrhosis is one of the major public health problems worldwide, with significant morbidity and mortality caused by life-threatening complications.[1,2] In the initial stages, it is asymptomatic. Still, there is a reduction of liver function as the disease advances, with an increased frequency of complications like liver failure, hepatic encephalopathy, ascites, variceal bleeding, and hepatorenal syndrome.[3] The arterial vasodilatation in patients with cirrhosis due to overproduction of circulating vasodilators may lead to reduced systemic vascular resistance and activation of renin-angiotensin-aldosterone system.[4,5,6] These hemodynamic changes resulted in increased cardiac output and heart rate and decreased systemic vascular resistance.[4] The persistent hyperdynamic circulation in patients with cirrhosis can cause functional and structural alteration of cardiac chambers.[7,8,9]

Cirrhotic cardiomyopathy is a clinical entity characterized by attenuated contractile responsiveness to stress and impaired diastolic function along with electrophysiological abnormalities in the absence of any structural cardiac disease.[4,10,11] The cardiac dysfunction affects the course and prognosis in patients with liver cirrhosis. Previous studies showed that cardiac abnormalities in liver cirrhosis adversely affected the outcome of invasive procedures such as transjugular intrahepatic portosystemic shunt insertion and liver transplantation.[12,13,14]

Left ventricular diastolic dysfunction (LVDD) has been an early cardiac disturbance in patients with cirrhosis occurring earlier than systolic dysfunction.[15] However, not much attention has been given to cardiac dysfunction in patients with cirrhosis. The hyperdynamic state of cirrhosis was previously thought to be caused either by thiamine deficiency caused by alcohol or related to endogenous vasoactive substances.[11,16] The previous studies that evaluated diastolic dysfunction in patients with liver cirrhosis were mostly from Western countries, and few are only from India. Hence, due to the scarcity of data in Southeast Asia and India, cardiac dysfunction in patients with cirrhosis was not well characterized in the Indian population. So, we performed a cross-sectional study to evaluate the cardiac status by echocardiography with tissue doppler imaging and assess the factors predictive of diastolic dysfunction in liver cirrhosis. This study also assessed the correlation between diastolic dysfunction and the severity of the liver disease.

MATERIALS AND METHODS

All the patients with cirrhosis attending the Gastroenterology and Hepatology outpatient or inpatient Department of Institute of Medical Sciences and SUM (Single word) Hospital from May 2015 to July 2018 were selected for the study, regardless of the etiology. The diagnosis of cirrhosis was based on clinical, laboratory, and imaging or histology findings. Those patients with age more than 70 years, diabetes mellitus, hypertension, chronic cardiac, pulmonary, or renal diseases, hepatocellular carcinoma, and active ethanol abuse were excluded from the study. The patients on β blocker therapy for oesophageal varices were instructed to stop medication 7 days prior to the cardiac function evaluation. Repeated sessions of variceal band ligation were undertaken to eradicate oesophageal varices. After exclusion, 104 patients with cirrhosis were selected for this study. Informed consent was obtained from all the participants enrolled in the study. The study was approved by the local ethics committee.

Demographic and clinical evaluation

A detailed history taking and thorough clinical examination were done at the time of the first visit. A complete blood count, liver function test, renal function test, coagulation parameters, and electrolytes were measured. Using these blood parameters, the model for end-stage liver disease (MELD) and child Pugh (CTP) scores were calculated.

Echocardiographic evaluation

All the patients with cirrhosis underwent two-dimensional echocardiography with tissue doppler imaging (TDI) (Vivid E9; General Electric, Boston, MA, USA) by an experienced cardiologist according to the recommendations of the American Society of Echocardiography (ASE).[17] Left ventricular ejection fraction (LVEF %) was calculated by the modified Simpson's rule, left atrium volume index (LAVI), peak early filling velocity (E), atrial filling velocity (A), calculated E/A ratio (E/A), deceleration time of the E wave (DT), early diastolic mitral inflow velocity/velocity of the septal and lateral sites (e') were estimated, and E/e' ratio was calculated. LVDD was defined and classified according to

Table 1: Demographic and clinical parameters in patients with cirrhosis, classified as per the presence of LVDD

Variables	No LVDD (n = 55)	Presence of LVDD (n = 49)	*p* value
Age in years	49.24 ± 11.02	51.96 ± 9.39	0.49
Male sex	39 (71%)	31 (63%)	0.33
H/o Alcohol	22 (40%)	15 (31 %)	0.12
Bilirubin (mg/dl)	1.92 ±0.95	2.68 ± 2.18	0.05
Albumin(gm/dl)	3.03 ± 0.68	2.50 ± 0.67	0.001
Presence of ascites	41%	67%	0.01
Child Pugh score	8.62 ± 1.97	9.77 ± 1.68	0.003
INR	1.49 ± 0.48	1.78 ± 0.60	0.01
MELD score	14.03 ± 5.07	18.10 ± 7.61	0.006
Creatinine(mg/dl)	0.98 ± 0.25	1.11 ± 1.05	0.1

Abbreviations: LVDD, left ventricular diastolic dysfunction; INR, international normalized ratio; Model for End-stage Liver Disease;

the recommendations of the ASE,[18] as follows: grade 1 LVDD: e' < 8 cm/sec, E/A ratio < 0.8, E/e'ratio < 9, and DT > 200 ms; grade 2 LVDD: e'< 8 cm/sec, E/A ratio 0.8–1.5, E/e' ratio 9–15, and DT 160–200 ms; and grade 3 LVDD: e' < 8 cm/sec, E/A ratio > 2,E/e' ratio > 15,and DT < 160ms.

Statistical analysis

The quantitative data with normal distribution were reported as mean ± SD, and comparisons were made by student t test. The qualitative data were compared by the Chi-square test, with Yates' correction as applicable. The predictors of LD dysfunction were calculated by the stepwise logistic regression model. Those variables with a p value < 0.05 in univariate analysis were subjected to multivariate analysis. Multivariate analysis was performed without including related variables as MELD, and CTP score includes multiple variables. All the statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL). A P value less than 0.05 was considered statistically significant.

Out of 104 patients with cirrhosis evaluated in this study, 34.6% had a history of alcohol consumption, and 17.3% had Hepatitis B virus (HBV) infection. The mean age of the patients was 51.41 ± 10.13 years. Most of the participants were male with a male: female ratio of 3.18:1. Of all patients, 57.6 % belonged to Child-Pugh class C, 31.7% belonged to class B, and 10.7% belonged to class A. The mean MELD score of the study population was 15.56 ± 7.9 with a range of 6-39. LVDD was observed in 47.11% of all patients. Demographic, clinical, and echocardiographic parameters, classified according to the presence of LVDD, are shown in table 1. The cirrhotic patients with LVDD had significantly higher child Pugh score (9.77 ± 1.68 vs. 8.62 ± 1.97, $p < 0.01$), MELD score (18.10 ± 7.61 vs. 14.03 ± 5.07, $p < 0.01$), INR (1.78 ± 0.60 vs. 1.49 ± 0.48, $p < 0.01$), serum bilirubin (2.68 ± 2.18 vs. 1.92 ± 0.95, $p < 0.05$), and lower serum albumin (2.50 ± 0.67 vs. 3.03 ± 0.68, $p < 0.001$) as compared with patients without LVDD. Age, percentage of the male sex, history of alcohol intake, and serum creatinine were similar in both groups of patients.

Table 2 depicts the echocardiographic abnormalities in patients with cirrhosis, based on the Child-Pugh score and MELD score. The patients with CTPC had significantly higher E/e' ratio and LAVI, and lower DT as compared with CTP B and A ($p < 0.01$). Similarly, cirrhotic patients with MELD ≥ 15 had significantly higher E/e' Ratio (11.79 ± 4.25 vs. 8.55 ± 3.22, $p = 0.002$) and LAVI (32.96 ± 8.4 vs. 25.98 ± 6.25, $p < 0.01$), and lower DT (186.43 ± 38.1 vs. 211.49 ± 33.25, $p < 0.001$) as compared with MELD < 15. There was an increased percentage of LVDD among patients with cirrhosis and higher child Pugh score, MELD scores, and ascites as depicted in figures 1, 2, and 3, suggesting a higher rate of LVDD in severe liver disease.

Table 3 reveals factors predictive of LVDD in patients with cirrhosis, as assessed by stepwise logistic regression analysis. Age, male sex, serum albumin, MELD score, presence of ascites, alcohol vs. other etiologies, and LVEF were the factors evaluated by univariate analysis. MELD score (OR = 1.11, 95%CI 1.04-1.19, $p < 0.001$), serum albumin (OR = 0.08, 95%CI 0.02-0.23, $p < 0.001$),

Table 2: Echocardiographic abnormalities of patients with cirrhosis classified based on Child-Pugh score and MELD score

	Child Pugh score			*p* Value	MELD score		*p* Value
	CTP A (n= 17)	CTP B (n=44)	CTP C (n=43)		MELD <15 (n=53)	MELD ≥ 15 (n=51)	
LVEF (%)	61.29 ± 3.2	62.20 ± 9.6	61.36 ± 9.17	0.92	60.01 ± 11.2	63.28 ± 5.71	0.92
E/A Ratio	1.18 ± 0.32	1.12 ± 0.33	1.29 ± 0.52	0.19	1.14 ± 0.43	1.39 ± 0.69	0.03*
E/e' Ratio	6.86 ± 0.74	8.32 ± 2.59	10.57 ± 4.38	0.002*	8.55 ± 3.22	11.79 ± 4.25	0.002*
LAVI,	22 ± 3.55	26.52 ± 7.12	30.88 ± 8.69	0.002*	25.98 ± 6.25	32.96 ± 8.4	0.002*
DT	229.14 ± 29.08	212.86 ± 30.09	191.60 ± 34.94	0.002*	211.49 ± 33.25	186.43 ± 38.1	0.001**

Abbreviations: LVEF, left ventricle ejection fraction; DT, deceleration time of E wave; E/e' ratio, the ratio of early diastolic annular velocity to peak early diastolic annular wave velocity; E/A ratio, the ratio of early diastolic annular velocity to peak late diastolic arterial filling velocity; LAVI, left atrium volume index;

Table 3: Stepwise logistic regression model for predicting diastolic dysfunction in patients with decompensated cirrhosis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	AOR	95% CI	*p* value
Age	0.98	0.94-1.01	0.3			
Male sex	0.56	0.16-1.76	0.45			
Albumin	0.08	0.02-0.23	0.001**	0.1	0.03-0.3	0.001
MELD	1.11	1.04-1.19	0.001**	1.12	1.03-1.22	0.007*
Presence of Ascites	3.91	1.67-9.18	0.002*	4.19	1.38-12.65	0.01*
Alcohol vs other etiologies	1.15	0.52-2.6	0.72			
LVEF	1.02	0.96-1.08	0.27			

Abbreviations: Model for End-stage Liver Disease; LVEF, left ventricle ejection fraction.

and presence of ascites (OR = 3.91, 95% CI 1.67-9.18, $p < 0.01$) were found to be predictors of LVDD in univariate analysis. In multivariate analysis, MELD score (AOR = 1.12, 95% CI 1.03-1.22, $p < 0.01$), serum albumin (AOR = 0.1, 95% CI 0.03-0.3, $p < 0.001$), and presence of ascites (AOR=4.19, 95% CI 1.38-12.65, $p < 0.01$) were also found to be independent predictors of LVDD in patients with cirrhosis.

RESULTS

Baseline clinical characteristics

Out of 104 patients with cirrhosis evaluated in this study, 34.6% had a history of alcohol consumption, and 17.3% had Hepatitis B virus (HBV) infection. The mean age of the patients was 51.41 ± 10.13 years. Most of the participants were male with a male: female ratio of 3.18:1. Of all patients, 57.6 % belonged to Child-Pugh class C, 31.7% belonged to class B, and 10.7% belonged to class A. The mean MELD score of the study population was 15.56 ± 7.9 with a range of 6-39. LVDD was observed in 47.11% of all patients. Demographic, clinical, and echocardiographic parameters, classified according to the presence of LVDD, are shown in table 1. The cirrhotic patients with LVDD had significantly higher child Pugh score (9.77 ± 1.68 vs. 8.62 ± 1.97, $p < 0.01$), MELD score (18.10 ± 7.61 vs. 14.03 ± 5.07, $p < 0.01$), INR (1.78 ± 0.60 vs. 1.49±0.48, p <0.01), serum bilirubin (2.68±2.18 vs. 1.92 ± 0.95, $p < 0.05$), and lower serum albumin (2.50 ± 0.67 vs. 3.03 ± 0.68, $p < 0.001$) as compared with patients without LVDD. Age, percentage of the male sex, history of alcohol intake, and serum creatinine were similar in both groups of patients.

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Table 3 reveals factors predictive of LVDD in patients with cirrhosis, as assessed by stepwise logistic regression

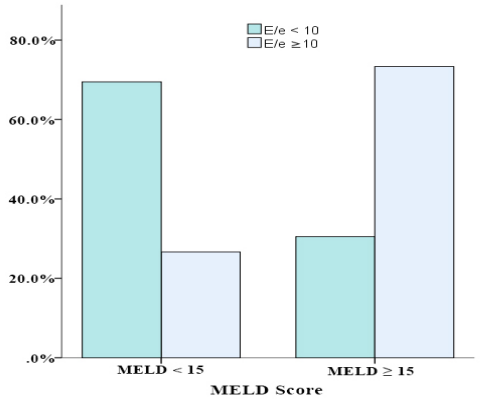

Fig. 1: Bar diagram showing percentage LV DD, as defined by E/e' ≥ 10 according to MELD status

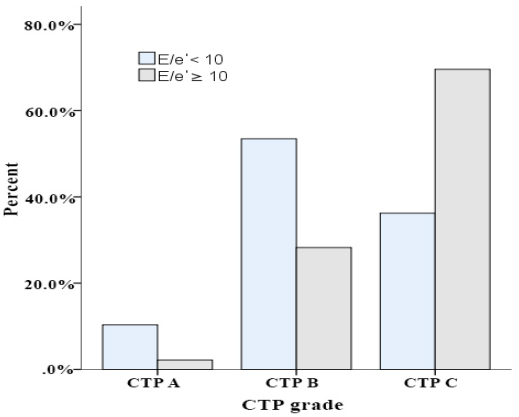

Fig. 2: Bar diagram showing percentage LV DD, definedby E/e' ≥ 10 according to Child Pugh status

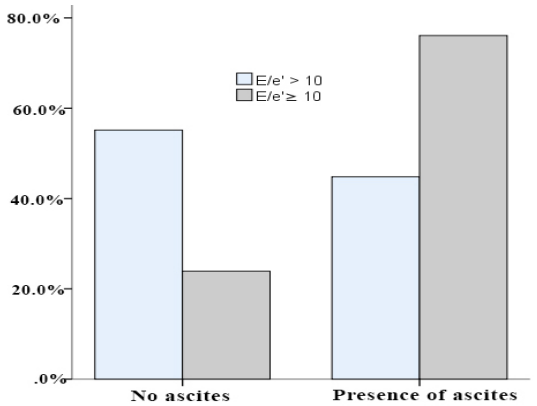

Fig. 3: Bar diagram showing percentage LV DD, defined by E/e' ≥ 10 according to ascites status

analysis. Age, male sex, serum albumin, MELD score, presence of ascites, alcohol vs. other etiologies, and LVEF were the factors evaluated by univariate analysis. MELD score (OR = 1.11, 95%CI 1.04-1.19, $p < 0.001$), serum albumin (OR = 0.08, 95%CI 0.02-0.23, $p < 0.001$), and presence of ascites (OR = 3.91, 95% CI 1.67-9.18, $p < 0.01$) were found to be predictors of LVDD in univariate analysis. In multivariate analysis, MELD score (AOR = 1.12, 95% CI 1.03-1.22, $p < 0.01$), serum albumin (AOR = 0.1, 95% CI 0.03-0.3, $p < 0.001$), and presence of ascites (AOR = 4.19, 95% CI 1.38-12.65, $p < 0.01$) were also found to be independent predictors of LVDD in patients with cirrhosis.

DISCUSSION

Liver cirrhosis is a state of hyperkinetic circulation associated with an increase in circulating blood volume and cardiac output and reduced systemic vascular resistance. Cirrhotic cardiomyopathy is an entity that includes both systolic and diastolic dysfunction in patients with liver cirrhosis. However, most previous studies have found diastolic dysfunction as the most common cardiac abnormality in patients with liver cirrhosis.[15,19,20] A combination of myocardial hypertrophy, fibrosis, and subendothelial edema often results in increased myocardial stiffness, causing diastolic dysfunction in patients with cirrhosis.[11,21] Systolic function as measured by ejection fraction is preserved in patients with liver cirrhosis, as reported in previous studies.[15,19,20]

In our study, the prevalence of diastolic dysfunction was 47% among patients with cirrhosis. This is on par with the study by Ruiz-Del-Arbol and colleagues from Spain.[22] However, one Indian study by Somani and co-workers reported a lower prevalence (30%) of LVDD in patients with cirrhosis.[11] We found a significant difference in MELD score and CTP grade between cirrhotic patients with LVDD and without LVDD, suggesting cardiac dysfunction in severe liver disease. Echocardiographic parameters like E/e' ratio, LAVI, and DT were significantly different between patients with higher MELD and child Pugh scores and lower MELD and Child-Pugh scores. Hence, cardiac function changes were related to the degree of liver failure, defined by higher MELD and Child-Pugh scores. Ruiz-Del-Arbol and colleagues found a significant difference in MELD scores between the patients with and

without LVDD, higher prevalence of ascites, hepatic encephalopathy, and hepatorenal syndrome in cirrhotic patients with grade 2 diastolic dysfunction than those with normal cardiac function.[22] One Indian study by Anish and others also found a higher prevalence of LVDD in patients with cirrhosis and MELD > 12, similar to the findings of our study.[23] A substantial number of studies have elaborated a significant correlation of child Pugh score with the severity of LVDD.[24,25,26,27] On the contrary, previous studies from India and Europe did not find any difference in the prevalence of LVDD with MELD score and Child-Pugh score.[11,28] However, diastolic dysfunction was the cardiac abnormality as a consequence of progressive liver disease, and a higher prevalence of LVDD is expected in more severe liver disease with higher MELD and CTP score, as found in our study.

In this study, we found that serum albumin, MELD score, and presence of ascites were independent predictors of LVDD in patients with cirrhosis. Advanced cirrhosis, as characterized by low serum albumin and high MELD score, causes splanchnic vasodilatation leading to circulatory dysfunction. Diastolic dysfunction plays an important role in the pathogenesis of ascites by impairing effective arterial blood volume in patients with cirrhosis.[9] Patients with ascites had a higher tendency to develop LVDD, as revealed by previous studies. A study by Ruız-Del-Arbol and colleagues showed a higher frequency of ascites in cirrhotic patients with grade 2 LVDD than those with grade 1 LVDD and normal LV function.[9] Few more studies also noticed a higher prevalence of LVDD in patients with ascites than those without it.[9,26,29] These findings indicate that LVDD plays a significant role in worsening the liver disease in the form of ascites.

E/A ratio was the echocardiographic parameter used to define diastolic dysfunction in older studies, but this ratio is load dependent and influenced by the age of the patients. And also, grade 2 diastolic dysfunction can be mistaken as normal (pseudonormal pattern) if the transmitral flow is studied alone. 30 We used tissue doppler imaging to evaluate diastolic dysfunction by the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, E/e' ratio.[18,23] A Korean study revealed that E/e' ratio is a useful marker to determine LVDD and also to predict survival in patients with cirrhosis.[15]

Our study has several limitations. The small sample size is a significant limitation of our study. Lack of follow-up data on the outcome of the patients and lack of stress testing also were major limitations of this study. Despite these limitations, this study appears to be promising as it is a prospective study and a real-life clinical practice study evaluating predictive factors for LVDD in patients with cirrhosis.

In conclusion, we demonstrated that serum albumin, MELD score, and presence of ascites were a significant predictor of developing LVDD in patients with cirrhosis. We also found a higher MELD and child Pugh score in patients with cirrhosis and LVDD than patients without LVDD, suggesting a significant correlation of severity of liver disease and LVDD. Hence, all cirrhotic patients with Child-Pugh class B and C and high MELD score should undergo a cardiovascular assessment by 2 D echocardiography with tissue doppler imaging to reduce mortality related to impaired cardiac function.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors have none to declare.

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