

# A case-cohort study of left ventricular diastolic dysfunction in patients with cirrhosis: the liver–heart axis

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## Abstract

**Background** Left ventricular diastolic dysfunction (LVDD) is an early manifestation of cirrhotic cardiomyopathy. Few studies have addressed its clinical significance in cirrhosis. We assessed the association of LVDD with the factors affecting cirrhosis patients' severity, complications, and survival.

**Methods** A total of 203 cirrhosis patients were enrolled and underwent investigations, including 2-dimensional echocardiography with tissue Doppler imaging, and 139 patients with LVDD (cases) were compared with 64 patients without LVDD (controls). Logistic regression and Kaplan-Meier analysis were applied.

**Results** Mean age was 52.76±10 years. Among LVDD patients, 56% had grade-1, and 44% had grade-2 LVDD. Cirrhosis related to NASH had a more significant association with LVDD ( $P<0.001$ ) than other etiologies. LVDD was significantly associated with a greater incidence of Child-Turcotte-Pugh (CTP) class C ( $P<0.001$ ), higher model for end-stage liver disease scores ( $P=0.001$ ), duration of cirrhosis >2 years since diagnosis ( $P=0.028$ ), ascites ( $P<0.001$ ), hepatic encephalopathy ( $P<0.010$ ), hepatorenal syndrome ( $P<0.001$ ), and a history of obesity ( $P=0.004$ ). Multivariate analysis showed that higher CTP score, ascitic fluid protein and prolonged QTc interval were independently associated with LVDD ( $P=0.009$ ;  $P=0.018$ ;  $P=0.016$ , respectively). Kaplan-Meier survival analysis showed significantly poorer survival status in patients with higher grades of LVDD ( $P<0.001$ ). The area under the receiver operating characteristic curve (0.78) was greatest for ascitic fluid protein in predicting LVDD, with a cutoff of >1 g/dL.

**Conclusions** Higher CTP score, prolonged QTc, higher ascitic fluid protein levels, and poor survival are significantly associated with LVDD. Ascitic fluid protein >1 g/dL could be an indicator for evaluating LVDD.

**Keywords** Left ventricular diastolic dysfunction, cirrhosis, survival, cardiomyopathy, predictors

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## Introduction

The characteristics of liver cirrhosis are chronic injury, inflammation, destruction, and regeneration of the hepatocytes. Decompensation sets in with the progressive worsening of liver cirrhosis and the development of portal hypertension secondary to increased hepatic resistance. Subsequently, the release of vasodilator mediators activates the renin–aldosterone–angiotensinogen axis and the sympathetic nervous system. These result in increased cardiac output and decreased systemic vascular resistance [1]. Cardiac function declines with the advancement of cirrhosis, which remains preserved in the initial stage of chronic liver disease [2,3]. The autonomic dysfunction, alterations in cell membrane composition, ion channel defects and overproduction of cardiodepressant factors result in an impaired cardiac response.

The Montreal Working Group (2005) defined cirrhotic cardiomyopathy as characterized by the following 3 factors:

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impaired contractile responsiveness to stress; diastolic dysfunction; and electrophysiological abnormalities with a prolonged QT interval [4,5]. Diastolic dysfunction is the earliest and indolent manifestation of cirrhotic cardiomyopathy. The consensus defined the E/A ratio (early filling to atrial filling flow velocities) as a measurement of diastolic dysfunction. However, it recognized its interdependence with fluid overload, which is common in cirrhosis. Later studies proposed tissue Doppler imaging (TDI) as a marker of left ventricular relaxation. This directly measures the velocity of myocardial displacement during left ventricular relaxation in diastole and is not dependent on volume status or left atrial pressure [6]. The E/e' index (ratio of early filling velocity to septal tissue velocity) is considered by the European Society of Cardiology (ESC) as a reliable parameter for diagnosing diastolic dysfunction [7]. The prevalence of diastolic dysfunction in cirrhosis in recent studies is 46-61% [8]. Recent studies based on TDI parameters have concluded that diastolic dysfunction is a sensitive marker for the development of type 1 hepatorenal syndrome (HRS). It is also a predictor of mortality in type 1 HRS [9,10] and spontaneous bacterial peritonitis (SBP) [11]. A recent Korean study in cirrhotic patients observed poor survival status in patients with LVDD and an E/e' ratio >10 [12]. These observations prompted us to scrutinize these veiled factors more comprehensively.

Hence, our study primarily aimed at assessing the association between LVDD and the factors associated with the severity of liver cirrhosis, its clinical complications, and the patients' survival. This information may help to prognosticate the patients more accurately and determine the relationship between cardiac dysfunction and different parameters. Therefore, it is necessary to fill this knowledge gap and assess the parameters, as they may be contributory factors and silent preventable causes of mortality in advanced chronic liver disease.

## Patients and methods

We conducted a descriptive cohort study that included 203 patients with ages ranging from 18-65 years, who attended the department of gastroenterology at a university hospital between October 2020 and December 2021. The patients had a diagnosis of cirrhosis based on clinical, biochemical, imaging, or histologic findings. We excluded from the study patients on cardiac medications that could interfere with cardiac function, as well as those with uncontrolled hypertension, a history of coronary artery disease or valvular heart disease, chronic kidney disease, chronic lung disease, hepatic and extrahepatic malignancies, or hypothyroidism. Patients with acute complications, such as infection, severe anemia or hepatic encephalopathy, were included once these conditions were treated. We stopped  $\beta$ -blockers and diuretics for 48 h before the study. All patients included in our study were inactive drinkers and abstained from alcohol for 6 months.

The sample size of 203 was calculated based on a study conducted in Korea [12], by SK Lee *et al*, assuming a

difference in mortality of 20% and a 95% confidence interval (CI). We received clearance from the Institutional Human Ethics Committee (HEC.No.05/36/2020/MCT) and obtained informed consent from all the patients.

All participants in the original cohort were divided into patients with LVDD (cases: n=139) and patients without LVDD (controls: n=64) at the end of follow up. A cardiologist assessed the patients' cardiovascular status.

## Demographic and clinical data

Complete history, physical examination, liver and renal function tests, coagulation profile, ultrasound of the abdomen, and an electrocardiogram were recorded at the time of enrollment. Standard laboratory parameters were performed to identify the etiology and complications of liver disease. In addition, Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores were calculated to assess the severity of the liver disease.

## Echocardiography data

All enrolled patients underwent 2-dimensional echocardiography with TDI using a Mindray DC-30 Machine with a 2.5 MHz transducer, according to the guidelines of the American Society of Echocardiography (ASE) and ESC [13]. Left ventricular ejection fraction was calculated by the modified Simpson's rule. Left atrium volume index, peak early filling velocity (E), atrial filling velocity (A), calculated E/A ratio (E/A), early diastolic mitral inflow velocity/velocity of the septal and lateral sites (e'), E/e' ratio (E/e'), and tricuspid regurgitation velocity were calculated. LVDD was classified as grade 1, 2 or 3, according to ESC guidelines. The pulmonary capillary wedge pressure (PCWP) was calculated using the E/e' ratio,  $PCWP = 1.24(E/e') + 1.9$ . Left ventricular filling pressure was considered elevated when the calculated PCWP was >15 mmHg [14]. The corrected QT interval (QTc) was calculated using Fridericia's formula ( $QTc = QT/(RR)^{1/3}$ ).

## Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences version 25.0 (IBM Corp). Continuous measurements were presented as mean  $\pm$  standard deviation if normally distributed and median (Interquartile range) if not, while categorical variables were expressed as proportions. The significance of the association was tested using the chi-square test and independent-samples *t*-test. Binary logistic regression multivariate analysis was carried out to predict the factors associated with the development of LVDD. Kaplan-Meier survival analysis was applied to determine the prognosis of cirrhotic patients with different grades of LVDD. The area under the receiver operating characteristic curve (AUROC) was computed

for the variables identified as significant in the multivariate analysis to determine a screening test for developing LVDD.

## Results

### Baseline clinical characteristics

Two hundred fifty consecutive patients were screened, of whom 203 patients were included (excluding 31 patients with hepatocellular carcinoma, 9 with coexistent heart disease, 4 with chronic lung disease, and 3 with chronic kidney disease). The baseline characteristics of the patients are listed in Table 1. The patients' mean age was 52.8±10 years and 85% were males. The most common cause of cirrhosis in the study population was alcohol (63.5%), with no active drinking, followed by nonalcoholic steatohepatitis (NASH) (18.7%), hepatitis B virus (HBV) (11.3%), hepatitis C virus (HCV) (3%), Wilson's disease (2%), and autoimmune hepatitis (1.5%). Regarding CTP classification, 44.8% belonged to class C, 45.3% to class B and 9.9% to class A. Of the 68.4% of patients (n=139) who had LVDD, 56% (n=78) had Grade-1, 44% (n=61) had Grade-2 and none had grade-3 LVDD. The mean MELD and CTP scores were (18.98±6.8 and 9.1±2.1, respectively).

### LVDD: correlation with cirrhosis etiology

The distribution of various etiologies of cirrhosis amongst patients with LVDD is given in Table 2. We observed a higher prevalence of LVDD in patients with NASH-related cirrhosis than in those with other etiologies. Hence, we further categorized study participants into NASH and non-NASH-related cirrhosis and found a significantly higher proportion of LVDD in the NASH-related cirrhosis group: 13.2% (n=5) had no LVDD, while 86.8% (n=33) had LVDD (odds ratio [OR] 3.67, 95%CI 1.361-9.916; P=0002). Among LVDD patients with NASH-related cirrhosis, a higher proportion of patients had Grade-2 (53%) than Grade-1 (47%) LVDD. Among patients with non-NASH-related cirrhosis, 41% had Grade-2 and 59% had Grade-1 LVDD.

### LVDD: correlation with cirrhosis severity

The relationship between severity of cirrhosis and grade of LVDD is given in Table 2. LVDD was significantly associated with a higher CTP class: 79.2% of CTP C, 65.2% of CTP B and 35% of CTP A class patients had LVDD. Patients with CTP B and C had a 4.3 times higher chance of developing LVDD than those with CTP A (OR 4.35, 95%CI 1.62-11.66; P=0.002). An independent samples *t*-test found a statistically significant difference in the mean CTP scores and MELD scores between patients with and without LVDD (9.5±2.1 vs. 8.4±2.0, P<0.001, and 20±6.6 vs. 16.6±6.6, P=0.001) (Table 3). One way ANOVA test found no statistically significant difference in CTP scores between Grade-1 and Grade-2 LVDD (P=0.457).

**Table 1** Baseline characteristics of the study participants (N=203)

Variables	Frequency/ Mean	Percentage (%)
Left ventricular diastolic dysfunction (LVDD) (N=203)		
Without LVDD	64	31.5
Grade-1 LVDD	78	38.4
Grade-2 LVDD	61	30
Sex (N=203)		
Male	172	84.7
Female	31	15.3
CTP class (N=203)		
A	20	9.9
B	92	45.3
C	91	44.8
Survival status (N=197)		
Survivors	139	70.6
Non survivors	58	29.4
Biochemical profile		
CTP	9.1±2.1	
MELD	18.9±6.8	
Serum Bilirubin(mg/dL)	9.1±2.1	
Serum Protein(g/dL)	6.2±0.95	
Serum albumin (g/dL)	2.7±0.62	
Prothrombin time (sec)	21.2±5.8	
INR	1.6±0.47	
Serum sodium (mEq/L)	134±5.8	
Creatinine	1.3±3.4	
Etiology (N=203)		
Alcohol	129	63.5
NASH	38	18.7
HBV	23	11.3
HCV	6	3
Wilson's disease	4	2
Autoimmune	3	1.5
Comorbidities (N=203)		
Diabetes mellitus	112	55.2
Hypertension	38	18.8
Dyslipidemia	16	7.9
History of obesity	68	35.8
Echocardiographic parameters		
LVEF (%)	64.6±7.8	
E/A	9.1±2.1	
E/e'	9.3±3.0	
TR velocity (cm/sec)	181±7.5	
LAVI (mL/m <sup>2</sup> )	36.9±6.8	
PCWP (mmHg)	13.4±3.8	

LVDD, left ventricular diastolic dysfunction; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; LVEF, left ventricular ejection fraction; E/A, early filling velocity/atrial filling velocity ratio; E/e', early filling velocity/medial wall velocity; TR, tricuspid regurgitation; LAVI, left atrial volume index; PCWP, pulmonary capillary wedge pressure

### LVDD: correlation with cirrhosis complications

We analyzed different complications of liver cirrhosis in patients with and without LVDD. The complications observed were ascites in 139, variceal bleeding in 105, hepatic encephalopathy (HE) in 71, jaundice in 59, SBP in 45, and HRS in 42 patients. All the complications had a higher incidence in patients with LVDD,

**Table 2** Factors associated with LVDD among cirrhotic patients

Variables	Without LVDD (Controls)	LVDD (Cases)		P-value
		Grade-1 LVDD	Grade-2 LVDD	
Sex				
Male	54 (84.4%)	67 (85.9%)	51 (83.6%)	0.93*, 0.924 <sup>#</sup>
Female	10 (15.6%)	11 (14.1%)	10 (16.4%)	
Cirrhosis duration				
<2 years	32 (50%)	28 (35.9%)	19 (24.1%)	0.076*, 0.028 <sup>#</sup>
≥2 years	32 (50%)	50 (64.1%)	42 (31.1%)	
Cirrhosis etiology				
Alcohol	44 (68.8%)	50 (64.1%)	35 (68.9%)	0.276*, 0.442 <sup>#</sup>
NASH	5 (7.8%)	16 (20.5%)	17 (27.9%)	
HBV	10 (15.6%)	8 (10.3%)	5 (8.2%)	
HCV	2 (3.1%)	2 (2.6%)	2 (3.3%)	
Wilson's disease	2 (3.1%)	1 (1.3%)	1 (1.6%)	
Autoimmune	1 (1.6%)	1 (1.3%)	1 (1.6%)	
NASH population				
Non-NASH	59 (92.2%)	63 (80.8%)	44 (72.1%)	0.007*, 0.041 <sup>#</sup>
NASH	5 (7.8%)	15 (19.2%)	17 (27.9%)	
CTP classes		4 (5.1%)		
A	13 (20.3%)	37 (47.4%)	3 (4.9%)	0.002*, <0.001 <sup>#</sup>
B	32 (50%)	37 (47.4%)	23 (37.7%)	
C	19 (29.7%)		35 (57.4%)	
Grades of ascites				
No ascites	35 (54.7%)	15 (19.2%)	14 (23%)	<0.001*, <0.001 <sup>#</sup>
Grade-1 ascites	28 (43.8%)	35 (44.9%)	5 (8.2%)	
Grade-2/3 ascites	1 (1.6%)	28 (35.9%)	42 (68.9%)	
Mortality				
Survivors	56 (90.3%)	55 (73.3%)	28 (46.7%)	<0.001*, <0.001 <sup>#</sup>
Non survivors	6 (9.7%)	20 (26.7%)	32 (53.3%)	
Comorbidities				
History of obesity	12 (19.7%)	24 (33.8%)	28 (48.3%)	0.004*, 0.005 <sup>#</sup>
Diabetes mellitus	30 (46.9%)	37 (47.4%)	34 (55.7%)	0.534*, 0.578 <sup>#</sup>
Hypertension	9 (14.1%)	16 (20.5%)	11 (18.3%)	0.602*, 0.342 <sup>#</sup>
Dyslipidemia	4 (6.2%)	5 (6.4%)	7 (11.5%)	0.460*, 0.558 <sup>#</sup>

\*P-value between LVDD vs. without LVDD group

# P-value between without LVDD, Grade-1 LVDD and Grade-2 LVDD

LVDD, left ventricular diastolic dysfunction; CTP, Child-Turcotte-Pugh; NASH, nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus

but the association was significant only for HRS, ascites, and HE (OR 12.52, 95%CI 2.06-17.7,  $P<0.001$ ; OR 4.57, 95%CI 2.41-8.68,  $P<0.001$ ; and OR 2.43, 95%CI 1.25-4.91,  $P=0.010$ , respectively). Jaundice and variceal bleeding were not significantly more frequent in patients with LVDD ( $P=0.142$ ,  $P=0.494$ , respectively). Patients with higher grades of ascites had more severe LVDD (OR 4.57, 95%CI 2.41-8.68;  $P<0.001$ ). Of patients with ascites grades 0/1, 2 and 3, 45.3%, 58.8% and 98.6%, respectively, had LVDD. Patients with moderate to severe ascites had a higher rate of LVDD (59.2%) than those with mild ascites (39.4%).

#### LVDD: correlation with cirrhosis duration

The duration of cirrhosis in years from the time of diagnosis was assessed. A Pearson chi-square test showed a significant association between the duration of cirrhosis and the development

of LVDD. Patients with cirrhosis for >2 years had a 1.95 times higher risk of developing LVDD than those with cirrhosis of shorter duration (OR 1.957, 95%CI 1.07-3.57;  $P=0.028$ ) (Table 2).

#### LVDD: correlation with comorbidities

Pearson chi-square analysis showed a significantly higher proportion of LVDD in patients with a history of obesity (OR 2.75, 95%CI 1.3-5.6;  $P=0.004$ ). However, no significant association was observed for the comorbidities diabetes mellitus ( $P=0.483$ ), hypertension ( $P=0.239$ ), or dyslipidemia ( $P=0.558$ ) (Table 2).

#### LVDD: correlation with cirrhotic patients' survival

All patients were followed up for 6 months or until death, whichever occurred first. At the end of the study, 6 patients

**Table 3** Clinical and biochemical parameters associated with LVDD among cirrhotic patients

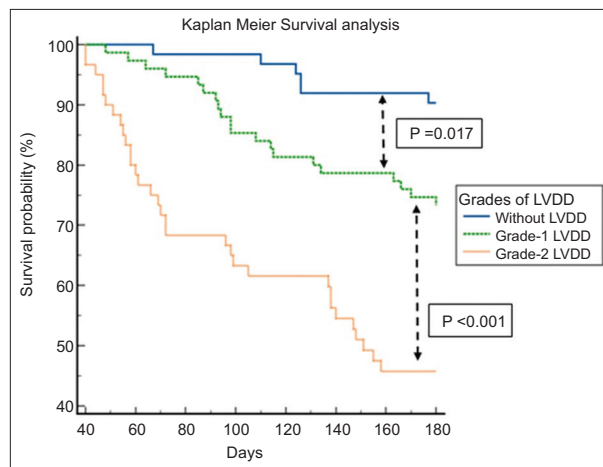
Parameters	No LVDD N=64	LVDD N=139	P-value
CTP score	8.4±2.0	9.5±2.1	<0.001
MELD	16.8±6.6	20±6.6	0.001
Hemoglobin (g/dL)	10.5±4.5	9.3±1.8	0.048
MCV (fL)	87.5±8.6	88.3±8.9	0.565
Platelet (counts/ $\mu$ L)	97746 $\times$ 10 <sup>4</sup>	86104 $\times$ 10 <sup>4</sup>	0.093
Serum protein (g/dL)	6.5±0.9	6.1±0.9	0.002
Serum albumin (g/dL)	2.9±0.5	2.6±0.6	0.005
Prothrombin time (sec)	20.6±5.3	21.5±6.0	0.335
INR	1.5±0.4	1.6±0.49	0.126
Serum creatinine (mg/dL)	1.6±0.6	1.1±0.8	0.054
Serum sodium (mEq/L)	135±5.5	134±5.9	0.205
Serum potassium (mEq/L)	4.0±0.43	4.1±0.64	0.284
SAAG	1.9±0.2	1.9±0.4	0.441
Ascitic fluid protein (g/dL)	0.84±0.3	1.2±0.3	<0.001
Ascitic fluid albumin (g/dL)	0.47±0.1	0.50±0.1	0.001
Serum bilirubin (mg/dL)	4.3 (1.1-4.1)		0.009
SGOT (U/L)	56 (23-52)		0.817
SGPT (U/L)	81 (42-91)		0.517
Blood urea (mg/dL)	38.4 (19-44)		0.073
Serum creatinine (mg/dL)	1.34 (0.7-1.2)		0.054

LVDD, left ventricular diastolic dysfunction; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; MCV mean corpuscular volume; INR, international normalized ratio; SAAG, serum ascites albumin gradient; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

were lost to follow up. All deaths (28.5%; n=58) were liver-related: hepatic failure 39.6% (n=23), HRS 20.6% (n=12), sepsis 22.4% (n=13), and variceal bleeding 17.2% (n=10). Among the patients who expired, 89.7% (n=52) had LVDD. In patients without LVDD, 90.3% (n=56) survived and 9.7% (n=6) died. In patients with grade-1 LVDD, 73.3% (n=55) survived and 26.7% (n=20) died, while in patients with grade-2, 46.7% (n=28) survived, and 53.3% (n=32) died. According to Fisher's exact test, LVDD had a significant association with patient mortality, with an OR of 5.84 for mortality in patients with LVDD as compared to those without (OR 5.84, 95%CI 2.35-14.5; P<0.001). Kaplan-Meier survival analysis showed poor survival status in patients with LVDD (log-rank P<0.001) (Fig. 1).

### LVDD and corrected QT interval

The mean QTc intervals for patients with and without LVDD were 441±59 msec and 410±65 msec, respectively. The mean QTc interval for Grade-2 LVDD was 452±39 msec. An

**Figure 1** Kaplan-Meier survival analysis of cirrhosis patients with left ventricular diastolic dysfunction (LVDD)

independent samples *t*-test, found a significant difference in the mean QTc interval between patients with and without LVDD ( $t=2.597$ ,  $P=0.010$ ).

### Predictors of LVDD

Binary multivariate logistic regression analysis was applied, using a model that included age, CTP score, HE, acute kidney injury, QTc interval, NASH etiology, and ascitic fluid protein. Higher CTP score, higher ascitic fluid protein, and prolonged corrected QT interval were independent predictors for the development of LVDD ( $P=0.009$ ,  $P=0.019$ ,  $P=0.015$ , respectively) (Table 4).

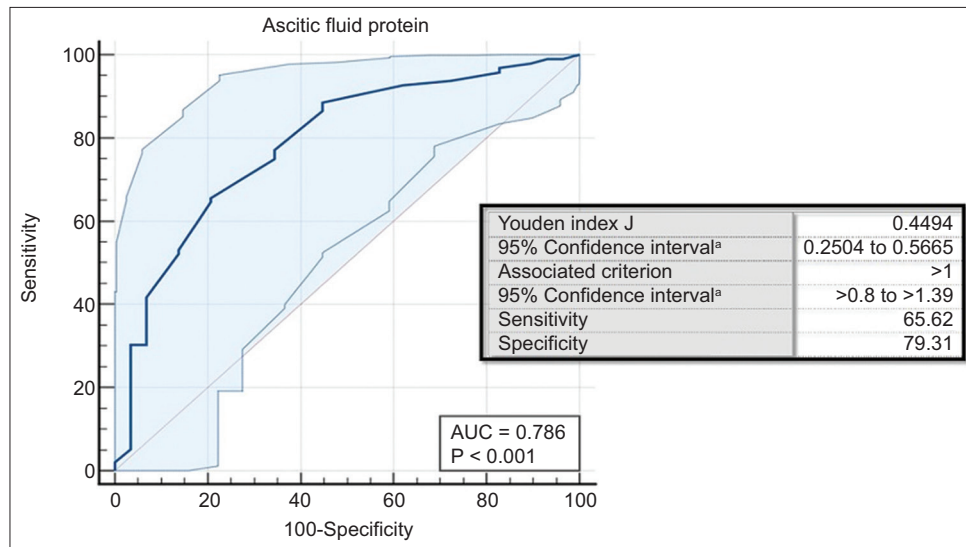
### AUROC curve to predict LVDD by ascitic fluid analysis

Mean ascitic fluid protein and ascitic fluid albumin in patients without LVDD ( $0.7\pm0.5$  g/dL and  $0.28\pm0.22$  g/dL), those with grade-1 LVDD ( $1\pm0.53$  g/dL and  $0.4\pm0.23$  g/dL) and those with grade-2 LVDD were ( $1.13\pm0.55$  g/dL and  $0.47\pm0.23$  g/dL). We observed a significant difference in the mean values of ascitic fluid protein and ascitic fluid albumin between the various grades of LVDD ( $P=0.001$  and  $P=0.002$ , respectively). The AUROC curve of these parameters was plotted. The AUROC was 0.78 for ascitic fluid protein and 0.68 for ascitic fluid albumin in predicting LVDD (Fig. 2). By Youden's index, the optimum cutoff for ascitic fluid protein to diagnose LVDD was >1 g/dL ( $P<0.001$ , sensitivity 65.62%, specificity 79.31%).

### Discussion

The prevalence of LVDD (68.4%) in our study was similar to that in a recent study from India by Behera *et al* [15] (66.3%)





**Figure 2** Area under the receiver operating characteristic curve (AUROC) to predict accuracy of ascitic fluid protein for left ventricular diastolic dysfunction (LVDD)

AUC, area under the curve

**Table 4** Binary logistic regression multivariate analysis for independent predictors of LVDD

Variables	P-value	Exp (B)	95% confidence interval	
			Lower	Upper
CTP score	0.008	2.33	1.25	4.34
Corrected QT interval	0.016	1.02	1.02	1.00
Obesity	0.221	0.294	0.42	2.08
Ascitic fluid protein	0.018	36.38	1.76	707.6
Age	0.356	1.04	0.957	1.130
HRS	0.167	7.81	0.422	144.7
HE	0.308	0.262	0.20	3.43
NASH	0.998	2.25	0.00	

LVDD, left ventricular diastolic dysfunction; CTP, Child-Turcotte-Pugh; NASH, nonalcoholic steatohepatitis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy

and higher than in previously reported studies [12,16]. The higher prevalence of LVDD reported in our study may be due to the fact that our study population included more patients with decompensated cirrhosis.

Alcohol consumption was our study's most common etiology of cirrhosis (84.7% of patients, perhaps because of the high prevalence of males in our study), followed by NASH (18.7%). In our study, the prevalence of HBV was 10.9% and HCV was 3%. Patients with HCV-related liver cirrhosis showed a greater tendency to have LVDD than those with HBV-related liver cirrhosis. These findings were in contrast to previous studies by Karagiannakis *et al*, Dadhich *et al* and Raevens *et al*, which showed no relation between LVDD and the etiology of liver cirrhosis [16-18].

NASH-related chronic liver disease is associated with elevated systemic proinflammatory cytokines such as interleukin [IL]-1 $\beta$ , IL-6, C-reactive protein-reactive protein and tumor necrosis factor- $\alpha$ , and with increased levels of dimethyl arginine, leading to endothelial dysfunction [19,20]. Proinflammatory cytokines, procoagulants and adhesion molecules produced during the necro-inflammatory phase of NASH seem to be implicated in changes in myocardial structure, ultimately increasing the stiffness of left ventricular myocardium [21]. NAFLD patients have low early diastolic relaxation and lower systolic velocity on TDI echocardiography, suggesting impaired diastolic function [22]. We found a significant association of LVDD with NASH compared to the non-NASH population, with an odds ratio of 3.67, 95%CI 1.361-9.916.

In our study, CTP class, higher CTP and MELD scores, elevated ascitic fluid albumin and ascitic fluid protein, a prolonged QTc interval, and low serum protein and serum albumin were significantly associated with the severity of LVDD. These variables correlate with the severity of liver disease, which directly translates to hyperdynamic circulation, volume overload, and increased systemic proinflammatory mediators.

In our study, CTP classes B and C had a significant association with LVDD, compared to class A patients (OR 4.35, 95%CI 1.62-11.66; P<0.001). Hence, decompensated liver cirrhosis is a significant risk factor for developing LVDD. The CTP class and the mean CTP scores help identify cirrhotic patients who are more prone to develop LVDD. Studies from India by Bhui *et al* [23] and Prashant *et al* [24] also reported a significant association of LVDD with the severity of cirrhosis. We found a significant correlation between the mean MELD scores in patients with and without LVDD (P=0.001). Our findings were consistent with the studies by Behera *et al* [15],

Ruiz-de-Arbor *et al* [25] ( $P < 0.01$ ) and Rimbasi *et al* [26] ( $P = 0.005$ ). The pathogenesis of our findings can be explained by the fact that spontaneous portosystemic shunts develop as the portal venous pressure increases with advanced liver cirrhosis. These shunts increase pulmonary flow and vasoactive mediator transit, causing pulmonary vasculature and cardiac remodeling, leading to left ventricular diastolic dysfunction.

All complications of liver cirrhosis were higher in patients with LVDD. The most significant association noted in our study was with HRS, ascites and HE complications (OR 12.52, 95%CI 2.06-17.7; OR 4.58, 95%CI 2.41-8.68; and OR 2.43, 95%CI 1.25-4.91 respectively). Recent Indian studies by Behera *et al* [12] and Premkumar *et al* [27] also showed a significant correlation between the degree of LVDD and complications of cirrhosis (HRS, sepsis, and HE). Moreover, in patients with ascites, higher grades are significantly associated with higher grades of LVDD (grade-2 > grade-1 > no LVDD). Diastolic dysfunction is associated with impaired cardiac chronotropic function, which significantly reduces effective arterial blood volume. This can lead to a decrease in renal perfusion and thus contribute to the pathogenesis of hepatorenal syndrome. The decreased effective arterial blood volume can cause water retention, which can further worsen the ascites [25,27,28]. The cardiac dysfunction is asymptomatic and manifests only during stress, such as transjugular intrahepatic portosystemic shunt or liver transplantation. It can manifest postoperatively as sudden heart failure and pulmonary edema [30]. However, we did not find an association with complications such as variceal bleeding, the number of endoscopic variceal band ligations, SBP, and jaundice. Most patients with a history of variceal bleeding were on  $\beta$ -blocker therapy, which could have protective effects against cardiac remodeling.

Patients were followed up for 6 months or until death, whichever occurred first. The liver-related mortality in our study was 28.5%. Patients with LVDD were more likely to die than those without, with an OR of 5.84, 95%CI 2.35-14.5. In addition, patients with grade-2 LVDD had higher mortality than those with grade-1 LVDD ( $P < 0.001$ ). These results were similar to those of a previous study by Lee *et al* [12]. According to the "window hypothesis", cardiac reserve decreases as the liver disease progresses, ultimately leading to an increase in mortality [2]. Moreover, these patients cannot compensate for stress stimuli such as sepsis, leading to higher mortality [29].

Our patients' left ventricular ejection fraction was within normal limits. This finding was in agreement with previous studies demonstrating that LVDD precedes systolic dysfunction. Patients with cirrhosis tend to form peripheral arterio-venous shunts. This could increase arterial blood flow and decrease systemic vascular resistance, leading to high cardiac output.

In this study, we found a statistically significant difference in mean QTc interval between patients with LVDD and those without. In addition, a history of obesity had a significant association with the presence of LVDD ( $P = 0.006$ ), suggesting a link between metabolic syndrome and LVDD. Patients

with a history of obesity had a 3.28 times higher chance of developing LVDD. On multivariate analysis, we found that a higher CTP score, higher ascitic fluid protein, and prolonged QTc interval were independent predictors for the development of LVDD, even after controlling with age as a confounding factor.

Ascitic fluid protein was the best predictor of LVDD (AUROC 0.78,  $P < 0.001$ ). The optimum cutoff for ascitic fluid protein to predict LVDD was  $> 1.0$  (sensitivity 65.62%, specificity 79.31%). Whether this is a cause or an effect of LVDD remains to be evaluated.

Compared to previous studies, our study has covered various variables, including etiology, duration of cirrhosis, severity parameters, survival status and higher sample size, which could give a better picture of the correlation between liver cirrhosis and LVDD. LVDD is a silent entity for mortality prediction, and highlighting these findings will help better categorise decompensated patients with cirrhotic cardiomyopathy for liver transplant listing. The severity parameters like CTP and MELD scores, ascitic fluid protein have proven to be the additional factors predicting the development of LVDD. Patients with NASH-related cirrhosis need a meticulous cardiac workup for better evaluation of prognosis.

One limitation of our study was the short follow-up period of 6 months. A longer follow-up time would have given more information on the prognostic effect of LVDD in cirrhotic patients. In addition, this study did not perform invasive cardiopulmonary pressure and neurohormonal measurements, such as like plasma renin levels, aldosterone levels, and brain natriuretic peptide levels, to assess the cardiac chronotropic response to circulatory dysfunction. This study did not screen cirrhotic patients for hepatopulmonary syndrome, which could subclinically affect LVDD.

In conclusion, patients with NASH-related cirrhosis have a propensity for the development of LVDD. The CTP and MELD scores help stratify risk and identify which liver cirrhosis patients are more prone to developing LVDD. Early detection and management of these patients could help prevent permanent damage from cirrhotic cardiomyopathy. The presence of LVDD is a good predictor of mortality. Therefore, patients with higher ascitic fluid protein levels and prolonged QTc interval should be screened for LVDD. An ascitic fluid protein level  $> 1.0$  g/dL could be an easy bedside tool to identify patients at high risk of developing LVDD.

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## Summary Box

### What is already known:

- The prevalence of left ventricular diastolic dysfunction (LVDD) is high in decompensated chronic liver disease
- Patients with higher Child-Turcotte-Pugh and model for end-stage liver disease scores have a greater chance of developing LVDD
- The presence of LVDD is predictive of poor survival status

### What the new findings are:

- Patients with cirrhosis caused by nonalcoholic steatohepatitis had a higher tendency to develop LVDD
- A cirrhosis duration >2 years was associated with a higher risk of developing LVDD
- Ascitic fluid protein >1 g/dL was an independent predictor of the presence of LVDD in cirrhosis
- LVDD grade was linearly correlated with poorer survival status

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