Left Ventricular Diastolic Dysfunction Increases the Risk of Medium-term Mortality in Patients with Cirrhotic Ascites

SHENG-HAO LI[1#], LU ZHANG[1#], HONG-JUAN LI[2], YE LI[1], YAN-MIN ZHENG[1], QING-QING WANG[3*]

[1] School of Public Health, School of Public Health, Dali University, no. 2, Hongsheng Road, Dali Town, Dali Bai Autonomous Prefecture, Dali City 671000, Yunnan Province, P.R. China
[2] Department of Palliative Medicine, The Third People's Hospital of Kunming/Yunnan Clinical Center for Infectious Diseases, no. 319 Wujing Road, Guandu District, Kunming City 650041, Yunnan Province, P.R. China
[3] Department of Hepatology 1, The Third People's Hospital of Kunming/Yunnan Clinical Center for Infectious Diseases, no. 319 Wujing Road, Guandu District, Kunming City 650041, Yunnan Province, P.R. China
[#]Authors contributed equally to this work
[*] Corresponding author

Abstract. Objective: To elucidate the impact of left ventricular diastolic dysfunction (LVDD) on the risk of medium-term poor prognosis in patients with cirrhotic ascites. **Methods:** A total of 194 patients with cirrhotic ascites were included in this retrospective study and categorized into two groups (LVDD and non-LVDD) based on echocardiography findings. Lasso and univariate Cox regression analyses were initially used to screen potential influencing factors of 1-year mortality from basic clinical data. Multivariate Cox regression was then performed to identify independent risk factors. Kaplan–Meier (K-M) and time-dependent receiver operating characteristic (ROC) curves were used to assess the predictive value of LVDD for 1-year mortality. Subgroup analysis was also conducted based on the presence or absence of hepatic malignancy. **Results:** (1) LVDD was present in 47.4% (92/194) of patients with cirrhotic ascites; (2) Regression analyses (Lasso, univariate Cox, and multivariate Cox) revealed that LVDD (hazard ratio = 2.109, 95% confidence interval [1.279–3.478], P = 0.003) was an independent risk factor for 1-year mortality; (3) Time-dependent ROC curves demonstrated that the predictive performance of LVDD for 360-day mortality, in the overall population and patients without hepatic malignancy, was comparable to that of traditional Child–Turcotte–Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores (P > 0.05 for all). **Conclusion:** LVDD increases the risk of 1-year mortality in patients with cirrhotic ascites, particularly in those without hepatic malignancy.

Keywords: cirrhotic ascites, hepato-cardiac disorder, left ventricular diastolic dysfunction, clinic risk factor, medium-term poor clinical outcome.

1. INTRODUCTION

Cirrhosis is one of the leading causes of death [1] worldwide, with at least one million deaths occurring each year [2]. Ascites, an important marker of progression to the decompensated stage in the natural course of cirrhosis, occurs in approximately 50% of patients with cirrhosis within 10 years [3]. Once ascites develops, patients with cirrhosis experience a sharp rise in mortality, with a 1-year and 5-year death rate of 20% [4] and 44%, respectively [5].

Although some treatment methods, such as the use of diuretics or albumin (ALB), have achieved remarkable progress in patients with cirrhotic ascites [6], the frequent relapses of ascites, high incidence of complications (including spontaneous bacterial peritonitis [SBP], hepatic encephalopathy [HE], and sepsis), high mortality rate, and poor quality of life currently remain major problems that trouble clinicians. Exploring the factors influencing adverse prognosis in such patients remains essential for providing breakthroughs for more effective management.

Patients with cirrhosis often have various complications related to abnormalities of cardiac structure or function [7], such as cirrhotic cardiomyopathy [8], arrhythmia [9], and portopulmonary hypertension [10]. In addition to liver function and traditional complications (such as SBP and HE), cardiovascular abnormalities can also contribute to poor clinical outcomes [11], highlighting the need to pay more attention to cardiac issues in patients with cirrhosis. LVDD,

occurring in 25.7–81.4% of patients with cirrhosis, is the earliest manifestation of cardiac insufficiency [12] and becomes more common when complicated by ascites. It is closely related to disease severity [13]. However, in a systematic review, Ieva S. *et al.* [13] proposed that LVDD, a characteristic of liver cirrhosis, has not yet received sufficient attention from clinicians. Particularly, the predictive value for prognosis of LVDD in cirrhotic patients after the onset of ascites, and whether it can be extended to subgroups of patients with or without concomitant hepatic malignancies, remains unclear.

Therefore, this study aimed to elucidate the impact of LVDD on the risk of medium-term poor prognosis in patients with cirrhotic ascites. Moreover, subgroup analyses stratified by the presence or absence of concomitant hepatic malignancy were also conducted. It explores new predictive markers for patients with cirrhotic ascites and provides a new perspective for treatment strategies.

2. MATERIALS AND METHODS

2.1. STUDY PARTICIPANTS

Patients with cirrhotic ascites admitted to the Hepatic Center of the Third People's Hospital of Kunming, Yunnan Province, China, were consecutively enrolled in this retrospective study between October 4, 2022, and October 3, 2023. The enrolled participants met the diagnostic criteria for cirrhotic ascites in the "Guidelines for the Diagnosis and Treatment of Cirrhotic Ascites (2023)" [14]. The exclusion criteria included: (1) Ascites not caused by liver cirrhosis; (2) Pregnancy; (3) Hypertension or diabetes mellitus; (4) Coronary heart disease, rheumatic heart disease, congenital heart disease, or a history of cardiac surgery; (5) Incomplete clinical data; and; (6) Refusal to sign the informed consent form.

2.2. ECHOCARDIOGRAPHIC EXAMINATION AND GROUPING

Transthoracic echocardiography (TTE) was performed by the same senior ultrasonologist to assess left ventricular diastolic function (LVDF) in all participants. Based on baseline TTE results, patients were categorized into two groups: LVDD and non-LVDD. The diagnostic criteria for LVDD followed the European "Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography (2009)" [15].

2.3. DATA COLLECTION

To obtain clinical outcomes, all participants were followed up for at least 12 months (deadline: October 3, 2024) via cellphone. Case report forms were used to record demographic data, basic clinical information, TTE parameters, and routine laboratory data (including liver and renal function, blood cell analysis, coagulation, inflammatory indexes, and alpha-fetoprotein). All datasets were entered into the EpiData database using manual double-entry.

2.4. STATISTICAL ANALYSIS

Datasets were analyzed using SPSS 26.0 or R 4.3.3 software. Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± s), and an independent samples t-test was used for comparison between the two groups if normally distributed. If not normally distributed, data are described as median (lower quartile, upper quartile) (M [P25, P75]), and the Mann–Whitney U test was used. Enumeration data are expressed as rates or percentages (%), and the chi-square test was used for comparison between groups.

LASSO regression was used to reduce collinearity and perform the preliminary variable selection. LASSO shrinks the coefficients of irrelevant variables to zero by introducing an L1 penalty term into the loss function and subsequently effectively removes them from the model. Specifically, when the absolute value of a variable's coefficient is less than the penalty parameter λ, it is shrunk directly to zero. The optimal β value was determined via 10-fold cross-validation, and the λ.1se criterion – the value of λ within one standard error of the minimum cross-validated error that yields the simplest model. Using one-year mortality as the dependent variable, we screened 75 candidate variables spanning 5 domains (demographics, basic clinical information, liver functions, laboratory findings, and cardiac parameters of TTE) and identified predictors with non-zero coefficients. The predictors with $|\beta| > \lambda$ and under the chosen penalty strength, which provide independent and meaningful information for explaining outcome variation, were used to construct the final multivariate model.

Furthermore, all the potential influencing factors selected via Lasso regression will be used in univariate Cox regression, through which those variables with $P < 0.05$ will then be included in multivariate Cox regression to ultimately identify

independent influencing factors for the 1-year mortality risk.

K-M curves were then used to visualize differences in mortality risk with or without LVDD. Finally, time-dependent receiver operating characteristic (ROC) curves were used to assess the predictive efficacy of LVDD for 1-year cumulative mortality risk in patients with cirrhotic ascites. The DeLong test was used to compare the areas under the ROC curves (AUCs) of LVDD with those of traditional liver function models, including the MELD score and CTP classification.

Statistical significance was set at $P < 0.05$. The K-M and time-dependent ROC curves were plotted using R 4.3.3 software.

3. RESULTS

3.1. DEMOGRAPHIC, BASIC CLINICAL CHARACTERISTICS, TTE PARAMETERS, AND BASELINE INFORMATION OF THE PARTICIPANTS

As shown in Table 1, a total of 194 patients with cirrhotic ascites met the inclusion and exclusion criteria and were enrolled in this study. The study included 135 males (69.5%) and 59 females (30.4%), with a median age of 55(47.00, 60.25) years (Table 1). Sixty-eight patients (35.1%) had grade 1 ascites (ascites depth < 3 cm), 114 (58.8%) had grade 2 ascites (depth 3–10 cm), and 12 (6.2%) had grade 3 ascites (depth > 10 cm). The MELD and CTP scores were 13.3 ± 5.2 and 9.2 ± 2.1, respectively.

To elucidate the influence of cardiac structure and function on mortality risk in patients with cirrhosis, TTE was performed, and relevant parameters were recorded, including stroke volume (70.0 [61.0, 80.0] mL), ejection fraction (68.0 [64.0, 73.0]%), end-systolic volume (31.0 [23.0, 40.0] mL), end-diastolic volume (100.5 [89.0, 117.2] mL), and E-wave/A-wave ratio (0.9 [0.7, 1.3]). Based on TTE results, participants were categorized into two groups: LVDD and non-LVDD. Approximately 47.4% (92/194) of participants were diagnosed with LVDD, while the remaining 52.6% (102/194) belonged to the non-LVDD group. Comparative analysis showed that the LVDD group had significantly lower ALB levels and significantly higher age, potassium, and blood urea nitrogen levels ($P < 0.05$). (Tables 1 and 2).

The baseline characteristics or other supporting datasets of demographics, basic clinical information, liver functions, laboratory findings, and cardiac parameters of TTE used in the following analyses were also provided in Tables 1 and 2.

Table 1

Demographic, basic clinical characteristics, and baseline information

Factors	Total (n = 194)	Non-LVDD group (n = 102)	LVDD group (n = 92)	t/Z/χ^2	*P*
Demographics					
Age, M(P25, P75) years	55.0(47.0, 60.2)	49.0(43.0, 57.3)	59.0(53.2, 65.7)	-5.936	<0.001
Male sex, n(%)	135(69.6)	77(75.5)	58(63)	3.541	0.060
Han ethnicity, n(%)	177(91.2)	96(94.1)	81(88)	2.232	0.135
BMI, M(P25, P75) kg/cm^2	22.0(20.3, 24.3)	22.0(20.0, 23.9)	22.4(20.4, 24.6)	-0.807	0.420
Smoking history, n(%)					
Yes	103(53.1)	60(58.9)	43(46.7)	3.204	0.202
No	84(43.3)	38(37.3)	46(50)		
Quit	7(3.6)	4(3.9)	3(3.3)		
Alcohol consumption, n(%)					
Yes	82(42.3)	48(47.1)	34(37)	2.849	0.241
No	91(46.9)	42(41.2)	49(53.3)		
Quit	21(10.8)	12(11.8)	9(9.8)		
Family history of hepatic malignant, n(%)	22(11.3)	13(12.7)	9(9.8)	0.422	0.516
Basic clinical information					
Etiology of cirrhosis, n(%)					
Viral hepatitis	144(74.2)	83(81.4)	61(66.2)	7.603	0.055
Alcohol	17(8.8)	6(5.9)	11(12)		

Table 1 (continued)

Factors	Total (n = 194)	Non-LVDD group (n = 102)	LVDD group (n = 92)	t/Z/χ^2	*P*
Virus + Alcohol	18(9.3)	9(8.8)	9(9.8)		
Others	15(7.7)	4(3.9)	11(12)		
Hepatic malignant, n(%)	124(63.9)	31(30.4)	39(42.4)	3.020	0.082
EGVB, n(%)	22(11.3)	12(11.8)	10(10.9)	0.039	0.844
Systolic blood pressure, M(P25, P75) mmHg	115.0(104.0, 128.0)	115.0(101.7, 122.0)	117.0(105.0, 134.0)	-1.752	0.080
Diastolic blood pressure, M(P25, P75) mmHg	72.0(66.0, 82.0)	71.0(65.0, 78.0)	74.0(68.0, 85.0)	-2.066	0.039
Heart rate, M(P25, P75) bpm	82.0(72.0, 92.0)	80.0(72.0, 91.0)	83.5(71.3, 92.0)	-0.334	0.738.
Liver function					
CTP, M(P25, P75) scores	9.0(8.0, 11.0)	9.0(7.0, 11.0)	9.0(8.0, 11.0)	-0.889	0.374
MELD, M(P25, P75) scores	12.6(10.0, 17.0)	12.4(10.1, 16.4)	12.6(9.5, 15.7)	-0.517	0.605
Laboratory findings					
TBIL, M(P25, P75) μmol/L	31.9(18.2, 64.5)	32.2(18.0, 77.8)	31.6(18.2, 58.1)	-0.142	0.887
DBIL, M(P25, P75) μmol/L	14.4(7.8, 36.0)	13.3(7.5, 44.6)	14.6(7.8, 28.8)	-0.187	0.852
ALT, M(P25, P75) U/L	35.0(23.0, 75.0)	37.0(24.8, 72.3)	32.5(23.0, 78.0)	-0.940	0.347
AST, M(P25, P75) U/L	54.0(37.8, 120.0)	58.5(37.0, 109.75)	51.0(38.0, 132.7)	-0069	0.945
GGT, M(P25, P75) U/L	96.0(40.8, 169.6)	80.5(38.7, 156.3)	103.5(46.4, 162.7)	-1.247	0.212
ALP, M(P25, P75) U/L	142.0(102.8, 201.2)	142.0(105.2, 195.0)	153(100.0, 217.0)	-0.513	0.608
TP, M(P25, P75) g/L	61.6(57.5, 67.4)	61.8(57.0, 67.1)	61.3(57.7, 68.2)	-0.133	0.894
PALB, M(P25, P75) g/L	76.1(49.1, 110.3)	77.0(46.4, 105.4)	71.1(52.1, 112.8)	-0.428	0.669
ALB, M(P25, P75) g/L	29.5(25.7, 33.3)	30.2(27.3, 35.0)	28.2(24.8, 31.8)	-2.596	0.009
GLOB, M(P25, P75) g/L	31.2(27.2, 36.7)	30.4(27.0, 35.5)	32.1(28.0, 37.8)	-1.629	0.103
CHE, M(P25, P75) U/L	2978.0(2136.8, 4008.3)	2978.0(2214.0, 3999.0)	2886.5(2089.7, 4253.5)	-0.636	0.525
PT, M(P25, P75) sec	16.6(15.3, 18.4)	16.6(15.3, 18.4)	16.6(15.4, 18.1)	-0.236	0.814
PTA, M(P25, P75) %	59.8(68.0, 50.7)	59.7(50.1, 69.9)	59.8(51.0, 68.0)	-0.008	0.994
INR, M(P25, P75)	1.4(1.3, 1.6)	1.4(1.2, 1.6)	1.4(1.2, 1.5)	-0.003	0.998
WBC, M(P25, P75) $\times10^9$/L	4.4(3.1, 7.3)	4.1(2.7, 7.9)	4.5(3.4, 7.4)	-1.694	0.092
RBC, ($\bar{x}\pm s$) $\times10^{12}$/L	3.6±0.8	3.6±0.7	3.5±0.8	0.556	0.579
HGB, M(P25, P75) g/L	115.0(97.8, 133.0)	117.5(95.0, 132.3)	115.0(99.3, 133.0)	0.080	0.937
PLT, M(P25, P75) $\times10^9$/L	89.5(59.7, 141.5)	83.5(53.7, 139.0)	100.0(71.2, 142.5)	-1.580	0.114
K, ($\bar{x}\pm s$) mmol/L	3.7±0.5	3.7±0.5	3.8±0.5	-2.053	0.041
Na, M(P25, P75) mmol/L	138.9(136.1, 141.1)	138.9(136.5, 141.2)	108.9(105.8, 140.8)	-0.690	0.490
Ca, ($\bar{x}\pm s$) mmol/L	2.1±0.2	2.0±0.1	2.09±0.2	-0.752	0.453
CL, M(P25, P75) mmol/L	106.9(136.1, 141.1)	106.9(103.9, 109.4)	106.5(103.1, 109.4)	-0.491	0.630
CO_2, M(P25, P75) mmol/L	23.3(21.5, 25.2)	23.2(21.7, 24.9)	23.4(21.3, 25.2)	-0.122	0.903
BUN, M(P25, P75) mmol/L	4.8(3.8, 7.1)	4.5(3.6, 6.5)	5.2(4.1, 8.5)	-2.768	0.006
Crea, M(P25, P75) μmol/L	61.5(52.0, 74.0)	60.0(49.0, 73.0)	63.5(53.0, 80.7)	-1.515	0.130
UA, M(P25, P75) μmol/L	295.0(244.0, 375.2)	290.5(243.7, 355.2)	301(242.2, 406.0)	-0.946	0.344
FPG, M(P25, P75) mmol/L	5.6(4.9, 7.4)	5.5(4.8, 7.1)	5.7(5.0, 8.2)	-1.375	0.169
TG, M(P25, P75) mmol/L	0.8(0.6, 1.3)	0.8(0.5, 1.2)	0.8(0.6, 1.2)	-1.204	0.229
CHOL, M(P25, P75) mmol/L	3.2(2.6, 3.9)	3.1(2.5, 3.5)	3.1(2.7, 4.2)	-2.427	0.015
HDL-C, M(P25, P75) mmol/L	0.8(0.5, 1.1)	0.7(0.4, 1.0)	0.7(0.5, 1.0)	-0.552	0.581
LDL-C, M(P25, P75) mmol/L	1.9(1.4, 2.5)	1.8(1.3, 2.2)	2.0(1.4, 2.8)	-2.957	0.003
CEA, M(P25, P75) μg/L	3.2(2.1, 4.8)	3.0(2.0, 4.5)	3.6(2.3, 5.0)	-2.300	0.021
AFP, M(P25, P75) μg/L	6.4(3.1, 66.7)	6.3(3.2, 38.9)	6.8(2.8, 100.4)	-0.391	0.696

Table 1 (continued)

Factors	Total (n = 194)	Non-LVDD group (n = 102)	LVDD group (n = 92)	t/Z/χ^2	*P*
CA125, M(P25, P75) U/mL	107.5(31.5, 276.5)	76.8(27.9, 228.2)	152.9(40.9, 442.8)	-2.944	0.003
CA199, M(P25, P75) U/mL	31.8(17.4, 68.5)	31.5(16.3, 72.9)	34.0(18.3, 67.2)	-0.210	0.834
LYMP, M(P25, P75) $\times 10^9$/L	0.9(0.6, 1.3)	0.9(0.5, 1.2)	0.9(0.5, 1.2)	-0.344	0.730
HCT, ($\bar{x}\pm s$) %	33.0±7.6	33.0±7.1	33.0±8.1	0.013	0.990
RDW, M(P25, P75) fL	15.7(14.4, 17.0)	15.7(14.4, 17.2)	15.3(14.2, 16.9)	-0.613	0.540

Note: Abbreviations: Body Mass Index (BMI), Esophageal GastroVariceal Bleeding (EGVB), White Blood Cell Count (WBC), Red Blood Cell Count (RBC), Hemoglobin (HGB), Platelet (PLT), Potassium (K), Sodium (Na), Blood Urea Nitrogen (BUN), Creatinine (Crea), Total Bilirubin (TBIL), Direct Bilirubin (DBIL), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Albumin (ALB), International Normalized Ratio (INR), Lymphocyte Count (LYMP), Hematocrit (HCT), Red Blood Cell Distribution Width (RDW), Calcium (Ca), Chloride (CL), Carbon Dioxide Content (CO_2), Uric Acid (UA), Fasting Plasma Glucose (FPG), Gamma-Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), Total Protein (TP), Prealbumin (PALB), Globulin (GLOB), Cholinesterase (CHE), Triglyceride (TG), CHOL, High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), Carcinoembryonic Antigen (CEA), Alpha-Fetoprotein (AFP), Cancer Antigen 125 (CA125), Cancer Antigen 19-9 (CA199), Prothrombin Time (PT), Prothrombin Time Activity (PTA).

Table 2

Cardiac parameters of TTE [M(P25, P75)]

Parameters of TTE	Total (n = 194)	Non-LVDD group (n = 102)	LVDD group (n = 92)	t/Z/χ^2	*P*
Aortic Valve Ring Internal Diameter, mm	23.0(22.0, 25.0)	23.0(22.0, 25.0)	24.0(21.2, 25.7)	-1.382	0.173
Ascending Aorta Internal Diameter, mm	25.0(23.0, 27.0)	25.0(23.0, 26.0)	25.5(23.0, 28.0)	-1.947	0.052
Mitral annulus diameter (MAD), mm	20.0(18.0, 22.0)	20.0(18.0, 22.0)	21.0(19.0, 22.0)	-0.897	0.370
Left Cardiac Chamber Diameter (LCD), mm	28.0(26.0, 31.0)	28.0(25.0, 31.0)	28.0(26.0, 31.0)	-0.435	0.663
Intrapericardial Pressure, mmHg	42.0(38.7, 46.0)	43.0(39.0, 46.0)	42.0(39.0, 46.0)	-0.785	0.432
Right Ventricular Diameter, mm	20.0(18.0, 22.0)	20.0(18.0, 22.0)	20.0(18.0, 21.7)	-0.784	0.433
Right Atrial Diameter, mm	32.0(30.0, 35.0)	32.5(30.0, 35.0)	32.0(29.0, 34.0)	-1.255	0.210
Right Ventricular Outflow Tract Diameter (RVOTD), mm	22.0(20.0, 24.0)	22.0(20.0, 24.0)	23.0(21.0, 25.0)	-1.573	0.116
Interventricular Septum Thickness, mm	9.0(8.0, 10.0)	9.0(8.0, 10.0)	9.0(8.0, 10.0)	-1.385	0.166
Left Posterior Wall Thickness, mm	9.0(8.0, 10.0)	9.0(8.0, 10.0)	9.0(8.0, 10.0)	-1.015	0.310
end-diastolic volume (EDV), ml	100.5(89.0, 117.2)	102.0(89.0, 113.0)	99.5(89.5, 121.0)	-0.320	0.749
end-systolic volume (ESV), ml	31.0(23.0, 40.0)	31.0(24.0, 40.0)	32.0(23.0, 42.5)	-0.238	0.812
ejection fraction (EF), %	68.0(64.0, 73.0)	69.0(64.0, 72.2)	67.0(63.0, 73.0)	-0.792	0.428
Fractional Shortening, %	38.0(34.0, 42.0)	38.0(35.0, 42.0)	37.0(34.0, 42.7)	-0.921	0.357
stroke volume (SV), ml	70.0(61.0, 80.0)	69.5(60.0, 78.6)	71.0(61.0, 80.0)	-0.353	0.724
E-point Septal Separation, mm	5.0(5.0, 6.0)	5.0(5.0, 6.0)	5.0(5.0, 6.0)	-1.358	0.174
Pulmonary Artery Systolic Pressure, mmHg	24.0(22.7, 28.0)	24.0(21.0, 28.0)	24.0(23.0, 28.0)	-0.116	0.908
Tricuspid Regurgitation (peak velocity), m/s	220.0(210.0, 246.0)	220.0(200.0, 240.0)	220.0(210.0, 240.0)	-0.275	0.783
Pulmonary Artery Valve Forward Flow Rate, m/s	113.0(96.7, 131.0)	111.0(94.7, 130.0)	113.0(100.0, 134.2)	-0.899	0.369
Pulmonary Pulmonic Valve Forward Flow Rate, m/s	90.0(80.0, 104.5)	90.5(80.7,102.2)	90.0(80.0, 106.7)	-0.193	0.847
E-wave/A-wave ratio (E/A)	0.9(0.7, 1.3)	1.2(1.0, 1.3)	0.7(0.6, 0.8)	-9.412	<0.001

3.2. IDENTIFICATION OF LVDD'S PREDICTIVE VALUE FOR 1-YEAR DEATH RISK IN PATIENTS WITH CIRRHOTIC ASCITES

Using 1-year mortality risk as the dependent variable, Lasso regression was used to reduce collinearity and identify potential influencing factors from 75 candidate variables across five dimensions (including demographics, basic clinical information, liver functions, laboratory findings, and cardiac parameters of TTE) listed in Tables 1 and 2. For the total cohort (Fig. 1A and B), the 10-fold cross-validation of Lasso regression shows that the log(λ.min) was -3.56, which corresponded to 19 model variables, and the log(λ.1se) was -2.90, which corresponded to 13 model variables. The model with a log(λ.1se) value of -2.90 was the optimal model we selected, and those 13 corresponding variables it contained, including BMI, hepatic malignancy, mitral annular disjunction (MAD), right ventricular outflow tract diameter (RVOTD), LVDD, WBC, PLT, Na, DBIL, GGT, ALP, CHE, and INR, were just the potential influencing factors screened out.

Subsequently, univariate Cox regression removed MAD, retaining 12 variables. Multivariate Cox regression further identified the following independent risk factors for 1-year mortality (Table 3): LVDD (*HR* = 2.109, 95% *CI* [1.279–3.478], *P* = 0.003), hepatic malignancy (*HR* = 1.863, 95% *CI* [1.107–3.141], *P* = 0.019) and RVOTD (*HR* = 1.077, 95% *CI* [1.018–1.139], *P* = 0.008), PLT (*HR* = 1.003, 95% *CI* [1.0002–1.0062], *P* = 0.035), and INR (*HR* = 7.031, 95% *CI* [2.504–19.748], *P* < 0.001). In contrast, BMI (*HR* = 0.876, 95% *CI* [0.808–0.950], *P* = 0.001) was a protective factor. MAD, WBC, Na, DBIL, GGT, ALP, and CHE were not retained in the final multivariate model.

To further elucidate the predictive value of LVDD for 1-year mortality, subgroup analyses were conducted based on the presence or absence of hepatic malignancy. For the subgroup without hepatic malignancy (Fig. 1C and D), the log(λ.min) and log(λ.1se) in Lasso regression were -3.10 and -2.54, corresponding to 12 and 10 model variables, respectively. Based on the log(λ.1se) of -2.54, the optimal model was screened out, and a total of 10 corresponding variables, including Etiology of cirrhosis, RVOTD, LVDD, RDW, CO2, CREA, TBIL, CHE, INR, and CTP score, were selected as the potential influence factors. Furthermore, the subsequent univariate and multivariate Cox regression revealed (Table 3) that LVDD was still an independent risk factor in the subgroup without hepatic malignancy (*HR* = 2.351, 95% *CI* [1.040–5.313], *P* = 0.040).

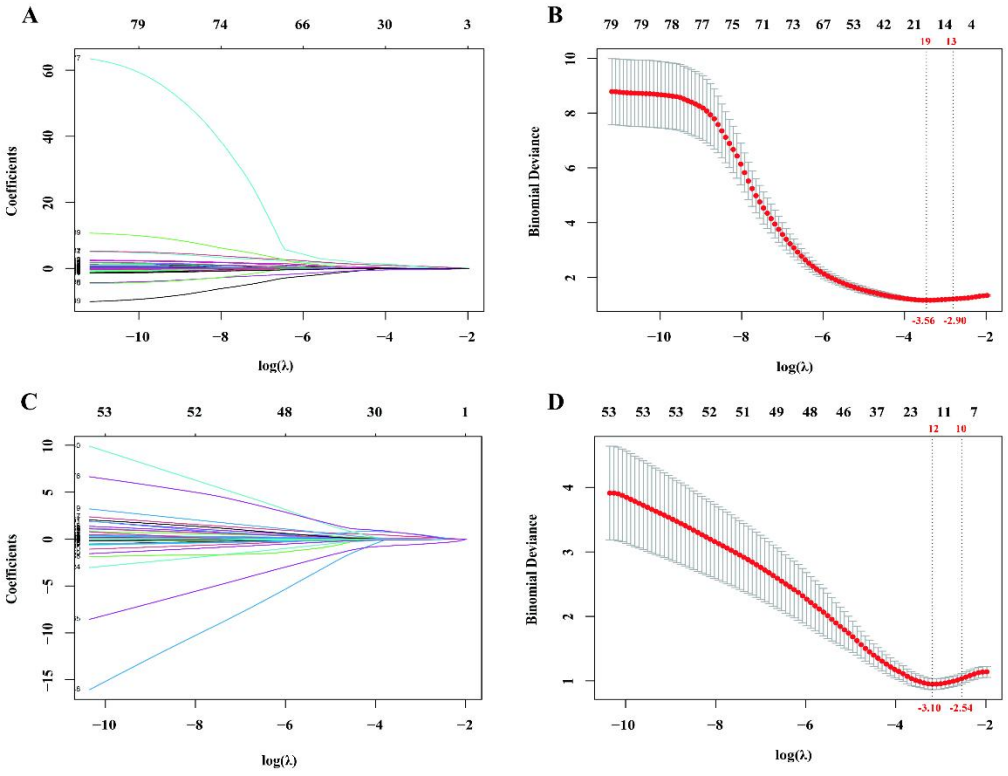

Figure 1. Lasso regression for screening potential influencing factors of 1-year mortality risk.

Note for figure 1: (A) and (B) belong to total cohort, and (C) and (D) belong to subgroup without hepatic malignancy. (A) and (C) are lasso coefficient plots. The vertical axis represents model coefficients, the lower horizontal axis shows the logarithm of λ, and the upper horizontal axis indicates the number of variables corresponding to each λ. λ is the regularization parameter, which controls the degree of penalty applied to model coefficients, thereby balancing the model's fitting ability and complexity. As λ increases, the penalty on model coefficients intensifies, compressing more coefficients toward zero or even setting them to zero. This achieves variable selection by eliminating relatively unimportant predictors, while variables not compressed to zero become the final retained model variables. (B) and (D) are 10-fold cross-validation plots. The vertical axis, Binomial Deviance (also known as Log loss), represents model error. This loss function measures the discrepancy between predicted and observed outcomes, quantifying the quality of model predictions. The lower horizontal axis displays the logarithm of λ, while the upper horizontal axis shows the number of variables corresponding to each λ. The left dashed vertical line indicates λ.min, where model error is minimized, but this model may be relatively complex and carry some risk of overfitting. The right dashed line corresponds to λ.1 standard error (λ.1se), the λ value where the evaluation metric is one standard error larger than that at λ.min. Models at λ.1se sacrifice some predictive accuracy (slightly higher than optimal prediction error) in exchange for a relatively simpler, more stable model with reliable generalization capabilities. Using 1-year mortality risk as the dependent variable, this study selected predictive models from 75 candidate variables across five dimensions (including demographics, basic clinical information, liver functions, laboratory findings, and cardiac parameters of TTE). After Lasso regression, the log(λ.min) and log(λ.1se) for the total cohort were -3.56 and -2.90, corresponding to 19 and 13 model variables, respectively, therefore, the 13 variables associated with log(λ.1se) were identified as potential influencing factors. For the subgroup without hepatic malignancy, log(λ.min) and log(λ.1se) were -3.10 and -2.54, corresponding to 12 and 10 model variables, respectively, so this study adopted the 10 variables corresponding to log(λ.1se) as potential influencing factors.

Table 3

Univariate and multivariate Cox regression of 1-year mortality risk

Participants	Factors	Univariate Cox			Multivariate Cox		
		HR	**95%*CI***	***P*-value**	***HR***	**95%*CI***	***P*-value**
Total	BMI	0.917	0.851–0.987	0.021	0.876	0.808–0.950	0.001
	Hepatic malignancy	2.579	1.635–4.069	<0.001	1.863	1.107–3.141	0.019
	MAD	1.069	0.999–1.155	0.088			
	RVOTD	1.087	1.039–1.137	<0.001	1.077	1.018–1.139	0.008
	LVDD	2.447	1.522–3.933	<0.001	2.109	1.279–3.478	0.003
	WBC	1.114	1.065–1.165	<0.001			
	PLT	1.004	1.002–1.006	<0.001	1.003	1.0002–1.0062	0.035
	Na	0.886	0.839–0.936	<0.001			
	DBIL	1.004	1.001–1.007	0.001			
	GGT	1.001	1.001–1.002	0.007			
	ALP	1.002	1.001–1.003	<0.001			
	CHE	0.352	0.213–0.580	<0.001			
	INR	4.713	2.197–10.110	<0.001	7.031	2.504–19.748	<0.001
Without hepatic malignancy	Etiology of cirrhosis				3.874	1.482–10.129	0.006
	viral hepatitis	1	–	–			
	alcohol	2.169	0.929–5.064	0.074			
	virus+alcohol	0.423	0.056–3.106	0.398			
	others	3.150	1.332–7.448	0.009			
	RVOTD	1.061	1.017–1.107	0.006			
	LVDD	3.020	1.441–6.332	0.003	2.351	1.040–5.313	0.040
	RDW	1.215	1.063–1.388	0.004			
	CO2	0.886	0.828–0.948	<0.001	0.840	0.764–0.922	<0.001
	CREA	1.003	1.001–1.004	0.003			
	TBIL	1.005	1.002–1.008	<0.001	1.007	1.003–1.011	0.001
	CHE	0.248	0.114–0.540	<0.001			
	INR	10.400	2.963–36.510	<0.001			
	CTP score	1.291	1.116–1.494	<0.001			

3.3. COMPARISON OF MORTALITY RISK BETWEEN LVDD AND NON-LVDD GROUPS VIA K–M CURVES

The cumulative mortality risk was statistically higher in the LVDD group than that of the non-LVDD group, as shown by the K-M curves and log-rank test ($P < 0.05$) for all participants (*HR* = 2.447, 95% *CI* [1.522–3.933]) and the subgroup without hepatic malignancy (*HR* = 3.020, 95% *CI* [1.441–6.332]). However, no statistically significant difference was observed in the subgroup with hepatic malignancy (Fig. 2).

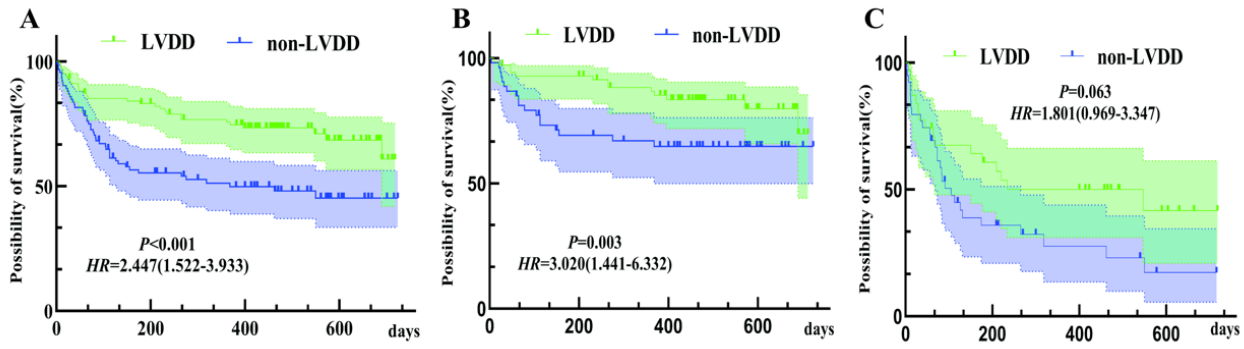

Figure 2. K-M curves showing the predictive value of LVDD vs. non-LVDD for 1-year mortality risk.
(A) Total participants; (B) Without hepatic malignancy; (C) With hepatic malignancy.

3.4. ANALYSIS OF TIME-DEPENDENT ROC CURVES TO ASSESS THE PREDICTIVE EFFICACY OF LVDD FOR MORTALITY

The Delong test (Fig. 3) showed that the AUC of the time-dependent ROC curve for LVDD predicting 360-day mortality was comparable to that of the MELD or CTP score, in the overall population (AUC_{LVDD} = 0.662 [95% *CI*: 0.589–0.735], AUC_{MELD} = 0.612 [95% *CI*: 0.524–0.700], and AUC_{CTP} = 0.674 [95% *CI*: 0.593–0.755]) and the subgroup without hepatic malignancy (AUC_{LVDD} = 0.674 [95% *CI*: 0.571–0.776], AUC_{MELD} = 0.638 [95% *CI*: 0.504–0.773], and AUC_{CTP} = 0.728 [95% *CI*: 0.599–0.836]), with all $P > 0.05$.

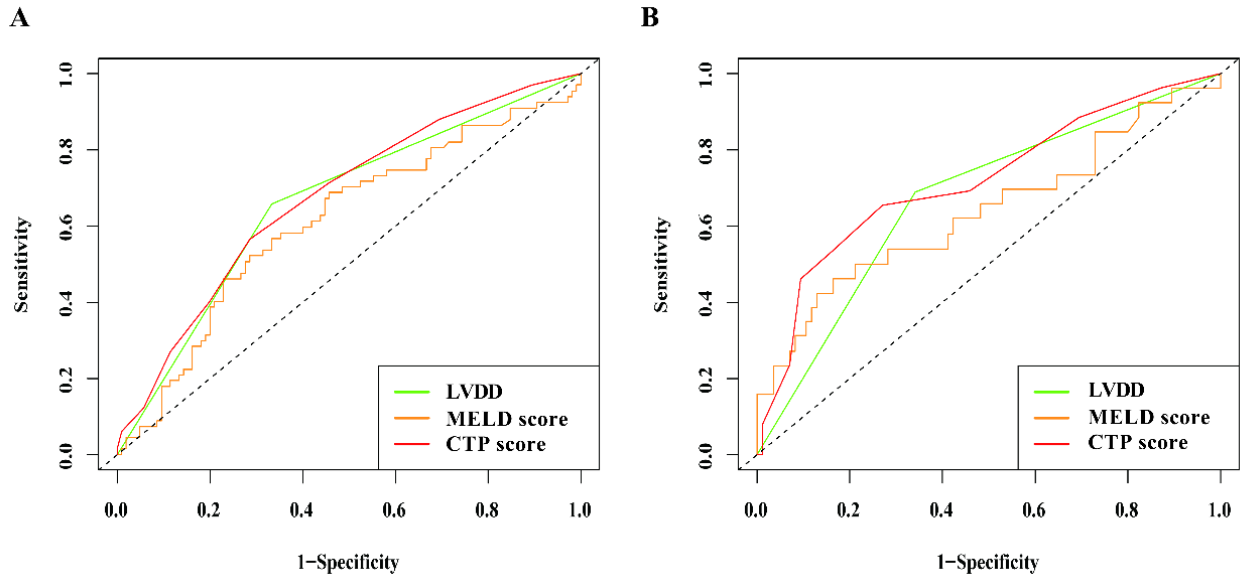

Figure 3. Time-dependent ROC curves showing the efficacy of LVDD in predicting 1-year mortality.
(A) Overall participants; (B) Subgroup without hepatic malignancy.

4. DISCUSSION

Cirrhotic ascites is associated with high mortality globally and is a major challenge to clinicians. Identifying new biomarkers to predict adverse outcomes remains one of the most important aspects of its management. Over the past decades, increasing attention has been directed toward hepato-cardiac disorders [16], opening new avenues for optimizing treatment and improving the prognosis of patients with liver cirrhosis [17].

LVDD, one of the most common cardiac disorders in patients with cirrhosis, has gained increasing attention in recent years [13] and appears to be associated with disease severity, the development of complications, and even mortality [18]. It is reported that the incidence of LVDD in cirrhosis ranges from 25.7% to 81.4% in general [13]. In this study, we observed 47.4% of the patients with cirrhotic ascites complicated with LVDD after the onset of ascites.

An Indian study involving 92 participants revealed that patients with decompensated cirrhosis and MELD scores ≥15 had higher E/e' ratios (an important echocardiographic parameter). Conversely, patients with E/e' ratios >10 had higher MELD and CTP scores, suggesting more severe LVDD in advanced cirrhosis. Cox multivariate analysis further revealed that E/e' ≥10 and serum ALB were independent predictors of mortality in these patients [19]. Other small-sample studies also found that patients with ≥ grade 2 LVDD had lower survival rates. [12] Innovatively and exclusively, this study focused on cirrhotic patients after the onset of ascites and furthermore elucidated the predictive value of LVDD for 1-year mortality risk, which provides a necessary complement to traditional CTP classification and MELD scoring in assessing poor prognosis. It also confirms that LVDD is not merely a consequence of cirrhosis but a contributor to its poor prognosis. Additionally, subgroup analysis was also performed and revealed that the predictive value of LVDD for 1-year mortality risk was applicable to cirrhotic ascites patients without hepatic malignancy.

As shown in Fig. 4, the intrinsic relationship between cirrhosis and LVDD and the corresponding mechanisms are extremely complicated. However, some progress has been made recently. Lower serum ALB, higher MELD scores, presence of ascites, and ascitic fluid protein levels are independent predictors of LVDD in patients with liver cirrhosis [20,21], which indicates that LVDD is closely related to the disease severity in such patients. High-dynamic circulation [22] and activation of the renin-angiotensin-aldosterone system (RAAS) [23] caused by cirrhosis can increase heart rate or cardiac output and subsequently induce myocardial remodelling such as cardiac hypertrophy, fibrosis, and edema [24,25], which is the main mechanism of LVDD development. Conversely, renin activity, glomerular filtration rate, and levels of serum lipopolysaccharide-binding protein, tumor necrosis factor-α, and noradrenaline can induce further gradations to LVDD [26], which can decrease the heart rate-to-norepinephrine ratio, impair cardiac chronotropic function, reduce effective blood volume [27] and renal perfusion (hepatorenal syndrome), and blunt the stress response during sepsis, ultimately leading to poorer outcomes [28] and an increased risk of death [29,30].

Based on our findings, we infer that managing or intervening in LVDD may be an effective approach to improving the prognosis of patients with cirrhotic ascites. Premkumar M. *et al.* [31] found that combining ivabradine with carvedilol improved LVDD, reduced the risk of encephalopathy and acute kidney injury, and improved survival in patients with cirrhosis. Non-selective beta blockers [32], such as propranolol or carvedilol, not only reduce portal pressure [33] but may also improve cirrhotic prognosis by improving LVDF.

In summary, LVDD is highly prevalent and is one of the most common cardiac manifestations in patients with cirrhotic ascites. It is not only a specific feature of cirrhosis but also an independent risk factor for mortality, making it a valuable predictor of medium-term poor outcomes. Although the predictive accuracy of LVDD, MELD, and CTP scores is not very high (AUC values around 0.61–0.67), LVDD can be considered an additional marker rather than a substitute indicator. More importantly, intervention in LVDD may offer another effective strategy for improving prognosis. However, this study also has certain limitations: we focused exclusively on LVDD caused by cirrhosis itself; the relationship between LVDD and prognosis in cirrhotic patients with underlying cardiovascular conditions remains an important area warranting further investigation. Moreover, we performed TTE assessment based on the European “Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography (2009)” rather than the updated guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging. However, this will not change the results of our study because the former includes more LVDD parameters and the latter

mainly focuses on simplifying the diagnostic process. Finally, the single-center retrospective nature of the study introduces the potential for selection bias, and larger multicenter perspective cohort studies with external validations are needed to further validate its predictive value. Moreover, basic research is required to elucidate the underlying mechanisms, and randomized controlled trials are necessary to determine whether LVDD interventions can truly reduce mortality.

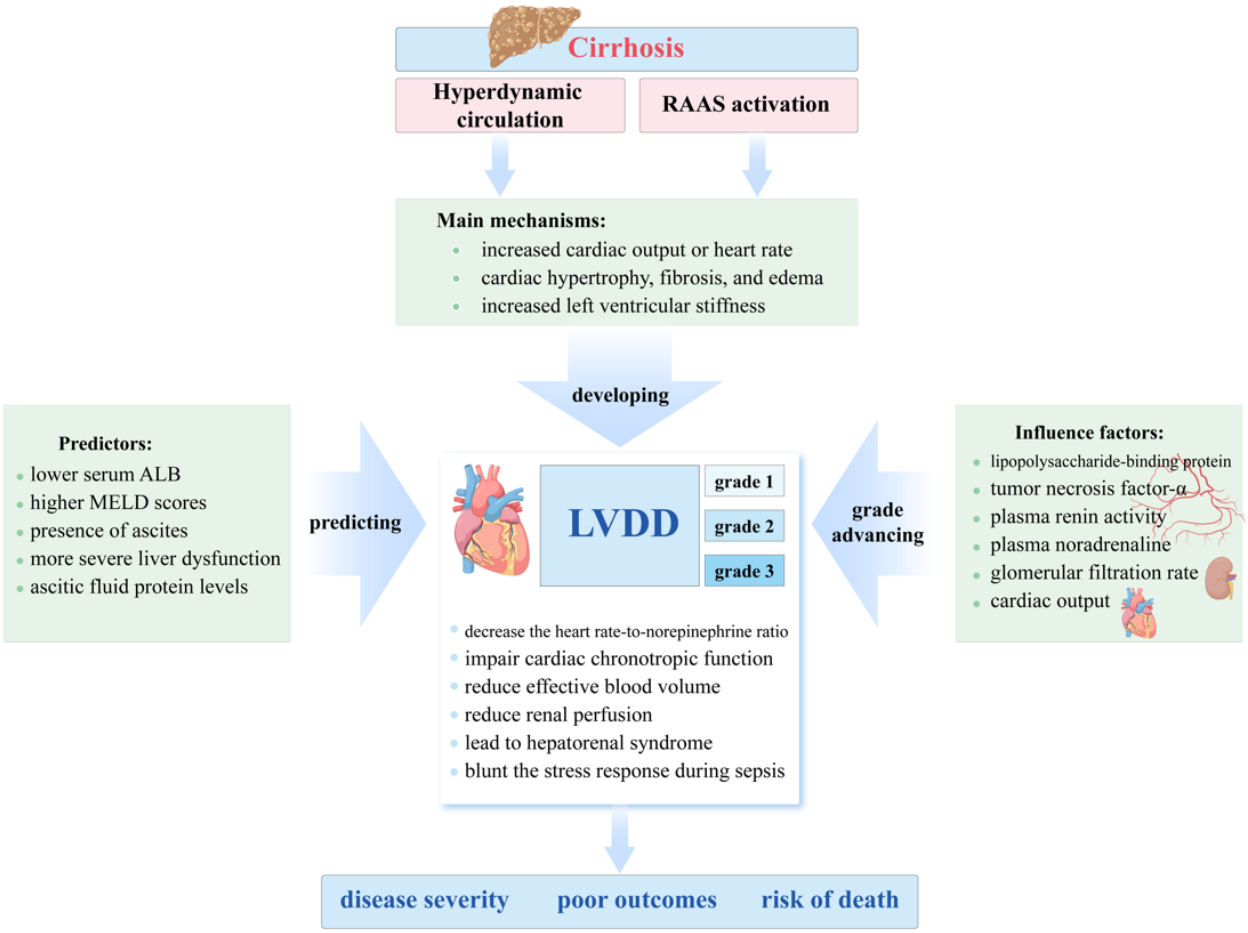

Figure 4. The intrinsic relationship between cirrhosis and LVDD and corresponding mechanisms.

5. CONCLUSION

LVDD increases the risk of 1-year mortality in patients with cirrhotic ascites, particularly in those without hepatic malignancy. Our study reveals new prognostic value for traditional LVDD parameters, indicating that targeting LVDD in cirrhotic patients may be one of the effective strategies to improve their prognosis.

Obiectiv: *Clarificarea impactului disfuncției diastolice ventriculare stângi (LVDD) asupra riscului de prognostic nefavorabil pe termen mediu la pacienții cu ascită de cauză cirotică.*

Metode: *Un total de 194 de pacienți cu ascită cirotică au fost incluși în acest studiu retrospectiv și împărțiți în două grupuri (cu LVDD și fără LVDD), pe baza rezultatelor ecocardiografice. Analizele Lasso și Cox univariată au fost utilizate inițial pentru a identifica potențialii factori influenți ai mortalității la un an, pornind de la datele clinice de bază. Ulterior, s-a efectuat o analiză Cox multivariată pentru identificarea factorilor de risc independenți. Curbele Kaplan–Meier (K–M) și curbele ROC dependente de timp au fost utilizate pentru a evalua valoarea predictivă a LVDD asupra mortalității la un an. S-a efectuat și o analiză pe subgrupuri în funcție de prezența sau absența malignității hepatice.*

Rezultate:
(1) LVDD a fost prezentă la 47,4% (92/194) dintre pacienții cu ascită cirotică;
(2) Analizele de regresie (Lasso, Cox univariată și Cox multivariată) au arătat că LVDD (raport de risc = 2,109; interval de încredere 95% [1,279–3,478]; p = 0,003) a reprezentat un factor de risc independent pentru mortalitatea la un an;
(3) Curbele ROC dependente de timp au demonstrat că performanța predictivă a LVDD pentru mortalitatea la 360 de zile, atât în populația generală, cât și la pacienții fără malignitate hepatică, a fost comparabilă cu cea a scorurilor clasice Child–Turcotte–Pugh (CTP) și Model for End-Stage Liver Disease (MELD) (p > 0,05 pentru toate).

Concluzie: *LVDD crește riscul de mortalitate la un an la pacienții cu ascită cirotică, în special la cei fără malignitate hepatică.*

Correspondece to: Qing-qing WANG, M.D, Department of Hepatology 1, The Third People's Hospital of Kunming/Yunnan Clinical Center for Infectious Diseases, no. 319 Wujing Road, Guandu District, Kunming City 650041, Yunnan Province, P.R. China
E-mail: wangqingqing1511@163.com

Declaration of interest: All authors declare no conflict of interest.

Ethics statement: This study was approved by the Ethics Committee of the Third People's Hospital of Kunming (Approval No. 2023032023) and was conducted in accordance with the local legislation and institutional requirements. All the participants provided their written informed consent to participate.

Funding: This study was supported by the National Natural Science Foundation of China (No. 82260408), Science Research Fund of Education Department of Yunnan Province (No. 2024J0863), and Health Research Project of Kunming Municipal Health Commission (No. 2025-02-04-001, 2025-03-03-005, and 2025-03-08-020).

REFERENCES

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 [J]. Lancet, 2018, 392(10159): 1789–858.
[2] GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 [J]. Lancet Gastroenterol Hepatol, 2020, 5(3): 245–66.
[3] D'AMICO G, GARCIA-TSAO G, PAGLIARO L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies [J]. J Hepatol, 2006, 44(1): 217–31.
[4] REIBERGER T, PÜSPÖK A, SCHODER M, BAUMANN-DURCHSCHEIN F, BUCSICS T, DATZ C, DOLAK W, FERLITSCH A, FINKENSTEDT A, GRAZIADEI I, HAMETNER S, KARNEL F, KRONES E, MAIERON A, MANDORFER M, PECK-RADOSAVLJEVIC M, RAINER F, SCHWABL P, STADLBAUER V, STAUBER R, TILG H, TRAUNER M, ZOLLER H, SCHÖFL R, FICKERT P. Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III) [J]. Wien Klin Wochenschr, 2017, 129(Suppl 3): 135–58.
[5] BENMASSAOUD A, FREEMAN SC, ROCCARINA D, PLAZ TORRES MC, SUTTON AJ, COOPER NJ, IOGNA PRAT L, COWLIN M, MILNE EJ, HAWKINS N, DAVIDSON BR, PAVLOV CS, THORBURN D, TSOCHATZIS E, GURUSAMY KS. Treatment for ascites in adults with decompensated liver cirrhosis: a network meta-analysis [J]. Cochrane Database Syst Rev, 2020, 1(1): Cd013123.
[6] BORAH GJ, PANDE G, MALAKAR S, KUMAR SR, YADAV RR, MOHINDRA S. Midodrine and weekly albumin therapy in patients with cirrhosis and diuretic intractable or recurrent ascites: a case-control study [J]. Cureus, 2025, 17(1): e76988.
[7] WU HHL, RAKISHEVA A, PONNUSAMY A, CHINNADURAI R. Hepatocardiorenal syndrome in liver cirrhosis: recognition of a new entity? [J]. World J Gastroenterol, 2024, 30(2): 128–36.
[8] RAZPOTNIK M, BOTA S, WIMMER P, HOFER P, HACKL M, FÜRSTNER M, ALBER H, MOHR R, WREE A, WALIA N, ENGELMANN C, DEMIR M, TACKE F, PECK-RADOSAVLJEVIC M. Development of liver-heart score for early detection of myocardial contractile dysfunction in cirrhosis by strain imaging [J]. Liver Int, 2025, 45(4): e70062.
[9] BARRERA N, JOU K, MALIK M, GALLEGOS-KOYNER F, CHAMAY S, ELFERT K, CERRUD-RODRIGUEZ RC, DI BIASE L. Safety of catheter ablation for atrial fibrillation in patients with liver cirrhosis [J]. J Cardiovasc Electrophysiol, 2025, 36(1): 103–10.
[10] EL KOOFY N, OKASHA SH, AGHA HM, ALI N, BEHAIRY AS, FOUAD HM, ZAWAM RH. Prevalence and predictors of pulmonary hypertension in children with portal hypertension: a single center study [J]. Pediatr Gastroenterol Hepatol Nutr, 2025, 28(2): 101–12.
[11] JIA Y, LIU L, ZHOU Y, YAO Y, CHENG Y, CHENG Y, SHEN C, YANG R, ZENG R, WAN Z, ZHAO Q, LI D, YUAN B, LIAO X. Prognostic implications of cardiac geometry in cirrhosis: findings from a large cohort [J]. Liver Int, 2025, 45(2): e16230.

[12] LEE SK, SONG MJ, KIM SH, AHN HJ. Cardiac diastolic dysfunction predicts poor prognosis in patients with decompensated liver cirrhosis [J]. Clin Mol Hepatol, 2018, 24(4): 409–16.
[13] STUNDIENE I, SARNELYTE J, NORKUTE A, AIDIETIENE S, LIAKINA V, MASALAITE L, VALANTINAS J. Liver cirrhosis and left ventricle diastolic dysfunction: Systematic review [J]. World J Gastroenterol, 2019, 25(32): 4779–95.
[14] [Guidelines on the management of ascites in cirrhosis (2023 version)] [J]. Zhonghua Gan Zang Bing Za Zhi, 2023, 31(8): 813–26.
[15] NAGUEH SF, APPLETON CP, GILLEBERT TC, MARINO PN, OH JK, SMISETH OA, WAGGONER AD, FLACHSKAMPF FA, PELLIKKA PA, EVANGELISA A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography [J]. Eur J Echocardiogr, 2009, 10(2): 165–93.
[16] FOUAD YM, YEHIA R. Hepato-cardiac disorders [J]. World J Hepatol, 2014, 6(1): 41–54.
[17] EL HADI H, DI VINCENZO A, VETTOR R, ROSSATO M. Relationship between heart disease and liver disease: a two-way street [J]. Cells, 2020, 9(3): 567.
[18] MØLLER S, BENDTSEN F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis [J]. Liver Int, 2018, 38(4): 570–80.
[19] BEHERA MK, SWAIN SN, SAHU MK, BEHERA GK, MISHRA D, NARAYAN J, SINGH A, AGARWAL S, MALLICK PK. Diastolic dysfunction is a predictor of poor survival in patients with decompensated cirrhosis [J]. Int J Hepatol, 2021, 2021: 5592376.
[20] BEHERA MK, NARAYAN J, SAHU MK, BEHERA SK, SINGH A, MISHRA D, AGARWAL S, UTHANSINGH K. Factors predicting cardiac dysfunction in patients with liver cirrhosis [J]. Middle East J Dig Dis, 2021, 13(3): 216–22.
[21] SOLANKI R, SREESH S, ATTUMALIL TV, MOHAPATRA SD, NARAYANAN V, MADHU D, CHAKRAVORTY A, PAL R, NAIR A, DEVADAS K. A case-cohort study of left ventricular diastolic dysfunction in patients with cirrhosis: the liver-heart axis [J]. Ann Gastroenterol, 2023, 36(6): 678–85.
[22] NØRSKOV MP, MØNSTED T, KIMER N, DAMGAARD M, MØLLER S. Can plasma volume determination in cirrhosis be replaced by an algorithm using body weight and hematocrit? [J]. Diagnostics (Basel), 2024, 14(8): 835.
[23] MØLLER S, BERNARDI M. Interactions of the heart and the liver [J]. Eur Heart J, 2013, 34(36): 2804–11.
[24] MØLLER S, HENRIKSEN J H. Cirrhotic cardiomyopathy [J]. J Hepatol, 2010, 53(1): 179–90.
[25] TIMOH T, PROTANO MA, WAGMAN G, BLOOM M, VITTORIO TJ. A perspective on cirrhotic cardiomyopathy [J]. Transplant Proc, 2011, 43(5): 1649–53.
[26] KALAMBOKIS G, CHRISTAKI M, TSIAKAS I, DESPOTIS G, LAKKAS L, TSIOURIS S, XOURGIA X, MARKOPOULOS GS, DOVA L, MILIONIS H. Association of left ventricular diastolic dysfunction with inflammatory activity, renal dysfunction, and liver-related mortality in patients with cirrhosis and ascites [J]. Eur J Gastroenterol Hepatol, 2024, 36(6): 775–83.
[27] RUÍZ-DEL-ÁRBOL L, ACHÉCAR L, SERRADILLA R, RODRÍGUEZ-GANDÍA M, RIVERO M, GARRIDO E, NATCHER JJ. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine [J]. Hepatology, 2013, 58(5): 1732–41.
[28] MØLLER S, WIESE S, HALGREEN H, HOVE JD. Diastolic dysfunction in cirrhosis [J]. Heart Fail Rev, 2016, 21(5): 599–610.
[29] LEE SS, LIU H. Cardiovascular determinants of survival in cirrhosis [J]. Gut, 2007, 56(6): 746–8.
[30] PREMKUMAR M, DEVURGOWDA D, VYAS T, SHASTHRY SM, KHUMUCKHAM JS, GOYAL R, THOMAS SS, KUMAR G. Left ventricular diastolic dysfunction is associated with renal dysfunction, poor survival and low health related quality of life in cirrhosis [J]. J Clin Exp Hepatol, 2019, 9(3): 324–33.
[31] PREMKUMAR M, RANGEGOWDA D, VYAS T, KHUMUCKHAM JS, SHASTHRY SM, THOMAS SS, GOYAL R, KUMAR G, SARIN SK. Carvedilol combined with ivabradine improves left ventricular diastolic dysfunction, clinical progression, and survival in cirrhosis [J]. J Clin Gastroenterol, 2020, 54(6): 561–8.
[32] TRIPATHI D, HANDLEY K, HOLDEN L, ABDALI Z, JOWETT S, MATHERS J, POYNER C, RICHARDSON P, FERGUSON J, ROWE I. Clinical trial: a multicentre randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE Trial) [J]. Aliment Pharmacol Ther, 2025, 61(11):1740–54.
[33] BERZIGOTTI A. Optimizing non-invasive monitoring of the therapeutic response to NSBBs in portal hypertension: is machine learning the answer? [J]. Hepatol Int, 2025, 19(2): 302–3.

Received: 17th August 2025