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Aortic Valve and Mitral Annular Calcification in Cirrhotic Patients and Potential Liver Transplant Recipients - A Single-Center Observational Study

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Abstract

Background/Objectives: Liver cirrhosis (LC), irrespective of its etiology, is associated with increased mortality from cardiovascular causes. In this study, we aimed to reveal the relationship between fatty LC (nonalcoholic and alcohol related liver diseases) and other causes of LC with aortic valve and mitral annular calcification. **Methods**: One hundred and twenty-three LC patients and an equal number of age- and sex-matched cardiovascular patients without cirrhosis or indications for heart valve surgery were included in the study. The two groups were compared in terms of demographic, clinical, and echocardiographic characteristics. In total, 70 female and 176 male patients, with a median age of 64.0 years (range, 58.0-70.0 years), were included in the analysis. **Results**: Binary logistic regression analyses revealed a significant association between fatty LC and aortic valve calcification, whereas LC, regardless of its cause, was associated with mitral annular calcification. Previous cardiac surgery due to atherosclerosis-related ischemic heart disease and mitral annular calcification were also associated with aortic valve calcification. In contrast, BMI, aortic valve calcification, aortic root calcification, and mitral valve calcification were related to the occurrence of mitral annular calcification. The findings also revealed a stark contrast in the burden of atherosclerotic cardiovascular disease risk factors between the two groups. **Conclusions**: The incidence of heart valve calcification should be considered in the management of cirrhosis patients as potential liver transplant recipients for more comprehensive preoperative risk stratification and postoperative follow-ups to identify patients that may benefit from either percutaneous or surgical valvular therapy.

Keywords: aortic valve calcification; mitral annular calcification; liver cirrhosis; liver transplantation

1. Introduction

Liver cirrhosis is a significant cause of morbidity and mortality, constituting around 2.4% of global death cases [1]. The primary causes of liver cirrhosis include metabolic-associated fatty liver disease (commonly referred to as MAFLD or nonalcoholic fatty liver disease), alcohol-related liver disease (AFLD), and chronic viral hepatitis [2–4]. Other causes of liver cirrhosis include autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, and medications. Many patients

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have overlapping causes, adding to the complexity of the condition [2–4]. There are also cases of cryptogenic liver cirrhosis of unknown etiology [5]. Regardless of the etiology of primary liver injury in cirrhotic patients, progressive liver fibrosis and subsequent metabolic impairment eventually lead to the development of a hyperdynamic circulatory state. This state can cause functional disturbances in multiple organ systems, including the development of hepatopulmonary and hepatorenal syndrome, both of which negatively impact patients' prognosis. [6–8]. Additionally, patients with liver cirrhosis may develop a condition known as cirrhotic cardiomyopathy. This condition is characterized by impaired heart contractility, encompassing both systolic and diastolic dysfunction, as well as abnormalities in the heart's electrical conduction, all of which occur in the absence of other heart diseases. [6,9,10]. The intricate interplay between the heart and liver, known as cardiohepatic interactions, often results in the coexistence of combined heart and liver dysfunctions in the context of primary heart and liver diseases. This highlights the importance of a multidisciplinary approach to managing these patients [11]. Data suggest that patients with liver cirrhosis and those with higher liver fibrosis scores face a greater risk of extensive and severe coronary atherosclerosis (CAD) and coronary calcification [12–15]. They are also more likely to experience myocardial infarction (MI) and have worse overall clinical outcomes compared to non-cirrhotic individuals [12–15]. However, a recent meta-analysis found no significant association between liver cirrhosis and the incidence of CAD and MI [16]. At the same time, traditional atherosclerotic risk factors such as advanced age, male sex, diabetes mellitus, hypertension, hyperlipidemia, and smoking history were all significantly associated with CAD in cirrhotic patients [16]. The same risk factors also increase the likelihood of calcific aortic valve disease (CAVD) and mitral annular calcification (MAC) in the general population [17]. However, the data regarding the incidence of aortic valve and mitral annular calcifications among liver cirrhosis patients are currently scarce. Therefore, this study aims to explore the prevalence and significance of aortic valve and mitral annular calcification in a cohort of patients with liver cirrhosis, particularly those with end-stage non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD), compared with an age- and sex-matched cardiovascular patient group without cirrhosis and indications for heart valve surgery.

2. Materials and Methods

2.1. Patients and Methods

The study included 123 potential liver transplant recipients with liver cirrhosis who were consecutively admitted to the Department of Internal Medicine, Division of Gastroenterology, at Clinical Hospital Merkur (CHM) in Zagreb, Croatia, between July 2019 and October 2021. Among them, 61 patients were diagnosed with fatty liver cirrhosis (alcoholic and nonalcoholic fatty liver disease) based on clinical, laboratory, instrumental, and/or histological features. The remaining 62 cases included liver cirrhosis patients of different etiology, such as autoimmune and viral hepatitis, hepatocellular carcinoma, polycystic liver and kidney disease, or cryptogenic liver cirrhosis. All patients underwent transthoracic echocardiography at the Department of Internal Medicine, Division of Cardiology and Intensive Care Unit, CHM, to determine the presence of aortic valve and mitral annulus calcification. Total calcium scoring was assessed using a semiquantitative algorithm developed by Pressman et al. (Table 1) [18]. The age- and gender-adjusted control group without liver cirrhosis consists of 123 cardiovascular patients who underwent routine check-ups and transthoracic echocardiography, accompanied by an assessment of total calcium scoring and evaluation of aortic and mitral annulus calcification using the same scoring algorithm [18]. Demographic and clinical data of all the patients included in the study were obtained from the hospital's electronic health records system. Patients were noted as having a history of hypertension, hyperlipidemia, diabetes, atrial fibrillation, peripheral vascular diseases, chronic obstructive pulmonary disease, cerebrovascular insult or transitory ischemic attack, cardiac surgery, or MI based on diagnoses in medical records. The stage of chronic kidney disease was assessed based on the glomerular filtration rate. All the

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subjects included in the study signed the informed consent, and the study was approved by the CHM local Ethics Committee (29-04-2019, no. 03/1-4558/2).

Table 1. The semiquantitative algorithm used for total calcium scoring of the aortic valve and mitral annular calcification.

Calcium scoring variable	*Value*
Posterior mitral annulus calcification	*None = 0; 1/3 calcified = 1; 2/3 calcified = 2; 3/3 calcified = 3*
Posterior mitral leaflet restriction	*No = 0; Yes = 1*
Anterior mitral annular calcification	*No = 0; Yes = 1*
Anterior mitral leaflet restriction	*No = 0; Yes = 1*
Mitral valve calcification	*No = 0; Mild = 1; More than mild = 2*
Subvalvular mitral apparatus calcification	*No = 0; Yes = 1*
Aortic valve calcification	*None = 0; Nodules in <3 leaflets = 1; Nodules in 3 leaflets = 2; Leaflet restriction = 3*
Aortic root calcification	*No = 0; Yes = 1*
Total	***13***

2.2. Statistical Analysis

The normality of the continuous data distribution was analyzed using the Shapiro-Wilk test. Data are presented as frequencies, medians with interquartile ranges, or as means with standard deviations (±SD). The groups were compared using a t-test for parametric and a Mann-Whitney test for non-parametric continuous variables, respectively. Intergroup relationships between categorical variables were assessed using the Pearson $\chi 2$ test or the Fisher exact test, as appropriate. Univariate and multivariate binary logistic regression analyses were employed to investigate the association between demographic and clinical variables and the occurrence of aortic valve and mitral annulus calcification, with the results presented as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided. The intergroup differences with $P<0.05$ were considered significant and corrected according to the Bonferroni procedure (the corrected significance level is $Pc = 0.05/N$; N- number of independent tests). Statistical analysis was performed using SPSS, Version 29 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patients' Characteristics

The study included 123 patients with liver cirrhosis and an equal number of age- and sex-matched cardiovascular patients without cirrhosis or indications for heart valve surgery that served as a control group. Their basic clinical and demographic characteristics are presented in Table 2.

The median age of both patient groups was 64.0 years (range, 58.0-70.0), with a predominance of male patients (71.5%). In the control group, a significantly higher number of patients with a history of smoking, and previous cardiovascular surgery, higher incidence of hypertension, hyperlipidemia, atrial fibrillation, peripheral vascular disease, chronic obstructive pulmonary disease, prior MI, lower left ventricular ejection fraction and higher number of patients with left ventricular ejection fraction <50% was found (Table 2). Following Bonferroni correction ($Pc = 0.05/27 = 0.0018$), no significant association was found in the incidence of peripheral vascular and chronic obstructive pulmonary disease between the control and cirrhotic patient groups. The control group also had a higher number of patients with the presence of mitral valve calcification, while the liver cirrhosis cohort exhibited a higher incidence of aortic valve calcification (Table 2). In contrast, no difference in the value of aortic and mitral valve Ca score, as well as total Ca score, was detected between the groups.

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Table 2. Demographic and clinical characteristics of patients included in the study.

Variable	All patients n = 246	Liver cirrhosis n = 123	Control group n = 123	P #
Age, years	64.0 (58.0-70.0)	64.0 (58.0-70.0)	64.0 (58.0-70.0)	>0.999
Gender, male	176 (71.5)	88 (71.5)	88 (71.5)	>0.999
BMI, kg/m^2	28.03±4.63	27.49±5.35	28.50±3.85	0.106
Cardiac surgery	18 (7.3)	1 (0.8)	17 (13.8)	<0.001##
Diabetes mellitus	74 (30.1)	44 (35.8)	30 (24.4)	0.070
Hypertension	149 (60.6)	51 (41.5)	98 (79.7)	<0.001##
Hyperlipidemia	103 (42.0)	29 (23.8)	74 (60.2)	<0.001##
AF	32 (13.1)	6 (4.9)	26 (21.1)	<0.001##
PVD	27 (11,0)	6 (4.9)	21 (17.1)	0.004
CVI or TIA	13 (5.3)	3 (2.5)	10 (8.1)	0.084
COPB	18 (7.3)	4 (3.3)	14 (11.4)	0.025
Smoking, yes	142 (60.4)	53 (46.9)	89 (73.0)	<0.001##
MI	51 (20.8)	5 (4.1)	46 (37.4)	<0.001##
CKD stage				0.812
I-II	212 (86.5)	104 (85.2)	108 (87.8)	
III	21 (8.6)	12 (9.8)	9 (7.3)	
IV	9 (3.7)	4 (3.3)	5 (4.1)	
V	3 (1.2)	2 (1.6)	1 (0.8)	
LVEF, %	65.0 (55.5-65.0)	65.0 (65.0-65.0)	59.0 (50.0-65.0)	<0.001##
LVEF <50%	25 (10.2)	3 (2.5)	22 (17.9)	<0.001##
Aortic valve calcification	125 (50.8)	79 (64.2)	46 (37.4)	<0.001##
Aortic root calcification	177 (72.0)	84 (68.3)	93 (75.6)	0.256
Total aortic valve Ca score	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.104
Posterior mitral annulus calcification	130 (52.8)	71 (57.7)	59 (48.0)	0.160
Posterior mitral leaflet restriction	11 (4.5)	4 (3.3)	7 (5.7)	0.538
Anterior mitral annular calcification	32 (13.0)	17 (13.8)	15 (12.2)	0.850
Anterior mitral leaflet restriction	3 (1.2)	1 (0.8)	2 (1.6)	>0.999
Mitral valve calcification	131 (53.3)	47 (38.2)	84 (68.3)	<0.001##
Subvalvular mitral apparatus calcification	107 (43.5)	51 (41.5)	56 (45.5)	0.607
Total mitral valve Ca score	2.0 (1.0-3.0)	2.0 (0.0-3.0)	2.0 (1.0-3.0)	0.253
Total Ca score	3.0 (2.0-5.0)	3.0 (1.0-5.0)	3.0 (2.0-4.0)	0.799

Data are presented as frequencies (n) and percentages (%), median with interquartile range or mean ± SD (standard deviation), AF - atrial fibrillation, BMI – body mass index, CKD – chronic kidney disease, COPB – chronic obstructive pulmonary disease, CVI – cerebrovascular insult, LVEF – left ventricular ejection fraction, MI - previous myocardial infarction, PVD – peripheral vascular disease, TIA -transitory ischemic attack, #Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/27 = 0.0018).

3.2. Liver Cirrhosis

Demographic and clinical characteristics of liver cirrhosis patients are presented in Table 3. Interestingly, excluding gender frequencies, following Bonferroni correction for multiple comparisons, no significant differences were found between cirrhotic patients subdivided into

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subgroups with fatty liver (alcoholic and nonalcoholic fatty liver disease) and other causes of liver cirrhosis (Table 3).

Table 3. Demographic and clinical characteristics of patients with liver cirrhosis.

Variable	LC n = 123	Fatty LC n = 61	Other causes of LC n = 62	P#
Age, years	64.0 (58.0-70.0)	64.0 (58.0-70.0)	64.5 (58.8-71.0)	0.748
Gender, male	88 (71.5)	53 (86.9)	35 (56.5)	<0.001##
BMI, kg/m^2	27.49±5.35	27.93 (25.26-32.32)	25.78 (22.73-29.65)	0.026
Cardiac surgery	1 (0.8)	1 (1,7)	0 (0.0)	0.492
Diabetes mellitus	44 (35.8)	23 (37.7)	21 (33.9)	0.709
Hypertension	51 (41.5)	22 (36.1)	29 (46.8)	0.273
Hyperlipidemia	29 (23.8)	20 (33.3)	9 (14.5)	0.019
AF	6 (4.9)	1 (1.7)	5 (8.1)	0.207
PVD	6 (4.9)	4 (6.7)	2 (3.2)	0.436
Previous CVI or TIA	3 (2.5)	1 (1.7)	2 (3.2)	>0.999
COPD	4 (3.3)	2 (3.3)	2 (3.2)	>0.999
Smoking, yes	53 (46.9)	28 (51.9)	25 (42.4)	0.349
Previous MI	5 (4.1)	3 (5.0)	2 (3.2)	0.677
CKD stage				0.648
I-II	104 (85.2)	49 (81.7)	55 (88.7)	
III	12 (9.8)	8 (13.3)	4 (6.5)	
IV	4 (3.3)	2 (3.3)	2 (3.2)	
V	2 (1.6)	1 (1.7)	1 (1.6)	
LVEF, %	65.0 (65.0-65.0)	65.0 (65.0-65.0)	65.0 (65.0-65.0)	0.394
LVEF <50%	3 (2.5)	1 (1,7)	2 (3.2)	>0999
Aortic valve calcification	79 (64.2)	41 (67.2)	38 (61.3)	0.574
Aortic root calcification	84 (68.3)	47 (77.0)	37 (59.7)	0.052
Total aortic valve Ca score	1.0 (1.0-2.0)	2.0 (1.0-2.0)	1.0 (0.75-2.0)	0.083
Posterior mitral annulus calcification	71 (57.7)	39 (63.9)	32 (51.6)	0.203
Posterior mitral leaflet restriction	4 (3.3)	2 (3.3)	2 (3.2)	>0999
Anterior mitral annular calcification	17 (13.8)	11 (18.0)	6 (9.7)	0.202
Anterior mitral leaflet restriction	1 (0.8)	1 (1.6)	0 (0.0)	0.496
Mitral valve calcification	47 (38.2)	23 (37.7)	24 (38.7)	>0999
Subvalvular mitral apparatus calcification	51 (41.5)	30 (49.2)	21 (33.9)	0.101
Total mitral valve Ca score	2.0 (0.0-3.0)	2.0 (1.0-3.0)	1.0 (0.0-3.0)	0.086
Total Ca score	3.0 (1.0-5.0)	3.0 (2.0-5.0)	3.0 (1.0-5.0)	0.043

Data are presented as frequencies (n) and percentages (%), median with interquartile range or mean ± SD (standard deviation), AF - atrial fibrillation, BMI – body mass index, CKD – chronic kidney disease, COPB – chronic obstructive pulmonary disease, CVI – cerebrovascular insult, LVEF – left ventricular ejection fraction, MI - previous myocardial infarction, PVD – peripheral vascular disease, TIA -transitory ischemic attack, #Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/27 = 0.0018).

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3.2. Aortic Valve Calcification

In overall patient group (data not shown) patients with aortic valve calcification (n = 125) were older [66.0 (62.0-71.0) vs. 62.0 (56.0-68.0), P <0.001], had a higher incidence of previous cardiac surgeries [16 (12.9 %) vs. 2 (1.7 %), P <0.001], and posterior mitral annulus calcification [89 (71.2 %) vs. 41 (33.9 %), P <0.001]. They also have higher aortic [2.0 (2.0-3.0) vs. 1.0 (0.0-1.0), P <0.001] and mitral valve [1.0 (0.0-2.0) vs. 0.0 (0.0-1.0), P <0.001] Ca score, as well as total Ca score values [4.0 (3.0-6.0) vs. 2.0 (1.0-3.0), P <0.001]. Clinical and demographic characteristics of cirrhotic and control patient cohorts, subdivided according to the presence of aortic valve calcification, are presented in Table 4.

Patients with liver cirrhosis (alcoholic and nonalcoholic fatty liver disease) and aortic valve calcification have a higher incidence of posterior mitral annulus calcification and mitral valve calcification, accompanied by a higher value of aortic and mitral valve Ca score, as well as total Ca score (Table 4). In contrast, control patients with aortic valve calcification had a higher incidence of previous cardiac surgeries and higher values of aortic valve and total Ca scores (Table 4). In both subgroups, patients with aortic valve calcification were older, but this did not remain significant after Bonferroni correction (Pc = 0.05/27 = 0.0018) for multiple comparisons was applied (Table 4).

Table 4. Demographic and clinical characteristics of liver cirrhosis and control subjects with and without aortic valve calcification.

Variable	LC n = 123	AVC n = 61	No AVC n = 62	P #	Control n = 123	AVC n = 61	No AVC n = 62	P #
Age, years	64.0 (58.0-70.0)	65.0 (60.0-71)	61.5 (53.3-65.8)	0.002	64.0 (58.0-70.0)	68.0 (62.8-72.3)	62.0 (57.8-68.5)	0.002
Gender, male	88 (71.5)	58 (73.4)	30 (68.2)	0.540	88 (71.5)	31 (67.4)	57 (74.0)	0.536
BMI, kg/m²	27.49±5.35	27.43±5.17	27.59±5.70	0.882	28.50±3.85	28.11±3.37	28.74±4.12	0.385
Cardiac surgery	1 (0.8)	1 (1.3)	0 (0.0)	>0.999	17 (13.8)	15 (32.6)	2 (2.6)	<0.001##
DM	44 (35.8)	28 (35.4)	16 (36.4)	>0.999	30 (24.4)	9 (19.6)	21 (27.3)	0.390
Hypertension	51 (41,5)	36 (45.6)	15 (34.1)	0.254	98 (79.7)	38 (82.6)	60 (77.9)	0.646
Hyperlipidemia	29 (23.8)	18 (23.1)	11 (25.0)	0.827	74 (60.2)	30 (65.29	44 (57.1)	0.448
AF	6 (4.9)	5 (6.4)	1 (2.3)	0.417	26 (21.1)	10 (21.7)	16 (20.8)	>0.999
PVD	6 (4.9)	5 (6.4)	1 (2.3)	0.417	21 (17.1)	13 (28.3)	8 (10.4)	0.014
CVI or TIA	3 (2.5)	3 (3.8)	0 (0.0)	0.552	10 (8.1)	7 (15.2)	3 (3.9)	0.039
COPD	4 (3.3)	2 (2.6)	2 (4.5)	0.619	14 (11.4)	6 (13.0)	8 (10.4)	0.771
Smoking, yes	53 (46.9)	33 (45.8)	20 (48.8)	0.845	89 (73.0)	32 (69.6)	57 (75.0)	0.534
MI	5 (4.1)	3 (3.8)	2 (4.5)	>0.999	46 (37.4)	17 (37.0)	29 (37.7)	>0,999
CKB stage				0.880				0.648
I-II	104 (85.2)	65 (83.3)	39 (88.6)		108 (87.8)	39 (84.8)	69 (89.6)	
III	12 (9.8)	8 (10.3)	4 (9.1)		9 (7.3)	4 (8.7)	5 (6.5)	
IV	4 (3.3)	3 (3.8)	1 (2.3)		5 (4.1)	2 (4.3)	3 (3.9)	
V	2 (1.6)	2 (2.6)	0 (0.0)		1 (0.8)	1 (2.2)	0 (0.0)	
LVEF, %	65.0 (65.0-65.0)	65.0 (65.0-65.0)	65.0 (65.0-65.0)	0.390	59.0 (50.0-65.0)	56.0 (50.0-62.25)	60 (51.0-66.0)	0.107
LVEF <50%	3 (2.5)	2 (2.6)	1 (2.3)	>0.999	22 (17.9)	10 (45.5)	12 (15.6)	0.468
Aortic root calcification	84 (68.3)	60 (75.9)	24 (55.5)	0.025	93 (75.6)	36 (78.3)	57 (74.0)	0.668

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Total aortic valve Ca score	1.0 (1.0-2.0)	2.0 (2.0-3.0)	1.0 (0.0-1.0)	<0.001##	1.0 (1.0-2.0)	2.0 (2.0-4.0)	1.0 (0.0-1.0)	<0.001##
Posterior mitral annulus calcification	71 (57.7)	71 (77.2)	10 (22.7)	<0.001##	59 (48.0)	28 (60.9)	31 (40.3)	0.040
Posterior mitral leaflet restriction	4 (3.3)	3 (3.8)	1 (2.3)	>0.999	7 (5.7)	2 (4.3)	5 (6.5)	0.711
Anterior mitral annulus calcification	17 (13.8)	13 (16.5)	4 (9.1)	0.291	15 (12.2)	7 (15.2)	8 (10.4)	0.570
Anterior mitral leaflet restriction	1 (0.8)	1 (1.3)	0 (0.0)	>0.999	2 (1.6)	2 (4.3)	0 (0.0)	0.138
Mitral valve calcification	47 (38.2)	39 (49.4)	8 (18.2)	<0.001##	84 (68.3)	31 (67.4)	53 (68.8)	>0.999
Subvalvular mitral apparatus calcification	51 (41.5)	37 (46.8)	14 (31.8)	0.128	56 (45.5)	22 (47.8)	34 (44.2)	0.712
Total mitral valve Ca score	2.0 (0.0-3.0)	2.0 (1.0-3.0)	0.0 (0.0-1.0)	<0.001##	2.0 (1.0-3.0)	2.0 (1-0-3.0)	1.0 (1.0-2.5)	0.062
Total Ca score	3.0 (1.0-5.0)	4.0 (3.0-6.0)	1.0 (0.0-2.0)	<0.001##	3.0 (2.0-4.0)	4.0 (4.0-6.0)	2.0 (1.5-3.0)	<0.001##

Data are presented as frequencies (n) and percentages (%), median with interquartile range or mean ± SD (standard deviation), AF - atrial fibrillation, BMI – body mass index, AVC – aortic valve calcification, CKD – chronic kidney disease, COPB – chronic obstructive pulmonary disease, CVI – cerebrovascular insult, DM – diabetes mellitus, LC - liver cirrhosis, LVEF – left ventricular ejection fraction, MI - previous myocardial infarction, PVD – peripheral vascular disease, TIA -transitory ischemic attack, # Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/27 = 0.0018).

Following the Bonferroni correction for multiple comparisons (Pc = 0.05/number of comparisons) the univariate binary logistic regression revealed significant association of older age, the presence of fatty liver cirrhosis (nonalcoholic and alcoholic fatty liver disease), and posterior mitral annulus calcification with the occurrence of aortic valve calcification (Table 5). As expected, the values of aortic and mitral valve Ca score, as well as the value of total Ca score, were also associated with the incidence of aortic valve calcification (Table 5).

Table 5. Univariate and multivariate binary logistic regression analysis of variables related to aortic valve calcification.

Variable	Univariate binary logistic regression			Variable	Multivariate binary logistic regression			
	OR	95 % CI	P#		Model	OR	95 % CI	P*
Age	1.072	1.039-1.106	<0.001##	Age	I	1.075	1.038-1.113	<0.001##
					IIa	1.043	1.004-1.084	0.030
					IIIa	1.040	0.996-1.087	0.076
Gender, male	0.966	0.555--1.681	0.903	Gender, male	I	1.043	0.548-1.982	0.899
					IIa	1.083	.554-2.116	0.816
					IIIa	1.734	.785-3.831	0.174

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BMI, kg/m²	0.970	0.917-1.027	0.296	BMI, kg/m²	I	0.958	0.899-1.021	0.187
					IIa	0.929	0.868-.995	0.036
					IIIa	0.906	0.837-.981	0.014
Fatty LC (NAFLD and AFLD)	3.432	1.796-6.556	<0.001##	Fatty LC (NAFLD and AFLD)	I	3.323	1.611-6.853	0.001##
					IIa	2.835	1.334-6.028	0.007##
					IIIa	3.873	1.529-9.807	0.004##
Other causes of LC	2.650	1.414-4.967	0.002	Other causes of LC	I	2.637	1.311-5.302	0.007##
					IIa	2.552	1.234-5.279	0.011
					IIIa	2.790	1.180-6.598	0.019
Previous cardiac surgery	8.815	1.981-39.225	0.004	Previous cardiac surgery	IIIa	26.363	4.907-141.635	<0.001##
Smoking	0.637	0.376-1.079	0.093	Smoking	IIIa	0.655	0.310-1.384	0.267
MI	0.558	0.298-1.047	0.069	MI	IIIa	0.464	0.177-1.215	0.118
PVD	2.113	0.909-4.910	0.082	PVD	IIIa	2.505	0.836-7.502	0.101
CVI or TIA	3.450	0.926-12.860	0.065	CVI or TIA	IIIa	4.141	0.744-23.049	0.105
Aortic root calcification	1.635	0.932-2.868	0.087	Aortic root calcification	IIIa	0.420	0.171-1.028	0.058
Posterior mitral annulus calcification	4.824	2.811-8.278	<0.001##	---	--	--	--	--
Mitral annulus calcification	4.364	2.54-7.477	<0.001##	Mitral annulus calcification	IIa	3.964	2.035-7.721	<0.001##
					IIIa	6.278	2.718-14.500	<0.001##
Aortic valve Ca score	2.113	1.736-2.572	<0.001##	---	--	--	--	--
Mitral valve Ca score	1.480	1.225-1.788	<0.001##	---	--	--	--	--
Total Ca score	2.113	1.736-2.572	<0.001##	---	--	--	--	--

Data are presented as odds ratio (OR), 95 % confidence interval (CI) and P values. Model I - controlling for age, gender, BMI and liver cirrhosis, Model IIa (controlling for age, gender, BMI, liver cirrhosis and mitral annulus calcification, Model IIIa - controlling for age, gender, and BMI, previous cardiac surgery, smoking history, myocardial infraction (MI), peripheral vascular diseases (PVD), previous cerebrovascular insult (CVI) or transitory ischemic attack (TIA), aortic root calcification and mitral annulus calcification. # Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/number of comparisons; Pc = 0.0018 for univariate, and 0.01 for Model I, 0.0083 for Model IIa, and 0.0042 for Model IIIa of multivariate binary logistic regression analysis, respectively).

Model I (controlling for age, gender, BMI and liver cirrhosis) IIa (controlling for age, gender, BMI, liver cirrhosis and mitral annulus calcification) and IIIa (controlling for age, gender, and BMI, previous cardiac surgery, smoking history, MI, peripheral vascular diseases, previous

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cerebrovascular insult or transitory ischemic attack, aortic root calcification and mitral annulus calcification) of multivariate binary logistic regression further confirmed the independent association of fatty (nonalcoholic and alcoholic liver disease) liver cirrhosis with the occurrence of aortic valve calcification in the overall patient group (Table 5). Model III of binary logistic regression also revealed the association of previous cardiac surgery and incidence of mitral annulus calcification (primarily driven by the posterior annulus calcification) with the occurrence of liver cirrhosis. Notably, other causes of liver cirrhosis were no longer significantly associated with the occurrence of aortic valve calcification after stringent Bonferroni corrections for multiple comparisons in Models II and III of binary logistic regression were applied.

3.3. Mitral Annular Calcification

In overall patient group (data not shown) patients with mitral annular calcification (n = 137) were older [68.0 (62.0-73.0) vs. 60.0 (54-0-65.0), P <0.001], and had a higher BMI index (28.9±4.5 vs. 26.9±4.6, P = 0.001), and lower LVEF(%) values [64.0 (53.0-65.0) vs. 65.0 (60.0-66.0), P <0.001]. They also exhibited a higher incidence of aortic valve [91 (66.4 %) vs. 34 (31.2 %), P <0.001], aortic root [123 (89.8 %) vs. 54 (49.5 %), P <0.001], mitral valve [92 (67.2 %) vs. 39 (35.8 %), P <0.001], and subvalvular mitral apparatus calcification [75 (54.7 %) vs. 32 (29. 4 %), P <0.001]. This was also accompanied with a higher values of aortic valve [2.0 (1.0-2.0) vs. 1.0 (0.0-1.0), P <0.001] and mitral valve Ca score [3.0 (2.0-3.0) vs. 1.0 (0.0-1.0), P <0.001] as well as higher value of total Ca score [5.0 (3.0-6.0) vs. 2.0 (1.0-2.0), P<0.001]. The overall patient group with mitral annular calcification also had a higher incidence of diabetes mellitus [50 (36.5 %) vs. 24 (22.0 %), P = 0.017), hyperlipidemia [68 (49.6 %) vs. 35 (32.4 %), P = 0.009], atrial fibrillation [24 (17.5 %) vs. 8 (7.4 %), P = 0.022], peripheral vascular disease [22 (16.1 %) vs. 5 (4.6 %), P = 0.007], chronic obstructive pulmonary disease [15 (10.9 %) vs. 3 (2.8 %), P = 0.024], and previous MI [37 (27.0 %) vs. 14 (13.0 %), P = 0.011] but this did not remain significant after Bonferroni correction (Pc = 0.05/27 = 0.00018) for multiple comparisons was applied.

Clinical and demographic characteristics of cirrhotic and control patient cohorts subdivided according to the presence of mitral annular calcification are presented in Table 6.

In general, patients with mitral annular calcification in both groups (control and patients with alcoholic and nonalcoholic fatty liver disease) were older and had a higher BMI. However, this remained significant only for age in the control patient subgroup after Bonferroni correction was applied. The patients with fatty liver cirrhosis and mitral annular calcification exhibit a higher incidence of aortic valve calcification, aortic root calcification, mitral valve calcification, and subvalvular mitral apparatus calcification. They also showed higher aortic valve Ca score, mitral valve Ca score, and total Ca score values (Table 6). These associations remained significant even after the Bonferroni correction was applied.

Table 6. Demographic and clinical characteristics of liver cirrhosis and control subjects with and without mitral annular calcification.

Variable	LC n = 123	MAC n = 61	No MAC n = 62	P #	Control n = 123	MAC n = 61	No MAC n = 62	P #
Age, years	64.0 (58.0-70.0)	65.0 (61.0-71.0)	62.0 (54.0-69-0)	0.006	64.0 (58.0-70.0)	69.5 (64.0-74.0)	58.0 (54.0-64.5)	<0.001##
Gender, male	88 (71.5)	55 (73.3)	33 (68.8)	0.683	88 (71.5)	43 (69.4)	45 (73.8)	0.690
BMI, kg/m^2	27.49±5.35	28.4±5.0	26.1±5.6	0.028	28.50±3.85	29.5±3.8	27.5±3.6	0.005
Previous cardiac surgery	1 (0.8)	1 (1.4)	0 (0.0)	>0.999	17 (13.8)	12 (19.4)	5 (8.2)	0.115
DM	44 (35.8)	31 (41.3)	13 (27.1)	0.126	30 (24.4)	19 (30.6)	11 (18.0)	0.141
Hypertension	51 (41,5)	33 (44.0)	18 (37.5)	0.574	98 (79.7)	57 (91,9)	41 (67.2)	<0.001##

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Hyperlipidemia	29 (23.8)	16 (21.3)	13 (27.7)	0.513	74 (60.2)0	52 (83.9)	22 (36.1)	<0.001##
AF	6 (4.9)	4 (5.3)	2 (4.3)	>0.999	26 (21.1)	20 (32.3)	6 (9.8)	0.004
PVD	6 (4.9)	5 (6.7)	1 (2.1)	0.404	21 (17.1)	17 (27.4)	4 (6.6)	0
CVI or TIA	3 (2.5)	3 (4.0)	0 (0.0)	0.284	10 (8.1)	7 (11.3)	3 (4.9)	0.323
COPD	4 (3.3)	2 (2.7)	2 (4.3)	0.639	14 (11.4)	13 (21.0)	1 (1.6)	0.001##
Smoking	53 (46.9)	35 (49.3)	18 (42.9)	0.562	89 (73.0)	50 (80.5)	39 (65.0)	0.067
MI	5 (4.1)	3 (4.0)	2 (4.3)	>0.999	46 (37.4)	34 (54.8)	12 (19.7)	<0.001##
CKD				0.919				0.001##
I-II	104 (85.2)	64 (85.3)	40 (85.1)		108 (87.8)	48 (77.4)	60 (98.4)	
III	12 (9.8)	8 (10.7)	4 (8.5)		9 (7.3)	8 (12.9)	1 (1.6)	
IV	4 (3.3)	2 (2.7)	2 (4.3)		5 (4.1)	5 (8.1)	0 (0.0)	
V	2 (1.6)	1 (1.3)	1 (2.1)		1 (0.8)	1 (1.6)	0 (0.0)	
LVEF, %	65.0 (65.0-65.0)	65.0 (65.0-65.0)	65.0 (65.0-65.0)	0.075	59.0 (50.0-65.0)	53.5 (49.8-60.0)	62.00 (58.0-66.5)	<0.001##
LFEF <50%	3 (2.5)	1 (1.4)	2 (4.2)	0.561	22 (17.9)	15 (24.2)	7 (11.5)	0.098
AVC	79 (64.2)	62 (82.7)	17 (35.4)	<0.001##	46 (37.4)	29 (46,8)	17 (27.9)	0.040
Aortic root calcification	84 (68.3)	63 (84.0)	21 (43.8)	<0.001##	93 (75.6)	60 (96.8)	033 (54.1)	<0.001##
Total aortic valve Ca score	1.0 (1.0-2.0)	2.0 (1.0-3.0)	1.0 (0.0-1.0)	<0.001##	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (0.0-1.0)	<0.001##
Posterior mitral leaflet restriction	4 (3.3)	3 (4.0)	1 (2.1)	>0.999	7 (5.7)	6 (9.7)	1 (1.6)	0.114
Anterior mitral leaflet restriction	1 (0.8)	0 (0.0)	1 (2.01)	0.390	2 (1.6)	2 (3.2)	0 (0.0)	0.496
Mitral valve calcification	47 (38.2)	44 (58.7)	3 (6.3)	<0.001##	84 (68.3)	48 (77.4)	36 (59.0)	0.034
Subvalvular mitral apparatus calcification	51 (41.5)	41 (54.7)	10 (20.8)	<0.001##	56 (45.5)	34 (54.8)	22 (36.1)	0.047
Total mitral valve Ca score	2.0 (0.0-3.0)	2.0 (1.0-3.0)	0.0 (0.0-0.75)	<0.001##	2.0 (1.0-3.0)	3.0 (2.0-4.0)	1.0 (1.0-1.0)	<0.001##
Total Ca score	3.0 (1.0-5.0)	5.0 (3.0-6.0)	1.0 (0.0-2.0)	<0.001##	3.0 (2.0-4.0)	4.0 (3.0-6.0)	2.0 (1.0-3.0)	<0.001##

Data are presented as frequencies (n) and percentages (%), median with interquartile range or mean ± SD (standard deviation), AF - atrial fibrillation, BMI – body mass index, AVC – aortic valve calcification, CKD – chronic kidney disease, COPB – chronic obstructive pulmonary disease, CVI – cerebrovascular insult, DM – diabetes mellitus, LC - liver cirrhosis, LVEF – left ventricular ejection fraction, MI - previous myocardial infarction, PVD – peripheral vascular disease, TIA -transitory ischemic attack, # Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/27 = 0.0018).

In the control patient subgroup with mitral annular calcification, a significantly higher incidence of hypertension, hyperlipidemia, chronic obstructive pulmonary disease, previous MI, chronic kidney disease stage III, IV, and V, and lower values of LVEF(%) were found. This patient subgroup also exhibited a higher incidence of aortic root calcification and had significantly higher values of

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aortic valve Ca score, mitral valve Ca score, and total Ca score values (Table 6). These associations remained significant even after the Bonferroni correction was applied.

The univariate binary logistic regression revealed significant association of older age, BMI index, diabetes mellitus, hyperlipidemia, atrial fibrillation, peripheral vascular disease, chronic obstructive pulmonary disease, previous cardiac surgery, chronic kidney disease stage III, left ventricular ejection fraction (%), aortic valve calcification, aortic root calcification, mitral valve calcification, subvalvular mitral apparatus calcification, fatty liver cirrhosis (nonalcoholic and alcoholic fatty liver disease), as well as aortic, mitral valve and total Ca score with the occurrence of mitral annular calcification (Table 7). However, excluding the aortic valve, mitral valve, and total Ca score, only older age, aortic valve calcification, aortic root calcification, mitral valve calcification, and subvalvular mitral apparatus calcification remained significantly associated with the occurrence of mitral annulus calcification following the Bonferroni correction for multiple comparisons.

Herein, as in the case of aortic valve calcification, the values of aortic valve and mitral valve Ca score, as well as the values of total Ca score, were not included in multivariate binary logistic regression analysis. Model I of multivariate binary logistic regression (controlling for age, gender, BMI, and liver cirrhosis) further confirmed the independent association of older age and BMI with the occurrence of mitral annulus calcification in the overall patient group (Table 7). Following Bonferroni correction, model IIb (controlling for age, gender, BMI, liver cirrhosis, aortic valve calcification, aortic root calcification, mitral valve calcification and subvalvular mitral apparatus calcification) of binary logistic regression further confirmed the association of older age, BMI, fatty liver cirrhosis (nonalcoholic and alcoholic liver disease), aortic valve calcification, aortic root calcification, and mitral valve calcification with the occurrence of mitral annulus calcification (Table 7).

However, following Bonferroni correction for multiple comparisons, model IIIb of multivariable binary logistic regression (controlling for age, gender, BMI, liver cirrhosis, aortic valve calcification, aortic root calcification, mitral valve calcification, subvalvular mitral apparatus calcification, posterior mitral leaflet restriction, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease stage, LVEF (%), and previous MI) both subgroups of liver cirrhosis etiology [fatty liver cirrhosis (nonalcoholic and alcoholic liver disease), and other causes of liver cirrhosis] as well as aortic valve calcification, and aortic root calcification were the only variables associated with the occurrence of mitral annulus calcification (Table 7).

Table 7. Univariate and multivariate binary logistic regression analysis of variables related to mitral annular calcification.

Variable	Univariate binary logistic regression			Variable	Multivariate binary logistic regression			
	OR	95 % CI	P#		Model	OR	95 % CI	P *
Age	1.140	1.094-1.187	<.001##	Age	I	1.141	1.092-1.193	<0.001##
					IIb	1.102	1.041-1.167	<0.001##
					IIIb	1.067	1.000-1.137	0.050
Gender, male	0.999	0.572-1.744	0.996	Gender, male	I	0.868	0.428-1.759	0.694
					IIb	0.715	0.303-1.684	0.442
					IIIb	0.439	0.157-1.228	0.117
BMI, kg/m^2	1.104	1.038-1.173	0.002	BMI, kg/m^2	I	1.102	1.026-1.183	0.008##
					IIb	1.166	1.067-1.273	<0.001##
					IIIb	1.169	1.061-1.288	0.002##

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DM	2.035	1.150-3.603	0.015	DM	IIIb	1.049	0.425-2.587	0.917
Hypertension	1.623	.969-2.719	0.066	Hypertension	IIIb	1.214	0.457-3.221	0.697
Hyperlipidemia	2.055	1.217-3.471	0.007	Hyperlipidemia	IIIb	2.423	0.900-6.521	0.080
AF	2.655	1.141-6.175	0.023	AF	IIIb	3.181	0.811-12.473	0.097
PVD	3.941	1.440-10.785	0.008	PVD	IIIb	1.708	0.352-8.286	0.506
COPD	4.303	1.212-15.274	0.024	COPD	IIIb	5.163	0.861-30.966	0.072
CKD III	2.857	1.010-8.082	0.048	CKD III	IIIb	0.726	0.1304.068	0.716
LVEF (%)	0.957	0.928-0.987	0.006	LVEF (%)	IIIb	0.969	0.923-1.016	0.194
MI	2.484	1.263-4.886	0.008	MI	IIIb	3.060	1.014-9.237	0.047
Fatty LC (NAFLD and AFLD)	2.017	1.063-3.828	0.032	Fatty LC (NAFLD and AFLD)	I	2.677	1.204-5.954	0.016
					IIb	4.461	1.573-12.656	0.005##
					IIIb	16.693	3.843-72.512	<0.001##
Other causes of LC	1.195	0.648-2.204	0.569	Other causes of LC	I	1.475	0.692-3.148	0.314
					IIb	3.173	1.135-8.871	0.028
					IIIb	12.719	3.068-52.736	<0.001##
AVC	4.364	2.547-7.477	<0.001##	AVC	IIb	5.307	2.444-11.522	<0.001##
					IIIb	8.079	3.263-20.004	<0.001##
Aortic root calcification	8.948	4.587-17.457	<0.001##	Aortic root calcification	IIb	7.185	2.827-18.257	<0.001##
					IIIb	15.987	4.630-55.203	<0.001##
Mitral valve calcification	3.670	2.161-6.232	<0.001##	Mitral valve calcification	IIb	4.790	2.077-11.044	<0.001##
					IIIb	4.229	1.634-10.947	0.003
Posterior mitral leaflet restriction	3.762	0.796-17.786	0.095	Posterior mitral leaflet restriction	IIIb	17.862	1.036-307.871	0.047

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Subvalvular mitral apparatus calcification	2.911	1.710-4.956	<0.001##	Subvalvular mitral apparatus calcification	IIb	1.901	0.910-3.972	0.087
					IIIb	1.458	0.640-3.321	0.369
Aortic valve Ca score	2.761	1.980-3.850	<0.001##	---	--	--	--	--
Mitral valve Ca score	13.895	7.248-26.638	<0.001##	---	--	--	--	--
Total Ca score	4.800	3.233-7.128	<0.001##	---	--	--	--	--

Data are presented as odds ratio (OR), 95 % confidence interval (CI) and P values. AVC – aortic valve calcification, DM – diabetes mellitus, Model I - controlling for age, gender, BMI and liver cirrhosis, Model IIa (controlling for age, gender, BMI, liver cirrhosis and mitral annulus calcification, Model IIIa - controlling for age, gender, and BMI, previous cardiac surgery, smoking history, myocardial infraction (MI), peripheral vascular diseases (PVD), previous cerebrovascular insult (CVI) or transitory ischemic attack (TIA), aortic root calcification and mitral annulus calcification. # Bonferroni non-adjusted P values, ##Bonferroni corrected P values (Pc = 0.05/number of comparisons; Pc = 0.0018 for univariate, and 0.01 for Model I, 0.0055 for Model IIb, and 0.0022 for Model IIIb of multivariate binary logistic regression analysis, respectively).

4. Discussion

Our study aimed to investigate the association between liver cirrhosis and calcification of the heart valves. Applying multivariate binary logistic regression analyses, we found a significant association, with fatty liver cirrhosis being linked to aortic valve calcification, and liver cirrhosis, regardless of its cause, being associated with mitral annular calcification. Multivariate binary logistic regression also identified other factors associated with aortic valve calcification in the overall patient group, including previous cardiac surgery due to atherosclerosis-related ischemic heart disease and mitral annular calcification. Conversely, BMI, aortic valve calcification, aortic root calcification, and mitral valve calcification were associated with the occurrence of mitral annular calcification. The patient cohort in our study was composed of liver cirrhosis patients [fatty liver (nonalcoholic and alcoholic liver disease) and other causes of liver cirrhosis] and an age- and sex-matched control composed of cardiovascular patients without cirrhosis or indications for heart valve surgery. The findings revealed a stark contrast in the burden of atherosclerotic cardiovascular disease risk factors between the two groups, underscoring the systemic impact of liver cirrhosis on overall health. The control group bore a significantly higher incidence of hyperlipidemia, cigarette smoking, and arterial hypertension. Moreover, the control group had a higher incidence of previous cardiac surgery and MI, and a higher number of patients with a lower LVEF. A higher incidence of peripheral atherosclerotic disease, cerebrovascular insult, or transitory ischemic attack was also noticed in the control group. Furthermore, the control patient group also exhibited a higher presence of mitral valve calcification, while the liver cirrhosis patient group exhibited a higher incidence of aortic valve calcification. However, no significant difference in the levels of aortic and mitral valve or total Ca score was found between the liver cirrhosis and control patient group. When the overall patient cohort was subdivided into subgroups with and without aortic valve or mitral annular calcification, patients in both the aortic valve and mitral annular calcification subgroups were older and showed significantly higher values of aortic valve and total calcium scores. In contrast, the mitral valve Ca score was higher only in the aortic valve calcification subgroup. Patients with aortic valve calcification also showed a higher incidence of previous atherosclerosis-related cardiac surgeries and posterior mitral annular calcification. In contrast, patients with mitral annular calcification had a higher BMI, lower left ventricular ejection fraction, and a higher incidence of calcification of the aortic valve, aortic root, mitral valve, and subvalvular mitral apparatus. Similarly, the patient subgroup

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with the concomitant presence of liver cirrhosis and mitral annular calcification was also characterized by higher BMI values and a higher incidence of calcification of the aortic valve, aortic root, mitral valve, and subvalvular mitral apparatus, Contrarily, the patient subgroup with concomitant presence of liver cirrhosis and aortic valve calcification showed higher incidence of mitral valve and posterior mitral annular calcification. Notably, higher values of aortic, mitral valve, and total calcium scores were observed in both patient subgroups. Higher values of aortic, mitral valve, and total calcium scores were also noticed in the control patient subgroup with mitral annular calcification. The control patient subgroup with mitral annular calcification was also characterized by significantly higher incidence of hypertension, hyperlipidemia, MI, and chronic kidney disease stage III-V, paralleled with lower values of LVEF. Distinctively, the control group with concomitant presence of aortic valve calcification showed significantly higher values of aortic valve and total Ca score, accompanied by a higher incidence of atherosclerosis-related cardiac surgeries. These findings underscore the adverse effects of liver cirrhosis, irrespective of its etiology, on heart valve calcification, mainly aortic valve calcification and mitral annular calcification, which are both associated with adverse cardiovascular outcomes [19–21]. Since liver cirrhosis and heart valve diseases are age-related phenomena with some overlapping risk factors, there is an increasing prevalence of patients who have both liver cirrhosis and severe valvular heart disease [22]. Previous findings revealed the association of nonalcoholic liver diseases with the occurrence of aortic and mitral valve calcification [23–25]. Bonapace et al. reported a positive and independent association of NAFLD with the presence of aortic valve sclerosis (defined as focal or diffuse thickening and calcification of the aortic leaflets without restriction of leaflet motion) in patients with type 2 diabetes mellitus [19,24]. This association remained significant even after adjusting for several established cardiovascular disease (CVD) risk factors (i.e., age, sex, BMI, smoking, alcohol consumption, hypertension, and dyslipidemia). However, in their study, no association between NAFLD and mitral annular calcification was detected. An independent association of NAFLD with an increased risk of aortic valve sclerosis in the general population was also reported by Markus et al. [23]. Similar to our study, Mantovani et al. also reported NAFLD as an independent predictor of cardiac calcification in both the aortic and mitral valves [25]. In their study, the presence of NAFLD was associated with a nearly threefold increased risk of prevalent aortic-valve sclerosis, mitral annular calcification, or both [25]. In addition, the reported association was independent of traditional CVD risk factors (age, sex, waist circumference, smoking, blood pressure, LDL-cholesterol), kidney function parameters (eGFR), diabetes-related variables (HbA1c), use of medications (i.e., hypoglycemic, lipid-lowering, and hypertensive drugs), and some relevant echocardiographic parameters (E/e' ratio used to assess left ventricular filling pressure and as a marker to diagnose diastolic heart failure) [25]. Positive association between NAFLD and incident aortic valve calcification was also reported by Hao et al.[26]. Their analysis of 4226 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) database also revealed the association between genetically predicted NAFLD and calcific aortic valve stenosis, but only after excluding genes associated with impaired very low-density lipoproteins (VLDL) secretion [26]. A study reported by Cozzolino et al. found that the prevalence of aortic valve stenosis in the pool of cirrhotic patients was about double that of non-cirrhotic patients, with approximately 12.5% and 6% of cirrhotic patients having mild-to-moderate aortic regurgitation and stenosis, respectively [27]. A similar frequency of patients with aortic valve lesions was recorded in studies of liver transplant recipients reported by Fukazawa et al. and Arman et al. [28,29]. Cozzolino et al. also reported that the prevalence of mitral valve regurgitation was higher in cirrhotic patients with more severe liver dysfunction, whereas the prevalence of mitral valve stenosis was not statistically different between the groups [27]. They also noticed a significantly higher incidence (> 90 %) and stage of mitral valve calcification in cirrhotic patients with a more advanced stage of liver disease compared to the remaining patients recruited in the study [27]. The association of NAFLD and fibrosis score (FIB 4) with the incidence of mitral annular calcification was also recently reported by Ergül et al [30]. Furthermore, NAFLD and/or FIB 4 were also associated with subclinical atherosclerosis, such as coronary artery calcification (CAC) and carotid intima-media thickening, and

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with coronary artery disease outcomes [30–41]. NAFLD was also associated with the occurrence of abdominal aortic calcification, as well as the incidence of arterial calcification [42–44]. The pathogenesis of NAFLD and AFLD is associated with various extra-hepatic risk factors such as age, gender, smoking, alcohol consumption, and metabolic syndrome encompassing obesity, type 2 diabetes mellitus, dyslipidemia, and chronic kidney disease [45,46]. Oxidative stress, insulin resistance, inflammation, dietary habits, genetic defects, and environmental factors also play an essential role [45,46]. However, the molecular mechanisms that promote disease progression, nor the mechanisms by which NAFLD and AFLD may directly contribute to the pathogenesis of cardiovascular diseases, including heart valve and other forms of ectopic cardiovascular calcification, have not been fully elucidated. Thus, a comprehensive understanding of NAFLD and AFLD signaling pathways will facilitate the identification of biomarkers and therapeutic targets for the early detection of disease progression and the management of its hepatic, systemic, and cardiovascular manifestations, including those related to the heart and other organs.

Regarding the limitations of this study, it's essential to acknowledge that the results, although not generalizable due to the small sample size and the study's single-center nature, lay the groundwork for future research in the field of liver cirrhosis and its impact on ectopic heart valve calcification. Further studies involving a larger number of subjects in both patient subgroups are needed to validate the results.

5. Conclusions

In conclusion, the findings of the present study demonstrate the involvement of liver cirrhosis in altering the structure and function of the heart valve. These findings have significant implications for patient care, particularly for cirrhosis patients who may be potential liver transplant recipients. The study found a significant association between fatty liver cirrhosis (nonalcoholic and alcoholic liver disease) and aortic valve calcification, as well as liver cirrhosis, regardless of its cause, with mitral annular calcification. Previous cardiac surgery due to atherosclerosis-related ischemic heart disease and mitral annular calcification were also related to aortic valve calcification, while BMI, aortic valve calcification, aortic root calcification, and mitral valve calcification were associated with the occurrence of mitral annular calcification. In addition, both the aortic valve and mitral annular calcification subgroups showed significantly higher values of aortic valve and total calcium scores, while the mitral valve Ca score was higher only in the aortic valve calcification subgroup. Higher values of aortic, mitral valve, and total calcium scores were also observed in liver cirrhosis subgroups with concomitant presence of aortic valve or mitral annular calcification, respectively. Elevated values of aortic, mitral valve, and total calcium scores were also noticed in the control cardiovascular patient subgroup with mitral annular calcification. In contrast, the control group with concomitant presence of aortic valve calcification showed significantly higher values of aortic valve and total Ca score, accompanied by a higher incidence of atherosclerosis-related cardiac surgeries. These data should be considered in perioperative management of cirrhosis patients as potential liver transplant recipients for more comprehensive preoperative risk stratification, but also postoperative detailed follow-ups and reviews to identify patients that may benefit from either percutaneous or surgical valvular therapy.

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Abbreviations

The following abbreviations are used in this manuscript:

AFLD	alcohol-related fatty liver disease
AVC	Aortic valve calcification
BMI	Body mass index
CAD	Coronary atherosclerosis
CAVD	Calcific aortic valve disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVI	Cerebrovascular insult
DM	Diabetes mellitus
LC	Liver cirrhosis
LVEF	Left ventricle ejection fraction
MAC	Mitral annular calcification
MAFLD	Metabolic-associated fatty liver disease
MI	Myocardial infarction
NAFLD	Nonalcoholic fatty liver disease
OR	Odds ratio
Pc	Bonferroni corrected P value
PVD	Peripheral vascular disease
SD	Standard deviation
TIA	Transitory ischemic attack

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