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ORIGINAL ARTICLE

Observational Study

Metabolic dysfunction-associated steatotic liver disease-associated fibrosis and cardiac dysfunction in patients with type 2 diabetes

Simona Cernea, Danusia Onișor, Andrada Larisa Roiban, Theodora Benedek, Nora Rat

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Abstract

BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD), particularly in the presence of liver fibrosis, increases the risk of cardiovascular morbidity and mortality, but the nature of the cardio-hepatic interaction in the context type 2 diabetes mellitus (T2DM) is not fully understood.

AIM
To evaluate the changes in cardiac morphology and function in patients with T2DM and MASLD-associated liver fibrosis.

METHODS
T2DM patients with MASLD underwent a medical evaluation that included an assessment of lifestyle, anthropometric measurements, vital signs, an extensive laboratory panel, and a standard echocardiography. Liver fibrosis was evaluated using two scores [Fibrosis-4 (FIB4) and Non-alcoholic fatty liver disease-Fibrosis Score (NFS)], and subjects were classified as having advanced fibrosis, no fibrosis, or an indeterminate risk. The correlations between structural and functional cardiac parameters and markers of liver fibrosis were evaluated through bivariate and multiple regression analyses. Statistical significance was set at $P < 0.05$.

RESULTS
Data from 267 T2DM-MASLD subjects with complete assessment was analyzed. Patients with scores indicating advanced fibrosis exhibited higher interventricular septum and left ventricular (LV) posterior wall thickness, atrial diameters, LV end-systolic volume, LV mass index (LVMi), and epicardial adipose tissue thickness (EATT). Their mean ejection fraction (EF) was significantly lower (49.19% ± 5.62% *vs* 50.87% ± 5.14% *vs* 52.00% ± 3.25%; $P = 0.003$), and a smaller proportion had an EF ≥ 50% (49.40% *vs* 68.90% *vs* 84.21%; $P = 0.0017$). Their total and mid LV wall motion score indexes were higher ($P < 0.05$). Additionally, they had markers of diastolic dysfunction, with a higher E/e' ratio [9.64 ± 4.10 *vs* 8.44 (2.43-26.33) *vs* 7.35 ± 2.62; $P = 0.026$], and over 70% had lateral e' values < 10 cm/second, though without significant differences between groups. In multiple regression analyses, FIB4 correlated with left atrium diameter (LAD; $\beta = 0.044$; $P < 0.05$), and NFS with both LAD ($\beta = 0.039$; $P < 0.05$) and right atrium diameter ($\beta = 0.041$; $P < 0.01$), Moreover, LVMi correlated positively with age and EATT ($\beta = 1.997$; $P = 0.0008$), and negatively with serum sex-hormone binding protein (SHBP) concentrations ($\beta = -0.280$; $P = 0.004$). SHBP also correlated negatively with LAD ($\beta = -0.036$; $P < 0.05$).

CONCLUSION
T2DM patients with markers of MASLD-related liver fibrosis exhibit lower EF and present indicators of diastolic dysfunction and cardiac hypertrophy. Additionally, LVMi and LAD correlated negatively with serum SHBP concentrations.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Type 2 diabetes mellitus; Liver fibrosis; Cardiac dysfunction; Sex-hormone binding protein

Core Tip: Metabolic dysfunction-associated steatotic liver disease (MASLD) is frequently associated with type 2 diabetes mellitus (T2DM), and both conditions are important risk factors for cardiovascular disease. However, the nature of the cardio-liver interaction, particularly in patients with T2DM, is not completely elucidated. In this study we found that T2DM patients with MASLD-associated fibrosis, quantified by accessible scores (Fibrosis-4 and Non-alcoholic fatty liver disease-Fibrosis Score), present markers of systolic and diastolic dysfunction, as well as cardiac hypertrophy, particularly increased left atrial diameter. The left ventricular mass index and left atrial dimension also correlated negatively with serum concentrations of sex-hormone binding protein, which may serve as a valuable prognostic biomarker. Mechanistic studies that explain the correlations between liver fibrosis and cardiac remodeling in MASLD patients, both with and without T2DM, are greatly needed.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined by the presence of hepatic steatosis in combination with at least one cardiometabolic risk factor, without other causes of steatotic liver disease[1]. It encompasses a spectrum of conditions from simple hepatic steatosis to steatohepatitis (which may involve varying degrees of fibrosis, from mild to severe/cirrhosis), and to hepatocellular carcinoma[1,2].

A core pathogenetic mechanism of MASLD is insulin resistance, which implies a cross-talk between the liver and peripheral tissues, favoring the accumulation of lipids in the liver[3,4]. In fact, MASLD is considered part of a multi-systemic disease, alongside other components of metabolic syndrome [*i.e.*, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, hypertension], for which insulin resistance is a key pathogenetic factor[5,6]. The relationship between T2DM and MASLD is bidirectional[6]. Literature data indicates that MASLD doubles the risk of T2DM, and the severity of hepatic fibrosis is independently correlated with a higher risk of incident diabetes[7,8]. On the other hand, T2DM increases the risk of MASLD by approximately two-fold and worsens the course of the disease toward more advanced stages (*i.e.*, advanced fibrosis/cirrhosis, hepatocellular carcinoma, liver-related hospitalizations, and deaths)[6,9-11].

Moreover, MASLD significantly increases the risk of cardiovascular disease (CVD) and mortality in both individuals with and without T2DM, independent of other risk factors[12-15]. In patients with T2DM, the presence of MASLD nearly doubles the risk of CVD, suggesting potential synergistic effects of these two conditions on cardiovascular risk[13,16]. The presence of MASLD in hospitalized patients with CVD significantly raises the risk of all-cause mortality [hazard ratio (HR): 2.08; 95% confidence interval (95%CI): 1.56-2.59, $P < 0.001$][17]. Furthermore, the severity of MASLD fibrosis is associated with a higher risk of overall mortality [unadjusted relative risk for stage F0 *vs* F4: 3.42 (95%CI: 2.63-4.46); adjusted HR for stage F0-2 *vs* F3-4: 2.24 (95%CI: 1.48-3.39)][18]. Emerging evidence also suggests that the severity of liver fibrosis has a significant impact on the risk of fatal or non-fatal CVD events, independent of other cardiometabolic risk factors [pooled random-effects HR: 2.50 (95%CI: 1.68-3.72)][15].

Nevertheless, the nature of the relationship between liver fibrosis and CVD, particularly in the context of T2DM, is not entirely clear, as the coexistence of other cardiovascular risk factors complicates the deciphering of the independent contributions of each condition to the incidence and progression of the other. Some authors even question the causal link between MASLD and CVD[19]. On the other hand, some data suggest that markers of CVD (such as carotid intima-media thickness) may predict liver fibrosis in MASLD patients with T2DM[20]. Therefore, understanding the nature of these associations is important, as early screening and intervention for one disease may potentially ameliorate the progression of the other. However, few studies have investigated the relationship between liver fibrosis and cardiac morphology and function in patients with T2DM. One study showed that liver fibrosis was independently associated with diastolic dysfunction [odds ratio (OR): 1.58 (95%CI: 1.07-2.34, $P = 0.022$), while another reported an association with subclinical myocardial remodeling in T2DM subjects[21,22].

The aim of this study was to evaluate cardiac morphology and function in relation to markers of liver fibrosis in T2DM patients with MASLD.

MATERIALS AND METHODS

Study population and data collection

The study enrolled patients with T2DM and NAFLD in the Outpatient Unit of the Emergency County Clinical Hospital of Târgu Mureș, Romania between July 2022 and July 2023. Patients were recruited from the Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, and the Gastroenterology Department of the County Clinical Hospital, Târgu Mureș. Inclusion criteria were as follows: Adult subjects aged 30 years or older, with a previous diagnosis of T2DM and NAFLD (based on patient history and liver ultrasound). NAFLD was defined by the presence of hepatic steatosis/steatohepatitis in the absence of other secondary causes of liver disease (including viral or autoimmune hepatitis, excessive alcohol intake of ≥ 30 g/day for men and ≥ 20 g/day for women, specific drugs, toxins, hemochromatosis, Wilson's disease or other known specific liver diseases). In July 2023, the term MASLD was proposed to replace NAFLD to better describe and classify the steatotic liver disease, potentially reducing stigma[23]. This new term was largely adopted thereafter, and emerging evidence indicates that the term MASLD can be used interchangeably with NAFLD[24]. Since our patients met the diagnostic criteria for MASLD (*i.e.*, had liver steatosis and at least one cardiometabolic risk factor, T2DM), we adopted the new term to describe their liver condition. Exclusion criteria for this study included other types of diabetes, other chronic liver diseases (including liver transplant), malignant diseases in the last 5 years, severe autoimmune diseases, severe valvulopathy, and significant pericardial collections. The study was approved by the Ethics Committees of the Emergency County Clinical Hospital of Târgu Mureș (nr. 8120/05.04.2022), the County Clinical Hospital of Târgu Mureș (nr. 4873/24.05.2022), and the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (nr. 1806/22.06.2022). All subjects signed an informed consent before being enrolled in the study.

The following data were collected: Demographic data, medical history (including therapy), lifestyle data (diet, coffee, tea and alcohol intake, physical exercise, sleep, smoking, stress) through general or specific questionnaires. Alcohol consumption was assessed using both a general questionnaire with secondary interview, and the AUDIT-C test. Anthropometric parameters (weight, height, waist circumference, hip circumference), heart rate, and blood pressure were measured using standard methods. The body mass index (BMI) was calculated as follows: Weight/height^2 (kg/m^2). The pO_2 was measured under standard conditions using a pulse oximeter.

Laboratory assessment

On the same day, fasting blood samples were collected between 7: 45 AM and 8: 15 AM, and serum aliquots were stored at -80 °C for subsequent analysis of the following parameters: Blood glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, C-peptide, uric acid, creatinine, sex-hormone binding protein (SHBP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (GGT), direct bilirubin, albumin, ferritin, and haptoglobin. Blood for HbA1c measurement was drawn on the same occasion and stored at -80 °C for up to three months for later measurement. The biochemical tests were analyzed using a

Cobas Integra 400plus (Roche Diagnostics, Germany). Albumin, haptoglobin, and HbA1c were measured using an immunoturbidimetric method, while uric acid, ASAT, ALAT, direct bilirubin, GGT, creatinine, glucose, and lipids were measured using a spectrophotometric method. C-peptide, ferritin and SHBP were analyzed on the Immulite 2000 XPI system (Siemens) using a solid-phase, two-site chemiluminescent immunometric assay. The complete blood count was analyzed shortly after the blood was drawn using a 5-differential hematology Mindray BC6200 analyzer. The Homeostatic Model Assessment (HOMA) for Insulin Resistance (HOMA-IR) was calculated by using the HOMA calculator version 2.2.3[25]. The estimated glomerular filtration rate (eGFR) was calculated based on the CKD-EPI 2021 formula[26].

The hepatic fibrosis was estimated using two well-known and validated indices. The fibrosis-4 (FIB4) score was calculated using the formula: Age (years) × ASAT (U/L)/[platelet (10^9/L) × ALT$^{1/2}$ (U/L)]. A FIB4 score < 1.3 rules out advanced fibrosis, a score > 2.67 indicates advanced fibrosis (F ≥ 2), while FIB4 values between 1.3 and 2.67 are considered to be indeterminate risk[27]. The NAFLD-Fibrosis Score (NFS) was calculated with the following formula: -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired glucose tolerance/diabetes (yes = 1; no = 0) + 0.99 × ASAT/ALAT - 0.013 × platelet (× 10^9/L) - 0.66 × albumin (g/dL). Values > 0.676 indicate significant liver fibrosis (> F2), scores < -1.455 indicate no significant fibrosis, while values between -1.455 and 0.676 are considered undetermined[28].

Echocardiographic assessment

The echocardiographic evaluation was performed on a subsequent day (within a 2-3 weeks interval) by an experienced cardiologist who was blinded to all other aspects of the study. The ultrasonographic assessment was conducted using a VIVID9 XDClear equipment (GE HealthCare). The quantification of cardiac chamber sizes and function was carried out in accordance with the recommendations of the ASE/EAC Guidelines[29].

The left ventricular (LV) ejection fraction (EF) was evaluated using the modified Simpson's rule calculated by dividing the stroke volume by the end-diastolic LV volume. An EF was considered normal if the values were ≥ 50%[30]. The dimensions of the ventricles and atria, as well as the epicardial adipose tissue thickness (EATT), were measured in the parasternal long-axis view. The LV end-diastolic and end-systolic volumes were measured using 2D echocardiography in the apical 4-chamber view and 2-chamber view at the end of diastole and systole.

The LV mass (LVM) was calculated using the following formula: LVM (g) = 0.80 × [1.04 × (PWd (cm)+ IVSd (cm) + LVDd (cm))^3 - (LVDd (cm))^3] + 0.6, where 1.04 is the density of heart muscle (g/cm^3), PWd is the LV posterior wall thickness at end-diastole, IVSd is the interventricular (IV) septum thickness at end-diastole, and LVDd is the LV end-diastolic dimension[29,31]. The LVM was indexed to the body surface area [LVM index (LVMi)] calculated using the DuBois formula[29,32]. The upper limits for normal values of LVMi were considered to be 95 g/m^2 in women and 115 g/m^2 in men[29].

The LV outflow tract (LVOT) velocity time integral was determined in the apical 5-chamber view using the pulsed-wave Doppler technique, with the pulse wave Doppler gate positioned at the LVOT level. Using the same technique in the apical 4-chamber view, the following parameters were determined on the Doppler curve: Maximum velocities of the E wave, A wave, e' septal, e' lateral, a' septal, a' lateral, and deceleration time (DcT). The E/A ratio e'/a' septal, and e'/a' lateral ratios were calculated. The average E/e' ratio was calculated as the ratio of E to the average e' (mean of e' septal and e' lateral).

Regional LV function was assessed in a 17-segment model. The basal and midventricular segments included anterior, anterolateral, anteroseptal, inferior, inferolateral, and inferoseptal segments, while the apical segments included anterior, septal, inferior, lateral, and the ''apical cap (apex)'' (myocardium beyond the end of the LV cavity)[29]. Total and segmental kinetics scores were calculated by assigning points according to the following grading: 1 point for normal kinetics; 2 points for hypokinesia, 3 points for akinesia. Total and segmental wall motion score indexes were calculated by dividing the wall motion scores by the number of segments.

Statistical analysis

Descriptive statistics were performed for all variables, and the normality of the data was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as the mean ± SD, while non-normally distributed variables are presented as median (min-max). Categorical variables are presented as frequency (%). Comparisons between groups were conducted using one-way ANOVA with Tukey post-test for normally distributed variables or Kruskal-Wallis test with Dunn post-test for non-normally distributed variables. The χ^2 test was employed to analyze categorical variables. The relationship between two variables of interest was investigated using Spearman's test, with data presented as correlation coefficients r (95%CI). Multiple regression analyses for more than two variables were employed to test the independent associations between liver fibrosis scores and cardiac parameters, as well as to evaluate the impact of independent variables on various echocardiographic parameters of interest. Statistical analyses were performed using GraphPad InStat 3 (GraphPad Software, United States). All tests were two-tailed, and statistical significance was assumed at $P < 0.05$.

RESULTS

In this study 278 T2DM patients with MASLD were enrolled. Of these, seven patients met the exclusion criteria, and four did not return for the cardiac ultrasound evaluation. Ultimately, data from 267 T2DM-MASLD patients were analyzed. The median age of the participants was 66 (36-82) years, and the median duration of diabetes was 10 (0-33) years. Of the total cohort, 45.32% were men, 76.40% lived in urban areas, 22.84% were employed, and 75.28% were retired. Their relevant medical history, lifestyle and other clinical characteristics are presented in Table 1.

Table 1 Lifestyle and clinical characteristics of the study population

Patients' characteristics	Value
Systolic/diastolic BP (mmHg)	135.0 (95.0-190.0)/80.0 (51.0-107.5)
Heart rate (beats/min)	74.0 (50.0-112.0)
pO_2 (%)	97.0 (90.0-99.0)
Lifestyle	
Smoking status	
Current smoker	28 (10.49)
Former smoker	107 (40.07)
Never smoked	132 (49.44)
Coffee intake (cups/day)	1.25 ± 0.80
Alcohol intake (g/day)	2.85± 5.37
Anthropometric parameters	
BMI (kg/m^2)	34.11 ± 5.30
Waist circumference (cm)	109.16 ± 11.72 (F)
	114.92 ± 10.83 (M)
Hip circumference (cm)	110.21 ± 10.55 (F)
	108.86 ± 9.98 (M)
Comorbidities	
Hypertension	251 (94.00)
Dyslipidemia	247 (92.51)
Coronary artery disease	137 (51.31)
Heart failure	99 (37.01)
Atrial fibrillation	17 (6.37)
Peripheral arterial disease	18 (6.74)
Stroke	19 (7.11)
Diabetic neuropathy	106 (39.70)
Diabetic retinopathy	36 (13.48)
Chronic kidney disease	49 (18.35)
Hyperuricemia	58 (21.72)
Antihyperglycemic therapy	
Metformin	262 (98.13)
GLP-1 RA	85 (31.83)
SGLT2 inhibitors	62 (23.22)
DPP-4 inhibitors	19 (7.12)
Sulphonylureas	27 (10.11)
Insulin	66 (24.72)

Data are presented as mean ± SD, median (min-max), or as *n* (%). BP: Blood pressure; F: Female; M: Male; BMI: Body mass index; GLP-1 RA: Glucagon-like peptide-1 receptor agonists; SGLT2: Sodium-glucose co-transporter 2; DPP-4: Dipeptidyl peptidase-4.

The median FIB4 value was 1.35 (0.4-17.3), and median NFS was 0.159 (-2.783 to 6.212). One FIB4 value was a significant outlier (134.15) and was excluded from further analysis. Among the study population, 11.2% had a FIB4 score > 2.67 suggesting advanced liver fibrosis, 44.2% had a FIB4 score between 1.3-2.67 (indicating an indeterminate risk of

advanced fibrosis) and 44.6% had a FIB4 score < 1.3 (which rules out significant fibrosis). Regarding the NFS, 31.8% of subjects had a score > 0.676 indicating advanced liver fibrosis, 61% had a score between 0.676 and -1.455 (undetermined risk of liver fibrosis), while 7.1% had NFS values < -1.455, which excludes fibrosis.

Correlation between markers of liver fibrosis and heart morphology and function

To ensure a proper selection of patients in the advanced fibrosis and no fibrosis categories, we divided the study population into three groups according to the two liver fibrosis scores: Group 1 consisted of patients with both FIB4 > 2.67 and NFS > -1.455 or both NFS > 0.676 and FIB4 > 1.3 [suggestive of significant (or advanced) fibrosis], Group 3 included patients with both FIB4 < 1.3 and NFS < -1.455 (indicating no significant fibrosis, F0-1), and Group 2, included the remaining subjects (with indeterminate risk of advanced fibrosis). The laboratory data are shown according to the liver fibrosis categories in Table 2. Subjects with more advanced hepatic fibrosis exhibited higher markers of liver injury, as well as increased insulin resistance, uric acid and triglyceride levels, and lower LDL cholesterol and eGFR values. There was no significant difference among the three groups in terms of the proportion of patients receiving therapy with glucagon-like peptide-1 receptor agonists (GLP-1 RA) and/or sodium-glucose co-transporter 2 (SGLT2) inhibitors (47.6% *vs* 48.8% *vs* 52.6%, $P = 0.9244$).

We first analyzed the ultrasound cardiac parameters evaluating the heart function and structure according to the liver fibrosis category (Table 3). The E, A and DcT were not measured in patients with atrial fibrillation, as this condition alters atrial filling. T2DM patients with MASLD and advanced liver fibrosis had significantly higher LVMi, left and right atrial diameters, IV septum thickness, and LV posterior wall thickness, LV end-systolic volume, and EATT. For other measurements of the LV, a similar trend was observed, but it did not reach statistical significance.

Moreover, patients with markers of advanced liver fibrosis had significantly lower EF (Figure 1A), and higher E/e' septal, as well as higher total a LV wall motion score index (mainly due to higher mid-ventricular wall motion scores), indicative of cardiac dysfunction and dyskinesia (Table 3 and Figure 1B). A higher proportion of T2DM patients with more advanced liver fibrosis had decreased EF (50.6% *vs* 31.1% *vs* 15.8%; $P_{trend} = 0.0004$; Figure 1C and Table 3).

Additionally, over half of the patients in each liver fibrosis category had increased LVMi values, with a slightly higher percentage in the advanced fibrosis group; however, the difference between the three groups was not significant (overall prevalence: 61.65%; Table 3). Moreover, a large proportion of patients in all three groups presented lateral e' values < 10 cm/second, indicative of LV diastolic dysfunction, but the differences between groups were not significant (65.79% in group 1 *vs* 72.84% in group 2 *vs* 70.59% in group 3; $P = 0.5384$). Higher percentages of patients in the advanced liver fibrosis and indeterminate risk of fibrosis groups presented e' septal values < 7 cm/second compared to the no liver fibrosis group, but the differences were not statistically significant (19.74% in group 1 *vs* 19.75% in group 2 *vs* 5.56% in group 3; $P = 0.3308$).

We further investigated the correlation between markers of liver fibrosis (using both FIB4 and NFS) and cardiac parameters by performing bivariate correlation and multiple regression analyses. The bivariate analyses indicated an association between markers of liver fibrosis and cardiac hypertrophy (mainly LVMi and atrial diameters), and dysfunction (primarily EF and LV kinetics score; Table 4 and Table 5). FIB4 also correlated positively with the mid and apical LV segmental kinetics scores [$r = 0.14$ (0.02; 0.26), and $r = 0.12$ (-0.002; 0.24), $P < 0.05$ for both]. A similar association was found for NFS [$r = 0.15$ (0.02; 0.27), $P < 0.05$, and $r = 0.18$ (0.06; 0.30), $P < 0.01$]. The cardiac parameters not mentioned in the table did not correlate with either of the fibrosis scores.

In the multiple regression analyses, atrial dimensions were independently associated with liver fibrosis markers. In model 1, which adjusted for several independent variables (sex, smoking status, systolic blood pressure, duration of diabetes, alcohol intake, presence of atrial fibrillation, serum creatinine), both FIB4 and NFS were independently associated with left atrium diameter (LAD; FIB4: $R^2 = 7.77\%$, $P = 0.0221$; NFS: $R^2 = 15.03\%$; $P < 0.0001$; Table 5). In model 2, which included cardiac parameters, as well as serum creatinine, C-peptide and LDL cholesterol values (correlated with both FIB4 and NFS in the bivariate analyses) as independent variables, liver fibrosis markers remained correlated with LAD, and C-peptide values (for FIB4; $R^2 = 11.19\%$, $P < 0.0001$) and right atrium diameter and creatinine values (for NFS; $R^2 = 12.56\%$, $P < 0.0001$), respectively (Table 5). The remaining parameters (not mentioned in Table 5) did not correlate with either of the fibrosis scores. In the multiple regression analyses, the LVMi was not associated significantly with either liver fibrosis scores.

In a separate bivariate analysis, LVMi correlated positively with uric acid values [$r = 0.13$ (0.010; 0.253), $P = 0.0295$], age [$r = 0.16$ (95%CI: 0.038; 0.279), $P = 0.0083$], and EATT [$r = 0.15$ (0.030; 0.272), $P = 0.0122$], while the negative correlation with SHBP concentration was not quite significant [$r = -0.12$ (-0.238; 0.005), $P = 0.0538$]. No other laboratory parameters or therapies with GLP-1 RA and/or SGLT2 inhibitors correlated with LVMi. In a multivariate regression analysis that included these parameters as independent variables, along with BMI and systolic blood pressure, the latter three were significantly correlated with LVMi ($R^2 = 10.77\%$, $P < 0.0001$): Age [$\beta = 0.599$ (95%CI: 0.227; 0.971), t ratio: 3.153, $P = 0.0018$], EATT [$\beta = 1.997$ (95%CI: 0.847; 3.146), t ratio: 3.405, $P = 0.0008$], and SHBP [$\beta = -0.280$ (95%CI: -0.469; -0.091), t ratio: 2.901, $P = 0.0040$].

To better understand the interrelationship between the liver and heart, we further investigated which liver-related and -independent factors had a significant impact on the LAD. Initially we performed bivariate correlation analyses and identified several parameters that were significantly associated with LAD (Table 6). Age, duration of diabetes, BMI, smoking status, alcohol intake and the other laboratory parameters mentioned in Table 2, as well as therapy with GLP-1RA and/or SGLT2 inhibitors were not correlated with LAD. Subsequently, the multiple regression analysis (which included as independent variables those factors found to be significantly correlated with LAD in the bivariate analysis) revealed that three of them remained independently correlated with LAD ($R^2 = 15.18\%$; $P < 0.0001$; Table 7). The presence of atrial fibrillation had the strongest impact, but higher serum values of GGT and lower SHBP concentrations also influenced LAD.

Table 2 Laboratory parameters in the study population according to the liver fibrosis category

Parameter	Group 1 (advanced fibrosis), *n* = 84	Group 2 (indeterminate risk of fibrosis), *n* = 164	Group 3 (without fibrosis), *n* = 19	*P* value
Uric acid (mg/dL)	6.13 ± 1.44	5.86 ± 1.48	5.29 (3.59-8.17)	0.0484
Albumin (g/dL)	4.59 ± 0.22[a]	4.68 ± 0.23[a]	4.70 ± 0.28	0.0118
ALAT (U/L)	17.22 (2.32-80.94)	18.02 (4.18-92.79)	25.36 ± 12.56	0.0921
ASAT (U/L)	22.54 (11.48-130.85)[b]	19.91 (9.75-49.95)[b]	19.30 (13.16-39.16)	0.0034
Direct bilirubin (mg/dL)	0.21 (0.07-0.59)[a]	0.20 (0.07-0.90)	0.17 ± 0.06[a]	0.0335
GGT (U/L)	32.78 (4.97-338.18)[a]	27.51 (4.02-313.66)[a]	27.13 (9.17-173.63)	0.0360
Total cholesterol (mg/dL)	147.20 (91.38-279.48)	155.45 (96.75-376.17)	175.16 ± 51.20	0.1347
HDL cholesterol (mg/dL)	43.98 (27.86-65.09)	43.75 (22.48-75.75)	48.04 ± 11.77	0.3977
LDL cholesterol (mg/dL)	73.71 (36.57-186.09)	84.73 (31.2-270.6)	104.01 ± 39.94	0.0488
Triglycerides (mg/dL)	156.02 (70.06-573.36)[a]	155.36 (62.37-609.08)[a]	117.83 (68.15-382.84)[a]	0.0305
Blood glucose (mg/dL)	137.59 (92.09-261.68)	136.58 (87.34-326.2)	142.75 ± 18.60	0.7290
HbA1c (%)	6.80 (4.6-10.01)	6.80 (5.7-10.20)	7.02 ± 0.72	0.5780
C-peptide (ng/mL)	3.68 (0.72-10.5)[a,b]	3.00 (0.28-8.83)[a]	2.62 ± 1.43[b]	0.0039
HOMA-IR	3.04 (0.66-8.4)[a]	2.61 (0.45-7.52)	2.23 ± 1.21[a]	0.0067
eGFR (mL/min/1.73m²)	82.53 (26.70-117.25)[b,c]	91.38 (40.36-114.59)[a,b]	97.17 ± 14.60[a,c]	< 0.0001
Haptoglobin (g/L)	1.59 ± 0.57	1.73 ± 0.61	1.73 ± 0.63	0.1997
Ferritin (ng/mL)	112.00 (8.79-781.00)	92.30 (6.41-811.00)	53.90 (9.72-543.0)	0.6226
SHBP (nmol/L)	37.41 ± 15.12	32.80 (7.62-118.00)	35.38 ± 15.68	0.3811

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
For triglycerides: Group 1 *vs* group 2, and group 2 *vs* group 3. Data are presented as mean ± SD or median (min-max). ASAT: Aspartate aminotransferase; ALAT: Alanine aminotransferase; GGT: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; SHBP: Sex-hormone binding protein.

DISCUSSION

MASLD is frequently associated with T2DM and has emerged as a risk factor for CVD, yet the nature of the cardio-liver interaction, particularly in patients with T2DM is not completely understood. In this study, which included T2DM patients with MASLD, we found that a higher proportion of patients with markers of advanced liver fibrosis had a reduced EF, and the mean EF values were lower in this category. Literature indicates that MASLD is associated with an increased risk of heart failure (HF), although there is limited information regarding the association between MASLD severity/fibrosis and HF phenotypes[33,34]. A recent cohort study suggested a stronger association of MASLD with HF with preserved EF (HFpEF) rather than HF with reduced EF (HFrEF); however, this study involved a healthcare database interrogation and not a direct echocardiographic evaluation of MASLD patients[35]. Another recent study in hospitalized patients with T2DM also showed a higher risk of HFpEF in MASLD [OR: 1.59 (95%CI: 1.22-2.08)], independent of cardiometabolic risk factors, primarily associated with more advanced liver fibrosis; however, this study did not specifically investigate the correlations of liver fibrosis with EF (or the risk of HFrEF)[36]. To our knowledge this is the first report of lower EF in T2DM patients with markers of advanced MASLD-related fibrosis. Nevertheless, existing literature is congruent with our findings. A small imaging study in T2DM and in MASLD patients, that employed high-resolution magnetic resonance imaging (MRI), tagging, and spectroscopy, demonstrated alterations in cardiac structure and function[37]. T2DM patients exhibited significant systolic dysfunction (shown by reduced stroke index), and diastolic dysfunction (reduced E/A)[37]. Moreover, a recent meta-analysis of 41 papers (n = 33891 patients who underwent echocardiography) demonstrated that patients with liver biopsy- or imaging-defined MASLD had lower EF [mean difference: -0.693 (95%CI: -1.112 to -0.274); P = 0.001] compared with patients without MASLD[38]. These patients also presented indicators of diastolic dysfunction, higher LVM and increased EATT[38]. Our study population also presented markers of diastolic dysfunction: Over 70% of subjects had lateral e' values < 10 cm/second, without differences between groups, while e' septal values were lower in the more advanced liver fibrosis group. Additionally, we have found that more than 60% of T2DM-MASLD patients included in this study had increased LVMi, and LVMi values were higher in subjects with markers of advanced hepatic fibrosis. A recent meta-analysis of twenty studies showed higher LVMi in

Table 3 Echocardiographic structural and functional parameters according to liver fibrosis categories

Echocardiographic parameters	Group 1 (advanced fibrosis), *n* = 84	Group 2 (indeterminate risk of fibrosis), *n* = 164	Group 3 (without fibrosis), *n* = 19	*P* value
Morphologic parameters				
LV diastolic diameter (mm)	51.37 ± 6.04	50.00 (38.00-71.00)	48.53 ± 4.50	0.1482
LV systolic diameter (mm)	37.00 (24.00-57.00)	36.00 (24.00-60.00)	34.89 ± 6.44	0.4832
IV septum thickness (mm)	12.00 (8.00-16.00)[b]	11.00 (7.00-16.00)	10.00 (9.00-13.00)[b]	0.0029
LV posterior wall thickness (mm)	12.00 (9.00-16.00)[a]	11.00 (7.00-17.00)[a]	11.00 (10.00-14.00)	0.0277
Left atrium diameter (mm)	39.07 ± 5.15[c]	37.00 (26.00-52.00)[a]	34.31 ± 4.26[a,c]	0.0008
Right atrium diameter (mm)	36.96 ± 6.03[a]	35.47 ± 5.28	33.47 ± 4.68[a]	0.0224
Right ventricle diameter (mm)	36.34 ± 5.50	35.00 (12.00-50.00)	37.00 ± 5.18	0.5209
Aortic annular diameter (mm)	32.00 (20.00-42.00)	32.00 (23.00-40.00)	31.11 ± 3.05	0.2201
Descending aorta diameter (mm)	18.00 (13.00-33.00)[b]	19.00 (10.00-30.00)[b]	18.11 ± 1.60	0.0066
LV end-diastolic volume (mm^3)	121.64 ± 31.18	109.00 (63.00-380.00)	108.74 ± 17.85	0.1388
LV end-systolic volume (mm^3)	66.70 ± 22.25[a]	57.00 (21.00-290.00)[a]	54.35 ± 14.16	0.0101
Stroke volume (mm^3)	55.42 ± 16.60	54.00 (24.00-112.00)	52.81 ± 13.48	0.7994
EATT (mm)	8.00 (3.00-17.00)[b]	7.00 (3.00-14.00)[b]	7.26 ± 2.51	0.0027
LVMi (g/m^2)	119.16 ± 27.36	113.23 ± 24.82	104.39 ± 22.32	0.0474
Increased LVMi, *n* (%)	55 (66.27%)	99 (60.37%)	10 (52.63%)	0.4687
Functional parameters				
EF, *n* (%)	49.19 ± 5.62	50.87 ± 5.14	52.00 ± 3.25[a]	0.0030
	49.00 (27.00-65.00)[a,b]	50.00 (23.00-61.00)[a,b]	52.00 (45.00-60.00)	
EF-normal range, *n* (%)	41 (49.40)	113 (68.90)	16 (84.21)	0.0017
E wave velocity (cm/second)	72.59 ± 19.24	70.00 (32.00-158.00)	71.83 ± 18.07	0.9292
A wave velocity (cm/second)	84.31 ± 21.25	86.10 ± 22.65	81.61 ± 27.54	0.6626
Mitral valve E/A	0.79 (0.38-1.52)	0.80 (0.44-2.07)	0.94 ± 0.28	0.5683
e′ septal (cm/second)	8.00 (3.00-16.00)[b]	8.00 (4.00-15.00)	10.50 ± 2.94[b]	0.0068
e′/a′ septal	0.70 (0.43-2.0)	0.78 (0.36-3.00)	0.84 ± 0.24	0.3637
E/e′ septal	9.64 ± 4.10[a]	8.44 (2.43-26.33)	7.35 ± 2.62[a]	0.0260
e′ lateral (cm/second)	8.00 (4.00-19.00)	8.00 (4.00-18.00)	8.00 (4.00-13.00)	0.9551
e′/a′ lateral	0.73(0.40-2.00)	0.71 (0.40-2.00)	0.79 ± 0.28	0.7655
E/e′ lateral	9.15 ± 3.76	8.27 (2.83-25.0)	8.15 (3.54-20.75)	0.8768
Average E/e′ ratio	9.17 ± 3.58	8.39 (2.62-22.57)	7.77 ± 2.34	0.3208
DcT (msec)	200.73 ± 59.07	194.59 ± 51.00	192.17 ± 43.19	0.6725
LVOT VTI (cm)	30.00 (11.20-78.00)	30.00 (11.90-76.00)	28.98 ± 7.27	0.5857
LV segmental kinetics				
Total wall motion score index	1.10 ± 0.17	1.06 ± 0.13	1.02 ± 0.06	0.0352
Basal wall motion score index	1.06 ± 0.18	1.03 ± 0.12	1.02 ± 0.05	0.6358
Mid wall motion score index	1.11 ± 0.21	1.06 ± 0.15	1.03 ± 0.1	0.0240
Apical wall motion score index	1.15 ± 0.26	1.10 ± 0.24	1.02 ± 0.06	0.0548

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

For ejection fraction (%): Group 1 *vs* group 2, and group 1 *vs* group 3. Data are presented as mean ± SD or median (min-max). Ejection fraction-normal range ≥ 50%. LV: Left ventricular; IV: Interventricular; EATT: Epicardial adipose tissue thickness; LVMi: Left ventricular mass index; EF: Ejection fraction; LVOT VTI: Left ventricular outflow tract velocity time integral; DcT: Deceleration time.

Table 4 The bivariate correlations of the two liver fibrosis scores with echocardiographic parameters in type 2 diabetes mellitus patients with Metabolic dysfunction-associated steatotic liver disease

	FIB4, *r* (95%CI)	NFS, *r* (95%CI)
LV diastolic diameter	0.09 (-0.03; 0.22)	0.14 (0.02; 0.26)[a]
IV septum thickness	0.19 (0.07; 0.31)[b]	0.23 (0.11; 0.35)[c]
LV posterior wall thickness	0.12 (-0.004; 0.24)	0.18 (0.06; 0.30)[b]
Left atrium diameter	0.19 (0.07; 0.31)[b]	0.17 (0.04; 0.29)[b]
Right atrium diameter	0.17 (0.05; 0.29)[b]	0.21 (0.09; 0.32)[d]
Aortic annular diameter	0.13 (0.001; 0.25)[a]	0.09 (-0.04; 0.21)
EATT	0.12 (-0.004; 0.24)	0.13 (0.01; 0.25)[a]
LV end-systolic volume	0.08 (-0.05; 0.20)	0.14 (0.01; 0.26)[a]
LVMi	0.15 (0.02; 0.26)[a]	0.19 (0.06; 0.30)[b]
EF (%)	-0.13 (-0.25; -0.01)[a]	-0.21 (-0.33; -0.09)[d]
e′ septal	-0.24 (-0.36; -0.12)[e]	-0.19 (-0.31; -0.07)[b]
a′ septal	-0.13 (-0.25; -0.004)[a]	-0.10 (-0.22; 0.03)
e′/a′ septal	-0.14 (-0.27; -0.02)[a]	-0.12 (-0.24; 0.01)
E/e′ septal	0.19 (0.06; 0.31)[b]	0.19 (0.07; 0.31)[b]
Total LV segmental kinetics score	0.14 (0.01; 0.26)[a]	0.16 (0.04; 0.28)[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P = 0.0001$.
[d]$P < 0.001$.
[e]$P < 0.0001$.
FIB4: Fibrosis-4; NFS: Non-alcoholic fatty liver disease-Fibrosis Score; 95%CI: 95% confidence interval; IV: Interventricular; LV: Left ventricle; EATT: Epicardial adipose tissue thickness; LVMi: Left ventricular mass index; EF: Ejection fraction.

MASLD; however, in patients with T2DM the differences in LVMi according to MASLD were not significant[39]. The potentially attenuated impact of MASLD on LVMi in T2DM may be due to T2DM itself being associated with higher LVM, particularly in the context of insulin resistance, longer duration of diabetes, and the presence of hypertension[40,41]. Notably, our study group of T2DM patients with more advanced liver fibrosis also had higher HOMA-IR values, indicative of significant insulin-resistance. Nonetheless, another meta-analysis of ten studies that included 1,800 T2DM patients reported higher LVMi in the presence of MASLD, accompanied by other markers of diastolic dysfunction[42]. However, neither of the two meta-analyses evaluated the relationship between LVMi and the severity of liver fibrosis.

It has also been suggested that high LVMi might lead to early LV diastolic dysfunction, which in turn is related to changes in left atrial dimensions and function, partly due to increased filling pressures and preload[42,43]. In our study, LAD was positively correlated with markers of liver fibrosis, and was significantly higher in T2DM patients with advanced liver fibrosis. This finding aligns with the research conducted by Fan *et al*[22], which showed a positive correlation between NFS and left atrial dimension, after adjusting for confounding factors, in patients with T2DM. Additionally, the study by Decoin *et al*[44] reported that patients with MASLD and higher liver fibrosis scores had an increased risk of atrial fibrillation recurrence after catheter ablation, along with increased left atrial remodeling with impaired histopathological, electrophysiological, and hemodynamic characteristics. Liver stiffness has been associated with atrial fibrillation in various studies[45,46]. Similarly, a Japanese study that included patients with severe tricuspid regurgitation, found that FIB4 scores positively correlated with the left atrial volume index, and the risk of major adverse cardiovascular events (MACE) [HR: 1.89 (95%CI: 1.01–3.54), $P = 0.046$][47]. In fact, a large prospective study that followed 4071 patients with MASLD for 6.6 years also reported that the risk of MACE increased progressively with higher FIB4 and NFS values ($P < 0.001$)[48].

In our study, LVMi and LAD negatively correlated with serum SHBP concentrations. Emerging evidence suggests that lower SHBP levels are associated with higher cardiovascular risk in men, and with elevated LVMi in post-menopausal women[49,50]. SHBP is a glycoprotein secreted by the liver (and other tissues, including the myocardium), that acts as a

Table 5 The multiple regression analyses with fibrosis-4 and non-alcoholic fatty liver disease-fibrosis score as dependent variables in two models

	β (95%CI); *t* ratio	*β* (95%CI); *t* ratio
Model 1		
Left atrium diameter	0.044 (0.007; 0.082); 2.307[a]	0.039 (0.004; 0.074); 2.180[a]
Right atrium diameter	0.019 (-0.014; 0.052); 1.107	0.041 (0.010; 0.072); 2.628[b]
Sex	0.137 (-0.273; 0.546); 0.654	-0.560 (-0.941; -0.179); 2.881[b]
Serum creatinine	0.748 (-0.025; 1.521); 1.897	1.467 (0.747; 2.186); 3.995[c]
Model 2		
Left atrium diameter	0.037 (0.0005; 0.073); 1.990[a]	0.030 (-0.005; 0.065); 1.695
C-peptide	0.175 (0.071; 0.280); 3.282[b]	0.099 (-0.002; 1.200); 1.920
Right atrium diameter	0.013 (-0.017; 0.043); 0.851	0.030 (0.001; 0.059); 2.021[a]
Serum creatinine	0.410 (-0.328; 1.148); 1.089	0.843 (0.133; 1.533); 2.326[a]

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.0001$.
Independent variables in Model 1: Left ventricular mass index (LVMi), left atrium diameter, right atrium diameter, sex, smoking status, systolic blood pressure, duration of diabetes, alcohol intake, atrial fibrillation, serum creatinine; in Model 2: LVMi, left atrium diameter, right atrium diameter, C-peptide, low-density lipoprotein cholesterol, serum creatinine). Only the parameters correlated with at least one score are mentioned in the table. 95%CI: 95% confidence interval; IV: Interventricular; LV: Left ventricle; LVMi: Left ventricular mass index; EF: Ejection fraction.

Table 6 Factors associated with left atrium diameter in the bivariate correlation analysis

Left atrium diameter	*r* (95%CI)
Uric acid	0.14 (0.01; 0.26)[a]
Direct bilirubin	0.15 (0.03; 0.27)[a]
GGT	0.15 (0.02; 0.27)[a]
HDL cholesterol	-0.13 (-0.25; -0.01)[a]
C-peptide	0.13 (0.005; 0.25)[a]
SHBP	-0.14 (-0.26; -0.02)[a]
Sex	0.23 (0.11; 0.34)[b]
Atrial fibrillation	0.16 (0.04; 0.28)[c]

[a]$P < 0.05$.
[b]$P = 0.0001$.
[c]$P < 0.01$.
95%CI: 95% confidence interval; GGT: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein; SHBP: Sex-hormone binding protein.

carrier for steroid hormones (androgens and estrogens, potentially influencing their availability and activity in specific tissues[51,52]. Additionally, *in vitro* experiments have shown that SHBP can bind to membrane receptors and activate intracellular signaling pathways, either through a putative G-protein-coupled receptor that increases intracellular cAMP levels, or through the megalin receptor, which induces the internalization of SHBG[51,53]. While the cardioprotective effects of sex hormones (primarily estrogens) are well established, the role of circulating SHBP in cardiovascular pathophysiology remains incompletely understood and warrants further investigation[54,55]. The findings of this research pave the way for subsequent mechanistic studies exploring the potential role of SHBP in linking liver fibrosis and cardiac remodeling.

Indeed, a mechanistic explanation for the correlation between liver fibrosis and remodeling of left atrium and left ventricle is still greatly needed. Perhaps shared pathogenetic mechanisms of cardiac and liver fibrosis, triggered by similar factors (such as inflammation/activation of inflammasomes or oxidative stress), leading to fibroblast activation and increased collagen formation, might explain these correlations (although causality remains a possibility)[56,57]. Increased visceral adiposity (particularly increased EATT), associated with insulin resistance and dysregulated adipokines, hepatokines or other molecules secreted by the liver (such as SHBP), and/or hemodynamic changes could also

Table 7 The multiple regression analysis with left atrium diameter as the dependent variable

	β (95%CI), *t* ratio
GGT	0.015 (0.003; 0.028); 2.343[a]
SHBP	-0.036 (-0.071; -0.001); 2.039[a]
Atrial fibrillation	3.481 (1.232; 5.729); 3.034[b]

[a]$P < 0.05$.
[b]$P < 0.01$.
95%CI: 95% confidence interval; GGT: Gamma glutamyl transpeptidase; SHBP: Sex-hormone binding protein.

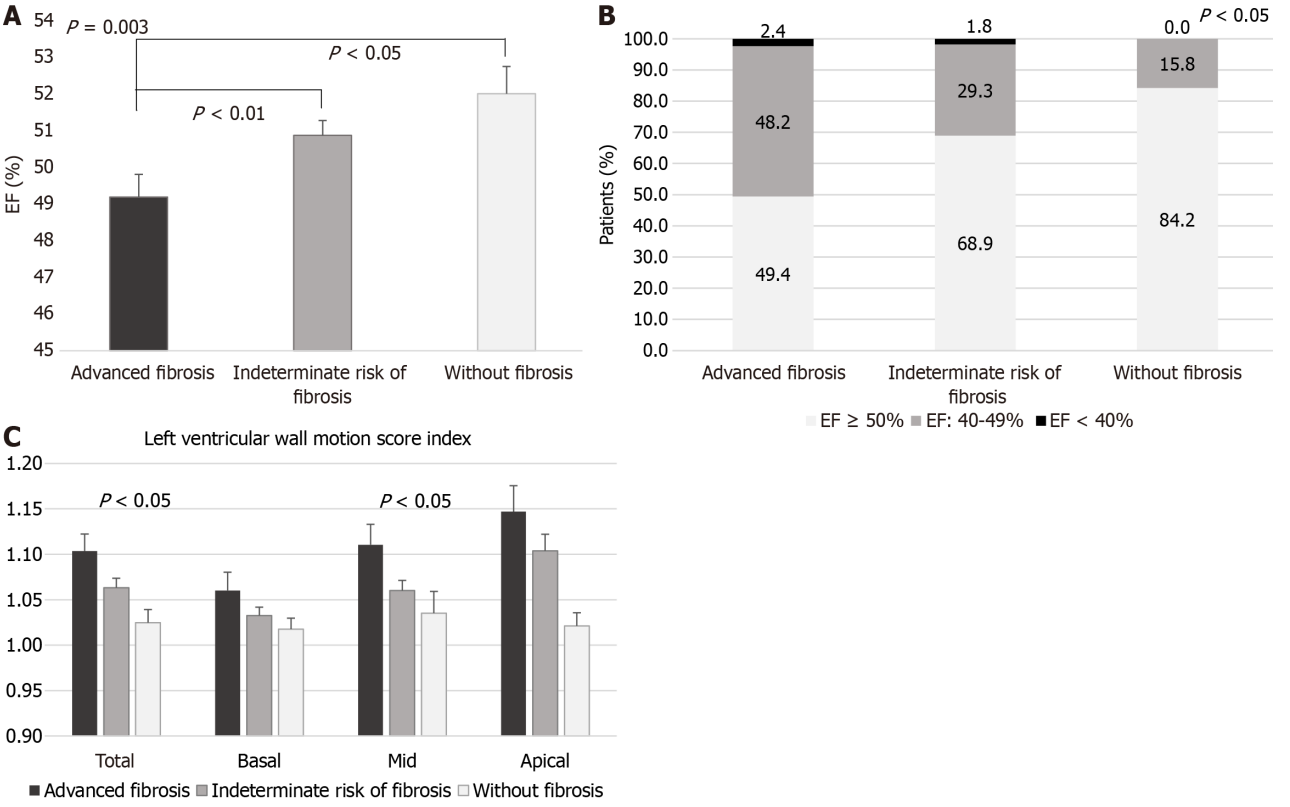

Figure 1 Association of metabolic dysfunction-associated steatotic liver disease-fibrosis categories with indicators of cardiac dysfunction and dyskinesia. A: Ejection fraction (%) according to the liver fibrosis categories in type 2 diabetes mellitus patients with metabolic dysfunction-associated steatotic liver disease; B: Proportion of patients with an ejection fraction (EF) ≥ 50% (normal), EF = 40%-49% (mild dysfunction), and EF < 40% (moderate dysfunction) in each liver fibrosis category; C: Total, basal, mid and apical left ventricular wall motion score indexes according to the liver fibrosis categories. EF: Ejection fraction.

be significant contributors[58-60]. Nevertheless, mechanistic and prospective studies are needed to better understand the interaction between liver fibrosis and cardiac remodeling and dysfunction in patients with and without T2DM. Additionally, interventional studies exploring the effects of various multidisciplinary therapeutic interventions could provide valuable insights regarding the liver-heart interaction in MASLD patients with T2DM.

We acknowledge several limitations of our study. First, the cross-sectional design did not permit a prospective evaluation of liver-heart cross-talk, and a cause-effect inference. Second, the liver fibrosis status was assessed using two fibrosis scores (FIB4 and NFS), resulting in a relatively high proportion of patients being classified as having indeterminate risk of advanced fibrosis. Nonetheless, these two scores are well validated and widely accepted in clinical practice, as FIB4 is the index of choice recommended by professional guidelines as the initial screening tool for MASLD fibrosis in patients with T2DM and other metabolic disorders[61,62]. By utilizing these two biomarkers we ensured proper classification of the advanced liver fibrosis group and the no liver fibrosis group. Another impediment of using non-invasive biological indexes was that the parameters used in the two formulas could not be included in the multivariable analyses (with the two scores as dependent variables). Thus, further studies employing different methods of liver fibrosis assessment should be undertaken. Thirdly, we did not have the opportunity to use more advanced cardiac imaging techniques (such as MRI) in this study; therefore, further research is needed to more accurately evaluate cardiac function and structure in patients with MASLD fibrosis.

CONCLUSION

T2DM patients with markers of MASLD-related liver fibrosis exhibit lower EF and present indicators of diastolic dysfunction, cardiac hypertrophy and dyskinesia. Additionally, LVMi and LAD negatively correlated with serum SHBP concentrations.

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FOOTNOTES

Author contributions: Cernea S design the study, acquired, analyzed and interpreted the data, wrote the manuscript, designed the figure; Onișor D, Roiban AL and Rat N acquired data and reviewed the paper for important intellectual content; Benedek T interpreted the data and reviewed the paper for important intellectual content.

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Informed consent statement: All subjects signed an informed consent before being enrolled in the study.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest related to this paper.

Data sharing statement: Data may be available upon request.

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