Hepatic T1-time, cardiac structure and function and cardiovascular outcomes in patients with dilated cardiomyopathy

Hepatic T1-time, cardiac structure and function and cardiovascular outcomes in patients with dilated cardiomyopathy

Riccardo M. Inciardi [a], Marco Merlo [b], Mariagiulia Bellicini [a], Martina Setti [c], Antonio De Luca [d], Nunzia Di Meo [e], Paolo Rondi [e], Matteo Pagnesi [a], Marianna Adamo [a], Carlo M. Lombardi [a], Jacopo Giulio Rizzi [b], Davide Farina [e], Alessandro Mantovani [f], Giovanni Targher [f,g], Gianfranco Sinagra [b], Marco Metra [a,*], on behalf of theNAFLD-DCM group[1]

[a] *ASST Spedali Civili di Brescia, Division of Cardiology and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy*
[b] *Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy*
[c] *Section of Cardiology, Department of Medicine, University of Verona, Verona, Italy*
[d] *Cardio-Thoraco-Vascular Department, University of Trieste, Trieste, Italy*
[e] *ASST Spedali Civili di Brescia, Division of Radiology and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy*
[f] *Department of Medicine, University of Verona, Verona, Italy*
[g] *Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella (VR), Italy*

ARTICLE INFO

Keywords:
Dilated cardiomyopathy
Magnetic resonance imaging
Heart Failure

ABSTRACT

Aim: Liver damage frequently occurs in patients with cardiovascular (CV) disease and is associated with adverse clinical outcomes. The associations of liver damage with cardiac structure/function measures and the risk of adverse CV events in patients with dilated cardiomyopathy (DCM) are poorly known.
Methods: We retrospectively enrolled consecutive patients with DCM undergoing cardiac magnetic resonance imaging (MRI). In addition to standard cardiac assessment, iron-corrected T1 mapping was also assessed in the liver. Cross-sectional associations between hepatic T1-time and cardiac structure and function were examined accounting for potential confounders. Longitudinal associations between hepatic T1-time and the risk of hospitalization for HF or CV death were also assessed.
Results: Overall, 120 stable patients with established DCM were included in the study (mean age 54.7 years, 26 % women). The mean hepatic iron-corrected T1-time was 563±73 ms. In linear regression analyses, measures of left atrial structure (LA maximal volume, $p = 0.035$, LA minimal volume=0.012), interventricular septum thickness ($p = 0.026$), and right ventricular ejection fraction ($p = 0.005$) were significantly associated with greater hepatic T1-time. Over a mean follow-up of 4.5 ± 1.8 years, 32 (27 %) died or were hospitalized for HF at a rate of 6.7 per 100 person-year. Higher hepatic iron-corrected T1-time was independently associated with a higher risk of adverse events (adjusted-hazard ratio 1.71, 95 % confidence interval: 1.14–2.56, $p = 0.009$). Patients with a hepatic T1-time ≥563 ms had a higher risk of CV events (log-rank $p = 0.03$).
Conclusion: Among stable patients with DCM, higher hepatic iron-corrected T1-time is associated with worse cardiac size and function and with higher rates of hospitalization for HF or CV death.
Condensed abstract: Limited data exist regarding the clinical value of hepatic T1-time in patients with dilated cardiomyopathy (DCM) undergoing cardiac Magnetic Resonance imaging (MRI). We found that higher hepatic iron-corrected T1-time is associated with worse cardiac size and function, even after accounting for clinical confounders. Over a mean follow-up of 4.5 ± 1.8 years, higher hepatic iron-corrected T1-time was independently

Abbreviations or acronyms: DCM, dilated cardiomyopathy; MRI, Magnetic Resonance imaging; LV, left ventricle; CV, cardiovascular; LA, left atrium; HF, heart failure; NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease.

* Correspondence author at: Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy.
E-mail address: metramarco@libero.it (M. Metra).

[1] **List of contributors**: Gianmarco Arabia[a], Manuela Iseppi[b], Emanuele Gavazzi[e], Laura Lupi[a], Daniela Tomasoni[a], Enrico Vizzardi[a].

associated with a higher risk of hospitalization for heart failure or cardiovascular death. Among stable patients with DCM, the evaluation of liver tissue by cardiac MRI may provide useful clinical information for CV risk stratification.

1. Introduction

Liver damage frequently occurs in patients with cardiovascular (CV) disease and predicts worse clinical outcomes [1,2]. In this context, liver damage may be mainly caused by elevated hepatic venous pressures due to increased cardiac filling pressures or by non-alcoholic fatty liver disease (NAFLD) [1]. NAFLD (recently renamed as metabolic dysfunction-associated fatty liver disease [MAFLD]) has become the most common chronic liver disease worldwide, affecting almost a third of the general adult population and up to ~70 %−90 % of patients with type 2 diabetes mellitus or severe obesity [3,4]. NAFLD/MAFLD represents a spectrum of progressive steatotic liver conditions, ranging from isolated steatosis to non-alcoholic steatohepatitis (NASH) with varying amounts of liver fibrosis, and cirrhosis, which may progress to end-stage liver disease. In addition to the risk of developing advanced liver disease, patients with NAFLD/MAFLD are also at increased risk of developing fatal and nonfatal CV events, and new-onset heart failure (HF) [5–9].

The "gold standard" for liver damage assessment is liver biopsy. However, due to the invasive nature of liver biopsy, non-invasive imaging methods, such as magnetic resonance imaging (MRI), are becoming a reliable alternative to measure hepatic tissue signals and estimate liver damage [10,11]. Iron-corrected T1 mapping (cT1 time) in the liver is a specific marker of chronic liver disease activity that reasonably correlates with histological liver inflammation and fibrosis [12–14]. Elevated values of hepatic iron-corrected T1-time have been also shown to be predictive of both major CV and liver-related clinical outcomes in patients with NAFLD/MAFLD or other chronic liver diseases of different etiology [15].

At present, little is known about the clinical value of hepatic iron-corrected T1-mapping, its association with cardiac structure and function measures, and the risk of adverse CV outcomes among patients with dilated cardiomyopathy (DCM). Therefore, the main aim of this exploratory study was to examine the relationships of hepatic T1 mapping with cardiac structure and function measures, and the risk of hospitalization for HF or CV death among stable patients with DCM referred for cardiac MRI.

2. Methods

2.1. Study population

This retrospective multicenter study includes consecutive patients referred for cardiac MRI during the work-up management according to the clinical practice at the Spedali Civili University Hospital of Brescia and the University Hospital of Trieste, which are two tertiary care centers with a high-volume multimodality imaging facility. Our study includes consecutive adult (age ≥18 years) patients with a diagnosis of HF (New york heart association [NYHA] functional class II-IV) due to DCM enrolled over a time period between 2016 and 2017. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. Only patients with DCM in stable clinical condition without overt cardiac decompensation requiring intravenous diuretic treatment were included in the study. Patients with excessive alcohol consumption, viral hepatitis B or C and other known chronic liver diseases were excluded.

2.2. Cardiac magnetic resonance imaging

A cardiac MRI was performed in all patients using 1.5 T scanners (Magnetom Aera Siemens Medical Solutions, Erlangen, Germany, and Philips Intera, Philips Medical Systems) with a dedicated cardiac coil. The cardiac MRI protocol included: cine-MRI sequences balanced steady-state free precession (bSSFP) in long-axis (LAX) and short-axis (SAX) stack, Modified Look-Locker Inversion Recovery (MOLLI) sequences (3 SAXs subset and four chamber LAX) before and 15 min after administration of 0.1 mmol/kg gadopentetate dimeglumine or gadobutrol, and T1-weighted PSIR (Phase-Sensitive Inversion-Recovery) sequences 10 min after administration of contrast medium for the quantification of late gadolinium enhancement (LGE). Left ventricular mass, left and right ventricular volumes, and ejection fraction are calculated using semiautomated software analyzing short-axis images and applying the Simpson's method. Left atrial (LA) volumes (maximal and minimal) were calculated using the biplane method. In addition to standard cardiac MRI measures, a region of interest (ROI) was performed on a representative single short axis MOLLI pre- and post-contrast sequences at the septum level and blood pool to calculate extracellular volume fraction (ECV). Furthermore, the other three ROIs were defined in the portion of the liver parenchyma and included in MOLLI sequences (away from hepatic vessels) before and after administration of the contrast medium to evaluate T1 relaxation times [7–9]. In a sub-group of 25 patients (21 %), measure of hepatic T1-time was assessed at a second MRI examination (mean follow-up 1.5 years). Notably, no significant differences were found between baseline and follow-up hepatic T1 times among these patients (hepatic T1-time at baseline: 580.5 ms vs. follow-up 548.2 ms, $p = 0.16$).

2.3. Clinical assessment

At the time of cardiac MRI, demographic data (age, sex, body mass index [BMI], body surface area [BSA]), and comorbidities were assessed. These comorbidities included hypertension, atrial fibrillation (AF, present at the time of cardiac MRI or documented in the medical history), diabetes, hyperlipidemia, smoking history, and coronary artery disease. The glomerular filtration rate (eGFR) was estimated using the simplified modification of diet in renal disease (MDRD) study equation (20). In addition, routine laboratory parameters, including serum creatinine, liver enzymes (aspartate aminotransferase, alanine aminotransferase and bilirubin), hemoglobin, potassium, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and fibrosis (FIB)−4 index (i.e., a widely used marker of advanced liver fibrosis) were assessed.

2.4. Primary outcome of the study

The primary outcome of the study was defined as a composite endpoint inclusive of the first hospitalization for HF or CV death. We retrieved dates and causes of death and hospitalizations from electronic medical records, in-hospital charts, and the national death registry.

2.5. Statistical analysis

Continuous data were expressed as means ± standard deviation (SD) or medians and interquartile ranges (IQR), and categorical variables were presented as percentages. Clinical characteristics and cardiac structure and function measures of patients were stratified by tertiles of hepatic iron-corrected T1-time. The Cochran–Armitage test was used to test-for-trend across groups for binary variables, and the Jonckheere–Terpstra test for continuous variables. Linear regression analyses were performed to test the cross-sectional associations between hepatic T1-

time and cardiac structure and function measures. These linear regression analyses were performed after adjusting for demographics (model 1) (i.e., age, sex, and body mass index) and for demographics and clinical features (model 2) (i.e., age, sex, and body mass index, hypertension, diabetes, eGFR, atrial fibrillation, and MRI-measured LVEF). Restricted cubic spline curves were created to visualize the continuous associations between hepatic T1-time and cardiac measures. The number of knots was chosen according to the lowest Akaike information criterion (AIC). Kaplan-Meier survival curves and Cox proportional-hazards regression analyses were used to prospectively investigate the association between hepatic T1 values and the risk of developing the primary study outcome (hospitalization for HF or CV death). For the Kaplan-Meier survival analysis, a hepatic T1-time cut-off of 563 ms was used according to our study patients' mean hepatic T1-time value. These analyses were adjusted for demographics, clinical confounders (as mentioned above) and finally, also for demographics, clinical features *plus* MRI-derived LA maximal volume, and right ventricular ejection fraction (model 3). The flexible continuous associations between hepatic T1-time and the composite of the hospitalization for HF or CV death were further assessed using restricted cubic splines with the number of knots selected to minimize the model AIC (3 to 6 knots tested). A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 16 (StataCorp, College Station, Texas).

3. Results

3.1. Characteristics of the study population

A total of 120 consecutive patients with DCM in stable clinical condition without overt cardiac decompensation requiring intravenous diuretic treatment (mean age 54.7 ± 14.9 years, 26 % women) were included in the study. Clinical and cardiac measures of the study population stratified by tertiles of hepatic T1-time are summarized in Table 1 and Table 2. The mean hepatic iron-corrected T1-time of patients was 563 ± 73 ms. Patients with higher hepatic T1-time (i.e., those in the upper tertile with a hepatic T1-time >586 ms) were more likely to be female than the other two patient groups. As for the MRI-derived cardiac measures, patients with higher hepatic T1-time also had significantly higher interventricular septum thickness, greater left atrial dimensions (i.e., LA area, LA maximal volume, and LA minimal volume), and lower right ventricular ejection fraction. Conversely, no significant differences were observed according to age, common CV risk factors, as well as MRI-derived LV mass index, LVEF, and pericardial fat area among the three patient groups.

3.2. Cross-sectional associations of hepatic T1-time with cardiac structure and function measures

The associations between cardiac structure and function measures and hepatic T1-time are shown in Table 3. After adjusting for age, sex and BMI, both the measures of LA structure (for each SD increase in LA area: β 26.3; 95 % confidence interval (CI) [13.7, 38.9]; $p < 0.001$; for each SD increase in LA maximal volume: β 20.5; 95 % CI [7.74, 33.3]; $p = 0.002$; for each SD increase in LA minimal volume: β 22.3; 95 % CI [9.47, 35.2]; $p = 0.001$) and the interventricular septum thickness (for each SD increase: β 18.9; 95 % CI [6.2, 31.6]; $p = 0.004$) were significantly associated with greater hepatic T1-time. These associations were linear (all p-values for non-linearity >0.05), such that larger LA measures and higher interventricular septum thickness were associated with a higher hepatic T1-time (Fig. 1). Right ventricular ejection fraction showed an inverse association with hepatic T1-time (for each SD increase: β −23.2; 95 % CI [−36.2, −10.22]; $p = 0.001$). Results were consistent even after adjusting for demographics and clinical features. No significant effect modification was observed by sex or baseline LVEF (all p-values for interaction >0.05).

Table 1
Clinical characteristics according to Hepatic T1 time in stable patients with DCM.

Clinical parameters	All patients ($n = 120$)	Hepatic T1 time 1° Tertile (369 – 524 ms) $N = 40$	Hepatic T1 time 2° Tertile (525 – 586 ms) $N = 40$	Hepatic T1 time 3° Tertile (587 – 758 ms) $N = 40$	p-value
		Better ↔ Worse			
Demographic Data					
Age, years	54.7 ± 14.9	55.7 ± 12.8	55.3 ± 17.3	53.0 ± 14	0.69
Female sex, n (%)	31 (25.8)	5 (12.5)	9 (22.5)	17 (42.5)	0.008
BMI, kg/m^2	26.7 ± 6.5	27.1 ± 5.2	25.6 ± 3.3	27.6 ± 9.4	0.34
Comorbidities					
History of CAD, n (%)	9 (7.5)	4 (10.0)	2 (5.0)	3 (7.5)	0.70
Dyslipidemia, n (%)	19 (15.8)	6 (15.0)	8 (20.0)	5 (12.5)	0.65
Type 2 diabetes, n (%)	12 (10.0)	4 (10.0)	3 (7.5)	5 (12.5)	0.76
Hypertension, n (%)	32 (26.7)	12 (30.0)	8 (20.0)	12 (30)	0.51
History of atrial fibrillation, n (%)	20 (16.7)	5 (12.5)	7 (17.5)	8 (20)	0.66
CKD, n (%)	39 (38)	10 (35.7)	14 (36.8)	15 (42.9)	0.81
Laboratory					
Creatinine, mg/dL	0.9 ± 0.3	0.9 ± 0.2	1.0 ± 0.3	0.9 ± 0.3	0.59
eGFR, ml/min/1.73 m^2	66.3 ± 20.3	70.1 ± 21.6	64.6 ± 16.1	65.0 ± 23.4	0.50
Potassium, mmol/L	4.1 [129, 773]	4.2 [4.0, 4.2]	4.0 [3.7, 4.2]	4.1 [3.8, 4.2]	0.39
Bilirubin, mg/dl	0.6 [0.5, 0.9]	0.6 [0.5, 0.9]	0.7 [0.4, 0.8]	0.6 [0.4, 1.0]	0.89
FIB-4 index	1.5 ± 2.1	1.0 ± 0.7	1.4 ± 1.3	1.9 ± 3.3	0.29
AST, U/L	21 [16, 32]	18.0 [14.5, 31.5]	19.0 [15.0, 26.0]	23.0 [19.0, 39.0]	0.08
ALT, U/L	30 [21, 50]	32.0 [22.0, 57.0]	28.0 [21.5, 40.0]	29.0 [19.0, 59.0]	0.79
NT-proBNP, ng/L	609 [300, 1460]	398.0 [99.0, 500.0]	478.0 [169.0, 888.0]	1701.0 [800.0, 2450.0]	0.001
Hematocrit,%	42 [38.5, 44]	42.3 [39.6, 44.0]	42.6 [40.0, 44.5]	40.1 [37.0, 42.7]	0.015
Hemoglobin, g/dL	14.2 ± 6.1	14.0 ± 1.3	15.5 ± 9.7	12.9 ± 1.7	0.20
Medical Treatments					
Diuretics,%	51 (44.3 %)	15 (38.5 %)	17 (44.7 %)	19 (50.0 %)	0.59
Diuretics dosage, mg/day	47 ± 35	46 ± 27	38 ± 29	56 ± 44	0.29
B-blockers,%	90 (75.0 %)	31 (77.5 %)	32 (80.0 %)	27 (67.5 %)	0.39
RAASi	87 (72.5 %)	27 (67.5 %)	32 (80.0 %)	28 (70.0 %)	0.42
MRA,%	65 (54.2 %)	19 (47.5 %)	21 (52.5 %)	25 (62.5 %)	0.39

Data are expressed as means ± SD, medians [interquartile ranges] or percentages.
Abbreviations: BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RAASi, renin-angiotensin-aldosterone system inhibitors; MRA, mineralocorticoid receptor antagonist.

Table 2
Cardiac structure and function measures according to hepatic T1 time in stable patients with DCM.

Cardiac structure and function	All patients (n = 120)	Hepatic T1 time 1° Tertile (369 – 524 ms) N = 40	Hepatic T1 time 2° Tertile (525 – 586 ms) N = 40	Hepatic T1 time 3° Tertile (587 – 758 ms) N = 40	p-value
		Better ↔ Worse			
Left Ventricle					
Interventricular septum thickness, cm	1.0 ± 0.1	1.02 ± 0.05	1.04 ± 0.05	1.06 ± 0.05	< 0.001
LV EDV, ml	244.2 ± 179.3	226.1 ± 67.1	235.7 ± 74.0	271.2 ± 296.1	0.51
LV Mass, g	152.2 ± 48.1	166.2 ± 43.5	142.8 ± 46.6	150.2 ± 51.7	0.14
LV Mass Index, g/m^2	80.6 ± 23.4	85.2 ± 20.5	76.2 ± 24.1	81.3 ± 24.7	0.30
LV EF,%	35.5 ± 11.0	34.5 ± 11.0	35.8 ± 9.7	36.1 ± 12.2	0.81
Left Atrium					
LA Area, cm^2	19.3 ± 7.5	17.9 ± 6.9	18.0 ± 6.1	22.1 ± 8.8	0.017
LA Volume max, ml	89.5 ± 38.7	82.4 ± 31.3	84.0 ± 33.0	102.0 ± 47.6	0.041
LA Volume min, ml	61.8 ± 40.0	58.4 ± 33.3	52.1 ± 31.2	74.8 ± 50.2	0.031
Right Ventricle					
RV EDV, ml	80.4 ± 25.3	76.2 ± 23.1	83.4 ± 21.8	81.4 ± 30.4	0.44
RV EF,%	38.8 ± 17.5	43.4 ± 13.0	39.6 ± 17.2	33.3 ± 20.44	0.035
Myocardial Tissue					
Epicardial fat Area, cm^2	9.6 ± 4.7	11.3 ± 5.0	8.3 ± 4.2	9.0 ± 4.4	0.016
Paracardial fat Area, cm^2	9.2 ± 6.8	10.3 ± 7.6	8.9 ± 7.1	8.1 ± 5.5	0.39
LGE evidence, n (%)	61 (53.5)	17 (43.6)	20 (55.6)	24 (61.5)	0.27
ECV,%	29.9 ± 6.5	28.2 ± 6.6	30.1 ± 5.4	31.4 ± 6.9	0.10

Data are expressed as means ± SD or percentages.
Abbreviations: EDV, end-diastolic volume; LV, left ventricle; EF, ejection fraction; LA, left atrium; ECV, extracellular volume; RV, right ventricle; LGE, late gadolinium enhancement.

3.3. Longitudinal association between higher hepatic T1-time and risk of hospitalization for HF or CV death

Over a mean follow-up period of 4.5 ± 1.8 years, 32 (27 %) patients experienced the composite study outcome of first hospitalization for HF or CV death at a rate of 6.7 per 100 persons-year. Twenty-six (22 %) patients experienced the outcome of hospitalization for HF alone at a rate of 5.5 per 100 persons-year. After adjusting for age, sex and BMI, a greater hepatic T1-time (hazard ratio (HR): 1.54; 95 % CI: 1.07–2.21; p-value=0.020) was significantly associated with a higher risk of the composite of the first hospitalization for HF or CV death (Table 4). This association was linear (p-value for non-linearity=0.69), such that higher hepatic T1-time values were associated with higher incidence rates of adverse CV events (Fig. 2). Notably, the association between hepatic T1-time and the risk of HF hospitalization or CV death remained significant even after adjustment for demographics, clinical features, LA maximal volume, and right ventricular ejection fraction (adjusted HR: 1.71; 95 % CI: 1.14–2.56; p-value=0.009). Similar results were also observed for the outcome of the first hospitalization for HF alone. Sex distribution, baseline plasma NT-proBNP level, LVEF, and degree of tricuspid regurgitation did not significantly modify the association between hepatic T1-time and the composite of first hospitalization for HF or CV death (p-value for interaction >0.05). Similarly, we found no significant interactions with the background use of diuretics and background HF medications (p-values for interaction > 0.05). By the Kaplan-Meier curve analysis, patients with a hepatic T1-time ≥ 563 ms were more likely to die or be hospitalized for HF than their counterparts with a hepatic T1-time <563 ms (Fig. 3; log-rank p-value=0.03).

4. Discussion

To our knowledge, this is the first study aimed to examine the associations between hepatic iron-corrected T1-time, a specific marker of chronic liver disease activity, with measures of cardiac structure and function and the risk of developing adverse CV outcomes in patients with DCM in stable clinical condition without overt cardiac decompensation requiring intravenous diuretic treatment.

The main and novel findings of our exploratory multicenter study are that among stable patients with DCM, the evaluation of liver tissue by cardiac MRI may provide useful clinical information for CV risk stratification. Higher hepatic iron-corrected T1-time was significantly associated with abnormal cardiac structure and function measures, especially impaired LV and LA structures and worse RV function. Moreover, higher baseline hepatic iron-corrected T1-time was significantly associated with a ~1.8-fold higher risk of CV death or hospitalization for HF during a mean follow-up of 4.5 years, even after adjusting for demographics and other important confounding factors. Therefore, the findings of our study suggest that among stable patients with DCM undergoing cardiac MRI, evaluation of liver structure can provide useful information for better CV risk stratification of this patient population.

In clinical practice, liver damage is frequently encountered among patients with chronic HF, and there has been growing scientific interest in the link between liver disease and HF in recent years [16,17]. The putative biological mechanisms underpinning the association between liver damage and HF are complex but mostly rely on hemodynamic parameters or the coexistence of NAFLD/MAFLD, which is the most common chronic liver disease worldwide. Passive hepatic congestion, mainly due to elevated central venous pressure and low arterial perfusion secondary to decreased cardiac output, may contribute to liver injury in patients with chronic HF [18]. Consequently, chronic congestion may cause hepatocyte damage, portal fibrosis, and eventually cirrhosis. It has also been reported that renin–angiotensin–aldosterone system activation is associated with greater liver fibrosis other than myocardial fibrosis in patients with chronic HF [17]. On the other hand, NAFLD/MAFLD is an emerging risk factor for HF and is also associated with an increased risk of adverse CV outcomes [2,7]. A recent meta-analysis of observational studies including more than 11 million middle-aged individuals from different countries showed that NAFLD was significantly associated with a 1.5-fold higher risk of developing new-onset HF after accounting for common risk factors for HF [9]. Multiple factors related to coexisting obesity, type 2 diabetes, intestinal dysbiosis, and systemic low-grade inflammation might modulate the association between NAFLD/MAFLD and the increased risk of new-onset HF [19]. Growing evidence indicates that NAFLD/MAFLD not only promotes accelerated coronary atherosclerosis but may also affect other anatomic structures of the heart, thereby conferring an increased risk of myocardial alterations (mainly cardiac remodeling and hypertrophy) that may lead to new-onset HF over time [2].

Previous studies highlighted the clinical importance of liver damage assessment in patients with HF [17,18,20]. It has been shown that cholestatic liver function parameters, such as circulating levels of total bilirubin, transaminases and albumin, were associated with an increased risk of all-cause death, CV death, and HF hospitalization in patients with HF [20]. However, liver tissue is rarely assessed histologically in these patients, and studying liver fibrosis in its earlier stage is challenging. Although liver biopsy remains the gold standard for quantifying liver damage and staging liver fibrosis, this invasive procedure is associated with risks of acute complications and possible sampling errors depending on the biopsy site. On the other hand, cholestatic liver function

Table 3
Cross-sectional associations between Hepatic T1 time and cardiac structure and function measures.

Cardiac parameters	B coefficient	B standardized coefficient	95 % Confidence Interval	p-value	B coefficient	B standardized coefficient	95 % Confidence Interval	p-value
	Adjusted Model 1				Adjusted Model 2			
Left Ventricle								
Interventricular septum, cm	18.9	0.271	6.28 - 31.63	0.004	17.1	0.246	2.12 - 32.2	0.026
LV EDV, ml	15.1	0.206	1.59 – 28.5	0.029	14.8	0.217	−0.39 – 30.8	0.056
LV Mass, g	−0.34	−0.005	−17.1 – 16.4	0.96	−10.7	−0.141	−32.2 – 10.8	0.32
LV Mass Index, g/m^2	1.56	0.022	−14.0 – 17.1	0.84	−7.13	−0.098	−26.9 – 12.6	0.47
LV EF,%	−4.57	−0.069	−17.1 – 7.99	0.47	−4.70	−0.070	−19.0 – 9.60	0.51
Left Atrium								
LA Area, cm^2	26.3	0.362	13.7 – 38.9	< 0.001	27.5	0.379	10.3 – 44.8	0.002
LA Volume max, ml	20.5	0.285	7.74 – 33.3	0.002	18.5	0.257	1.38 – 35.7	0.035
LA Volume min, ml	22.3	0.305	9.47 – 35.2	0.001	24.3	0.337	5.51 – 43.1	0.012
Right Ventricle								
RV EDV, ml	6.63	0.093	−6.55 – 19.8	0.32	7.02	0.100	−7.75 – 21.8	0.34
RV EF,%	−23.2	−0.326	−36.2 – −10.22	0.001	−21.5	−0.316	−36.3 – −6.83	0.005
Myocardial Tissue								
Epicardial fat Area, cm^2	−12.1	−0.217	−23.9 – −0.35	0.044	−12.6	−0.244	−25.2 – −0.15	0.047
Paracardial fat Area, cm^2	−4.81	−0.073	−18.6 – 8.99	0.49	2.89	0.042	−13.8 – 19.6	0.73
Evidence of LGE, n (%)	16.4	0.110	−11.8 - 44.6	0.25	15.8	0.104	−18.5 - 50.2	0.36
ECV,%	7.61	0.102	−6.73 – 21.9	0.29	7.05	0.096	−9.35 – 23.4	0.39

B coefficients are expressed for each SD increase in MRI-derived cardiac measures. Model 1 was adjusted for age, sex and BMI. Model 2 was further adjusted for hypertension, LVEF, diabetes, atrial fibrillation, and eGFR.
Abbreviations: EDV, end-diastolic volume; LV, left ventricle; EF, ejection fraction; LA, left atrium; ECV, extracellular volume; RV, right ventricle; LGE, late gadolinium enhancement.

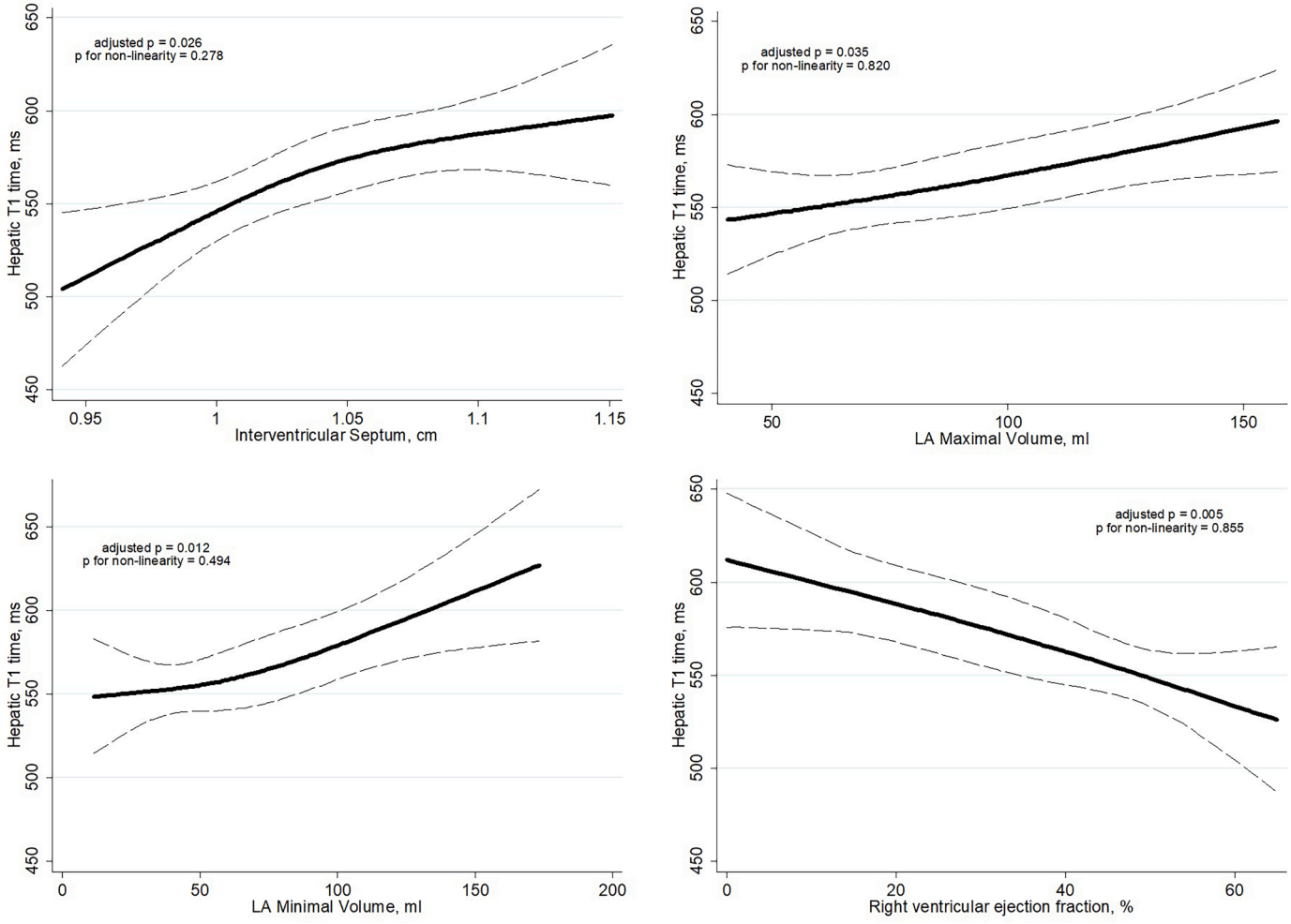

Fig. 1. Association between hepatic T1-time and cardiac structure and function measures. The dotted black lines indicate the 95 % CIs.

Table 4
Longitudinal associations between hepatic T1 time and the risk of adverse cardiovascular outcomes.

	Model 1				Model 2				Model 3			
	HR	95 % CI	p	|Z|	HR	95 % CI	p	|Z|	HR	95 % CI	p	|Z|
First Hospitalization for HF or CV death - 32 events; event rate per 100 person-years: 6.7 (4.78 – 9.57)												
Hepatic T1 time, ms	1.54	1.07–2.21	0.020	2.33	1.67	1.15–2.43	0.007	2.71	1.71	1.14–2.56	0.009	2.60
First Hospitalization for HF - 26 events; event rate per 100 person-years: 5.5 (3.74 – 8.07)												
Hepatic T1 time, ms	1.79	1.20–2.66	0.004	2.89	2.02	1.33–3.08	0.001	3.30	2.03	1.28–3.22	0.003	3.01

Regression Model 1 was adjusted for age, sex, and body mass index (BMI). Model 2 was further adjusted for hypertension, LVEF, diabetes, atrial fibrillation, and eGFR. Model 3 was adjusted for Model 2's covariates + MRI-derived left atrial maximal volume and right ventricular ejection fraction.
HRs are expressed for each SD increase in hepatic T1-tim.

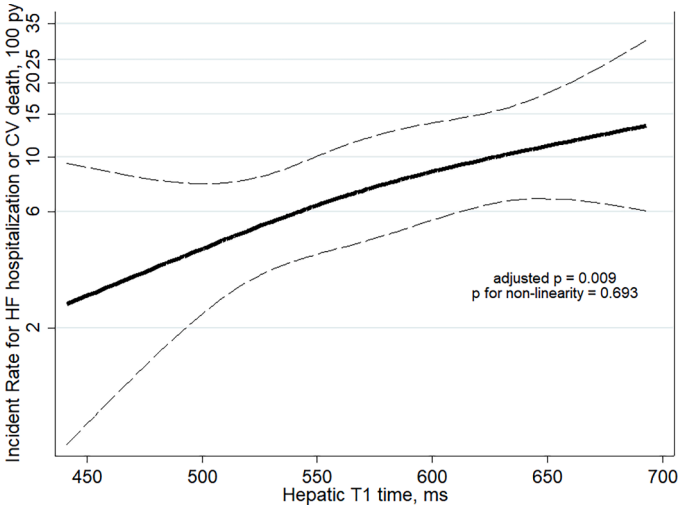

Fig. 2. Association between hepatic T1-time and the risk of hospitalization for HF or CV death. The dotted black lines indicate the 95 % CIs.

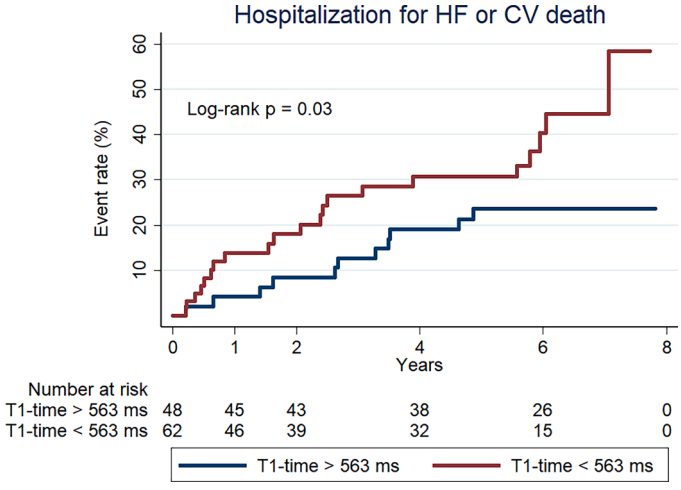

Fig. 3. Kaplan-Meier survival curve analysis of hepatic T1-time and the risk of developing hospitalization for HF or CV death.

parameters alone or in combination with other biochemical risk factors may have limited sensitivity and specificity for non-invasively detecting liver inflammation and fibrosis. Currently, cardiac MRI is widely used in the diagnostic work-up of patients with HF. It allows precise structural and functional myocardial assessment, including tissue characterization with T1 mapping. Hepatic tissue is also displayed on the standard cardiac T1-map. Hepatic iron-corrected T1 mapping has been shown to correlate significantly with hepatocyte ballooning, liver inflammation and fibrosis [12] and has been associated with histological disease activity in NASH [21]. Hepatic T1-time has since been recognized by endocrinology and gastroenterology guidelines in the assessment of NAFLD/MAFLD [22,23].

So far, few prospective studies have reported on using liver T1-maps in patients referred for cardiac MRI, showing promising results. The Multi-Ethnic Study of Atherosclerosis (MESA) study revealed that hepatic T1-time of patients with a history of atrial fibrillation, HF, or coronary artery disease was prolonged compared to disease-free participants [10]. In a recent Austrian prospective register study of patients with different CV risk profiles undergoing cardiac MRI, hepatic T1-time was associated with abnormal cardiac size and function measures, comorbidities, natriuretic peptides, and independently predicted CV mortality [24]. Finally, in the UK Biobank imaging sub-study, an elevation of hepatic T1-time was associated with an increased risk of new-onset CV disease, specifically incident atrial fibrillation, HF, CV hospitalization, and all-cause mortality [25], thus further suggesting that hepatic T1-time has a promising role to play in risk stratification of subjects at greatest risk of CV morbidity and mortality.

To our knowledge, the associations of hepatic T1-time with cardiac structure/function measures, and the risk of adverse CV clinical outcomes in a population with DCM have never been explored. Therefore, we extended the results of previous studies by confirming the feasibility of hepatic T1-time assessment and showing a strong association of hepatic T1-time with cardiac abnormalities and the risk of developing adverse CV outcomes in patients with DCM. Our results suggest the usefulness of liver structure evaluation in the clinical assessment of stable patients with DCM. Future studies should also assess the clinical implications of hepatic T1-time changes over time, in the context of repeated cardiac MRI evaluation during the clinical follow-up of HF patients. Although our study revealed a substantial stability of hepatic T1-time in a subgroup of patients with DCM in stable clinical condition without overt cardiac decompensation, larger patient populations are required for definite conclusions.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have significantly reduced all-cause mortality, cardiovascular mortality, and hospitalization for HF [26–28]. Experimental data also reported favorable effects of SGLT-2 inhibitors on hepatic steatosis and fibrosis. In this regard, a recent meta-analysis of twelve randomized controlled trials reported that compared to placebo/reference therapy, treatment with SGLT-2 inhibitors for a median period of 24 weeks was associated with significant reductions in serum liver enzyme levels and the absolute percentage of liver fat content on magnetic resonance-based techniques [28]. That said, future studies are needed to explore whether treatment with SGLT-2 inhibitors would also determine a histological improvement of liver structure in patients with DCM.

4.1. Study limitations

The data presented have been collected in a patient population of two tertiary HF centers. Future research in larger cohorts of patients with DCM is required to further validate the use of hepatic T1-time and the cut-off (i.e., hepatic T1-time $\geq$ 563 ms) identified in our study. The assessment of liver imaging data has not been centralized; therefore, a

possible center-specific bias cannot be excluded. Assessment of T1-times can be potentially biased by using two different 1.5T scanners. Hepatic fibrosis could be segmental within the liver, so it is possible that some misclassification of hepatic T1-time occurred based on the ROIs examined. Another potential limitation of the study is the lack of confirmatory liver biopsy. However, following the guiding medical principle of *"primum non nocere"*, it is not surprising in a study of patients with DCM and fairly normal serum aminotransferase concentrations. Although we included only stable patients with DCM without overt cardiac decompensation, some patients may have had subclinical congestion. Finally, given the hypothesis-generating nature of our study, the present data do not prove causation.

5. Conclusions

Among stable patients with DCM undergoing cardiac MRI, assessment of liver structure by hepatic iron-corrected T1-time is feasible and may provide additional clinical information for CV risk stratification of this patient population. In this exploratory multicenter study, we showed that higher hepatic iron-corrected T1-time was significantly associated with impaired cardiac structure and function measures and a greater risk of hospitalization for HF or CV mortality over a mean follow-up of 4.5 years. Further prospective and mechanistic studies are needed to better elucidate the possible implications of effective HF and NAFLD/MAFLD pharmacotherapies on liver structure and function.

Conflict of Interest Disclosures

The authors declare they have no conflict of interest

Acknowledgements and funding/support

Nothing to declare

References

[1] Targher G, Byrne CD. Circulating markers of liver function and cardiovascular disease risk. Arterioscler Thromb Vasc Biol 2015;35(11):2290–6. Nov.

[2] Mantovani A, Byrne CD, Benfari G, Bonapace S, Simon TG, Targher G. Risk of heart failure in patients with nonalcoholic fatty liver disease: JACC review topic of the week. J Am Coll Cardiol 2022;79(2):180–91. Jan 18.

[3] Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, Pryke R, Hutchinson SJ, Sangro B, Martin NK, Cecchini M, Dirac MA, Belloni A, Serra-Burriel M, Ponsioen CY, Sheena B, Lerouge A, Devaux M, Scott N, Hellard M, Verkade HJ, Sturm E, Marchesini G, Yki-Järvinen H, Byrne CD, Targher G, Tur-Sinai A, Barrett D, Ninburg M, Reic T, Taylor A, Rhodes T, Treloar C, Petersen C, Schramm C, Flisiak R, Simonova MY, Pares A, Johnson P, Cucchetti A, Graupera I, Lionis C, Pose E, Fabrellas N, Ma AT, Mendive JM, Mazzaferro V, Rutter H, Cortez-Pinto H, Kelly D, Burton R, Lazarus JV, Ginès P, Buti M, Newsome PN, Burra P, Manns MP. The EASL-lancet liver commission: protecting the next generation of Europeans against liver disease complications and premature mortality. Lancet 2022;399(10319):61–116. Jan 1.

[4] Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77(4):1335–47. Apr 1.

[5] Ma J, Hwang SJ, Pedley A, et al. Bi-directional analysis between fatty liver and cardiovascular disease risk factors. J Hepatol 2017;66:390–7.

[6] Stahl EP, Dhindsa DS, Lee SK, Sandesara PB, Chalasani NP, Sperling LS. Nonalcoholic fatty liver disease and the heart: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:948–63.

[7] Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;6:903–13.

[8] Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. Diabetes Obes Metab 2021. https://doi.org/10.1111/dom.14484. Published online July 29.

[9] Mantovani A, Petracca G, Csermely A, Beatrice G, Bonapace S, Rossi A, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. Gut 2022. Jul 25: gutjnl-2022-327672.

[10] Ostovaneh MR, Ambale-Venkatesh B, Fuji T, et al. Association of liver fibrosis with cardiovascular diseases in the general population: the multi-ethnic study of atherosclerosis (MESA). Circ Cardiovasc Imaging 2018;11:e007241.

[11] Chacko L, Boldrini M, Martone R, et al. Cardiac magnetic resonance-derived extracellular volume mapping for the quantification of hepatic and splenic amyloid. Circ Cardiovasc Imaging 2021. Circimaging121012506.

[12] Dennis A, Kelly MD, Fernandes C, Mouchti S, Fallowfield JA, Hirschfield G, Pavlides M, Harrison S, Chakravarthy MV, Banerjee R, Sanyal A. Correlations between MRI biomarkers PDFF and cT1 with histopathological features of non-alcoholic steatohepatitis. Front Endocrinol (Lausanne) 2021;11:575843. Jan 27.

[13] Li Z, Sun J, Hu X, Huang N, Han G, Chen L, Zhou Y, Bai W, Yang X. Assessment of liver fibrosis by variable flip angle T1 mapping at 3.0T. J Magn Reson Imaging 2016;43:698–703. https://doi.org/10.1002/jmri.25030.

[14] Tunnicliffe EM, Banerjee R, Pavlides M, Neubauer S, Robson MD. A model for hepatic fibrosis: the competing effects of cell loss and iron on shortened modified look-locker inversion recovery T1 (shMOLLI-T1) in the liver. J Magn Reson Imaging 2017;45:450–62. https://doi.org/10.1002/jmri.25392.

[15] Jayaswal ANA, Levick C, Selvaraj EA, Dennis A, Booth JC, Collier J, Cobbold J, Tunnicliffe EM, Kelly M, Barnes E, Neubauer S, Banerjee R, Pavlides M. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. Liver Int 2020;40(12):3071–82. Dec.

[16] Samsky MD, Patel CB, DeWald TA, Smith AD, Felker GM, Rogers JG, Hernandez AF. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol 2013;61:2397–405.

[17] Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. Curr Heart Fail Rep 2014;11:236–40.

[18] Nikolaou M, Parissis J, Yilmaz MB, Seronde MF, Kivikko M, Laribi S, Paugam-Burtz C, Cai D, Pohjanjousi P, Laterre PF, Deye N, Poder P, Cohen-Solal A, Mebazaa A. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. Eur Heart J 2013;34:742–9.

[19] Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2018;15(7):425–39.

[20] Liang W, He X, Wu D, Xue R, Dong B, Owusu-Agyeman M, Zhao J, Cai L, You Z, Dong Y, et al. Prognostic implication of liver function tests in heart failure with preserved ejection fraction without chronic hepatic diseases: insight from TOPCAT Trial. Front Cardiovasc Med 2021;8:618816. https://doi.org/10.3389/fcvm.2021.618816.

[21] Andersson A, Kelly M, Imajo K, Nakajima A, Fallowfield JA, Hirschfield G, Pavlides M, Sanyal AJ, Noureddin M, Banerjee R, Dennis A, Harrison S. Clinical utility of magnetic resonance imaging biomarkers for identifying nonalcoholic steatohepatitis patients at high risk of progression: a multicenter pooled data and meta-analysis. Clin Gastroenterol Hepatol 2022;20(11):2451–61. Nove3.

[22] Long MT, Noureddin M, Lim JK. AGA clinical practice update: diagnosis and management of nonalcoholic fatty liver disease in lean individuals: expert review. Gastroenterology 2022;163(3):764–74. Sepe1.

[23] Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, Kashyap S, Mechanick JI, Mouzaki M, Nadolsky K, Rinella ME, Vos MB, Younossi Z. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the american association for the study of liver diseases (AASLD). Endocr Pract 2022;28(5):528–62. May.

[24] Mascherbauer K, Donà C, Koschutnik M, Dannenberg V, Nitsche C, Duca F, Heitzinger G, Halavina K, Steinacher E, Kronberger C, Bardach C, Beitzke D, Loewe C, Waldmann E, Trauner M, Barkto P, Goliasch G, Mascherbauer J, Hengstenberg C, Kammerlander A. Hepatic T1-time predicts cardiovascular risk in all-comers referred for cardiovascular magnetic resonance: a post-hoc analysis. Circ Cardiovasc Imaging 2022;15(10):e014716. Oct.

[25] Roca-Fernandez A, Banerjee R, Thomaides-Brears H, Telford A, Sanyal A, Neubauer S, Nichols TE, Raman B, McCracken C, Petersen SE, Ntusi NA, Cuthbertson DJ, Lai M, Dennis A, Banerjee A. Liver disease is a significant risk factor for cardiovascular outcomes - a UK Biobank study. J Hepatol 2023. Jun 20: S0168-8278(23)00420-8.

[26] Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet 2022;400(10354):757–67.

[27] Vaduganathan M, Claggett BL, Inciardi RM, Fonarow GC, McMurray JJV, Solomon SD. Estimating the benefits of combination medical therapy in heart failure with mildly reduced and preserved ejection fraction. Circulation 2022;145(23):1741–3. Jun 7.

[28] Mantovani A, Petracca G, Csermely A, Beatrice G, Targher G. Sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Metabolites 2020;11(1). Epub 2021/01/06.