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REVIEW

Liver stiffness as a cornerstone in heart disease risk assessment

Joost Boeckmans[1,2] | Laurent Sandrin[3] | Christian Knackstedt[4,5] | Jörn M. Schattenberg[1,6]

[1]Metabolic Liver Research Center, Department of Medicine, University Medical Center Mainz, Mainz, Germany

[2]In Vitro Liver Disease Modelling Team, Department of In Vitro Toxicology and Dermato-Cosmetology, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium

[3]Echosens, Paris, France

[4]Department of Cardiology, Maastricht University Medical Center+, Maastricht, the Netherlands

[5]Faculty of Health, Medicine, and Life Sciences, CARIM School for Cardiovascular Diseases, Maastricht, the Netherlands

[6]Department of Medicine II, Saarland University Medical Center, Homburg, Germany

Correspondence
Jörn M. Schattenberg, Metabolic Liver Research Center, I. Department of Medicine, University Medical Center Mainz, Mainz and Department of Medicine II, Saarland Univeristy Medical Center, both Germany.
Email: joern.schattenberg@unimedizin-mainz.de

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) typically presents with hepatic fibrosis in advanced disease, resulting in increased liver stiffness. A subset of patients further develops liver cirrhosis and hepatocellular carcinoma. Cardiovascular disease is a common comorbidity in patients with MASLD and its prevalence is increasing in parallel. Recent evidence suggests that especially liver stiffness, whether or not existing against a background of MASLD, is associated with heart diseases. We conducted a narrative review on the role of liver stiffness in the prediction of highly prevalent heart diseases including heart failure, cardiac arrhythmias (in particular atrial fibrillation), coronary heart disease, and aortic valve sclerosis. Research papers were retrieved from major scientific databases (PubMed, Web of Science) until September 2023 using 'liver stiffness' and 'liver fibrosis' as keywords along with the latter cardiac conditions. Increased liver stiffness, determined by vibration-controlled transient elastography or hepatic fibrosis as predicted by biomarker panels, are associated with a variety of cardiovascular diseases, including heart failure, atrial fibrillation, and coronary heart disease. Elevated liver stiffness in patients with metabolic liver disease should lead to considerations of cardiac workup including N-terminal pro–B-type natriuretic peptide/B-type natriuretic peptide determination, electrocardiography, and coronary computed tomography angiography. In addition, patients with MASLD would benefit from heart disease case-finding strategies in which liver stiffness measurements can play a key role. In conclusion, increased liver stiffness should be a trigger to consider a cardiac workup in metabolically compromised patients.

KEYWORDS
atrial fibrillation, coronary heart disease, heart failure, liver stiffness, metabolic dysfunction-associated steatotic liver disease

Abbreviations: AF, atrial fibrillation; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CHD, coronary heart disease; CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; FAST, FibroScan-AST; FIB-4, fibrosis-4; FLI, fatty liver index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MAST, magnetic resonance imaging-AST; MEFIB, magnetic resonance elastography plus FIB-4; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NIT, non-invasive test; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; T2D, type 2 diabetes; TAVI, transcatheter aortic valve implantation; VCTE, vibration-controlled transient elastography.

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an increasing health problem affecting up to one-third of the world's population.[1] Recently, the nomenclature of NAFLD was changed to metabolic dysfunction-associated steatotic liver disease (MASLD), in which liver steatosis should be present in combination with at least one cardiometabolic condition, including impaired glucose regulation, overweight, hypertension, hypertriglyceridemia, or dyslipidaemia, underscoring the importance of cardiovascular disease (CVD) in these patients.[2] Of note, approximately, 99% of patients with NAFLD also meet the MASLD criteria, suggesting that existing literature on NAFLD can be taken under the novel MASLD nomenclature.[3] To avoid confusion in terminology and to promote uniformity in future research, the MASLD nomenclature is used throughout this article.

MASLD encompasses a spectrum of slowly progressing disease stages including hepatic steatosis, inflammatory metabolic dysfunction-associated steatohepatitis (MASH) with or without fibrosis, and cirrhosis potentially resulting in hepatocellular carcinoma.[4] The economic burden of MASH is high with especially the late-stage disease patients being responsible for accumulating healthcare costs.[5] Multiple factors have been proposed to be at the interface between MASLD and heart disease development including adipose-derived and diabetes-related factors, intestine-derived factors, thrombogenic molecules, and pro-inflammatory and oxidative stress-related components.[6] Within the MASLD spectrum, liver fibrosis severity and especially the presence of cirrhosis are the most potent determinants of disease-specific mortality.[7,8] Current guidelines recommend screening for advanced fibrosis in high-risk groups for MASLD using non-invasive tests (NITs).[9] Among the NITs, vibration-controlled transient elastography (VCTE) and the blood-based Fibrosis-4 (FIB-4) index are the most widely used. VCTE directly assesses liver stiffness and multiple studies have described the correlation with hepatic fibrosis,[10–12] while the FIB-4 index is based on age, aspartate aminotransferase, alanine aminotransferase, and platelet count.[9,13]

The presence of MASLD and advanced fibrosis increase the risk of CVD, while CVD is a primary cause of death in patients with MASLD.[14,15] As a result, the management of MASLD requires a multidisciplinary approach including hepatologists, primary care providers, diabetologists, dieticians, and cardiologists.[16]

Increasing evidence suggests that MASLD is a contributor to the onset and/or progression of CVD,[17] including heart failure (HF),[18] coronary heart disease (CHD),[19] atherosclerosis,[20] and arrhythmias.[21] In addition, MASLD is associated with an increased prevalence and incidence of chronic kidney disease, which is a known risk factor for CVD.[22–25] Furthermore, subclinical portal hypertension can occur in non-cirrhotic MASLD, which can impair renal vasoregulation.[26,27]

Recently, it was shown that hepatic steatosis does not predict incident CVD and related mortality when taking into account changes in cardiovascular risk factors over time,[28] suggesting that especially MASLD-related hepatic inflammation and fibrosis with resulting liver stiffness are the most important contributors to the onset and progression of CVD.[29–33]

Key points

- Metabolic dysfunction-associated steatotic liver disease (MASLD) and heart diseases are tightly interrelated.
- MASLD typically presents with hepatic fibrosis in advanced disease resulting in elevated liver stiffness. Venous hepatic congestion is also a source of liver stiffness.
- Increased liver stiffness relates to heart failure, atrial fibrillation, and coronary heart disease.
- Non-invasive tests for liver fibrosis can aid the multidisciplinary management of MASLD patients.
- Elevated liver stiffness should be a cue to consider a cardiac workup.

Of note, increased liver stiffness does not solely result from liver disease-related fibrogenesis but also from increased central venous pressure and congestive hepatopathy.[34,35] Consequently, measuring liver stiffness could be a convenient tool for counteracting cardiovascular sequelae through active surveillance and case finding in metabolically compromised patients.[30,36]

This Review summarizes the evidence for the relation between increased liver stiffness in patients with cardiometabolic risk factors and MASLD and the incidence, prevalence, and prognosis of related heart diseases. Finally, we propose considerations for cardiac workup based on finding elevated liver stiffness using NITs.

Relevant scientific literature was retrieved from major scientific databases (PubMed, Web of Science) using 'liver stiffness', 'liver fibrosis' and the respective heart diseases as keywords until September 2023.

2 | HEART FAILURE

2.1 | Chronic heart failure

MASLD has been found to increase the risk for incident HF by 1.5 times independent of common cardiovascular risk factors.[18] Considering the poor prognosis of HF,[37] it is important to retrieve the driving force behind MASLD that promotes its onset. A handful of studies investigated if increased liver stiffness determined by NITs, whether or not accompanied by evident hepatic steatosis, could be related to the increasing incidence and poor prognosis of HF.

Liver stiffness determined by VCTE has been evaluated in the Rotterdam study, a large cohort study in the Netherlands, for its possible association with mortality in elderly patients with HF. The

authors reported that increased liver stiffness measurement (LSM) (≥8.0 kPa) was solely a poor prognostic factor for mortality in patients with HF (hazard ratio (HR): 2.48, 95% confidence interval (CI): 1.15–5.35), and not in those without HF (HR: 1.07, 95% CI: 0.70–1.64),[38] indicating the relevance of measuring liver stiffness in this population and providing a basis for liver VCTE in the risk assessment for HF (Figure 1). VCTE has been employed in other smaller studies with inpatients that substantiate the role of liver stiffening in the course of HF. In a prospective study consisting of 171 hospitalized participants and a median follow-up of 203 days, VCTE of the liver was performed before discharge with subsequent stratification of the study participants liver stiffness tertiles with cut-offs of 4.7 and 6.9 kPa. Patients in the high liver stiffness category had an HR of 3.57 (95% CI: 1.93–6.83) for mortality and HF rehospitalization when compared with the lower LSM tertiles, which remained significant in different multivariable models. Here, it was also demonstrated that increased liver stiffness (>6.9 kPa) was associated with a higher New York Heart Association (NYHA) functional class, jugular venous distention, tricuspid regurgitation, and a large inferior vena cava diameter in patients with HF compared with the lower tertiles. VCTE-determined liver stiffness thus reflects right-sided filling pressure and liver congestion and is predictive for shorter-term mortality in HF in this population.[39] In a similar setup with 53 hospitalized patients with HF and a follow-up of 24 months, an HR of 4.81 (95% CI: 1.69–13.7) was found for the composite endpoint of death and rehospitalization because of HF for patients in the high liver stiffness group.[40] Yet, it is unclear whether the increased liver stiffness was due to incomplete recompensation or pre-existing liver disease.

Similar results were obtained when using the FIB-4 index as a surrogate for liver fibrosis/stiffness. In a study with 1058 HF inpatients, the FIB-4 index was used to group the study population in tertiles with FIB-4 index <1.72, FIB-4 index ≥1.72 and F<3.01, and FIB-4 index ≥3.01. After a mean follow-up period of 1047 days, the FIB-4 index was found to associate with increased all-cause mortality in a stepwise manner, suggesting that the presence of hepatic fibrosis in HF underlies a worse outcome.[41] In terms of cardiovascular outcomes, NAFLD fibrosis score (NFS) quartiles predicted cardiovascular events (deaths due to progressive HF, myocardial infarction, stroke, sudden cardiac death, and rehospitalization due to worsening of HF) in 516 patients with chronic HF and a median follow-up of 464 days (HR: 1.126, 95% CI: 1.014–1.250), suggesting a prominent role of liver fibrosis and CVD progression.[42]

Since increased liver stiffness could arise from architectural remodelling in the liver because of venous congestion,[34] it would be relevant to investigate if liver stiffness specifically caused by MASLD also contributes to a worse outcome in patients with HF instead of being part of a slowly-progressing liver disease. When comparing patients having HF and MASLD-fibrosis as determined by a fatty liver index (FLI) ≥ 60, and a BARD score ≥2, to patients fulfilling the same criteria with a BARD score <2, an HR for all-cause mortality of 1.597 (95% CI: 1.001–2.548) was found,[43] indicating that hepatic fibrosis can be at the basis of a worse prognosis in patients with both MASLD and HF. In addition, advanced hepatic fibrosis (BARD ≥ 2) in patients with MASLD was also predictive of increased incident HF (HR: 1.116, 95% CI: 1.037–1.201). Nevertheless, whether hepatic fibrogenesis occurred solely through advancing liver disease or long-lasting venous congestion, remains a point of discussion.

Since most studies investigating the role of MASLD and liver stiffness in HF describe the HF syndrome as one continuum, it is difficult to understand their pathophysiological links. A meta-analysis covering 280 645 individuals reported an OR of 2.02 (95% CI: 1.47–2.79) to have diastolic dysfunction when suffering from MASLD, suggesting a potent role of metabolic liver disease in HF with preserved ejection fraction (HFpEF).[44] In addition, a study comprising 3300 individuals undergoing echocardiography and liver ultrasonography in the setting of a health screening program showed that the prevalence of left ventricular diastolic dysfunction increased along with increasing NAFLD fibrosis grade according to the NFS (30.4% in participants without MASLD, 35.2% in participants with MASLD and low probability of advanced fibrosis (NFS < −1.445), and 57.4% in participants with MASLD and intermediate-high probability of advanced fibrosis (NFS ≥ −1.455), $p < .001$),

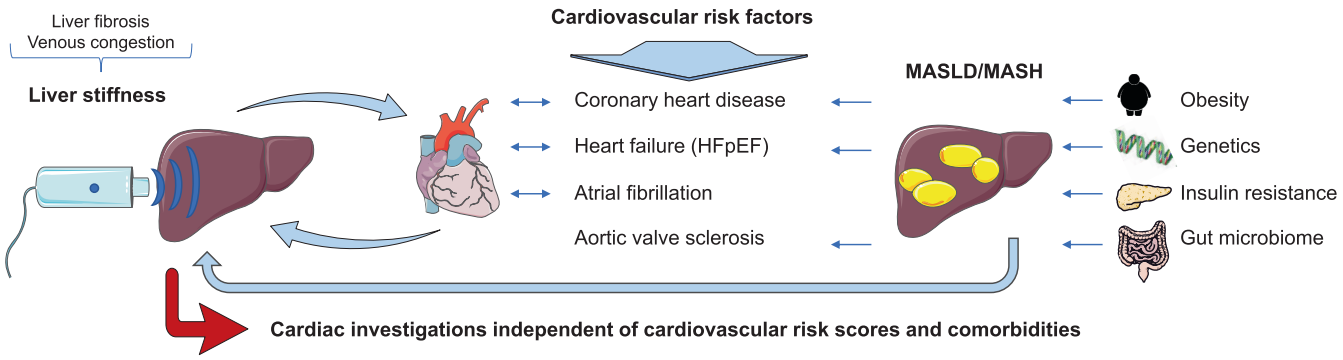

FIGURE 1 Liver stiffness as a cue fo the need for cardiac investigations. Multiple factors, including both liver disease-related and heart disease-related, contribute to stiffening of the liver. Since MASLD, whether or not accompanied by hepatic fibrosis, can contribute to the onset and course of multiple heart diseases, increased liver stiffness is an important sign of a dysregulated liver-heart axis and hence a valuable indicator of the need for cardiac investigations. HFpEF, heart failure with preserved ejection fraction; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

indicating that left ventricular diastolic dysfunction is even more prevalent in advanced MASLD.[45] In recent years, it became indeed clear that patients with MASLD are especially at an increased risk for developing HFpEF compared with HF with reduced ejection fraction (HFrEF) (HR HFpEF: 1.24, 95% CI: 1.14–1.34; HR HFrEF: 1.09, 95% CI: 0.98–1.2).[46] Therefore, studies evaluating liver stiffness in cohorts consisting only of HFpEF patients are of importance to gain insights into the liver-heart axis at the basis of this phenomenon. A study covering 1423 patients with HFpEF showed a prevalence of advanced fibrosis in 37.57% determined by the NFS (>0.675) and 8.02% determined by the FIB-4 index (>3.25), indicating a high prevalence of liver fibrosis in these patients.[47] Another study with 116 HFpEF patients reported that an increase in FIB-4 index was associated with right ventricular dysfunction and 2.202-fold (95% CI 1.110;4.368) risk to develop major adverse cardiovascular events (FIB-4 index ≥3.11 vs. <3.11), which substantiates the previous finding.[48] Remarkably, when comparing HFpEF to HFmrEF and HFrEF, the FIB-4 index (<1.3, 1.3–2.67, >2.67) only predicted total cardiovascular events in HFpEF (HR: 1.09, 95% CI: 1.03–1.15).[49]

In a prospective observational study with 492 hospitalized patients suffering from HFpEF, it was found that the NFS predicted all-cause mortality when comparing the fourth to first quartile (HR: 2.784, 95% CI: 1.343–5.775) while hepatic fibrosis was also associated with increased central venous pressure and circulating markers of systemic fibrosis among which procollagen type III peptide, type IV collagen 7S, and hyaluronic acid. Therefore, collagen turnover with associated fibrogenesis could be the link between MASLD and HFpEF,[50] which has been raised by others as well.[41] This mechanistic basis of HFpEF exacerbation in patients with MASLD could explain the concurrence of advanced HFpEF and fibrosis in MASLD, as shown in a prospective study including 181 patients.[51]

The association between increased liver stiffness whether or not accompanied by MASLD, with incident HF and associated mortality is clear. Yet, it remains unclear whether hepatic inflammation and fibrosis in MASLD effectively contribute to cardiac remodelling in the course of HF. Sparse data are available to substantiate this interaction, although one prospective study including 92 MASLD patients undergoing two-dimensional transthoracic echocardiography implemented with speckle-tracking echocardiography analysis and VCTE of their liver, elegantly showed that increased liver stiffness (≥5.5 kPa) can identify those patients with subclinical myocardial dysfunction.[52]

2.2 | Acute heart failure

Elderly patients with MASLD admitted for acute HF showed to be especially at risk for mortality when having MASLD-fibrosis (determined using ultrasonography, FIB-4 index, and aspartate aminotransferase (AST) to platelet ratio index (APRI)), suggesting a role to also measure liver stiffness in the context of acute HF.[53] The predictive role of the FIB-4 index for mortality in acute HF was investigated in 1854 patients and seemed to be limited to patients with HFpEF (HR per SD: 1.069, 95% CI: 1.047–1.092) and HFmrEF (HR per SD: 1.036, 95% CI: 1.002–1.072), and not of use in HFrEF (HR per SD: 1.005, 95% CI: 0.997–1.012).[54]

Yet, if MASLD-related fibrosis apart from fluid overload potently contributes to the exacerbation of acute HF remains to be clarified, especially considering that VCTE-determined liver stiffness was found to decrease along with N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels during hospitalization in patients with acute decompensated HF.[55] This has been substantiated in a study including 877 patients hospitalized for acute HF that separated the cohort based on the reduction of FIB-4 index during hospitalization (low (<1.0%, $n=293$), middle (1.0%–27.4%, $n=292$), and high (>27.4%, $n=292$) reduction of FIB-index). The authors showed that patients from the low (HR: 2.16, 95% CI: 1.41–3.32, $p<.001$) and middle (HR: 1.70, 95% CI: 1.10–2.63) group were at an increased risk to die from all causes or to get rehospitalized because of HF within 180 days compared with patients from the high reduction in FIB-4 index group.[56]

Therefore, the determination of liver stiffness using NITs in acute HF could predict short-term prognosis[53,54,56,57] and can help inform about adequate venous decongestion prior to discharge.[58,59]

3 | CARDIAC ARRHYTHMIAS

Most evidence linking MASLD to cardiac arrhythmias is present for atrial fibrillation (AF), although associations exist as well for ventricular arrhythmias and cardiac conduction defects.[21]

Metabolic dysfunction-associated steatotic liver disease has been related to an increased risk of incident AF in a prospective cohort study consisting of 400 patients with type 2 diabetes (T2D) who were followed over a period of 10 years (odds ratio (OR): 6.38, 95% CI: 1.7–24.2).[60] The association between incident AF and MASLD was later confirmed in other studies, among which one based on a large primary care database in Germany, reporting an HR of 1.15 (95% CI: 1.04–1.26) when having MASLD[23] and another one based on a large Korean sample reporting an HR of 1.55 (95% CI: 1.19–2.03) for the fourth versus first quartile of the FLI,[61] resulting in an absolute risk increase of about 1.3 (95% CI: 0.5–2.1) per 1000 person-years.[62] Although it is fair to conclude from these reports that MASLD impacts incident AF, the individual roles of hepatic steatosis and fibrosis were not taken into account. In addition, the association between MASLD and HF can impact its association with AF as well.[63]

Notably, the relation between hepatic steatosis and incident AF has been investigated over a period of 12 years in 2122 participants of the Framingham Heart Study. Here, hepatic steatosis was determined using computed tomography (CT) with a liver phantom cut-off of 0.33. After adjusting for age, sex, BMI, and a set of well-established cardiovascular risk factors, no significant association was found between the presence of hepatic steatosis and incident AF (HR: 0.96, 95% CI: 0.64–1.45).[64] This finding was confirmed in the Rotterdam study covering 5825 participants of which 35.7% had

hepatic steatosis determined by abdominal ultrasound (HR for incident AF: 0.88, 95% CI: 0.59–1.33). On cross-sectional analysis, liver steatosis was neither associated with prevalent AF (OR: 0.80, 95% CI: 0.62–1.03), in contrast to liver stiffness determined by VCTE (OR: 1.09 per 1.0 kPa, 95% CI: 1.03–1.16). Remarkably, the association between increased liver stiffness and prevalent AF was only persistent in the absence of hepatic steatosis (OR: 1.18 per kPa, 95% CI: 1.08–1.29),[65] which points to the value of referring patients with isolated increased liver stiffness for electrocardiography. Nonetheless, the authors justly stated that the exact origin and pathophysiological basis of the observed increased liver stiffness in these patients remain elusive. These data confirm an earlier smaller study with elderly people, showing that liver stiffness is significantly higher in individuals with existing AF (VCTE stiffness with AF: 9.3 kPa; without AF: 6.3 kPa, $p = .018$). Conspicuously, when ranking the VCTE-based liver stiffness value based on i. having no MASLD or AF, ii. MASLD but no AF, iii MASLD and AF and iv. no MASLD with AF, the highest liver stiffness was observed among those having both MASLD and AF ($p = .019$).[66] Although the study was limited in the number of participants ($n = 73$), it points to the possible relevance of defining VCTE-based cut-offs for liver stiffness in cardiovascular risk assessment in specific populations. Yet, as AF is also a driving factor in HF, it is important to adjust for it which was not done in the former study.[63] In terms of laboratory-based NITs, the FIB-4 index (in categories <1.30, 1.3–2.67, >2.67) showed to associate with the risk of AF in patients with MASLD (adjusted OR: 2.255, 95% CI: 1.744–2.915).[67]

Limited data are available for the association between liver stiffness and other cardiac arrhythmias.

A retrospective study with 751 patients suffering from T2D who were discharged from the hospital investigated if MASLD (determined by abdominal ultrasound), and accompanying advanced fibrosis (evidenced by a FIB-4 index >2.67), were associated with prevalent heart block, defined as at least one block among first-degree atrio-ventricular block, second-degree block, third-degree block, left bundle branch block, right bundle branch block, left anterior hemi-block or left posterior hemi-block. The authors found a three-fold increased risk for prevalent heart block in patients with MASLD after adjusting for confounders (OR: 3.04, 95% CI: 1.81–5.10). Furthermore, MASLD patients with a FIB-4 index being indicative of advanced fibrosis (FIB-4 > 2.67) had a significantly higher prevalence of heart blocks compared with patients with a lower FIB-4 index,[68] suggesting an exacerbating role for hepatic fibrosis in patients with MASLD.

In a large cross-sectional study with 31 116 individuals from the general population, it was observed that MASLD severity, by means of ultrasonographic criteria (i.e. increased parenchymal brightness compared with the right renal cortex and the ability to visualize portal venule walls[69]), was associated with a higher risk for heart rate-corrected QT (QTc) prolongation, going up to an extension of 12.13 ms in QTc interval,[70] implying also a role for MASLD in ventricular arrhythmias. Later, liver stiffness determined by VCTE in patients with chronic liver disease, most of them having MASLD or chronic viral hepatitis, appeared to be a predictor for QTc prolongation (spearman's correlation coefficient $\rho = 0.137$ with $p = .011$) while hepatic steatosis determined by the controlled attenuation parameter (CAP) did not (spearman's correlation coefficient $\rho = 0.019$ with $p = .718$). Although these results support the role of liver stiffening in QT prolongation, they must be interpreted with caution to draw conclusions regarding specific liver diseases because of the heterogeneous study population.[71]

4 | CORONARY HEART DISEASE

MASLD is a well-known contributor to progressive coronary artery atherosclerosis[72,73] and consequently associates with an increased incidence of myocardial infarction (adjusted HR: 1.54, 95% CI: 1.11–2.14).[74] In terms of NITs and early effects of MASLD on CHD, the FLI predicts both clinical and subclinical atherosclerosis.[75]

In a study with 120 patients having symptoms of CHD, hepatic steatosis and fibrosis were determined using ultrasonography and shear stress elastography, respectively, while making the definite diagnosis of CHD with coronary angiography or CT angiography. Although the study made use of different techniques to objectivate the presence of CHD and was of cross-sectional nature, the authors found an association between the degree of liver stiffness and the presence of CHD ($\beta = 1.404$ with $p < .001$).[76] The predictivity of liver stiffness for CHD was later substantiated in another cross-sectional study including 105 patients with MASLD, determined by magnetic resonance imaging proton density fat fraction (MRI-PDFF) of at least 5% while liver stiffness was measured using magnetic resonance elastography (MRE). Here, it was found that liver stiffness is an independent predictor of coronary artery calcification (coronary artery calcification score >0) determined using cardiac CT (OR: 2.16, 95% CI: 1.29–4.09).[77] Furthermore, a study including 142 MASLD patients reported that LSM by VCTE was as well independently associated with the coronary artery calcification score ($\beta = 0.311$, $p = .001$).[78] Similar results were obtained in a smaller study with 49 MASLD patients using both VCTE and a non-invasive biomarker panel (NFS).[79] In addition, multiple liver fibrosis scores including the FIB-4 index and NFS, showed to correlate with coronary artery calcification progression and severity[80,81] and cardiovascular risk scores (among which the Framingham risk score) in patients with MASLD.[82,83] In the general population, the FIB-4 index predicted the onset of ischemic heart disease in individuals with liver steatosis determined by ultrasonography with a follow-up of 10 years (HR: 1.42, 95% CI: 1.13–1.77) allowing to take early preventive measures in primary care.[84] Altogether, these data indicate that liver stiffness determination using VCTE or blood-based NITs suggestive of hepatic fibrosis should be implemented for cardiovascular risk assessment in patients with MASLD.

However, there exist also some conflicting data on the contribution or predictive value of liver stiffness in CHD from a well-designed prospective cohort study of 576 patients who underwent coronary angiography and liver VCTE. Here, MASLD was diagnosed based on a CAP of at least 234 dB/m, and advanced fibrosis as a LSM of at

least 7.9 kPa. Patients with clinically relevant coronary artery stenosis, implying a reduction of at least 75% of the luminal diameter, had moderately but significantly higher median CAP values (273 ± 61 vs. 260 ± 66 dB/m; $p = .038$), while MASLD was also more prevalent in this group compared with patients without or with a lower coronary artery stenosis grade (75.0% vs. 63.1%, $p = .0068$). To differentiate MASLD-related hepatic fibrosis from other causes of liver stiffening, patients with congestive hepatopathy and other causes of increased liver stiffness were excluded from the analysis of MASLD-specific fibrosis. Based on a well-defined subset of 392 patients, the authors found no significantly higher prevalence of MASLD-related advanced fibrosis among patients with CHD with a luminal reduction of at least 75% compared with less-affected subjects (10.7% vs. 12.5%, $p = .60$).[85] Since the stringent criteria for CHD in this study might have overridden the modifying effect of liver stiffness in the early course of the disease, one might question whether the presence of MASLD-related liver stiffness could effectively contribute to increased mortality in these patients. Indeed, although increased liver stiffness appears to associate with the development and progression of CHD, its effect on mortality in patients living with CHD was found to be insignificant in the Rotterdam study (HR: 1.43, 95% CI: 0.58–3.49 for liver stiffness ≥8 kPa determined by VCTE), although a trend towards an increased risk of mortality could be observed.[38]

Remarkably, patients suspected of MASLD with a FIB-4 index ≥2.67 that underwent percutaneous coronary intervention (PCI) within 24 h after the onset of acute myocardial infarction had a 3.45-fold (95% CI: 1.07–11.00) higher chance for rehospitalization because of HF within 13 months, compared with patients with a FIB-4 index <2.67).[86] These results suggest a prognostic role of liver stiffness in patients with advanced CHD undergoing PCI but await confirmation given the wide confidence interval and lack of adjustment for sex, age, and cardiovascular risk factors. Overall, liver stiffness whether or not resulting from MASLD seems to especially contribute to the early phases of CHD while its role in more advanced disease is less clear.

5 | AORTIC VALVE SCLEROSIS AND STENOSIS

The association between hepatic steatosis and aortic valve sclerosis has been described already a decade ago. In a cross-sectional analysis of 2212 individuals of the general population with available abdominal ultrasound data, subjects with hepatic steatosis had 33% (95% CI: 6%–66%) higher odds of having aortic valve sclerosis determined by echocardiography, compared with those without evident hepatic steatosis.[87] This association was replicated in a study sample of 120 patients with T2D, reporting an OR of 3.04 (95% CI: 1.3–7.3) to have aortic valve sclerosis based on the presence of hepatic steatosis determined by ultrasonography.[88] Later, a meta-analysis showed that MASLD patients have an OR of 2.28 (95% CI: 1.21–4.28) to have aortic valve sclerosis.[89] The association between MASLD and aortic valve sclerosis seems therefore evident, but the contribution of hepatic fibrosis or liver stiffness was not taken into account in these studies and should be elucidated in future research.

Liver fibrosis has been studied regarding aortic valve sclerosis/stenosis for its prognostic value related to mortality after transcatheter aortic valve implantation (TAVI). In a study with 538 patients who underwent CT before valve implantation, MASLD was defined as a liver-to-spleen attenuation ratio <1.0 on CT without contrast while hepatic fibrosis was assessed using the NFS. Based on a follow-up period of 47 months, MASLD did not predict all-cause mortality (HR: 1.32, 95 CI: 0.97–1.97), nor did the NFS (HR for NFS < −1.455 vs. >0.676 = 1.54, 95% CI: 0.82–2.91),[90] suggesting that the existence of liver fibrosis in MASLD should not withhold patients for undergoing TAVI. In contrast, another study with 480 participants reported that a FIB-4 index with a cut-off value of 1.82 predicts 1-year all-cause mortality in patients receiving a novel aortic valve via TAVI with an HR of 1.75 (95% CI: 1.18–2.59) after adjusting for most relevant confounders. Yet in this study, patients with a FIB-4 index >1.82 also had a significantly higher rate of pulmonary hypertension (43.8% vs. 31.8%), right-ventricular systolic dysfunction (29.5% vs. 19.2%), and larger inferior vena cava diameter (1.6 ± 0.6 vs. 1.3 ± 0.6 cm) compared with patients with a FIB-4 index ≤1.82,[91] suggesting that the increased liver stiffness and poor prognosis were rather related to the existence of long-term cardiac impairment instead of liver disease. Therefore, the exact role of liver stiffness in the prognosis of patients undergoing TAVI needs to be clarified in future studies.

6 | DISCUSSION

NITs to stage MASLD and fibrosis are gaining *momentum* in the field.[13] Among the available NITs, especially VCTE seems to be a convenient tool in daily medical practice since it allows ad hoc determination of liver stiffness. Considering that heart diseases, among which HF, arrhythmias, and CHD are important comorbidities and/or causes of death in MASLD (Figure 2),[30] it is crucial to identify the cues in routine medical practice that reflect their interplay. Hitherto, most evidence is available for liver stiffness, instead of fatty liver, being at the nexus of liver and heart disease. Therefore, the use of liver VCTE and blood-based NITs suggestive of hepatic fibrosis[92] could assist in guiding cardiovascular risk assessment. As a confounding factor, venous congestion and congestive hepatopathy can increase liver stiffness.[93] Accordingly, the finding of increased liver stiffness without a liver disease, could be an indicator of underlying CVD and urge immediate clinical investigations. An argument that corroborates this statement emanates from the often poor prognosis of heart diseases that can underlie increased liver stiffness.[94,95] This assertion is largely substantiated by experimental data from well-designed studies covering different cardiac pathologies. For example, VCTE-determined liver stiffness in elderly patients with HF showed to increase the risk for all-cause mortality solely in patients with HF,[38] which indicates that increased liver stiffness should not be regarded as an innocent bystander of a slowly progressing disease in this population. On that basis, elevated liver stiffness

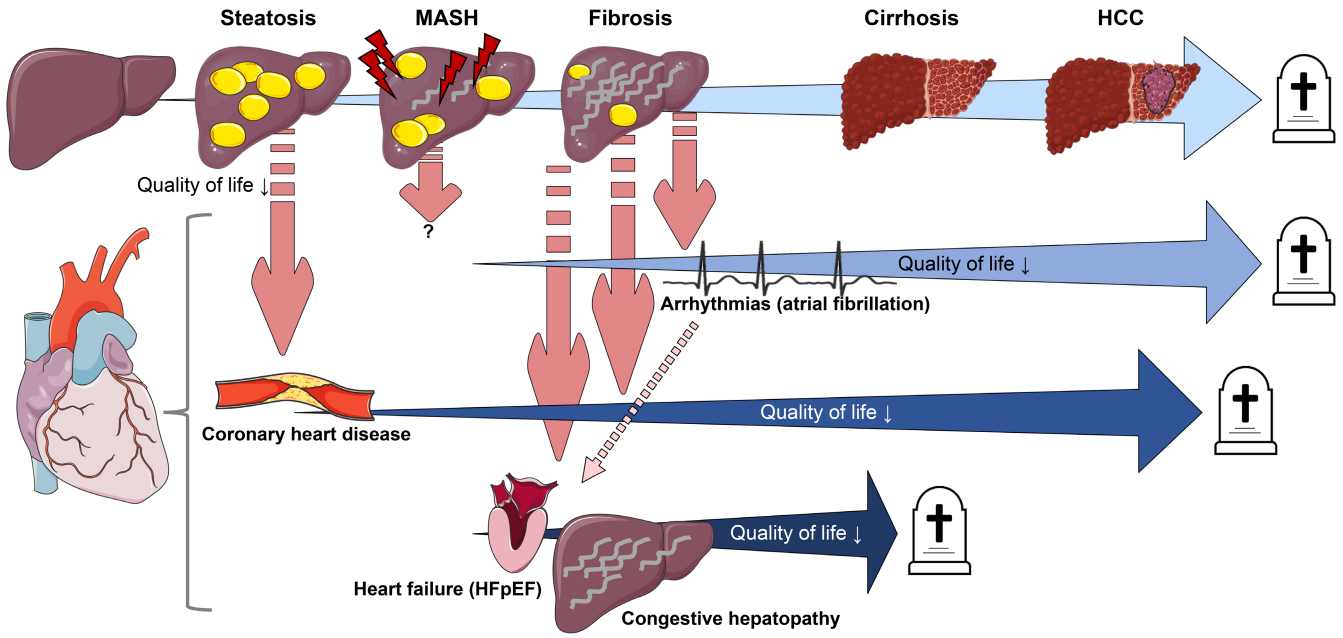

FIGURE 2 Current concepts in the emerging role of MASLD in the landscape of highly prevalent heart diseases. MASLD increases the incidence of CHD and subsequent myocardial infarction. Liver stiffness due to fibrogenesis or venous congestion associates with HF and is a poor prognostic factor. Elevated liver stiffness is associated with prevalent AF. Quality of life is impaired in both MASLD and heart disease. AF, atrial fibrillation; CHD, coronary heart disease; HCC, hepatocellular carcinoma; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MASH, metabolic dysfunction-associated steatohepatitis.

determined by VCTE was found to associate with prevalent AF, especially in those without hepatic steatosis.[65] Although cardiovascular scoring systems remain useful tools for risk assessment, hepatic fibrosis determined by NITs showed to correlate with cardiovascular risk scores, including the Framingham risk score,[82,83] suggesting that measuring liver stiffness can fulfil a role in the assessment of long-term cardiovascular risks.

One should keep in mind the predictive value of liver stiffness in specific populations for estimating short- and long-term risks related to heart disease. Elevated liver stiffness in a population without metabolic or other liver-related risk factors might rather be a consequence of hepatic venous congestion, urging immediate aggressive curative cardiovascular treatment. On the other hand, patients suffering from obesity and T2D are more likely to have MASLD-related advanced fibrosis[96] as their underlying cause of abnormal liver stiffness measurements. As MASLD might lay at the basis of early cardiac remodelling[97] and is a predictive factor for incident HF,[18] liver-directed therapies could be initiated in these types of patients in the context of cardiovascular risk management.

Furthermore, variable fibrosis risks exist based on age and sex, and knowledge on these disparities seem essential to select patients for further cardiac investigations. Women of reproductive age are protected from MASLD with a risk reduction of approximately 50% compared with men, while also being protected from fibrosis development in the occasion that MASLD develops.[98,99] In contrast, postmenopausal women with MASLD loose this protection and are at higher risk for advanced fibrosis than men, reflecting the hepato- and cardioprotective properties of oestrogen to among others suppress lipogenesis, increase fatty acid oxidation and ameliorate insulin sensitivity.[99–101] The sexual dimorphism in cardiometabolic disease is at least partly attributable to the different adipose tissue distribution between women and men, since an elevated BMI in premenopausal women can be based on relatively benign subcutaneous adipose tissue, compared with android visceral adipose tissue in men.[102] Consequently, women suffering from the polycystic ovarium syndrome, a reproductive disorder associated with excess androgens, also have a higher prevalence of the metabolic syndrome and MASLD with more severe MASH and advanced fibrosis,[103–105] as well as CVD on the long-term.[106] In addition, metabolic profiles associated with the risk of advanced liver fibrosis in MASLD differ among age groups, which can influence as well the risk for heart diseases.[107]

7 | CONSIDERATIONS

Increased liver stiffness can be an indicator to consider a cardiovascular workup in patients with metabolic risk factors. In addition, and as proposed by others,[77] patients with MASLD and elevated liver stiffness should be considered for cardiovascular risk assessment independently of other traditional cardiovascular risk scores. In the primary care setting, NITs with cut-offs suggestive of hepatic fibrosis[108,109] could inform general practitioners on the risk for prevalent and incident heart disease in patients with suspected MASLD or heart disease and as a result, initiate preventive actions or refer for a cardiovascular workup in specialty care (Figure 3).[9,110–113] Although

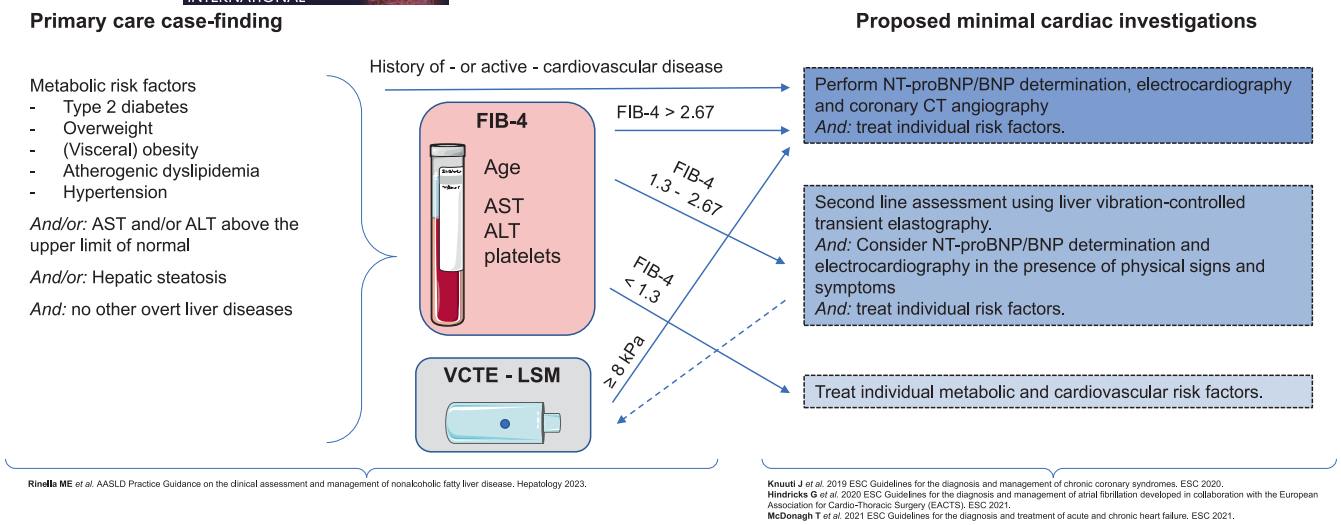

FIGURE 3 Proposed minimal cardiac investigations based on primary care case finding in metabolically compromised patients. Implementation of a simple blood-based non-invasive test in primary care for patients at risk of MASLD-related fibrosis can assist in preventing heart diseases or enable early treatment. AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography; FIB-4, fibrosis-4; LSM, liver stiffness measurement; NT-proBNP, N-terminal pro–B-type natriuretic peptide; VCTE, vibration-controlled transient elastography.

the current NITs are better at ruling out than ruling in hepatic fibrosis and their accuracy can be affected by concurrent T2D,[83,114] their determination would allow for the initiation of referral pathways based on age, sex, comorbidities and physical signs and symptoms of heart disease and could therefore be a convenient tool to initiate a personalized diagnostic path.[16,35,36,115]

Nevertheless, these recommendations and cut-offs for liver stiffness in the view of cardiovascular risk assessment are still arbitrary as there is no conclusive data on the utility of such an approach.

8 | PERSPECTIVES AND CONCLUSION

Efforts are currently being made in the LiverScreen project covering 30 000 participants from eight European countries to investigate the usefulness and cost-effectiveness of liver stiffness measurement in the general population for identifying subjects with asymptomatic advanced liver disease. Since the study is of prospective nature and also targets CVD in a secondary endpoint, the results could be extrapolated to gain insights in the value of performing liver VCTE in cardiovascular risk assessment in the general population.[116,117]

Although the source of increased liver stiffness is not always obvious and can be the result of a complex interplay between hepatic, cardiac, and systemic factors, hepatic inflammation in MASH could also compromise cardiac health and contribute to the initiation of heart disease.[50,118,119] Therefore, one might question whether referral to specialty care for cardiovascular risk assessment based on liver stiffness in MASLD should be rather based on a NIT that can identify patients with MASH,[120,121] independent of evident liver stiffness. Unfortunately, no laboratory NIT is available that can accurately identify patients with MASH[122,123] and consequently, identifying patients in the primary care setting at risk of MASLD-related fibrosis would be the best strategy to take aggressive cardiovascular preventive or curative measures as early as possible.

The FIB-4 index and LSM by VCTE are currently the most widely used NITs to test for advanced fibrosis and especially have good negative predictive values with a relatively high number of false positives. NITs that combine VCTE-based LSM with routine blood-based laboratory markers, including Agile 3+ and Agile 4 appear to have better positive predictive values to rule in advanced fibrosis and cirrhosis in patients with MASLD, but their use is limited to specialized care centers.[124] In that perspective, the FibroScan-AST (FAST) score, combining LSM, CAP and AST levels, can non-invasively identify patients at risk of progressive MASH and perhaps even earlier identify patients also at risk for CVD in secondary and tertiary care.[120] In the specialized care setting, elevated magnetic resonance-based scores to detect at-risk MASH and advanced fibrosis in individuals with MASLD, of which MRE plus FIB-4 (MEFIB) seems to outperform the magnetic resonance imaging-AST (MAST) and also FAST score,[125] should led to referral for cardiovascular risk management.

Sparse data are available on the mechanisms linking MASLD-derived liver stiffness to heart disease that could be targeted using pharmacological therapies. Using bioinformatics, efforts have been made to identify common pathophysiological pathways between MASLD and HFpEF. By comparing transcriptomics data of epicardial adipose tissue of patients suffering from HFpEF with data obtained from liver tissue of MASLD/MASH patients, the authors concluded that bosentan, eldecalcitol, ramipril, and probucol could be possible treatment options to target both diseases.[126] Yet, these data await validation and future controlled clinical studies are required to define the most appropriate approach.

Biomarkers for monitoring patients with combined liver and CVD would as well be of practical use. Fetuin-A has been earlier proposed as a biomarker for liver and vascular fibrosis progression

in MASLD,[127] and hepatic hypoperfusion and cardiac outcomes in HF,[128] but requires validation for these purposes. Gamma glutamyl transferase has been as well highlighted as a marker of cardiometabolic health, although interpretation of its elevation is highly unspecific and can be the result of multiple other liver-related conditions including cholestatic and alcoholic liver disease.[129]

Regardless of targeting common pathophysiological pathways, the link between (advanced) MASLD and the increased incidence and prevalence of heart disease with resulting mortality fuels the need for an approved anti-MASH drug in the multidisciplinary treatment of metabolically compromised patients.[130–132] In addition, both entities are typified by impaired quality of life[133–137] along with financial pressure on healthcare systems[138,139] which further emphasizes the need for holistic management of these patients (Figure 2).

In conclusion, determining liver stiffness in the context of a personalized multidisciplinary approach[16,140] will improve cardiovascular outcomes in patients with metabolic risk factors and MASLD by allowing for preventive strategies or early curative treatments.

AUTHOR CONTRIBUTIONS

Conceptualization: Joost Boeckmans and Jörn M. Schattenberg; Investigation: Joost Boeckmans and JMS; Methodology: Joost Boeckmans and Jörn M Schattenberg; Project administration: Joost Boeckmans and Jörn M. Schattenberg; Supervision: Jörn M. Schattenberg; Writing – original draft: Joost Boeckmans Writing – review & editing: all authors.

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CONFLICT OF INTEREST STATEMENT

JB does not report a conflict of interest. Independent of this review, LS is a full-time employee of Echosens. Independent of this review, CK has served as advisor to TOMTEC Imaging systems, Alnylam, Bristol Myers Squibb and Pfizer. Also, he has received unrestricted grants, paid to institute from Astra Zeneca and Pfizer, and travel grants from TOMTEC Imaging systems. Also, his scientific work has been supported by software and hardware grants from TOMTEC Imaging systems and Medis Imaging. Independent of this review, JMS has acted as consultant to Apollo Endosurgery, Astra Zeneca, Bayer, Boehringer Ingelheim, Gilead Sciences, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers; has received research Funding from Gilead Sciences, Boehringer Ingelheim, Siemens Healthcare GmbH and Speaker Honorarium from Boehringer Ingelheim, Echosens, MedPublico GmbH, Novo Nordisk, Madrigal Pharmaceuticals.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Joost Boeckmans https://orcid.org/0000-0001-8399-5872
Laurent Sandrin https://orcid.org/0000-0002-0433-736X
Christian Knackstedt https://orcid.org/0000-0002-5457-3010
Jörn M. Schattenberg https://orcid.org/0000-0002-4224-4703

REFERENCES

1. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7(9):851-861.
2. Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023. In press. doi:10.1016/j.jhep.2023.06.003
3. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. *J Hepatol*. 2023. In press. doi:10.1016/j.jhep.2023.08.026
4. Parthasarathy G, Revelo X, Malhi H. Pathogenesis of nonalcoholic steatohepatitis: an overview. *Hepatol Commun*. 2020;4(4):478-492.
5. Schattenberg JM, Lazarus JV, Newsome PN, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: a cost-of-illness analysis. *Liver Int*. 2021;41(6):1227-1242.
6. 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):180-191.
7. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology*. 2015;61(5):1547-1554.
8. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. *Gastroenterology*. 2018;155(2):443-457.
9. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797-1835.
10. Siddiqui MS, Vuppalanchi R, Van Natta ML, et al. Vibration-controlled transient Elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2019;17(1):156-163.e2.
11. Mózes FE, Lee JA, Selvaraj EA, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut*. 2021;71(5):1006-1019.
12. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29(12):1705-1713.
13. Vali Y, Lee J, Boursier J, et al. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. *Lancet Gastroenterol Hepatol*. 2023;8(8):714-725.
14. Long MT, Zhang X, Xu H, et al. Hepatic fibrosis associates with multiple cardiometabolic disease risk factors: the Framingham heart study. *Hepatology*. 2021;73(2):548-559.
15. Kasper P, Martin A, Lang S, et al. NAFLD and cardiovascular diseases: a clinical review. *Clin Res Cardiol*. 2021;110(7):921-937.
16. Schattenberg JM, Allen AM, Jarvis H, et al. A multistakeholder approach to innovations in NAFLD care. *Commun Med*. 2023;3(1):1.

17. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut*. 2020;69(9):1691-1705.
18. Mantovani A, Petracca G, Csermely A, et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. *Gut*. 2022;72(2):372-380.
19. Arslan U, Yenerçağ M. Relationship between non-alcoholic fatty liver disease and coronary heart disease. *World J Clin Cases*. 2020;8(20):4688-4699.
20. Brea A, Mosquera D, Martín E, et al. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler Thromb Vasc Biol*. 2005;25(5):1045-1050.
21. Chen Z, Liu J, Zhou F, et al. Nonalcoholic fatty liver disease: an emerging driver of cardiac arrhythmia. *Circ Res*. 2021;128(11):1747-1765.
22. Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. *J Hepatol*. 2020;72(4):785-801.
23. Labenz C, Huber Y, Michel M, et al. Impact of NAFLD on the incidence of cardiovascular diseases in a primary care population in Germany. *Dig Dis Sci*. 2020;65(7):2112-2119.
24. Kaps L, Labenz C, Galle PR, Weinmann-Menke J, Kostev K, Schattenberg JM. Non-alcoholic fatty liver disease increases the risk of incident chronic kidney disease. *United European Gastroenterol J*. 2020;8(8):942-948.
25. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. *Gut*. 2022;71(1):156-162.
26. Lonardo A, Mantovani A, Targher G, Baffy G. Nonalcoholic fatty liver disease and chronic kidney disease: epidemiology, pathogenesis, and clinical and research implications. *Int J Mol Sci*. 2022;23(21):13320.
27. Francque S, Verrijken A, Mertens I, et al. Visceral adiposity and insulin resistance are independent predictors of the presence of non-cirrhotic NAFLD-related portal hypertension. *Int J Obes (Lond)*. 2011;35(2):270-278.
28. Ahmed HS, Wang N, Carr JJ, et al. The association between hepatic steatosis and incident cardiovascular disease, cancer, and all-cause mortality in a US multicohort study. *Hepatology*. 2023;77(6):2063-2072.
29. Shroff H, VanWagner LB. Cardiovascular disease in nonalcoholic steatohepatitis: screening and management. *Curr Hepatol Rep*. 2020;19(3):315-326.
30. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut*. 2017;66(6):1138-1153.
31. Ostovaneh MR, Ambale-Venkatesh B, Fuji T, et al. Association of liver fibrosis with cardiovascular diseases in the general population. *Circ Cardiovasc Imaging*. 2018;11(3):e007241.
32. 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(11):903-913.
33. Simon TG, Roelstraete B, Hagström H, Sundström J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. *Gut*. 2022;72(9):1867-1875.
34. Lemmer A, VanWagner L, Ganger D. Congestive hepatopathy: differentiating congestion from fibrosis. *Clin Liver Dis (Hoboken)*. 2017;10(6):139-143.
35. Millonig G, Friedrich S, Adolf S, et al. Liver stiffness is directly influenced by central venous pressure. *J Hepatol*. 2010;52(2):206-210.
36. Boursier J, Guillaume M, Leroy V, et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. *J Hepatol*. 2019;71(2):389-396.
37. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart*. 2022;108(17):1351-1360.
38. van Kleef LA, Sonneveld MJ, Zhu F, Ikram MA, Kavousi M, de Knegt RJ. Liver stiffness is associated with excess mortality in the general population driven by heart failure: the Rotterdam Study. *Liver Int*. 2023;43(5):1000-1007.
39. Taniguchi T, Ohtani T, Kioka H, et al. Liver stiffness reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure. *JACC Cardiovasc Imaging*. 2019;12(6):955-964.
40. Wang Q, Song Y, Wu Q, Dong Q, Yang S. Liver stiffness for predicting adverse cardiac events in chinese patients with heart failure: a two-year prospective study. *BMC Cardiovasc Disord*. 2022;22(1):51.
41. Sato Y, Yoshihisa A, Kanno Y, et al. Liver stiffness assessed by Fibrosis-4 index predicts mortality in patients with heart failure. *Open Heart*. 2017;4(1):e000598.
42. Takahashi T, Watanabe T, Shishido T, et al. The impact of non-alcoholic fatty liver disease fibrosis score on cardiac prognosis in patients with chronic heart failure. *Heart Vessels*. 2018;33(7):733-739.
43. Park J, Kim G, Kim H, et al. The association of hepatic steatosis and fibrosis with heart failure and mortality. *Cardiovasc Diabetol*. 2021;20(1):197.
44. Wijarnpreecha K, Lou S, Panjawatanan P, et al. Association between diastolic cardiac dysfunction and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Dig Liver Dis*. 2018;50(11):1166-1175.
45. Chung GE, Lee JH, Lee H, et al. Nonalcoholic fatty liver disease and advanced fibrosis are associated with left ventricular diastolic dysfunction. *Atherosclerosis*. 2018;272:137-144.
46. Fudim M, Zhong L, Patel KV, et al. Nonalcoholic fatty liver disease and risk of heart failure among medicare beneficiaries. *J Am Heart Assoc*. 2021;10(22):e021654.
47. Peters AE, Pandey A, Ayers C, et al. Association of liver fibrosis risk scores with clinical outcomes in patients with heart failure with preserved ejection fraction: findings from TOPCAT. *ESC Heart Fail*. 2021;8(2):842-848.
48. Nakashima M, Sakuragi S, Miyoshi T, et al. Fibrosis-4 index reflects right ventricular function and prognosis in heart failure with preserved ejection fraction. *ESC Heart Fail*. 2021;8(3):2240-2247.
49. Takae M, Fujisue K, Yamamoto E, et al. Prognostic significance of liver stiffness assessed by fibrosis-4 index in patients with heart failure. *ESC Heart Fail*. 2021;8(5):3809-3821.
50. Yoshihisa A, Sato Y, Yokokawa T, et al. Liver fibrosis score predicts mortality in heart failure patients with preserved ejection fraction. *ESC Heart Fail*. 2018;5(2):262-270.
51. Miller A, McNamara J, Hummel SL, Konerman MC, Tincopa MA. Prevalence and staging of non-alcoholic fatty liver disease among patients with heart failure with preserved ejection fraction. *Sci Rep*. 2020;10(1):12440.
52. Sonaglioni A, Cerini F, Cerrone A, et al. Liver stiffness measurement identifies subclinical myocardial dysfunction in non-advanced non-alcoholic fatty liver disease patients without overt heart disease. *Intern Emerg Med*. 2022;17(5):1425-1438.
53. Valbusa F, Agnoletti D, Scala L, et al. Non-alcoholic fatty liver disease and increased risk of all-cause mortality in elderly patients admitted for acute heart failure. *Int J Cardiol*. 2018;265:162-168.
54. Tseng CH, Huang WM, Yu WC, et al. The fibrosis-4 score is associated with long-term mortality in different phenotypes of acute heart failure. *Eur J Clin Invest*. 2022;52(12):e13856.
55. Colli A, Pozzoni P, Berzuini A, et al. Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. *Radiology*. 2010;257(3):872-878.
56. Maeda D, Kanzaki Y, Sakane K, et al. Prognostic impact of a reduction in the fibrosis-4 index among patients hospitalized with acute heart failure. *Heart Vessels*. 2023;38(10):1235-1243.

57. Saito Y, Kato M, Nagashima K, et al. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. *Circ J*. 2018;82(7):1822-1829.
58. Soloveva A, Kobalava Z, Fudim M, et al. Relationship of liver stiffness with congestion in patients presenting with acute decompensated heart failure. *J Card Fail*. 2019;25(3):176-187.
59. Dhillon JK, Fong MW, Fong TL. Use of liver stiffness measurements in acute decompensated heart failure: new applications of a non-invasive technique. *ESC Heart Fail*. 2022;9(5):2800-2807.
60. Targher G, Valbusa F, Bonapace S, et al. Non-alcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes. *PloS One*. 2013;8(2):e57183.
61. Roh JH, Lee JH, Lee H, et al. Association between non-alcoholic fatty liver disease and risk of new-onset atrial fibrillation in healthy adults. *Liver Int*. 2020;40(2):338-346.
62. Cai X, Zheng S, Liu Y, Zhang Y, Lu J, Huang Y. Nonalcoholic fatty liver disease is associated with increased risk of atrial fibrillation. *Liver Int*. 2020;40(7):1594-1600.
63. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J*. 2015;36(46):3250-3257.
64. Long MT, Yin X, Larson MG, et al. Relations of liver fat with prevalent and incident atrial fibrillation in the Framingham heart study. *J Am Heart Assoc*. 2017;6(5):e005227.
65. van Kleef LA, Lu Z, Arfan Ikram M, de Groot NMS, Kavousi M, de Knegt RJ. Liver stiffness not fatty liver disease is associated with atrial fibrillation: the Rotterdam study. *J Hepatol*. 2022;77(4):931-938.
66. Käräjämäki AJ, Kettunen O, Lepojärvi S, et al. Presence of atrial fibrillation is associated with liver stiffness in an elderly Finnish population. *PloS One*. 2017;12(3):e0173855.
67. Park HE, Lee H, Choi SY, Kim HS, Chung GE. The risk of atrial fibrillation in patients with non-alcoholic fatty liver disease and a high hepatic fibrosis index. *Sci Rep*. 2020;10(1):5023.
68. Mantovani A, Rigolon R, Pichiri I, et al. Nonalcoholic fatty liver disease is associated with an increased risk of heart block in hospitalized patients with type 2 diabetes mellitus. *PloS One*. 2017;12(10):e0185459.
69. Needleman L, Kurtz AB, Rifkin MD, Cooper HS, Pasto ME, Goldberg BB. Sonography of diffuse benign liver disease: accuracy of pattern recognition and grading. *AJR Am J Roentgenol*. 1986;146(5):1011-1015.
70. Hung CS, Tseng PH, Tu CH, et al. Nonalcoholic fatty liver disease is associated with QT prolongation in the general population. *J Am Heart Assoc*. 2015;4(7):e001820.
71. Bellan M, Rigamonti C, Giacomini GM, et al. Liver stiffness, not fat liver content, predicts the length of QTc interval in patients with chronic liver disease. *Gastroenterol Res Pract*. 2019;2019:6731498.
72. 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):425-439.
73. Ren Z, Simons PIHG, Wesselius A, Stehouwer CDA, Brouwers MCGJ. Relationship between NAFLD and coronary artery disease: a Mendelian randomization study. *Hepatology*. 2023;77(1):230-238.
74. Sinn DH, Kang D, Chang Y, et al. Non-alcoholic fatty liver disease and the incidence of myocardial infarction: a cohort study. *J Gastroenterol Hepatol*. 2020;35(5):833-839.
75. Lonardo A, Ballestri S, Bedogni G, Bellentani S, Tiribelli C. The fatty liver index (FLI) 15 years later: a reappraisal. *Metab Target Organ Damage*. 2021;1:10.
76. Song Y, Dang Y, Wang P, Tian G, Ruan L. CHD is associated with higher grades of NAFLD predicted by liver stiffness. *J Clin Gastroenterol*. 2020;54(3):271-277.
77. Park JG, Jung J, Verma KK, et al. Liver stiffness by magnetic resonance elastography is associated with increased risk of cardiovascular disease in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2021;53(9):1030-1037.
78. You SC, Kim KJ, Kim SU, et al. Hepatic fibrosis assessed using transient elastography independently associated with coronary artery calcification. *J Gastroenterol Hepatol*. 2015;30(10):1536-1542.
79. Perdomo CM, Ezponda A, Núñez-Córdoba JM, et al. Transient elastography and serum markers of liver fibrosis associate with epicardial adipose tissue and coronary artery calcium in NAFLD. *Sci Rep*. 2022;12(1):6564.
80. Lee J, Kim HS, Cho YK, et al. Association between noninvasive assessment of liver fibrosis and coronary artery calcification progression in patients with nonalcoholic fatty liver disease. *Sci Rep* 2020;10(1):18323.
81. Lu C, Chen Y, Zhang Y, Zhao X. Liver fibrosis scores and coronary artery disease: novel findings in patients with metabolic dysfunction-associated fatty liver disease. *Diabetes Metab Syndr Obes*. 2023;16:2627-2637.
82. Dogan S, Celikbilek M, Yilmaz YK, et al. Association between liver fibrosis and coronary heart disease risk in patients with nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. 2015;27(3):298-304.
83. Ballestri S, Mantovani A, Baldelli E, et al. Liver fibrosis biomarkers accurately exclude advanced fibrosis and are associated with higher cardiovascular risk scores in patients with NAFLD or viral chronic liver disease. *Diagnostics*. 2021;11(1):98.
84. Higashiura Y, Tanaka M, Mori K, et al. High fibrosis-4 index predicts the new onset of ischaemic heart disease during a 10-year period in a general population. *Eur Heart J Open*. 2022;2(3):oeac030.
85. Friedrich-Rust M, Schoelzel F, Maier S, et al. Severity of coronary artery disease is associated with non-alcoholic fatty liver disease: a single-blinded prospective mono-center study. *PloS One*. 2017;12(10):e0186720.
86. Nunohiro T, Furukawa K, Uchida M, et al. Liver stiffness assessed by Fibrosis-4 index predicts heart failure in AMI patients. *Eur Heart J*. 2022;43(S1):i96.
87. Markus MRP, Baumeister SE, Stritzke J, et al. Hepatic steatosis is associated with aortic valve sclerosis in the general population: the study of health in pomerania (SHIP). *Arterioscler Thromb Vasc Biol*. 2013;33(7):1690-1695.
88. Bonapace S, Valbusa F, Bertolini L, et al. Nonalcoholic fatty liver disease is associated with aortic valve sclerosis in patients with type 2 diabetes mellitus. *PloS One*. 2014;9(2):e88371.
89. Di Minno MND, Di Minno A, Ambrosino P, Songia P, Tremoli E, Poggio P. Aortic valve sclerosis as a marker of atherosclerosis: novel insights from hepatic steatosis. *Int J Cardiol*. 2016;217:1-6.
90. Nabeta T, Myagmardorj R, Hirasawa K, et al. Prognostic value of nonalcoholic fatty liver disease in patients with severe aortic stenosis who underwent transcatheter aortic valve implantation. *Am J Cardiol*. 2023;186:176-180.
91. Sudo M, Shamekhi J, Sedaghat A, et al. Predictive value of the Fibrosis-4 index in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Clin Res Cardiol*. 2022;111(12):1367-1376.
92. Lazarus JV, Castera L, Mark HE, et al. Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice. *JHEP Rep*. 2023;5(1):100596.
93. Lemmer A, VanWagner LB, Ganger D. Assessment of advanced liver fibrosis and the risk for hepatic decompensation in patients with congestive hepatopathy. *Hepatology*. 2018;68(4):1633-1641.
94. Zeitouni M, Clare RM, Chiswell K, et al. Risk factor burden and long-term prognosis of patients with premature coronary artery disease. *J Am Heart Assoc*. 2020;9(24):e017712.
95. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017;390(10106):1981-1995.
96. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and

hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol*. 2023;78(3):471-478.
97. Jamialahmadi O, Tavaglione F, Rawshani A, Ljungman C, Romeo S. Fatty liver disease, heart rate, and cardiac remodelling: evidence from the UK biobank. *Liver Int*. 2023;43(6):1247-1255.
98. Mauvais-Jarvis F, Merz NB, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *Lancet*. 2020;396:565-582.
99. Lonardo A, Nascimbeni F, Ballestri S, et al. Sex differences in nonalcoholic fatty liver disease: state of the art and identification of research gaps. *Hepatology*. 2019;70(4):1457-1469.
100. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have a lower risk of nonalcoholic fatty liver disease but a higher risk of progression vs men: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(1):61-71.e15.
101. Eng PC, Forlano R, Tan T, Manousou P, Dhillo WS, Izzi-Engbeaya C. Non-alcoholic fatty liver disease in women – current knowledge and emerging concepts. *JHEP Rep*. 2023;5(10):100835.
102. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol*. 2021;17(1):47-66.
103. Sarkar M, Terrault N, Chan W, et al. Polycystic ovary syndrome (PCOS) is associated with NASH severity and advanced fibrosis. *Liver Int*. 2020;40(2):355-359.
104. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2006;91(1):48-53.
105. Kasarinaite A, Sinton M, Saunders PTK, Hay DC. The influence of sex hormones in liver function and disease. *Cell*. 2023;12(12):1604.
106. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nat Rev Endocrinol*. 2011;7(4):219-231.
107. Petta S, Eslam M, Valenti L, et al. Metabolic syndrome and severity of fibrosis in nonalcoholic fatty liver disease: an age-dependent risk profiling study. *Liver Int*. 2017;37(9):1389-1396.
108. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2021;161(5):1657-1669.
109. Sripongpun P, Kim WR, Mannalithara A, et al. The steatosis-associated fibrosis estimator score: a tool to detect low-risk NAFLD in primary care. *Hepatology*. 2022;77(1):256-267.
110. Knuuti J, Wijns W, Sarate A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
111. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
112. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373-498.
113. Hill SA, Balion CM, Santaguida P, et al. Evidence for the use of B-type natriuretic peptides for screening asymptomatic populations and for diagnosis in primary care. *Clin Biochem*. 2008;41(4–5):240-249.
114. Boursier J, Canivet CM, Costentin C, et al. Impact of type 2 diabetes on the accuracy of noninvasive tests of liver fibrosis with resulting clinical implications. *Clin Gastroenterol Hepatol*. 2023;21(5):1243-1251.e12.
115. Ballestri S, Mantovani A, Di Girolamo M, Baldelli E, Capitelli M, Lonardo A. Liver fibrosis in nonalcoholic fatty liver disease patients: noninvasive evaluation and correlation with cardiovascular disease and mortality. *Metab Target Organ Damage*. 2023;3:1.
116. Graupera I, Thiele M, Ma AT, et al. LiverScreen project: study protocol for screening for liver fibrosis in the general population in European countries. *BMC Public Health*. 2022;22(1):1385.
117. Ginès P, Thiele M, Graupera I, et al. Screening for fibrosis to diagnose liver diseases early: the LIVERSCREEN project. *Nat Med*. 2023;29(4):774-775.
118. Simon TG, Bamira DG, Chung RT, Weiner RB, Corey KE. Nonalcoholic Steatohepatitis is associated with cardiac remodeling and dysfunction. *Obesity*. 2017;25(8):1313-1316.
119. Gehrke N, Schattenberg JM. Metabolic inflammation—a role for hepatic inflammatory pathways as drivers of comorbidities in nonalcoholic fatty liver disease? *Gastroenterology*. 2020;158(7):1929-1947.e6.
120. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol*. 2020;5(4):362-373.
121. Tavaglione F, Jamialahmadi O, De Vincentis A, et al. Development and validation of a score for fibrotic nonalcoholic Steatohepatitis. *Clin Gastroenterol Hepatol*. 2023;21(6):1523-1532.e1.
122. Pennisi G, Enea M, Falco V, et al. Noninvasive assessment of liver disease severity in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes. *Hepatology*. 2023;78(1):195-211.
123. Younossi Z, Alkhouri N, Cusi K, et al. A practical use of noninvasive tests in clinical practice to identify high-risk patients with nonalcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2023;57(3):304-312.
124. Sanyal AJ, Foucquier J, Younossi ZM, et al. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. *J Hepatol*. 2023;78(2):247-259.
125. Kim BK, Tamaki N, Imajo K, et al. Head-to-head comparison between MEFIB, MAST, and FAST for detecting stage 2 fibrosis or higher among patients with NAFLD. *J Hepatol*. 2022;77(6):1482-1490.
126. Wang A, Li Z, Sun Z, et al. Heart failure with preserved ejection fraction and non-alcoholic fatty liver disease: new insights from bioinformatics. *ESC Heart Fail*. 2023;10(1):416-431.
127. Sato M, Kamada Y, Takeda Y, et al. Fetuin-A negatively correlates with liver and vascular fibrosis in nonalcoholic fatty liver disease subjects. *Liver Int*. 2015;35(3):925-935.
128. Tomita Y, Misaka T, Yoshihisa A, et al. Decreases in hepatokine Fetuin-A levels are associated with hepatic hypoperfusion and predict cardiac outcomes in patients with heart failure. *Clin Res Cardiol*. 2022;111(10):1104-1112.
129. Lonardo A, Ndrepepa G. Concise review: gamma-glutamyl transferase-evolution from an indiscriminate liver test to a biomarker of cardiometabolic risk. *Metab Target Organ Damage*. 2022;2:17.
130. Drenth JPH, Schattenberg JM. The nonalcoholic steatohepatitis (NASH) drug development graveyard: established hurdles and planning for future success. *Expert Opin Investig Drugs*. 2020;29(12):1365-1375.
131. Yang L, Hao Y, Boeckmans J, Rodrigues RM, He Y. Immune cells and their derived microRNA-enriched extracellular vesicles in nonalcoholic fatty liver diseases: novel therapeutic targets. *Pharmacol Ther*. 2023;243:108353.
132. Boeckmans J, Natale A, Rombaut M, et al. Anti-NASH drug development hitches a lift on PPAR agonism. *Cell*. 2020;9(1):37.
133. Papatheodoridi M, Pallini G, Aithal G, et al. Health-related quality of life in patients with nonalcoholic fatty liver disease: a prospective multi-center UK study. *Clin Gastroenterol Hepatol*. 2023;21(12):3107-3114.e3.
134. Johansson I, Joseph P, Balasubramanian K, et al. Health-related quality of life and mortality in heart failure the global congestive heart failure study of 23000 patients from 40 countries. *Circulation*. 2021;143(22):2129-2142.
135. Freeman JV, Simon DN, Go AS, et al. Association between atrial fibrillation symptoms, quality of life, and patient outcomes: results from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes*. 2015;8(4):393-402.

136. Sajobi TT, Wang M, Awosoga O, et al. Trajectories of health-related quality of life in coronary artery disease. *Circ Cardiovasc Qual Outcomes*. 2018;11(3):e003661.
137. Thrall G, Lane D, Carroll D, Lip GYH. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med*. 2006;119(5):448.e1-448.e19.
138. Luo F, Chapel G, Ye Z, Jackson SL, Roy K. Labor income losses associated with heart disease and stroke from the 2019 panel study of income dynamics. *JAMA Netw Open*. 2023;6(3):e232658.
139. Slavin SD, Khera R, Zafar SY, Nasir K, Warraich HJ. Financial burden, distress, and toxicity in cardiovascular disease. *Am Heart J*. 2021;238:75-84.
140. Lonardo A, Byrne CD, Targher G. Precision medicine approaches in metabolic disorders and target organ damage: where are we now, and where are we going? *Metab Target Organ Damage*. 2021;1:3.

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