Lonardo *et al. Metab Target Organ Damage* 2024;4:41
DOI: 10.20517/mtod.2024.42

Metabolism and Target Organ Damage

Review

Open Access

Liver fibrosis as a barometer of systemic health by gauging the risk of extrahepatic disease

Amedeo Lonardo[1,#], Stefano Ballestri[2,#], Gyorgy Baffy[3,#], Ralf Weiskirchen[4,#]

[1]Department of Internal Medicne Azienda, Ospedaliero-Universitaria di Modena (-2023), Modena 41100, Italy.
[2]Internal Medicine Unit, Hospital of Pavullo, Azienda USL of Modena, Modena 41026, Italy.
[3]Department of Medicine, VA Boston Healthcare System, Harvard Medical School, Boston, MA 02130, USA.
[4]Institute of Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry (IFMPEGKC), Rheinisch-Westfälische Technische Hochschule (RWTH), University Hospital Aachen, Aachen D-52074, Germany.
[#]Authors contributed equally.

Correspondence to: Prof. Amedeo Lonardo, Department of Internal Medicne Azienda, Ospedaliero-Universitaria di Modena (-2023), Via Giardini 1135, Modena 41100, Italy. E-mail: a.lonardo@libero.it

How to cite this article: Lonardo A, Ballestri S, Baffy G, Weiskirchen R. Liver fibrosis as a barometer of systemic health by gauging the risk of extrahepatic disease. *Metab Target Organ Damage* 2024;4:41. https://dx.doi.org/10.20517/mtod.2024.42

Received: 28 May 2024 **First Decision:** 21 Oct 2024 **Revised:** 26 Oct 2024 **Accepted:** 5 Nov 2024 **Published:** 15 Nov 2024

Academic Editor: Sonia Najjar **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

This review article proposes the theory that liver fibrosis, the abnormal accumulation of excessive extracellular matrix, is not just an indicator of liver disease but also a negative reflection of overall systemic health. Liver fibrosis poses a heavy financial burden on healthcare systems worldwide and can develop due to chronic liver disease from various causes, often due to sustained inflammation. Liver fibrosis may not generate symptoms and become apparent only when it reaches the stage of cirrhosis and is associated with clinically significant portal hypertension and leads to decompensation events or promotes the development of hepatocellular carcinoma. While chronic viral hepatitis and excessive alcohol consumption were once the primary causes of chronic liver disease featuring fibrosis, this role is now increasingly taken over by metabolic dysfunction-associated steatotic liver disease (MASLD). In MASLD, endothelial dysfunction is an essential component in pathogenesis, promoting the development of liver fibrosis, but it is also present in endothelial cells of other organs such as the heart, lungs, and kidneys. Accordingly, liver fibrosis is a significant predictor of liver-related outcomes, as well as all-cause mortality, cardiovascular risk, and extrahepatic cancer. Physicians should be aware that individuals seeking medical attention for reasons unrelated to liver health may also have advanced fibrosis. Early identification of these at-risk individuals can lead to a more comprehensive assessment and the use of various treatment options, both approved and investigational, to slow or reverse the progression of liver fibrosis.

Keywords: Biomarkers, cancer, cardiovascular disease, diabetes, liver fibrosis, MASH, MASLD mortality, vibration-controlled transient elastography

DEFINITIONS, HISTORY, BURDEN, AND AIM

Liver fibrosis is defined as the accumulation of excessive collagen and other extracellular matrix (ECM) proteins[1]. It serves to preserve tissue integrity by circumscribing offending agents and results from ongoing liver insults of viral, toxic, autoimmune, genetic, or metabolic origin. Therefore, it is a final common outcome of all types of chronic liver disease (CLD) regardless of etiology[2,3]. Initially clinically silent and insidious, advanced liver fibrosis is associated with profoundly distorted hepatic architecture and markedly compromised liver physiology[1,4]. When it progresses to cirrhosis, advanced fibrosis predisposes to portal hypertension, liver failure, and hepatocellular carcinoma (HCC), and may necessitate liver transplantation in some cases[1].

Hepatic stellate cells (HSCs), also known as "Sternzellen" or "Ito cells", were first described by von Kupffer in 1876 (as reported by Geerts *et al.* and Sufleţel *et al.*)[5,6] and well characterized in humans, fishes, monkeys, and rats by Ito *et al.* and Tanuma, *et al.* in the 1950s[7-10]. In the 1980s, HSCs were identified as the main collagen-producing intrahepatic cell types, with their dramatic phenotypic changes associated with cell activation and the development of fibrogenic activity[11]. However, other cell types, such as portal myofibroblasts and cells of bone marrow origin, have also been acknowledged to exhibit fibrogenic potential[12,13]. Clinically, liver fibrosis may progress with remarkable individual variability due to genetic and environmental risk modifiers that modulate the risk of developing fibrosis and the speed of its progression in the context of CLD of various etiologies[14].

Initially believed to be an irreversible condition, early cirrhosis has instead been proven to be reversible after the removal of the inciting agent[15-17]. This discovery has sparked the interest of clinical and translational researchers in identifying antifibrotic therapies that target HSCs in preclinical models, antifibrotic programs, and clinical trials involving patients with CLD[1,18].

The severe clinical outcomes associated with advanced liver fibrosis, namely portal hypertension, liver failure, and HCC, largely explain why cirrhosis represents a leading cause of mortality and impaired quality of life worldwide. It imposes a major and ever-increasing financial burden on healthcare systems globally[19-21].

It is widely acknowledged that the stage of fibrosis, ranging from F0 (absence of fibrosis) to F4 (cirrhosis), plays a crucial role in determining the prognosis of CLD and liver-related outcomes[3]. Therefore, this review article will specifically address the recent recognition that the presence and severity of liver fibrosis are strongly associated with, and probably determine, significant extrahepatic outcomes, such as the risk of developing cardiometabolic events and cancer.

ETIOLOGY AND PATHOMECHANISM OF LIVER FIBROSIS

Recently, we have witnessed major epidemiological trends owing to the prevailing burden of CLD due to metabolic dysfunction. These types of CLD, previously alluded to as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), are now renamed metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). NAFLD/NASH is a diagnosis of exclusion (nonalcoholic), while MAFLD/MASH is a diagnosis based on positive criteria (metabolic dysfunction); additionally, the adjective "steatotic" replaces "fatty liver" to avoid any concerns regarding the risk of stigmatization[22]. Although NAFLD and MASLD are differently defined, they identify an almost identical patient population[23]. Therefore, these two nomenclatures will be used

interchangeably in the present review. While the global burden of cirrhosis is higher in men, the age-standardized incidence and mortality rates of MASH cirrhosis in women are now comparable to those of men[24]. A study conducted in Sweden during the years 2004 to 2017 found a shift among the leading etiologies of cirrhosis, with an approximately 30% relative reduction in cirrhosis related to infection with Hepatitis C Virus (HCV) contrasted with a more than 150% increase in NAFLD-cirrhosis, while alcohol-related cirrhosis maintained its leading position[25]. These findings clearly illustrate the notion that a complex mixture of sex, environmental factors (including higher rates of eradication of HCV infection with direct-acting antivirals), and lifestyle habits (i.e., drinking and eating habits, sedentary behavior) determine the outcomes of fibrosing CLD[26].

Mechanistic concepts of liver fibrosis

In acute liver injury, fibrosis is a self-limited and reversible multicellular repair mechanism that provides mechanical scaffolding to replace dead cells and guide reparative processes[27,28]. This response is characterized by the activation and transdifferentiation of HSCs into myofibroblasts[29]. In healthy livers, HSCs are non-proliferative perisinusoidal cells with a star-like shape and many cytoplasmic lipid droplets[30]. However, following liver injury, HSCs progressively lose their typical stellate morphology and lipid droplets while secreting abundant components of the ECM and pro-inflammatory mediators[3]. Persistent HSC activation leads to ECM deposition that overcomes fibrosis dissolution, resulting in the progression of liver fibrosis[31]. An essential trigger of HSC activation is the loss of tonic inhibition due to diminished availability of nitric oxide (NO) caused by endothelial dysfunction[32].

The high number of activated HSCs and contractibility of myofibroblasts impair sinusoidal blood flow, leading to the depletion of oxygen and nutrients, which contributes to liver dysfunction in advanced stages of fibrosis[3]. Different subpopulations of macrophages (M1 expressing pro-inflammatory cytokines, and M2 anti-inflammatory mediators) coincide in the liver and contribute to different phases of liver fibrosis[33]. The activation of macrophages fuels a closed circuit of ongoing inflammation by secreting cytokines to stimulate HSCs, which, in turn, produce pro-inflammatory cytokines to perpetuate pro-fibrotic macrophage activity[34]. Additionally, HSCs directly interact with immune cells via adhesion molecules, resulting in amplified pro-fibrogenic response[35]. Lymphocytes also participate in the fibrogenic process, as demonstrated by the finding that the depletion of intrahepatic lymphocytes results in impaired liver fibrosis[3]. It is increasingly recognized that HSC activation in MASLD involves mechanosensitive components from shear, compression, and stretch forces related to steatosis, hepatocellular ballooning, and inflammatory infiltration leading to impaired microcirculation, feedback amplification loops, and a pro-fibrogenic milieu[36].

The role of endothelial dysfunction as a main driver of liver fibrosis is remarkable, since recognition of this relationship may offer preventive and therapeutic targets in early-stage MASLD. The sinusoidal endothelium holds a unique position as it is directly exposed to vasoregulatory, pro-inflammatory, immunogenic, and toxic substances from the gut microbiota via the portal circulation[37]. While liver sinusoids represent a highly specialized form of endothelium, liver sinusoidal endothelial cells (LSECs) share structural, functional, and regulatory features with endothelial cells of other organs such as the heart, lungs, and kidneys[38]. From a holistic perspective, vascular endothelium can be viewed as the gatekeeper of organ function, while its dysfunction is associated with a wide range of ailments, playing a prominent role in the pathogenesis of cardiometabolic disorders[39]. Arteriolar dysfunction and the propensity for atherosclerosis have been strongly associated with obesity, diabetes, dyslipidemia, and MASLD. Diabetic nephropathy is a vascular manifestation of metabolic dysregulation in the kidneys. Activation of angiocrine signaling pathways is a prerequisite for the continual growth of digestive cancers, disproportionately seen in obesity-associated disorders such as MASLD. The emergence of liver fibrosis from the dysfunction of LSECs

is, therefore, a plausible indicator of the overall health of the integrated endothelial system. In other words, the extent to which liver fibrosis reflects the disrupted sinusoidal homeostasis may also gauge the dysfunction of vascular endothelium across the entire organism.

Intestinal dysbiosis, defined as decreased diversity of intestinal microbiota, is involved in the progression of liver fibrosis through a variety of mechanisms including disrupted intestinal homeostasis, increased intestinal permeability, relative overgrowth of potentially pathogenic bacteria, delivery of pathogen-associated molecular patterns, and intestinal deconjugation of bile acids, leading to increased production of secondary bile acids[3]. The so-called gut microbiota - bile acid axis is intricately involved with hepatic fibrogenesis[40]. For example, patients with liver fibrosis exhibit significant gut dysbiosis, and increased intestinal permeability allowing bacteria or bacterial antigens to reach the liver from the intestinal lumen via the portal blood, thereby contributing to fibrosis progression[41,42]. Additionally, subjects with liver fibrosis exhibit a dysregulated metabolism of bile acids, which is also involved in hepatic fibrogenesis via multiple signaling pathways[40]. Of interest, the gut microbiota affects bile acid metabolism by influencing both bile acid synthesis and conversion of primary bile acids to secondary bile acids via various catalyzed chemical reactions[43]. In their turn, bile acids affect the abundance and composition of the gut microbiota, and act as chemical messengers bridging the liver and intestine[44]. These fundamental changes do not occur in isolation; instead, they represent pathophenotypes[45] that impact other organs and overall health.

Studies have identified the molecular signaling pathways involved in liver fibrogenesis, paving the way for innovative therapeutics targeting sterile inflammation[46]. These pathways included platelet-derived growth factor (PDGF) signaling[47], transforming growth factor-β (TGF-β) signaling[48], oxidative stress, and the Inflammasome (NLRP3)-Caspase1 pathway, which have been described in detail elsewhere[3,49,50]. For example, the understanding that PDGF is produced by platelets suggests the use of direct oral anticoagulants and aspirin as antifibrotic agents[51-53].

ASSESSMENT OF LIVER FIBROSIS

Liver fibrosis can be either assessed invasively through liver biopsy or non-invasively using "wet" (fibrosis biomarkers) or "dry" (elastography) techniques[54]. While liver biopsy is considered the "gold standard" for diagnosing and evaluating the severity of liver disease, including staging liver fibrosis, it is expensive, not always well-received by patients, and carries serious risks (3% hospitalization and 0.3% mortality)[55]. Additionally, there is a risk of sampling error in up to one-fourth of patients with MASLD, as histopathological lesions may be evenly distributed in the liver[56]. Due to these limitations, liver biopsy is not ideal for epidemiological studies or monitoring treatment responses over time in clinical settings. It should be reserved for cases with diagnostic uncertainties or for patients at high risk of significant liver fibrosis.

Biomarkers of liver fibrosis

Several liver fibrosis biomarkers are available. Some biomarkers, such as FibroTest, FibroMeter NAFLD, enhanced liver fibrosis (ELF) test, and others, are based on the direct measurement of ECM products, but they are not widely available and may incur payment as they are patented tools. Other freely and universally available biomarkers are based on a combination of biometric and laboratory data, including the aspartate to alanine amino-transferase (AST/ALT) ratio, AST-to-platelet ratio Index (APRI), fibrosis-4 (FIB-4) index, Forns index, BARD score, and Hepamet fibrosis score (HFS)[4]. Almost all these biomarkers have achieved a diagnostic accuracy of at least 0.80 for advanced fibrosis (F3-F4) compared to liver biopsy[4,57]. Liver fibrosis biomarkers have a high negative predictive value (more than 80%-90%) in excluding advanced fibrosis/cirrhosis, while their positive predictive value is suboptimal[57,58]. A relevant percentage of patients fall into

an indeterminate zone between cut-off values ruling out or ruling in advanced fibrosis[55]. False positive results may occur in patients with normal alanine aminotransferase levels[58] and accuracy may be lower in diabetic patients[59]. FIB-4 is the best-validated fibrosis biomarker for MASLD patients[60].

Elastometry

Elastographic techniques estimate liver fibrosis through liver stiffness measurement (LSM) and are more accurate than biomarkers for non-invasive staging of liver fibrosis[58,61]. There are three main LSM methods: (1) vibration-controlled transient elastography (VCTE) (patented as Fibroscan®); (2) shear wave elastography (SWE) including point-SWE (pSWE) such as acoustic radiation force impulse (ARFI) and two-dimensional-SWE (2D-SWE) such as supersonic shear imaging (SSI); and (3) magnetic resonance (MR) elastography (MRE)[62,63]. The accuracy of VCTE and SWE measurements may be limited by overweight/obesity, liver inflammation, congestion, and cholestasis, which can increase liver stiffness independently of fibrosis[62,63]. MRE has the highest accuracy among elastographic techniques and is not influenced by obesity or other confounders, but it is expensive and not widely available[58].

LSM by VCTE can be used to diagnose compensated CLD by ruling in (> 15 kPa) or ruling out (< 10 kPa) the condition, as well as to rule out clinically significant portal hypertension (< 15 kPa and normal platelet count) according to the Baveno VII consensus[64]. Available evidence suggests that combining biomarkers and elastographic techniques increases the accuracy of non-invasive assessment of liver fibrosis.

Current guidelines suggest that patients with MASLD who are at intermediate to high risk of advanced fibrosis (FIB-4 ≥ 1.3) and have a LSM ≥ 8 should be evaluated for liver biopsy or MRE. Those with low risk (FIB-4 < 1.3 or LSM < 8) do not need a referral and can be reassessed every 2 years[58,65,66]. FAST (FibroScan-AST) score may improve the detection of fibrotic MASH[67]. A recent meta-analysis showed that a sequential combination of FIB-4 and LSM-VCTE with lower cut-offs to rule out advanced fibrosis (< 1.3; < 8.0 kPa) and upper cut-offs to rule in cirrhosis (≥ 3.48; ≥ 20.0 kPa) can reduce the need for liver biopsies from 33% to 19% in MASLD patients[68].

Limitations and future directions

Historically developed to identify significant fibrosis in chronic hepatitis C, subsequently refined for use in NAFLD and further adapted for prognostication in CLD, those biomarkers discussed above have several limitations including variability, inadequate accuracy, and risk factors for error[69]. Of concern is that these biomarkers were not designed to reflect the dynamic process of fibrogenesis, accurately differentiate among adjacent disease stages, identify MASH, or longitudinally follow changes in fibrosis occurring because of either the natural course of disease or treatment[69].

Age is a confounding factor for the accurate diagnosis of advanced fibrosis with biomarkers[70]. Additionally, patients with type 2 diabetes (T2D) represent an area of specific concern and specific biomarkers of fibrosis should be used in this patient population, for whom a decreased accuracy of fibrosis biomarkers is noted[59]. Similarly, obesity impacts the accuracy of non-invasive diagnosis of liver fibrosis[71] and is a common reason for failures to measure liver elastometry, although the XL probe may permit successful measurements in most obese subjects[72].

Understanding the strengths and limitations of these non-invasive tests will enable more judicious interpretation in the clinical context, while prompting precision medicine approaches to identify the best technique to assess liver fibrosis in any given individual.

LIVER FIBROSIS IMPACTS ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY

The severity of liver fibrosis modulates the risk of some of the principal causes of death among MASLD patients, including cardiovascular disease, extrahepatic cancer, and liver-related conditions[73,74], as discussed below.

Liver fibrosis and all-cause mortality

It is universally acknowledged that liver fibrosis is strongly linked to liver-related outcomes[75]. However, given that MASLD has multifactorial pathogenesis (often associating genetic predisposition with endocrine and metabolic dysfunction) and multisystem extension[76], it is logical to postulate that surrogate markers of liver fibrosis are a barometer of general health status. In agreement, all-cause mortality was already associated with the extent of fibrosis by Dulai *et al.* in 2017[77]. Mechanistically, this finding is likely due to the association of liver fibrosis with cardiovascular mortality and extrahepatic cancers, as discussed below. Recent studies have pointed out an association of liver fibrosis with all-cause mortality [Table 1][78-81].

Liver fibrosis and cardiovascular mortality

A large body of evidence indicates that, irrespective of the method used to identify it, i.e., either algorithms or imaging techniques, liver fibrosis is associated with cardiovascular mortality in MASLD independent of confounding factors [Table 2][78,82-91].

Liver fibrosis and cardiovascular disease are interconnected through several mechanisms, primarily involving inflammation, oxidative stress, and metabolic dysregulation[92-94]. In liver fibrosis, the accumulation of ECM proteins leads to scar tissue formation, which can disrupt normal liver function. This condition often results in increased portal hypertension and systemic inflammation, contributing to endothelial dysfunction, a key factor in cardiovascular disease[95,96]. Additionally, liver fibrosis is associated with altered lipid metabolism and insulin resistance, which can exacerbate atherogenic processes and promote coronary artery disease[97]. Furthermore, the release of pro-inflammatory cytokines from fibrotic liver tissue can lead to systemic effects that increase the risk of cardiovascular events. Overall, the interplay between these two conditions highlights the importance of addressing liver health as part of cardiovascular disease prevention and management strategies.

Liver fibrosis and extrahepatic cancers

Compared to data pertaining to cardiovascular mortality, data on the association of NAFLD with extrahepatic cancers appear to be less robust [Table 3][98-106].

According to Thomas *et al.*, unlike HCC, the higher risk of extrahepatic cancer in NAFLD occurs independent of the liver fibrosis stage[104,107]. Although evidence on the excess risk of extrahepatic cancer among NAFLD subjects compared to NAFLD-free controls is limited, the disproportionate burden of extrahepatic cancer relative to HCC in NAFLD should be emphasized[107] as this may shape precision medicine follow-up protocols. Accordingly, additional investigation is warranted.

ASSESSING LIVER FIBROSIS TO GAUGE CARDIOVASCULAR RISK

Liver steatosis of viral (such as HCV) and/or metabolic (such as MASLD) origin has been strongly associated with insulin resistance and cardiovascular risk[108,109]. A large meta-analysis (36 longitudinal studies; nearly 6 million middle-aged subjects; 6.5 years of follow-up) has shown that MASLD (diagnosed by imaging, ICD diagnosis coding, or histology) is associated with increased incidence of fatal or non-fatal cardiovascular disease (CVD) events, more pronounced in advanced MASLD, especially in higher fibrosis stages[110].

Table 1. Recent studies illustrating the notion that surrogate biomarkers of liver fibrosis predict all-cause mortality

Author, year [ref]	Study population	Indexes of liver fibrosis	Findings	Conclusions
Ciardullo *et al.*, 2024[78]	4,229 MASLD individuals (free from a medical history of heart failure) from the general population who participated in the 1999-2004 NHANES.	FIB-4.	At the LRA, elevated FIB-4 (≥ 2.67) and elevated NT-ProBNP levels (≥ 125 pg/mL) were both independently associated with higher risks of all-cause mortality (HR: 2.2, 95%CI: 1.5-3.2 and HR: 1.6, 95%CI: 1.4-2.0, respectively) irrespective of age, sex, and obesity.	In subjects with MASLD, both FIB-4 and NT-ProBNP were independently associated with higher mortality.
Collier *et al.*, 2023[79]	UK retrospective cohort study of 12,589 patients, with follow-up from January 2012 until November 2021.	FIB-4, NFS, and APRI.	The overall adjusted all-cause mortality HRs [95%CI: in the high-risk of fibrosis compared to low-risk groups were 3.69 (1.95-2.75), 4, 2.32 (2.88-4.70), and 3.92 (2.88-5.34) for FIB-4, NFS, and APRI, respectively].	All three fibrosis risk scores were positively associated with all-cause mortality in people with T2DM.
Choi *et al.*, 2022[80]	7,702 Korean adults enrolled in the Dong-gu Study.	NFS, FIB-4, APRI, and BARD score.	Overall mortality increased in parallel with increasing NFS level (aHR: 4.3, 95%CI: 3.3-5.5 for high risk *vs.* low risk), increasing FIB-4 level (aHR: 3.5, 95%CI: 2.9-4.4 for high risk *vs.* low risk), and increasing APRI level (aHR: 3.5, 95%CI: 2.1-5.8 for high risk *vs.* low risk) but not with BARD score.	NFS, FIB-4, and APRI showed a significant relationship with the overall mortality.
Vieira Barbosa *et al.*, 2022[81]	Analysis of a cohort of 81,108 subjects extracted from a US real-world nationwide database with data of 30 million individuals.	FIB-4.	At LRA, FIB-4 ≥ 2.67 was significantly and independently associated with all-cause mortality (HR: 2.49, 95%CI: 2.20-2.82, $P < 0.001$).	FIB-4 ≥ 2.67 strongly predicted all-cause mortality independently of confounding factors.

aHR: Adjusted hazard ratio; APRI: aspartate aminotransferase to platelet ratio index; BARD: body mass index, AST/ALT ratio, and presence of diabetes; CI: confidence interval; FIB-4: Fibrosis-4; HR: hazard ratio; LRA: logistic regression analysis; NFS: nonalcoholic fatty liver disease fibrosis score; NHANES: National Health and Nutrition Examination Survey; NAFLD: nonalcoholic fatty liver disease; NT-ProBNP: N-terminal pro-B-type natriuretic peptide; T2DM: type 2 diabetes mellitus; UK: United Kingdom; US: United States; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Liver biopsy

Two recent prospective histological studies investigated the association between liver fibrosis and cardiometabolic risk with positive findings. The first study, which included 285 MASLD patients with a median follow-up time of 5.2 years, found that F3-F4 fibrosis on biopsy and a higher NAFLD fibrosis score (but not FIB-4, AST/ALT, APRI) independently predicted incident CVD at multivariable analysis [sub hazard ratio (HR) 2.86, 95%CI: 1.36-6.04], after adjusting for traditional risk factors and cardiovascular risk scores[111]. The second study, which included an even larger sample (2,850 MASLD patients and 10,648 controls) with a longer follow-up time (median 13.6 years), reported a significantly increased risk of incident major adverse cardiovascular events (MACE) in MASLD compared to controls (24.3 *vs.* 16.0/1,000 person-years; adjusted hazard ratio (aHR) 1.63, 95%CI: 1.56-1.70), including coronary heart disease (CHD), stroke, heart failure (HF), or cardiovascular (CV) mortality rates. The risk of MACE increased progressively with worsening MASLD (MASH without fibrosis: Ahr = 1.52; non-cirrhotic fibrosis: aHR 1.67; cirrhosis: aHR 2.15)[112]. Conversely, a previous smaller study with a sample size of 603 biopsy-proven MASLD patients matched to 6,269 controls found that MASLD, but not histological parameters, independently predicted incident CVD (HR: 1.54, 95%CI: 1.30-1.83) during a mean follow-up of 18.6 years[113].

Fibrosis biomarkers

The association between non-invasively assessed liver fibrosis (specifically fibrosis biomarkers and elastographic techniques) and CVD has been extensively reviewed elsewhere[4].

Advanced fibrosis assessed by fibrosis biomarkers [FIB-4, Forns index, nonalcohol fatty liver disease fibrosis score (NFS), and HFS] as well as liver biopsy or LSM is associated with increased CV risk scores, such as 10-year atherosclerotic cardiovascular disease (ASCVD) risk, Systematic COronary Risk Evaluation (SCORE)

Table 2. Recent evidence linking liver fibrosis to mortality owing to cardiovascular causes

Author, year [ref]	Study population and follow-up	Assessment of liver fibrosis	Findings	Conclusions
Baik *et al.*, 2020[82]	2,504 patients with first-ever IS or TIA recruited were followed for a median of 1.2 years.	Advanced liver fibrosis was defined as a FIB-4 > 3.25.	Advanced liver fibrosis was associated with an increased risk of all-cause mortality (HR: 3.98, 95%CI: 2.40-6.59), CVM (HR: 4.48, 95%CI: 1.59-12.65), and IS recurrence (HR: 1.95, 95%CI: 1.05-3.65).	Advanced liver fibrosis is associated with unfavorable long-term prognosis, including increased risk of CVM and overall mortality.
Cao *et al.*, 2021[83]	3,718 consecutive patients with previous MI were enrolled and followed for a mean of 47.4 ± 24.8 months.	FIB-4, NFS, Forns score, HUI score, and BARD score.	Regarding cardiovascular outcomes, aHRs of the highest group of FIB-4, NFS, Forns score, HUI score, and BARD score were 1.75 (1.32-2.33), 2.37 (1.70-3.33), 2.44 (1.61-3.73), 1.58 (1.16-2.14), and 1.27 (1.03-1.57), respectively, *vs.* the lowest score group. These liver fibrosis scores were also independent predictors of CVM and all-cause mortality.	Liver fibrosis scores independently predict CVM and all-cause mortality.
Jin *et al.*, 2021[84]	5,143 consecutive subjects with stable CAD were followed up for 7 years.	NFS, FIB-4.	Subjects with intermediate and high NFS and FIB-4 values had a higher risk of CVEs and CVM.	NFS and FIB-4 scores are associated with CVEs and CVM.
Oh *et al.*, 2021[85]	4,163 subjects from the KGES were followed biannually over 16 years.	FIB-4, NFS, and APRI.	Both FIB-4 and NFS were significantly associated with liver-specific mortality, particularly in subjects with BMI < 25 kg/m^2, but not CVM.	FIB-4 and NFS, while predicting liver-specific mortality, do not predict CVM.
Chung *et al.*, 2022[86]	1,607,232 T2DM subjects were enrolled and followed up for a mean of 6.9 years.	AAR.	Compared to those with AAR < 0.8, overall mortality and CVM significantly increased in those with AAR ≥ 1.4 in both non-CKD (HR: 2.16, 95%CI: 2.06-2.25 and HR: 1.93, 95%CI: 1.73-2.15) and CKD groups (HR: 2.36, 95%CI: 2.20-2.52 and HR: 2.57, 95%CI: 2.21-2.98).	High AAR is associated with CVM and overall mortality.
Yan *et al.*, 2022[87]	Metanalytic review comprising 12 cohort studies, totaling 25,252 individuals with CVD.	FIB-4, NFS.	The highest values of FIB-4 or NFS were associated with a greater risk of CVM (FIB-4, HR: 2.07, 95%CI: 1.19-3.61, I^2 = 89%; NFS, HR: 3.72, 95%CI: 2.62-5.29, I^2 = 60%) and all-cause mortality (FIB-4, HR: 1.81, 95%CI: 1.24-2.66, I^2 = 90%; NFS, HR: 3.49, 95%CI: 2.82-4.31, I^2 = 25%).	Among CVD patients, higher levels of FIB-4 and NFS are associated with a higher risk of CVM and all-cause mortality.
Mascherbauer *et al.*, 2022[88]	1,075 subjects were included (972 patients, 50 controls, 53 participants with transient elastography). Follow-up duration: 58 ± 31 months.	T1-times on standard CMR.	High hepatic T1-times were associated with a higher risk of events (aHR: 1.66, 95%CI: 1.45-1.89) per 100 ms increase; P < 0.001), even when adjusted for confounding factors. On ROC analysis and RCS, a hepatic T1-time > 610 ms was associated with excessive risk.	Hepatic T1-times > 610 ms on standard CMR scans independently predict CVM.
Lee *et al.*, 2023[89]	35,531 individuals with suspected NAFLD, from the KNAHNES 2007-2015, and followed for a mean 8.1-year follow-up.	FIB-4, NFS.	When NFS and FIB-4 were combined, the high NFS + high FIB-4 group was significantly associated with higher odds of all-cause mortality (HR: 1.85, 95%CI: 1.42-2.43) and CVN (HR: 2.04, 95%CI: 1.23-3.39) compared to the low NFS + low FIB-4 controls, although these associations were attenuated among those with high-quality diet.	In NAFLD, advanced liver fibrosis independently predicts all-cause mortality and CVM. However, this association is affected by a high-quality diet.
Seo *et al.*, 2023[90]	46,456 individuals from the KNANHES database were included, with a median follow-up period of 8.6 years.	FIB-4.	FIB-4, ≥ 2.67 was associated with all-cause mortality (HR: 1.64, 95%CI: 1.23-2.18), CVM (HR: 2.96, 95%CI: 1.60-5.46), and LRM (HR: 10.50, 95%CI: 4.70-23.44), but not cancer mortality, after adjusting for confounding factors.	FIB-4 is strongly associated with all-cause, CVM, and LRM.
Guan *et al.*, 2023[91]	Cross-sectional study of 3,471 subjects with T2D from the NHANES database.	FIB-4.	The risk of all-cause mortality (HR: 1.24, 95%CI: 1.17-1.32) and CVM (HR: 1.17, 95%CI: 1.04-1.31) increased with each FIB-4 SD increase after full adjustment. Stratified analysis showed that FIB-4 was a risk factor for individuals > 60 years old (HR: 1.14, 95%CI: 1.01-1.29).	FIB-4 is associated with all-cause and CVM in the T2D population, and this association is significantly affected by age.
Ciardullo *et al.*, 2024[78]	4,229 MASLD subjects (free from a history of HF heart failure who participated in the 1999-2004 cycles of the NHANES and were followed	FIB-4.	Both FIB-4 ≥ 2.67 and NT-ProBNP levels ≥ 125 pg/mL were independently associated with higher all-cause mortality (HR: 2.1, 95%CI: 1.2-3.7) and CVM (HR: 2.1, 95%CI: 1.5-2.9) irrespective of age, sex, and obesity.	Both FIB-4 and NT-ProBNP are independently associated with higher mortality among MASLD subjects, supporting the combined use of these

	over a median of 15.6 years.	biomarkers to risk-stratify patients.

AAR: AST/ALT ratio; aHR: adjusted HR; BARD: BMI, AST/ALT ratio, diabetes; APRI: aspartate aminotransferase to platelet ratio index; CAD: coronary artery disease; CKD: chronic kidney disease; CI: confidence interval; CMR: cardiac magnetic resonance; CVD: cardiovascular disease; CVEs: cardiovascular events; CVM: cardiovascular mortality; FIB-4: Fibrosis 4; HF: heart failure; HR: hazard ratio; HUI: health utility index; IS: ischemic stroke; NHANES: National Health and Nutrition Examination Survey; KNHANES: Korea National Health and Nutrition Examination Survey; KGES: Korean Genome and Epidemiology Study; KTRs: kidney transplant recipients; LRM: liver-related mortality; MI: myocardial infarction; NFS: nonalcohol fatty liver disease fibrosis score; NT-ProBNP: N-terminal pro-B-type natriuretic peptide; RCS: restricted cubic splines; ROC: receiver operating characteristic; SD: standard deviation; TIA: transient ischemic attack; T2D: type-2-diabetes; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

model, and the Framingham risk score (FRS)[57,114,115]. Advanced fibrosis assessed by liver fibrosis biomarkers (FIB-4 and NAFLD fibrosis score) has been significantly and independently associated with subclinical atherosclerosis [high-risk carotid intima-media thickness (cIMT) ≥ 1.2 mm] in patients with biopsy-proven MASLD. The diagnostic performance of biomarkers was like that of histological fibrosis staging[116]. Interestingly, two recent large sample meta-analyses have shown that FIB-4 and NFS independently predicted incident CVD in MASLD patients, as well as in subjects with established CVD, including CHD, nonvalvular atrial fibrillation (AF), and HF[87,117].

A longitudinal study of the UK Biobank cohort consisting of 325,129 participants with a median follow-up of 12.8 years, revealed that metabolic dysfunction-associated fatty liver disease (MAFLD) as defined by fatty liver index (FLI) significantly predicted the occurrence of myocardial infarction (MI) (HR: 1.35, 95%CI: 1.29-1.41) and stroke (HR: 1.26, 95%CI: 1.18-1.33). Importantly, there was a clear association between liver fibrosis biomarkers (NFS/FIB-4) and the risk of MI and stroke within specific MAFLD subtypes, such as diabetics and overweight patients with metabolic abnormalities[118].

Some studies have specifically explored the association between biomarkers of liver fibrosis and CVD in patients with type 2 diabetes mellitus (T2DM). In a population of 120,256 patients with new-onset T2DM, persistent advanced liver fibrosis determined by the BARD score was associated with increased risk of CVD (such as stroke and HF) and mortality. Conversely, regression of liver fibrosis was associated with a decreased risk of CVD and mortality[119]. Higher FIB-4 scores have been significantly associated with various CVD events such as MACE, hospitalization for HF/CV death, CV death, and hospitalization for HF among 8,246 patients with T2DM and ASCVD included in a post-hoc analysis of the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV)[120].

Cross-sectional studies have found that target organ damage in T2DM, such as diabetic nephropathy, retinopathy, or neuropathy, was independently associated with liver fibrosis staging assessed by FIB-4[121,122].

A milestone meta-analysis showed that MASLD is associated with an increased risk of prevalent AF (overall) and incident AF (only in T2DM)[123]. Recent data suggest that liver fibrosis may drive AF risk in patients with fatty liver. Higher FIB-4 has been significantly associated with an increased risk of AF independently of cardiometabolic risk factors (aOR 2.26; 95%CI: 1.74-2.92) in MASLD patients[124]. Intermediate-high NFS and FIB-4 independently predicted AF recurrence in NAFLD patients[125]. Advanced baseline liver fibrosis assessed by NFS has been significantly associated with incident new-onset AF among patients with preserved ejection fraction HF[126].

MASLD is associated with an increased risk of incident HF, as confirmed by recent meta-analytic studies[127,128]. The FIB-4 score has been positively and significantly correlated with serum BNP levels,

Table 3. Recent studies addressing the risk of extrahepatic cancers among those with NAFLD

Author, year [Ref]	Method	Types of cancers associated with NAFLD	Conclusion
Kim *et al.*, 2017[98]	Historical cohort study of 25,947 subjects (33.6% of whom with NAFLD) followed up for a median of 7.5 years at a tertiary hospital in South Korea.	Further to HCC, NAFLD was strongly associated with CRC in males (HR: 2.01, 95%CI: 1.10-3.68; $P = 0.02$) and BRC in females (HR: 1.92, 95%CI: 1.15-3.20, $P = 0.01$).	A high NFS and a high FIB-4 score showed a strong association with the development of all cancers and HCC.
Peleg *et al.*, 2018[99]	Single-center retrospective study of 32 subjects followed up for a mean time of 100 months.	At MVA, the occurrence of malignancies was associated with higher APRI ($P < 0.001$), FIB-4 ($P < 0.001$), and NFS ($P = 0.008$) scores, but not with histologically determined advanced fibrosis ($P = 0.105$).	In NAFLD patients, non-invasive scoring systems are good predictors of the development of hepatic and EHCs.
Liu *et al.*, 2020[100]	Meta-analysis of 26 studies.	CRC and adenomas (OR: 1.72, 95%CI: 1.40-2.11 and OR: 1.37, 95%CI: 1.29-1.46, respectively). ICC and ECC (OR: 2.46, 95%CI: 1.77-3.44 and OR: 2.24, 95%CI: 1.58-3.17, respectively). BRC (OR: 1.69, 95%CI: 1.44-1.99) was associated with NAFLD. Additionally, NAFLD was also tightly associated with the risk of GC, PAC, PRC, and EC.	NAFLD is one of the influencing factors during the clinical diagnosis and treatment of EHCs.
Lee *et al.*, 2020[101]	Retrospective analysis of 8,120,674 Koreans (11.5% of whom had NAFLD defined with FLI ≥ 60), followed up for 7.2 years.	Compared to NAFLD-free controls, all-cause mortality in patients with EC (HR: 1.46, 95%CI: 1.28-1.67), GC (HR: 1.26, 95%CI: 1.18-1.34), and CRC (HR: 1.16, 95%CI: 1.10-1.22) was significantly increased in subjects with NAFLD.	NAFLD is burdened with excess mortality owing to EHCs.
Veracruz *et al.*, 2021[102]	Meta-analysis of 13 studies.	Significant heterogeneity in assessing EHCs prevented applying meta-analysis methods. However, NAFLD seemed to be associated with an increased risk of BRC and CRCs.	There appears to be an increased risk of BRC and CRC.
Mantovani *et al.*, 2022[103]	Meta-analysis of 10 cohort studies, totaling 182,202 middle-aged individuals (24.8% with NAFLD) and 8,485 incident cases of EHCs over a median follow-up of 5.8 years.	NAFLD was significantly associated with a nearly 1.5-fold to 2-fold increased risk of developing EC, GC, PAC, or CRC. Furthermore, NAFLD was associated with an approximately 1.2-fold to 1.5-fold increased risk of lung, breast, gynecological, or urinary system cancers. All risks were independent of confounding factors.	This large meta-analysis suggests that NAFLD is associated with a moderately increased risk of developing certain EHCs over a median follow-up period of 6 years.
Thomas *et al.*, 2022[104]	64 studies involving 41,027 patients were eligible for analysis of EHC incidence.	The pooled extrahepatic cancer incidence rate was 10.58 per 1,000 person-years (95%CI: 8.14 to 13.02, $I^2 = 97.1\%$). The most frequently occurring extrahepatic cancers were uterine, breast, PRC, CRC, and lung cancers. However, EHC incidence rates were not higher among NAFLD subjects with advanced liver fibrosis or cirrhosis.	Extrahepatic cancers are over eight-fold more frequent than HCC in NAFLD and not associated with liver fibrosis stage.
Muhamad *et al.*, 2023[105]	Meta-analysis of 11 studies totaling 222,523 adults and 3 types of cancer: HCC, BRC, and other types of EHC.	NAFLD and breast cancer had the highest prevalence out of the 3 forms of cancer at 30% (95%CI: 14%-45%), while the pooled prevalence for NAFLD and other cancers was 21% (95%CI: 12%-31%).	NAFLD subjects may be exposed to a higher risk of cancer not only of the liver but also of the breast and bile ducts.
Xie *et al.*, 2024[106]	Two-sample MRA to assess the causal effects of NAFLD on 22 EHCs.	Genetically predicted NAFLD was significantly associated with female breast cancer (OR: 15.99, 95%CI: 9.58-26.69); with cervical and laryngeal cancers using the inverse variance weighting method, and the ORs were 2.44 (95%CI: 1.43-4.14) and 1.94 (95%CI: 1.35-2.78), respectively. PNPLA3 -driven and TMSF2-driven NAFLD forms were associated ($P < 0.05$) with increased risks of leukemia, lung cancer, and PRC.	Genetically predicted NAFLD is associated with an increased risk of female BRC, cervical, laryngeal, leukemia, lung, and PRC.

APRI: AST to platelet ratio index; BRC: breast cancer; CRC: colorectal cancer; EC: esophageal cancer; EHC: extrahepatic cancer; ECC: extrahepatic cholangiocarcinoma; FIB-4: Fibrosis 4; FLI: fatty liver index; GC: gastric cancer; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; MRA: mendelian randomization analysis; MVA: multivariate analysis; NFS: nonalcoholic fatty liver disease fibrosis score; NAFLD: nonalcoholic fatty liver disease; PAC: pancreatic cancer; PNPLA3: patatin-like phospholipase domain-containing protein 3; PRC: prostate cancer; HR: hazard ratio; OR: odd ratio; CI: confidence interval.

suggesting it may serve as a risk marker for HF development[129].

Elastography

Liver stiffness has recently been reviewed as a cornerstone in assessing CVD risk[130]. In a study of 3,276 adult subjects from the Framingham Heart Study, liver fibrosis assessed by VCTE was independently associated with multiple cardiometabolic risk factors. These factors included low high-density lipoprotein cholesterol (OR: 1.47), metabolic syndrome (OR: 1.49), hypertension (OR: 1.52), obesity (OR: 1.82), and diabetes (OR: 2.67; 95%CI: 1.21-3.75), after adjusting for demographic variables, physical activity, smoking status, alcohol intake, aminotransferases, and liver steatosis as assessed by controlled attenuation parameter (CAP)[131].

Liver fibrosis severity, as defined by VCTE, has been associated with various ultrasonographic cardiovascular structure and function parameters, including subclinical atherosclerosis evaluated with cIMT. This association remained significant even after adjusting for traditional cardiovascular risk factors in a prospective study conducted on a population-based cohort of young adults[132]. Moreover, the severity of liver fibrosis, as assessed by VCTE, was found to be directly correlated with the ultrasonographic burden of carotid and systemic atherosclerosis in a small cohort of patients aged 40 to 64 years[133].

Evidence on the association between liver fibrosis severity, as assessed by VCTE-LSM, and CVD has been somewhat conflicting in patients with MASLD who do not have T2DM[4,134-137]. However, in patients with T2DM, cross-sectional and longitudinal studies suggest that VCTE-LSM can independently predict the risk of diabetic macro-microvascular complications[4].

VCTE-LSM but not ultrasonographic fatty liver disease was associated with AF (OR: 1.09 per kPa, 95%CI: 1.03-1.16) in a large prospective cohort (Rotterdam Study)[138]. However, this association persisted only among those without fatty liver (OR: 1.18 per kPa, 95%CI: 1.08-1.29). It was hypothesized that venous congestion due to AF, rather than fibrosis, may have caused increased LSM in these subjects.

Conversely, studies using MR imaging have consistently found an association between liver fibrosis severity and CVD. In the large prospective Multi-Ethnic Study of Atherosclerosis (MESA) study, a subsample of subjects underwent T1-mapping MR after 10 years. Liver fibrosis indicators (higher extracellular volume fraction and native T1) were associated with the development of HF, AF, and CHD. However, the latter relationship was weakened after adjusting for the coronary artery calcium score[139]. Another recent retrospective study on 428 patients showed that moderate to advanced fibrosis increased the risk of CVD, while cirrhosis decreased it, with cirrhosis conversely having the highest risk of liver-related events such as HCC and decompensation[140].

In conclusion, evidence from histological, biomarker measurements, and elastographic studies taken collectively strongly supports the association of liver fibrosis with an increased cardiometabolic risk.

ASSESSING LIVER FIBROSIS TO GAUGE THE RISK OF EXTRAHEPATIC CANCERS

In the setting of MASLD, liver fibrosis is a significant factor in determining the risk of developing HCC. However, MASLD-HCC often occurs in individuals with non-cirrhotic MASLD[141]. Notably, the cancer risk among MASLD patients also includes extrahepatic cancers, with evidence supporting a link between NAFLD and colorectal cancer (CRC) where the risk is approximately 50% higher compared to MASLD-free controls[142,143]. Other extrahepatic cancers linked to MASLD comprise cancers of the gastrointestinal and urinary tracts, lungs, and the female genital tract[144,145].

It has been hypothesized that MASLD shares a pro-inflammatory systemic environment with extrahepatic cancers, associated with metabolic derangements as a common precursor. Alternatively, it is suggested that MASLD plays an active role in the initiation, development, and progression of cancer[144]. Among the various pathomechanisms involved, liver fibrosis is considered a major factor, along with genetics, obesity, insulin resistance, oxidative stress, cardiovascular risk, socio-demographic characteristics, and hormonal status[145].

The connection between liver fibrosis and extrahepatic malignancies, such as CRC, is increasingly recognized in medical research[146,147]. Liver fibrosis, often resulting from CLD such as hepatitis or alcohol abuse, creates a pro-inflammatory environment characterized by elevated cytokines and growth factors that can influence tumorigenesis beyond the liver. This inflammatory milieu may promote systemic changes, including alterations in immune surveillance and increased oxidative stress, which can facilitate the development of cancers in other organs[148]. Specifically, patients with advanced liver fibrosis often exhibit metabolic syndrome features - such as obesity and insulin resistance - that are also risk factors for CRC[148]. Additionally, the gut-liver axis plays a crucial role; dysbiosis associated with liver disease can lead to increased intestinal permeability and translocation of bacterial products, further heightening the risk of CRC through mechanisms such as inflammation and immune modulation[149]. Consequently, individuals with liver fibrosis may have an elevated risk of developing extrahepatic malignancies, underscoring the need for vigilant screening and management strategies in this population. The association of MASLD with extrahepatic cancers has been extensively covered in other sources[103,143-145].

CONCLUSION AND RESEARCH AGENDA

Diagnosis and management of conventional CVD risk factors such as low-density lipoprotein (LDL)-cholesterol, blood pressure, and glycemia are crucial in cardiovascular medicine[150]. However, there remains a "residual CVD risk", which refers to the odds of recurrent vascular events that persist despite achieving target treatment of traditional risk factors[151]. Could assessing liver fibrosis provide additional insights into this "residual CVD risk"? Or could liver fibrosis potentially replace conventional CVD risk factors altogether[152]? While traditional CVD risk factors are still important, incorporating liver-specific parameters shows promise in enhancing risk assessment and guiding targeted interventions to reduce the significant burden of CVD in high-risk populations[152].

Liver fibrosis, the often-dysfunctional wound-healing hepatic response, may be triggered by metabolic dysfunction, among other inciting stimuli. Liver fibrosis is typically defined histologically and is a strong predictor of various liver-related clinical outcomes such as cirrhosis, clinically significant portal hypertension, liver failure, transplantation, and HCC, as well as liver-related mortality[153]. Revolutionizing previous paradigms of risk prediction, the severity of liver fibrosis is also associated with increased cardiovascular risk and all-cause mortality. Moreover, liver fibrosis can now be identified by imaging techniques or accurate biomarkers. The utilization of fibrosis as an emerging non-invasive biomarker of all-cause mortality in MASLD-associated cirrhosis, where the primary cause of death is cardiovascular disease, is therefore a highly relevant question.

We may wonder if there is a direct connection between cardiovascular disease and liver fibrosis. Mendelian Randomization analysis (MRA) studies published so far have provided conflicting results regarding the association between MASLD and CVD[154-156]. Among these, the study by Ren *et al.* stands out as the most methodologically robust[156]. These investigators conducted a two-sample MRA analysis to evaluate the link between genetically predicted MASLD, such as chronically elevated serum alanine aminotransferase levels (cALT), and imaging-based and biopsy-confirmed MASLD, and the risk of CVD. Interestingly, after

excluding genes associated with impaired very-low-density lipoprotein (VLDL) cholesterol secretion that are protective against CVD, the authors consistently found associations between genetically predicted MASLD (regardless of the diagnostic method used). Despite some uncertainty, the strongest evidence that more advanced liver fibrosis stages are linked to a higher long-term risk of fatal or non-fatal CVD events comes from the updated meta-analytic review by Mantovani *et al.*[110]. This review was based on 36 studies globally involving 5,802,226 middle-aged individuals who were followed up for a median of 6.5 years, during which 99,668 incident cases of fatal and non-fatal CVD events occurred.

The mechanistic relationship between liver fibrosis and the increased risk of CVD remains incompletely understood. One important factor to consider is that endothelial dysfunction caused by metabolic factors may serve as a common link between liver disease and CVD. Endothelial cells are specialized for the unique functions of different tissues, with each vascular bed having its own structural and functional properties[38]. However, there are general characteristics that suggest the importance of considering vascular endothelium at an organismal level, which could explain shared features between metabolic dysfunction-related liver and cardiovascular issues. Discussions about disease trajectories in MASLD have traditionally focused on the process of liver cell injury followed by fibrogenesis, with less attention given to vascular compromise. However, progressive damage of the hepatic microvasculature is likely fundamental to disease progression in metabolic dysfunction. Small-vessel obstruction plays a crucial role in CLD and may lead to congestion and sinusoidal portal hypertension. Furthermore, compromised sinusoidal capillary flow due to external compression, capillarization, and interstitial edema bears resemblance to the primary vascular lesions seen in atherosclerosis underlying CVD[157].

LSECs play a crucial role in maintaining the microvascular health of the liver through various mechanisms[158,159]. The liver serves as the primary organ responsible for collecting and processing information from digested food and the gut microbiota[160,161]. LSECs act as a vital filter for nutrition-derived and microbiota-associated biomolecules that enter the liver. These cells have multiple scavenger receptors that can become impaired in cases of metabolic dysfunction[162]. This impairment can expose other liver cell components to pathogen-associated and damage-associated molecular patterns, leading to the activation of the innate immune system and processes that may contribute to disease progression. Furthermore, insulin resistance, atherogenic dyslipidemia, and the increased synthesis and release of various bioactive lipids into the bloodstream (such as fatty acyl-coenzyme A molecules, diacylglycerides and ceramides), along with proatherogenic, procoagulant, pro-inflammatory factors, hepatocyte-derived extracellular vesicles containing microRNAs and dysregulated secretion of hepatokines (such as fetuin A, fibroblast growth factor 21, follistatin, selenoprotein P, and liver-derived coagulation factor XI) may either predict or facilitate CVD events[163]. Finally, the discovery that aspirin may specifically protect against both CVD events and liver fibrosis provides indirect evidence for a role played by platelets and PDGF[52]. Together, these studies support a "common soil" that predisposes individuals to both fibrosing MASLD/MASH and CVD, suggesting that MASLD may precede incident CVD both chronologically and mechanistically.

Endothelial dysfunction may be a common factor in the development of both hepatic and cardiovascular diseases. Fibrosis can be considered a useful biomarker for monitoring chronic vascular changes and reparative processes, thus serving as an indicator of cardiovascular risk. With our current methodological armamentarium, it is more challenging to detect and track changes in sinusoidal microvasculature than to detect and follow the severity of fibrosis. Importantly, recent technological advances in the non-invasive detection of liver fibrosis may make it a non-inferior marker of CVD risk compared to the traditional parameters established by cardiologists for risk assessment.

We may also need to consider the possibility that fibrosis is not the best liver-related predictor of non-liver disease compared to other biomarkers derived from inflammation or increased portal pressure. Therefore, we should approach investigations with an open mind, exploring all possible directions. It is important to remember that, in addition to fibrosis, other fundamental components of the pathobiology of MASLD, such as steatosis and steatohepatitis, may also play such a role[164-168]. The idea that portal hypertension could lead to accelerated atherogenesis was first suggested many years ago based on experimental evidence[169]. This concept should be further explored using new insights from mechanobiology[36,170].

The endothelial cell, as a potential origin of commonalities between pathological changes in hepatic and systemic circulation, also has important implications for the management of cardiovascular disease associated with metabolic dysfunction and advanced liver fibrosis. Any pharmaceutical intervention that can reduce intrahepatic venous resistance and sinusoidal pressure may prove beneficial[170,171]. This strategy, which may protect LSECs and mitigate endothelial dysfunction with statin use, has been increasingly recognized and applied in the management of advanced liver disease associated with MASLD and other etiologies[171]. It is likely to augment the beneficial impact of anti-inflammatory medications that reduce the degree of microcirculatory damage and interstitial fluid collection.

The astute physician should promptly recognize individuals who, while seeking medical advice for non-hepatic conditions such as MACE, diabetic retinopathy, diabetic neuropathy, or chronic kidney disease, may also have unsuspected advanced liver fibrosis[2]. Early identification of at-risk syndromic representations can aid in developing comprehensive multi-organ assessments, determining surveillance protocols, and utilizing a wide range of licensed and investigational diagnostic strategies and management options[2,19,172-174].

DECLARATIONS

Authors' contributions

Wrote the first draft of the manuscript: Lonardo A, Ballestri S
Performed study revision and editing: Baffy G, Ballestri S, Lonardo A, Weiskirchen R
All authors contributed equally to the conception and design of the study

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Lonardo A is the Editor-in-Chief of *Metabolism and Target Organ Damage*. However, he was not involved in any steps during the editorial handling of the manuscript, inviting Reviewers, or making editorial decisions regarding this submission. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Bataller R, Brenner DA. Liver fibrosis. *J Clin Invest* 2005;115:209-18. DOI PubMed PMC
2. Lonardo A. Liver fibrosis: more than meets the eye. *Ann Hepatol* 2024;29:101479. DOI PubMed
3. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. *Cells* 2020;9:875. DOI PubMed PMC
4. Ballestri S, Mantovani A, Girolamo MD, 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. DOI
5. Geerts A. History, heterogeneity, developmental biology, and functions of quiescent hepatic stellate cells. *Semin Liver Dis* 2001;21:311-35. DOI PubMed
6. Sufleţel RT, Melincovici CS, Gheban BA, Toader Z, Mihu CM. Hepatic stellate cells - from past till present: morphology, human markers, human cell lines, behavior in normal and liver pathology. *Rom J Morphol Embryol* 2020;61:615-42. DOI PubMed PMC
7. ITO T, NEMOTO M. [Kupfer's cells and fat storing cells in the capillary wall of human liver]. *Okajimas Folia Anat Jpn* 1952;24:243-58. DOI PubMed
8. Tanuma Y, Ito T, Shibasaki S. Further electron-microscope studies on the human hepatic sinusoidal wall with special reference to the fat-storing cell. *Arch Histol Jpn* 1982;45:263-74. DOI PubMed
9. Tanuma Y, Ohata M, Ito T. Electron microscopic studies on the sinusoidal cells in the monkey liver. *Arch Histol Jpn* 1983;46:401-26. DOI PubMed
10. Ito T, Itoshima T, Ukida M, et al. Scanning electron microscopy of Ito's fat-storing cells in the rat liver. *Acta Med Okayama* 1984;38:1-9. DOI PubMed
11. Friedman SL, Roll FJ, Boyles J, Bissell DM. Hepatic lipocytes: the principal collagen-producing cells of normal rat liver. *Proc Natl Acad Sci U S A* 1985;82:8681-5. DOI PubMed PMC
12. Ramadori G, Saile B. Portal tract fibrogenesis in the liver. *Lab Invest* 2004;84:153-9. DOI PubMed
13. Forbes SJ, Russo FP, Rey V, et al. A significant proportion of myofibroblasts are of bone marrow origin in human liver fibrosis. *Gastroenterology* 2004;126:955-63. DOI PubMed
14. Bataller R, North KE, Brenner DA. Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal. *Hepatology* 2003;37:493-503. DOI PubMed
15. Montfort I, Pérez-Tamayo R. Collagenase in experimental carbon tetrachloride cirrhosis of the liver. *Am J Pathol* 1978;92:411-20. PubMed PMC
16. Pérez-Tamayo R. Cirrhosis of the liver: a reversible disease? *Pathol Annu* 1979;14:183-213. PubMed
17. Hammel P, Couvelard A, O'Toole D, et al. Regression of liver fibrosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct. *N Engl J Med* 2001;344:418-23. DOI PubMed
18. Bataller R, Brenner DA. Hepatic stellate cells as a target for the treatment of liver fibrosis. *Semin Liver Dis* 2001;21:437-51. DOI PubMed
19. Trivella JP, Martin P, Carrion AF. Novel targeted therapies for the management of liver fibrosis. *Expert Opin Emerg Drugs* 2020;25:59-70. DOI PubMed
20. Lan Y, Wang H, Weng H, et al. The burden of liver cirrhosis and underlying etiologies: results from the Global Burden of Disease study 2019. *Hepatol Commun* 2023;7:e0026. DOI PubMed PMC
21. Wu XN, Xue F, Zhang N, et al. Global burden of liver cirrhosis and other chronic liver diseases caused by specific etiologies from 1990 to 2019. *BMC Public Health* 2024;24:363. DOI PubMed PMC
22. Rinella ME, Sookoian S. From NAFLD to MASLD: updated naming and diagnosis criteria for fatty liver disease. *J Lipid Res* 2024;65:100485. DOI PubMed PMC
23. Ciardullo S, Perseghin G. From NAFLD to MAFLD and MASLD: a tale of alcohol, stigma and metabolic dysfunction. *Metab Target Organ Damage* 2024;4:30. DOI
24. Tan D, Chan KE, Wong ZY, et al. Global Epidemiology of cirrhosis: changing etiological basis and comparable burden of nonalcoholic steatohepatitis between males and females. *Dig Dis* 2023;41:900-12. DOI PubMed PMC
25. Hagström H, Lindfors A, Holmer M, et al. Etiologies and outcomes of cirrhosis in a large contemporary cohort. *Scand J Gastroenterol* 2021;56:727-32. DOI PubMed
26. Lonardo A, Singal AK, Osna N, Kharbanda KK. Effect of cofactors on NAFLD/NASH and MAFLD. A paradigm illustrating the pathomechanics of organ dysfunction. *Metab Target Organ Damage* 2022;2:12. DOI PubMed PMC
27. Weiskirchen R, Weiskirchen S, Tacke F. Recent advances in understanding liver fibrosis: bridging basic science and individualized treatment concepts. *F1000Res* 2018;7:921. DOI PubMed PMC
28. Weiskirchen R, Weiskirchen S, Tacke F. Organ and tissue fibrosis: molecular signals, cellular mechanisms and translational implications. *Mol Aspects Med* 2019;65:2-15. DOI PubMed
29. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008;134:1655-69. DOI PubMed PMC

30. Testerink N, Ajat M, Houweling M, et al. Replacement of retinyl esters by polyunsaturated triacylglycerol species in lipid droplets of hepatic stellate cells during activation. *PLoS One* 2012;7:e34945. DOI PubMed PMC
31. Delgado ME, Cárdenas BI, Farran N, Fernandez M. Metabolic reprogramming of liver fibrosis. *Cells* 2021;10:3604. DOI PubMed PMC
32. Shah V, Haddad FG, Garcia-Cardena G, et al. Liver sinusoidal endothelial cells are responsible for nitric oxide modulation of resistance in the hepatic sinusoids. *J Clin Invest* 1997;100:2923-30. DOI PubMed PMC
33. Chávez-Galán L, Olleros ML, Vesin D, Garcia I. Much more than M1 and M2 macrophages, there are also $CD169^+$ and TCR^+ macrophages. *Front Immunol* 2015;6:263. DOI PubMed PMC
34. Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol* 2014;5:491. DOI PubMed PMC
35. Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. *Best Pract Res Clin Gastroenterol* 2011;25:195-206. DOI PubMed PMC
36. Mitten EK, Baffy G. Mechanotransduction in the pathogenesis of non-alcoholic fatty liver disease. *J Hepatol* 2022;77:1642-56. DOI PubMed
37. Baffy G, Portincasa P. Gut microbiota and sinusoidal vasoregulation in MASLD: a portal perspective. *Metabolites* 2024;14:324. DOI PubMed PMC
38. Aird WC. Phenotypic heterogeneity of the endothelium: II. Representative vascular beds. *Circ Res* 2007;100:174-90. DOI PubMed
39. Augustin HG, Koh GY. A systems view of the vascular endothelium in health and disease. *Cell* 2024;187:4833-58. DOI PubMed
40. Zhang YL, Li ZJ, Gou HZ, Song XJ, Zhang L. The gut microbiota-bile acid axis: a potential therapeutic target for liver fibrosis. *Front Cell Infect Microbiol* 2022;12:945368. DOI PubMed PMC
41. Arab JP, Arrese M, Shah VH. Gut microbiota in non-alcoholic fatty liver disease and alcohol-related liver disease: current concepts and perspectives. *Hepatol Res* 2020;50:407-18. DOI PubMed PMC
42. Costa CFFA, Sampaio-Maia B, Araujo R, et al. Gut microbiome and organ fibrosis. *Nutrients* 2022;14:352. DOI PubMed PMC
43. Winston JA, Theriot CM. Diversification of host bile acids by members of the gut microbiota. *Gut Microbes* 2020;11:158-71. DOI PubMed PMC
44. Larabi AB, Masson HLP, Bäumler AJ. Bile acids as modulators of gut microbiota composition and function. *Gut Microbes* 2023;15:2172671. DOI PubMed PMC
45. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011;12:56-68. DOI PubMed PMC
46. Ouyang X, Ghani A, Mehal WZ. Inflammasome biology in fibrogenesis. *Biochim Biophys Acta* 2013;1832:979-88. DOI PubMed
47. Borkham-Kamphorst E, Weiskirchen R. The PDGF system and its antagonists in liver fibrosis. *Cytokine Growth Factor Rev* 2016;28:53-61. DOI PubMed
48. Schon HT, Weiskirchen R. Immunomodulatory effects of transforming growth factor-β in the liver. *Hepatobiliary Surg Nutr* 2014;3:386-406. DOI PubMed PMC
49. Kang H, Seo E, Oh YS, Jun HS. TGF-β activates NLRP3 inflammasome by an autocrine production of TGF-β in LX-2 human hepatic stellate cells. *Mol Cell Biochem* 2022;477:1329-38. DOI PubMed PMC
50. Blas-García A, Apostolova N. Novel therapeutic approaches to liver fibrosis based on targeting oxidative stress. *Antioxidants* 2023;12:1567. DOI PubMed PMC
51. Ballestri S, Capitelli M, Fontana MC, et al. Direct oral anticoagulants in patients with liver disease in the era of non-alcoholic fatty liver disease global epidemic: a narrative review. *Adv Ther* 2020;37:1910-32. DOI PubMed PMC
52. Lonardo A, Zheng MH. Does an aspirin a day take the MASLD away? *Adv Ther* 2024;41:2559-75. DOI PubMed
53. Oh H, Park HE, Song MS, Kim H, Baek JH. The therapeutic potential of anticoagulation in organ fibrosis. *Front Med* 2022;9:866746. DOI PubMed PMC
54. Weiskirchen R, Tacke F. The role of radiologic modalities in diagnosing nonalcoholic steatohepatitis (NASH) and fibrosis. *Curr Hepatology Rep* 2018;17:324-35. DOI
55. Nascimbeni F, Ballestri S, Machado MV, et al. Clinical relevance of liver histopathology and different histological classifications of NASH in adults. *Expert Rev Gastroenterol Hepatol* 2018;12:351-67. DOI PubMed
56. Ratziu V, Charlotte F, Heurtier A, et al; LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005;128:1898-906. DOI PubMed
57. 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;11:98. DOI PubMed PMC
58. Sanyal AJ, Castera L, Wong VW. Noninvasive assessment of liver fibrosis in NAFLD. *Clin Gastroenterol Hepatol* 2023;21:2026-39. DOI PubMed
59. 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;21:1243-51.e12. DOI PubMed
60. Sun W, Cui H, Li N, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: a meta-analysis study. *Hepatol Res* 2016;46:862-70. DOI PubMed
61. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to

detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. *Hepatology* 2017;66:1486-501. DOI PubMed

62. Ferraioli G, Wong VW, Castera L, et al. Liver ultrasound elastography: an update to the world federation for ultrasound in medicine and biology guidelines and recommendations. *Ultrasound Med Biol* 2018;44:2419-40. DOI PubMed
63. Ballestri S, Nascimbeni F, Lugari S, Lonardo A, Francica G. A critical appraisal of the use of ultrasound in hepatic steatosis. *Expert Rev Gastroenterol Hepatol* 2019;13:667-81. DOI PubMed
64. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. *J Hepatol* 2022;76:959-74. DOI PubMed PMC
65. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. *Gastroenterology* 2023;165:1080-8. DOI PubMed
66. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guideline Panel; Chair:; EASL Governing Board representative:; Panel members:. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021;75:659-89. DOI PubMed
67. 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;5:362-73. DOI PubMed PMC
68. Mózes FE, Lee JA, Selvaraj EA, et al; LITMUS Investigators. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut* 2022;71:1006-19. DOI PubMed PMC
69. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. *JHEP Rep* 2020;2:100067. DOI PubMed PMC
70. McPherson S, Hardy T, Dufour JF, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol* 2017;112:740-51. DOI PubMed PMC
71. Petta S, Wai-Sun Wong V, Bugianesi E, et al. Impact of obesity and alanine aminotransferase levels on the diagnostic accuracy for advanced liver fibrosis of noninvasive tools in patients with nonalcoholic fatty liver disease. *Am J Gastroenterol* 2019;114:916-28. DOI PubMed
72. Zhang X, Wong GL, Wong VW. Application of transient elastography in nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2020;26:128-41. DOI PubMed PMC
73. 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;155:443-57.e17. DOI PubMed
74. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut* 2024;73:691-702. DOI PubMed
75. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1611-25.e12. DOI PubMed
76. Cianci N, Subhani M, Hill T, et al. Prognostic non-invasive biomarkers for all-cause mortality in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *World J Hepatol* 2022;14:1025-37. DOI PubMed PMC
77. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology* 2017;65:1557-65. DOI PubMed PMC
78. Ciardullo S, Cannistraci R, Muraca E, Zerbini F, Perseghin G. Liver fibrosis, NT-ProBNP and mortality in patients with MASLD: a population-based cohort study. *Nutr Metab Cardiovasc Dis* 2024;34:963-71. DOI PubMed
79. Collier A, Curran C, Cameron L, Wild SH, Byrne CD. Liver fibrosis markers and all cause mortality in people with type 2 diabetes: a population based study (The Ayrshire Diabetes Outcomes Cohort (ADOC) study). *Diabetes Obes Metab* 2023;25:2659-68. DOI PubMed
80. Choi SW, Kweon SS, Lee YH, Ryu SY, Nam HS, Shin MH. Association of liver fibrosis biomarkers with overall and CVD mortality in the Korean population: the Dong-gu study. *PLoS One* 2022;17:e0277729. DOI PubMed PMC
81. Vieira Barbosa J, Milligan S, Frick A, et al. Fibrosis-4 index as an independent predictor of mortality and liver-related outcomes in NAFLD. *Hepatol Commun* 2022;6:765-79. DOI PubMed PMC
82. Baik M, Nam HS, Heo JH, et al. Advanced liver fibrosis predicts unfavorable long-term prognosis in first-ever ischemic stroke or transient ischemic attack. *Cerebrovasc Dis* 2020;49:474-80. DOI PubMed
83. Cao YX, Zhang M, Zhang HW, et al. Impact of liver fibrosis score on prognosis in patients with previous myocardial infarction: a prospective cohort study. *Liver Int* 2021;41:1294-304. DOI PubMed
84. Jin JL, Zhang HW, Cao YX, et al. Liver fibrosis scores and coronary atherosclerosis: novel findings in patients with stable coronary artery disease. *Hepatol Int* 2021;15:413-23. DOI PubMed
85. Oh TJ, Kim K, Moon JH, Choi SH, Cho NH, Jang HC. Liver fibrosis indices for the prediction of mortality in korean subjects: a 16-year prospective cohort study. *J Endocr Soc* 2021;5:bvab123. DOI PubMed PMC
86. Chung GE, Han K, Lee KN, et al. Combined effects of chronic kidney disease and nonalcoholic fatty liver disease on the risk of cardiovascular disease in patients with diabetes. *Biomedicines* 2022;10:1245. DOI PubMed PMC
87. Yan Z, Liu Y, Li W, et al. Liver fibrosis scores and prognosis in patients with cardiovascular diseases: a systematic review and meta-analysis. *Eur J Clin Invest* 2022;52:e13855. DOI PubMed
88. Mascherbauer K, Donà C, Koschutnik M, et al. Hepatic T1-time predicts cardiovascular risk in all-comers referred for cardiovascular magnetic resonance: a post-hoc analysis. *Circ Cardiovasc Imaging* 2022;15:e014716. DOI PubMed

89. Lee J, Jo G, Park D, Jun HJ, Bae JH, Shin MJ. The association between advanced liver fibrosis and mortality is modified by dietary quality among Korean adults: results from the Korea National Health and Nutrition Examination Survey with mortality data. *Nutrients* 2023;15:1501. DOI PubMed PMC
90. Seo YG, Polyzos SA, Park KH, Mantzoros CS. Fibrosis-4 index predicts long-term all-cause, cardiovascular and liver-related mortality in the adult Korean population. *Clin Gastroenterol Hepatol* 2023;21:3322-35. DOI PubMed
91. Guan L, Li L, Zou Y, Zhong J, Qiu L. Association between FIB-4, all-cause mortality, cardiovascular mortality, and cardiovascular disease risk among diabetic individuals: NHANES 1999-2008. *Front Cardiovasc Med* 2023;10:1172178. DOI PubMed PMC
92. Nakashima M, Nakamura K, Nishihara T, et al. Association between cardiovascular disease and liver disease, from a clinically pragmatic perspective as a cardiologist. *Nutrients* 2023;15:748. DOI PubMed PMC
93. Roca-Fernandez A, Banerjee R, Thomaides-Brears H, et al. Liver disease is a significant risk factor for cardiovascular outcomes - a UK Biobank study. *J Hepatol* 2023;79:1085-95. DOI PubMed
94. 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;16:2627-37. DOI PubMed PMC
95. Mitten EK, Portincasa P, Baffy G. Portal hypertension in nonalcoholic fatty liver disease: challenges and paradigms. *J Clin Transl Hepatol* 2023;11:1201-11. DOI PubMed PMC
96. Wan Y, Li X, Slevin E, et al. Endothelial dysfunction in pathological processes of chronic liver disease during aging. *FASEB J* 2022;36:e22125. DOI PubMed PMC
97. Cetin EG, Demir N, Sen I. The relationship between insulin resistance and liver damage in non-alcoholic fatty liver patients. *Sisli Etfal Hastan Tip Bul* 2020;54:411-5. DOI PubMed PMC
98. Kim GA, Lee HC, Choe J, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. *J Hepatol* 2017;68:140-6. DOI PubMed
99. Peleg N, Sneh Arbib O, Issachar A, Cohen-Naftaly M, Braun M, Shlomai A. Noninvasive scoring systems predict hepatic and extra-hepatic cancers in patients with nonalcoholic fatty liver disease. *PLoS One* 2018;13:e0202393. DOI PubMed PMC
100. Liu SS, Ma XF, Zhao J, et al. Association between nonalcoholic fatty liver disease and extrahepatic cancers: a systematic review and meta-analysis. *Lipids Health Dis* 2020;19:118. DOI PubMed PMC
101. Lee JM, Park YM, Yun JS, et al. The association between nonalcoholic fatty liver disease and esophageal, stomach, or colorectal cancer: national population-based cohort study. *PLoS One* 2020;15:e0226351. DOI PubMed PMC
102. Veracruz N, Hameed B, Saab S, Wong RJ. The association between nonalcoholic fatty liver disease and risk of cardiovascular disease, stroke, and extrahepatic cancers. *J Clin Exp Hepatol* 2021;11:45-81. DOI PubMed PMC
103. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. *Gut* 2022;71:778-88. DOI PubMed
104. Thomas JA, Kendall BJ, Dalais C, Macdonald GA, Thrift AP. Hepatocellular and extrahepatic cancers in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Cancer* 2022;173:250-62. DOI PubMed
105. Muhamad NA, Maamor NH, Leman FN, et al. The global prevalence of nonalcoholic fatty liver disease and its association with cancers: systematic review and meta-analysis. *Interact J Med Res* 2023;12:e40653. DOI PubMed PMC
106. Xie J, Gao H, Liu C, Pan Y, Xu C, Xu L. Causal association of nonalcoholic fatty liver disease with 22 extrahepatic cancers: a Mendelian randomization study. *Hepatol Res* 2024;54:261-71. DOI PubMed
107. Thomas JA, Kendall BJ, El-Serag HB, Thrift AP, Macdonald GA. Hepatocellular and extrahepatic cancer risk in people with non-alcoholic fatty liver disease. *Lancet Gastroenterol Hepatol* 2024;9:159-69. DOI PubMed
108. Loria P, Marchesini G, Nascimbeni F, et al. Cardiovascular risk, lipidemic phenotype and steatosis. A comparative analysis of cirrhotic and non-cirrhotic liver disease due to varying etiology. *Atherosclerosis* 2014;232:99-109. DOI PubMed
109. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016;31:936-44. DOI PubMed
110. 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. DOI PubMed
111. Henson JB, Simon TG, Kaplan A, Osganian S, Masia R, Corey KE. Advanced fibrosis is associated with incident cardiovascular disease in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2020;51:728-36. DOI PubMed PMC
112. 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;71:1867-75. DOI PubMed
113. Hagström H, Nasr P, Ekstedt M, et al. Cardiovascular risk factors in non-alcoholic fatty liver disease. *Liver Int* 2019;39:197-204. DOI PubMed
114. Park JH, Koo BK, Kim W, Kim WH; Innovative Target Exploration of NAFLD (ITEN) Consortium. Histological severity of nonalcoholic fatty liver disease is associated with 10-year risk for atherosclerotic cardiovascular disease. *Hepatol Int* 2021;15:1148-59. DOI PubMed
115. Han E, Lee YH, Lee JS, et al. Fibrotic burden determines cardiovascular risk among subjects with metabolic dysfunction-associated fatty liver disease. *Gut Liver* 2022;16:786-97. DOI PubMed PMC
116. Arai T, Atsukawa M, Tsubota A, et al. Liver fibrosis is associated with carotid atherosclerosis in patients with liver biopsy-proven nonalcoholic fatty liver disease. *Sci Rep* 2021;11:15938. DOI PubMed PMC

117. Yi M, Peng W, Teng F, Kong Q, Chen Z. The role of noninvasive scoring systems for predicting cardiovascular disease risk in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2022;34:1277-84. DOI PubMed
118. Chen S, Xue H, Huang R, Chen K, Zhang H, Chen X. Associations of MAFLD and MAFLD subtypes with the risk of the incident myocardial infarction and stroke. *Diabetes Metab* 2023;49:101468. DOI PubMed
119. Park J, Kim G, Kim BS, et al. The association between changes in hepatic steatosis and hepatic fibrosis with cardiovascular outcomes and mortality in patients with new-onset type 2 diabetes: a nationwide cohort study. *Diabetes Res Clin Pract* 2022;194:110191. DOI PubMed
120. Corbin KD, Dagogo-Jack S, Cannon CP, et al. Cardiorenal outcomes by indices of liver steatosis and fibrosis in individuals with type 2 diabetes and atherosclerotic cardiovascular disease: analyses from VERTIS CV, a randomized trial of the sodium-glucose cotransporter-2 inhibitor ertugliflozin. *Diabetes Obes Metab* 2023;25:758-66. DOI PubMed
121. Li J, Xiang Y, Han J, et al. Retinopathy as a predictive indicator for significant hepatic fibrosis according to T2DM status: a cross-sectional study based on the national health and nutrition examination survey data. *Ann Hepatol* 2024;29:101478. DOI PubMed
122. Trivedi HD, Tran Q, Fricker Z, Curry MP, Li JX, Lai M. Type 2 diabetes complications are associated with liver fibrosis independent of hemoglobin A1c. *Ann Hepatol* 2023;28:101087. DOI PubMed
123. Mantovani A, Dauriz M, Sandri D, et al. Association between non-alcoholic fatty liver disease and risk of atrial fibrillation in adult individuals: an updated meta-analysis. *Liver Int* 2019;39:758-69. DOI PubMed
124. 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;10:5023. DOI PubMed PMC
125. Wang Z, Wang Y, Luo F, et al. Impact of advanced liver fibrosis on atrial fibrillation recurrence after ablation in non-alcoholic fatty liver disease patients. *Front Cardiovasc Med* 2022;9:960259. DOI PubMed PMC
126. Liu X, Chen W, Shao W, et al. Liver fibrosis scores and atrial fibrillation incidence in heart failure with preserved ejection fraction. *ESC Heart Fail* 2022;9:3985-94. DOI PubMed PMC
127. 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;79:180-91. DOI PubMed
128. Salah HM, Pandey A, Van Spall HGC, Michos ED, McGarrah RW, Fudim M. Meta-analysis of nonalcoholic fatty liver disease and incident heart failure. *Am J Cardiol* 2022;171:180-1. DOI PubMed
129. Iwasaki Y, Shiina K, Matsumoto C, et al. Correlation of the fatty liver index with the pathophysiological abnormalities associated with cardiovascular risk markers in japanese men without any history of cardiovascular disease: comparison with the fibrosis-4 score. *J Atheroscler Thromb* 2021;28:524-34. DOI PubMed PMC
130. Boeckmans J, Sandrin L, Knackstedt C, Schattenberg JM. Liver stiffness as a cornerstone in heart disease risk assessment. *Liver Int* 2024;44:344-56. DOI PubMed
131. Long MT, Zhang X, Xu H, et al. Hepatic fibrosis associates with multiple cardiometabolic disease risk factors: the framingham heart study. *Hepatology* 2021;73:548-59. DOI PubMed PMC
132. Tang R, Abeysekera KWM, Howe LD, Hughes AD, Fraser A. Non-alcoholic fatty liver and fibrosis is associated with cardiovascular structure and function in young adults. *Hepatol Commun* 2023;7:e0087. DOI PubMed PMC
133. Kuznetsova A, Dolgushina A, Savochkina A, et al. Liver stiffness is associated with the burden of carotid and systemic atherosclerosis in an unorganized cohort of patients 40-64 years old. *Diagnostics* 2022;12:2336. DOI PubMed PMC
134. 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;54:271-7. DOI PubMed PMC
135. Shili-Masmoudi S, Wong GL, Hiriart JB, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int* 2020;40:581-9. DOI PubMed
136. Ciardullo S, Cannistraci R, Mazzetti S, Mortara A, Perseghin G. Nonalcoholic fatty liver disease, liver fibrosis and cardiovascular disease in the adult US population. *Front Endocrinol* 2021;12:711484. DOI PubMed PMC
137. Petta S, Sebastiani G, Viganò M, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with nonalcoholic fatty liver disease and compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol* 2021;19:806-15.e5. DOI PubMed
138. Kleef LA, Lu Z, Ikram MA, 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;77:931-938. DOI PubMed
139. 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. DOI PubMed PMC
140. Tamaki N, Higuchi M, Kurosaki M, Loomba R, Izumi N; MRCH Liver Study Group. Risk difference of liver-related and cardiovascular events by liver fibrosis status in nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2022;20:1171-73.e2. DOI PubMed PMC
141. Lugari S, Baldelli E, Lonardo A. Metabolic primary liver cancer in adults: risk factors and pathogenic mechanisms. *Metab Target Organ Damage* 2023;3:5. DOI
142. Hagström H, Kechagias S, Ekstedt M. Risk for hepatic and extra-hepatic outcomes in nonalcoholic fatty liver disease. *J Intern Med* 2022;292:177-89. DOI PubMed
143. Mantovani A, Lonardo A, Stefan N, Targher G. Metabolic dysfunction-associated steatotic liver disease and extrahepatic

gastrointestinal cancers. *Metabolism* 2024;160:156014. DOI PubMed
144. Lonardo A. Extra-hepatic cancers in metabolic fatty liver syndromes. *Explor Dig Dis* 2023;2:11-7. DOI
145. Lonardo A. Is liver fibrosis a risk factor for gynecological cancers? *Metab Target Organ Damage* 2024;4:7. DOI
146. Kim MC, Park JG, Jang BI, Lee HJ, Lee WK. Liver fibrosis is associated with risk for colorectal adenoma in patients with nonalcoholic fatty liver disease. *Medicine* 2019;98:e14139. DOI PubMed PMC
147. Chakraborty D, Wang J. Nonalcoholic fatty liver disease and colorectal cancer: correlation and missing links. *Life Sci* 2020;262:118507. DOI PubMed PMC
148. Ait-ahmed Y, Lafdil F. Novel insights into the impact of liver inflammatory responses on primary liver cancer development. *Liver Research* 2023;7:26-34. DOI
149. Yu J, Chen X, Yang X, Zhang B. Understanding gut dysbiosis for hepatocellular carcinoma diagnosis and treatment. *Trends Endocrinol Metab* 2024;35:1006-20. DOI PubMed
150. Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the atherosclerosis risk in communities study, multi-ethnic study of atherosclerosis, and jackson heart study. *Diabetes Care* 2016;39:668-76. DOI PubMed PMC
151. Siniawski D, Masson G, Masson W, et al. Residual cardiovascular risk, use of standard care treatments, and achievement of treatment goals in patients with cardiovascular disease. *Int J Cardiol Cardiovasc Risk Prev* 2023;18:200198. DOI PubMed PMC
152. Jamalinia M, Lonardo A. Perspective article: Determinants and assessment of cardiovascular risk in steatotic liver disease owing to metabolic dysfunction-addressing the challenge. *Metab Target Organ Damage* 2024;4:23. DOI
153. Moreno-Del Castillo MC, Sanchez-Rodriguez A, Hernandez-Buen Abad JJ, et al. Importance of evaluating cardiovascular risk and hepatic fibrosis in patients with newly diagnosed nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2019;17:997-9. DOI PubMed
154. Lauridsen BK, Stender S, Kristensen TS, et al. Liver fat content, non-alcoholic fatty liver disease, and ischaemic heart disease: Mendelian randomization and meta-analysis of 279 013 individuals. *Eur Heart J* 2018;39:385-93. DOI PubMed
155. Yeung SL, Borges MC, Wong THT, Lawlor DA, Schooling CM. Evaluating the role of non-alcoholic fatty liver disease in cardiovascular diseases and type 2 diabetes: a Mendelian randomization study in Europeans and East Asians. *Int J Epidemiol* 2023;52:921-31. DOI PubMed PMC
156. Ren Z, Simons PIHG, Wesselius A, Stehouwer CDA, Brouwers MCGJ. Relationship between NAFLD and coronary artery disease: a Mendelian randomization study. *Hepatology* 2023;77:230-8. DOI PubMed PMC
157. Wanless IR. The role of vascular injury and congestion in the pathogenesis of cirrhosis: the congestive escalator and the parenchymal extinction sequence. *Curr Hepatology Rep* 2020;19:40-53. DOI
158. Poisson J, Lemoinne S, Boulanger C, et al. Liver sinusoidal endothelial cells: physiology and role in liver diseases. *J Hepatol* 2017;66:212-27. DOI PubMed
159. Adolph TE, Grander C, Moschen AR, Tilg H. Liver-microbiome axis in health and disease. *Trends Immunol* 2018;39:712-23. DOI PubMed
160. Hammoutene A, Rautou PE. Role of liver sinusoidal endothelial cells in non-alcoholic fatty liver disease. *J Hepatol* 2019;70:1278-91. DOI PubMed
161. Hsu CL, Schnabl B. The gut-liver axis and gut microbiota in health and liver disease. *Nat Rev Microbiol* 2023;21:719-33. DOI PubMed PMC
162. Pandey E, Nour AS, Harris EN. Prominent receptors of liver sinusoidal endothelial cells in liver homeostasis and disease. *Front Physiol* 2020;11:873. DOI PubMed PMC
163. Stefan N, Lonardo A, Targher G. Role of steatotic liver disease in prediction and prevention of cardiometabolic diseases. *Nat Rev Gastroenterol Hepatol* 2024;21:136-7. DOI PubMed
164. Alkhouri N, Tamimi TA, Yerian L, Lopez R, Zein NN, Feldstein AE. The inflamed liver and atherosclerosis: a link between histologic severity of nonalcoholic fatty liver disease and increased cardiovascular risk. *Dig Dis Sci* 2010;55:2644-50. DOI PubMed
165. Arulanandan A, Ang B, Bettencourt R, et al. Association between quantity of liver fat and cardiovascular risk in patients with nonalcoholic fatty liver disease independent of nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2015;13:1513-20.e1. DOI PubMed
166. Bril F, Sninsky JJ, Baca AM, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. *J Clin Endocrinol Metab* 2016;101:644-52. DOI PubMed
167. Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? *J Hepatol* 2018;68:335-52. DOI PubMed
168. Jamalinia M, Zare F, Noorizadeh K, Bagheri Lankarani K. Systematic review with meta-analysis: steatosis severity and subclinical atherosclerosis in metabolic dysfunction-associated steatotic liver disease. *Aliment Pharmacol Ther* 2024;59:445-58. DOI PubMed
169. las Heras N, Aller MA, Arias J, Lahera V. The risk association between experimental portal hypertension and an aortic atherosclerosis-like disease. *Hepatology* 2013;57:421-2. DOI PubMed
170. Mitten EK, Baffy G. Mechanobiology in the development and progression of non-alcoholic fatty liver disease: an updated review. *Metab Target Organ Damage* 2023;3:2. DOI
171. Gracia-Sancho J, Maeso-Díaz R, Fernández-Iglesias A, Navarro-Zornoza M, Bosch J. New cellular and molecular targets for the treatment of portal hypertension. *Hepatol Int* 2015;9:183-91. DOI PubMed

172. Sharpton SR, Loomba R. Emerging role of statin therapy in the prevention and management of cirrhosis, portal hypertension, and HCC. *Hepatology* 2023;78:1896-906. DOI PubMed
173. Lonardo A, Roncucci L. The "obese liver" and gastrointestinal cancer risk. *Transl Gastroenterol Hepatol* 2020;5:44. DOI PubMed PMC
174. Tadokoro T, Morishita A, Masaki T. Diagnosis and therapeutic management of liver fibrosis by microRNA. *Int J Mol Sci* 2021;22:8139. DOI PubMed PMC