Jamalinia *et al. Metab Target Organ Damage* 2024;4:23
DOI: 10.20517/mtod.2024.34

Metabolism and Target Organ Damage

Perspective

Open Access

Check for updates

Perspective article: determinants and assessment of cardiovascular risk in steatotic liver disease owing to metabolic dysfunction-addressing the challenge

Mohamad Jamalinia[1], **Amedeo Lonardo**[2]

[1]Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz 7193635899, Iran
[2]Department of Internal Medicine, Azienda Ospedaliero-Universitaria of Modena, Modena 41100, Italy.

Correspondence to: Dr. Mohamad Jamalinia, Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, 9th floor, Mohammad Rasoul Allah Research Tower, Khalili St., Shiraz 7193635899, Iran. E-mail: m_jamalinia@sums.ac.ir

How to cite this article: 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. https://dx.doi.org/10.20517/mtod.2024.34

Received: 24 Apr 2024 **First Decision:** 24 May 2024 **Revised:** 27 May 2024 **Accepted:** 13 Jun 2024 **Published:** 26 Jun 2024

Academic Editor: Giovanni Targher **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) stands as an independent risk factor for cardiovascular disease (CVD), which is the leading cause of mortality among MASLD patients. The diverse spectrum of cardio-nephro-metabolic and vascular manifestations inherent in MASLD highlights the complex profile of CVD risk associated with this condition. However, current approaches to assessing CVD risk in MASLD lack specificity, predominantly relying on traditional markers. Although it is widely accepted that patients with advanced fibrosis are more prone to CVD risk, recent evidence suggests that this isolated focus may overlook the remarkable phenotypic variability of this CVD risk across the entire MASLD population. Emerging data indicate a progressive escalation of CVD risk in parallel with the severity of MASLD, highlighting the need for precise disease staging to inform accurate risk assessment. To address this challenge, we propose a novel sequential approach to CVD risk assessment in MASLD. While traditional CVD risk factors remain essential, incorporating liver-specific parameters enhances risk stratification and guides targeted interventions to mitigate the substantial burden of cardiovascular disease in this vulnerable population. This approach involves initial screening using FIB-4 and NAFLD fibrosis score, followed by assessment of liver fibrosis with imaging-based non-invasive techniques in individuals at intermediate-high risk for advanced fibrosis and liver fat quantification in low-risk individuals. Future prospective investigations should focus on the simultaneous use of liver biomarkers and imaging modalities to evaluate, in a sex-specific manner, the efficacy of the proposed approach and to determine optimal thresholds of

liver fibrosis and steatosis for optimal CVD risk assessment.

Keywords: Biomarkers, cardiovascular risk, elastometry, fibroscan, liver fibrosis, steatosis, ultrasonography

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a significant public health concern affecting up to one-third of the global population, with its prevalence rising alongside type 2 diabetes mellitus in a mutual and bidirectional manner over the past two decades[1-3]. MASLD encompasses a spectrum of liver histology changes, ranging from benign hepatic steatosis, characterized by intrahepatocyte lipid accumulation, to more severe forms such as metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma. Although liver-related events are common in patients with advanced MASLD forms, the leading cause of mortality in MASLD is cardiovascular disease (CVD)[4,5]. Recent recognition of MASLD as an independent risk factor for CVD has further underscored the urgency of understanding its pathophysiology and implementing effective risk assessment strategies[6-9].

Despite growing awareness of the cardiovascular implications of MASLD, there is ongoing debate regarding the optimal strategy for assessing CVD risk in affected individuals. While traditional risk factors for CVD are well-established[10], there is increasing recognition of the importance of incorporating liver-specific parameters into CVD risk assessment algorithms for MASLD patients[11-13]. These hepatological parameters may offer unique insights into the complex interplay between metabolic dysfunction, steatotic liver disease (SLD), and cardiovascular health.

Aiming to direct future investigations, the present perspective article seeks to address this knowledge gap. To this end, published studies on CVD risk assessment strategies in MASLD are critically discussed, with due emphasis on the possible role of liver-related parameters. Our specific objective is to elucidate the most effective approaches for identifying and stratifying CVD risk in individuals with MASLD, as these are virtually useful for developing targeted interventions to mitigate the substantial burden of CVD in this vulnerable population.

MASLD *VS.* MAFLD IN PREDICTING CVD RISK

The recent changes in NAFLD terminology, schematically illustrated in Table 1, have resulted in different CVD risk profiles within the realm of SLD owing to metabolic dysfunction. The criteria for metabolic dysfunction-associated fatty liver disease (MAFLD), introduced in 2020[14,15], have identified patients with metabolically complicated liver conditions, irrespective of alcohol consumption, and have consequently shown higher CVD risk than NAFLD[16,17].

In addition, the criteria for MASLD, introduced in 2023 under the umbrella term SLD[18], further differentiate patients with MASLD and increased alcohol consumption, termed metALD, which has been associated with elevated CVD risk compared to MASLD alone[19-23]. Moon *et al.*, in a nationwide cohort study spanning a median follow-up of 9 years, observed an incremental risk of incident CVD from MASLD (SHR: 1.19) to metALD (SHR: 1.28)[19]. These findings imply that the MASLD nomenclature, compared to MAFLD, offers a more homogenous risk profile by acknowledging the impact of alcohol on CVD risk.

Moreover, MAFLD criteria, compared to MASLD, may overlook a significant proportion of lean patients with NAFLD[24-26], who are equally important in predicting CVD risk[27-29]. A meta-analysis of 21 studies revealed that individuals with lean NAFLD exhibited a 50% increase in the odds of cardiovascular mortality

Table 1. Definitions of NAFLD/MAFLD/MASLD

	NAFLD	MAFLD	MASLD
Years	1988	2020	2023
Alcohol level	< 20 g/d (w) or < 30 g/d (m)	No specific limit on alcohol	< 20 g/d (w) or < 30 g/d (m)
definition	Steatosis without other causes	steatosis with the presence (or treatment of) any of the following:	steatosis with the presence (or treatment of) any of the following:
		1. overweight	1. overweight or increased WC
		2. T2DM	2. T2DM or prediabetes
		3. at least 2 metabolic abnormalities:	3. increased BP
		increased WC	4. elevated TG
		increased BP	5. low HDL
		elevated TG	
		low HDL	
		elevated FBS	
		elevated HOMA-IR score	
		elevated CRP	

NAFLD: non-alcoholic fatty liver disease; MAFLD: metabolic associated fatty liver disease; MASLD: metabolic dysfunction-associated fatty liver disease; WC: waist circumference; BP: blood pressure; TG: triglycerides; HDL: high-density lipoprotein; FBS: fasting blood sugar; HOMA-IR: homeostatic model assessment for insulin resistance; CRP: C-reactive protein; T2DM: type 2 diabetes mellitus

compared to their non-lean counterparts[30]. Furthermore, Kang *et al.* found that both MASLD and MAFLD were associated with coronary artery calcification (CAC) > 0, whereas only MASLD showed an association with severe CAC (> 300) (aOR: 1.38)[31].

In summary, recent data indicate that MASLD may offer better predictive value for CVD risk than MAFLD. MASLD provides a more homogeneous risk profile within SLD subcategories, captures lean NAFLD patients who also exhibit high CVD risk, and shows associations with a higher risk of ASCVD. However, it is essential to note that the superiority of MASLD over MAFLD in predicting CVD risk requires further validation.

SPECTRUM AND PATHOMECHANISMS OF CARDIOVASCULAR MANIFESTATIONS OF MASLD

The spectrum of cardio-nephro-metabolic and vascular manifestations of MASLD is wider than originally thought and embraces a variety of risk factors and damage to target organs. Figure 1 illustrates the principal

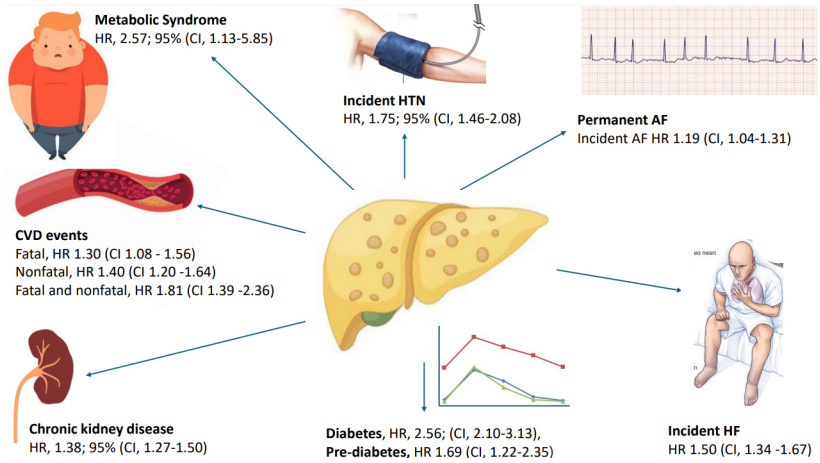

Figure 1. Spectrum of cardio-nephro-metabolic and vascular manifestations of MASLD[32-36]. AF: atrial fibrillation; CVD: cardiovascular disease; HF: heart failure; HTN: arterial hypertension; MASLD: metabolic dysfunction-associated steatotic liver disease.

cardiometabolic outcomes spanning from the full-blown metabolic syndrome to its individual components (arterial hypertension, diabetes, and prediabetes) and from major cardiovascular events (MACE) (both fatal and non-fatal) to atrial fibrillation, heart failure, and chronic kidney disease[32,33]. Further to these, heart valve calcifications (predominantly aortic valve sclerosis), left ventricular diastolic dysfunction and hypertrophy have also been reportedly associated with MASLD[34-36].

A cause-and-effect relationship between at least some of these cardiovascular manifestations is demonstrated by a Mendelian Randomization study[37] as well as by the finding that bariatric surgery in MASLD patients is associated with a significant reduction in incident cardiovascular events[38] and adverse hepatic outcomes[39].

The putative pathomechanisms associating MASLD with the various cardiovascular manifestations named above are incompletely defined and the succession of such mechanisms, postulated to act in parallel, remains speculative[33]. Interestingly, cardiovascular manifestations of MASLD tend to worsen in parallel with increasing liver fat content, the progression from simple steatosis to steatohepatitis and more advanced stages of liver fibrosis[33,40-43]. These findings may be useful both in the diagnostic and therapeutic arena.

The pathomechanics underlying cardiovascular manifestations of MASLD include, further to liver histology changes, the Metabolic Syndrome (and its individual features), underlying insulin resistance, accompanying lipotoxicity, systemic oxidative stress, and systemic (often sub-clinical) pro-inflammatory and pro-thrombotic milieu[33]. Additional mechanisms include genetic polymorphisms, pro-inflammatory diets, gut dysbiosis, and extracellular vesicles[44-47].

VARIABLE CARDIOVASCULAR RISK IN MASLD

Cofactors, i.e., genetics and epigenetics, lifestyle habits, viruses, immunity, drugs, and gut microbiota, determine organ dysfunction in the setting of MASLD[48]. Sex is a strong genetic factor that modulates the risk of cardiovascular (CV) disease (CVD) in the context of MASLD[49]. Desai *et al.*, based on a population of 409,130 hospitalizations with MASLD, found different sex distribution of CV risk factors (with women, compared to men, displaying higher levels of obesity and uncomplicated diabetes) and major CV and cerebrovascular events (which were more common among men)[50]. Interestingly, in this connection,

Kammerlander *et al.*, in their study involving 3,482 participants in the Framingham Heart Study, found that cardiometabolic and CVD risk associated with visceral obesity could be adequately captured by simple anthropometric measures (such as waist circumference and body mass index) in men, while in women, measurement of abdominal visceral adipose tissue with computed tomography permitted more accurate assessment of obesity-associated cardiometabolic and CVD risk[51]. Collectively, these studies strongly suggest the need for sex-specific analyses of the interactions between cardio-metabolic risk, MACE, and MASLD.

Two common conditions document the notion that comorbidities with either chronic obstructive pulmonary disease (COPD) or chronic kidney disease (CKD) strongly affect the risk of CVD in MASLD.

COPD, an acknowledged CV risk factor, has several commonalities with MASLD and these two conditions are reportedly associated[52,53]. Viglino *et al.*, in their prospective study of 111 COPD patients, found through multivariate analysis that after a 5-year follow-up, patients with liver fibrosis had more CV events and higher mortality than those with no fibrosis (HR [95%CI]: 2.94 [1.18; 7.33]), implying that early assessment of liver health might potentially improve CV outcomes in COPD[54].

CKD is a common CVD risk factor and a feared incident complication in the course of MASLD[55]. Miyamori *et al.* in their large population study have reported that only concomitant MASLD and CKD were independently associated with an increased risk of ischemic heart disease (HR, 1.51, 95%CI: 1.02-2.22), while either MAFLD or CKD alone were not[56]. Strategies aimed at preventing and contrasting the development and progression of CKD among those with MASLD have recently been discussed[55].

CURRENT STRATEGIES FOR CARDIOVASCULAR RISK ASSESSMENTS IN MASLD

In 2010, the pioneering Italian NAFLD guidelines stated that *"NASH patients should undergo periodic evaluation of cardiovascular risk"*[57]. CVD is indeed the leading cause of mortality of these patients, particularly among those aged 45 to 54 years[58,59], and up to 10% of NAFLD individuals die from CVD, which is a 2-fold to almost 4-fold increased risk of CVD *vs.* non-NAFLD subjects[60-62], indicating that MASLD is a non-traditional CVD risk factor[63,64].

Presently, CVD risk assessment and management, preferentially as a hospital-based, multi-disciplinary approach[65,66], is universally endorsed by Scientific Societies as a key requirement in the care of MASLD patients[6,67-71].

Accumulating evidence indicates that both NAFLD and MAFLD are epidemiologically and causally associated with CVD, as proven by Mendelian randomization studies; therefore, NAFLD/MAFLD/MASLD must be considered as "high-risk" conditions for CVD like diabetes, which justifies aggressive correction of cardiometabolic risk factors among these patients[72].

However, whether the same CVD risk scoring systems should be used among MASLD individuals as those proposed for use in the general population remains uncertain. Indeed, elevated C-reactive protein levels are associated with CVD risk in MASLD[73], but the pro-inflammatory, insulin-resistant and hypertriglyceridemic components of NAFLD are generally neglected by available CVD risk scoring systems which, additionally, need to be locally validated[74]. Consistent with this concern, a Japanese study conducted among subjects with T2D and suspected coronary artery disease found that NAFLD, in addition to coronary artery calcium scores and FRS, improved the risk classification of cardiovascular events[75]. Similarly, a Korean population study found that the severity of steatosis diagnosed with ultrasound and NAFLD scoring

systems correlated with increased CVD risk[76].

The CVD risk is not homogenous across the MASLD population. Men, postmenopausal women, and those with the more advanced stages of fibrosis are more prone to the odds of MACE[77-80]; lean NAFLD, and NAFLD with concurrent sarcopenia are associated with more severe risk of ASCVD[81,82]. Moreover, changes in the NAFLD/MAFLD/MASLD nomenclature identify different CVD risk profiles[19,83-85]; metabolomic signatures predict distinctive CVD risk profiles[86], and "metabolic" (as opposed to "genetic") MASLD is causally associated with the risk of MACE[37,87].

Two major validated CVD risk scoring systems have been proven useful among MASLD individuals: the Framingham Risk Score (FRS)[88] and the atherosclerotic CVD risk score (ASCVD)[89]. Both FRS and ASCVD predict the risk of incident MACE at 10 years based on patient demography, medical history, and routine clinical-laboratory assessment, making them practical tools for risk prediction[90].

However, validation in the specific MASLD setting would request additional investigation involving larger patient populations who should be fully characterized according to the so-called "LDE" paradigm assessing liver-related ("L"), disease determinants "D", and extrahepatic features of disease ("E")[91].

Non-invasive assessment of liver fibrosis is a major tool for CVD risk assessment, and various non-invasive, non-patented methods for early identification of liver fibrosis are available. These include APRI (based on AST, platelets), FIB-4 (AST, ALT, age, Platelets), NFS (based on age, body mass index, impaired fasting glucose/T2D, AST, ALT, platelets, and albumin), and VCTE (i.e. liver stiffness), whose differing characteristics have recently been thoroughly evaluated elsewhere[92]. Niederseer *et al.*, in a large Austrian cohort, found that NFS was correlated with FRS ($r = 0.29$; $P < 0.001$), and a one-point increase in NFS strongly predicted high-risk FRS independent of confounding factors (OR 1.30, 95%CI 1.09-1.54; $P = 0.003$)[93]. A meta-analysis of 9 published studies, totaling 155,382 NAFLD cases, found that FIB-4 and NFS (rather than APRI) are useful for identifying individuals with NAFLD who are exposed to a higher CVD risk[11]. Further to biomarkers of liver fibrosis, the MELD-Na score also predicts MACE among NAFLD patients, and when added to the FRS, it may better define NAFLD-associated CVD risk[94].

Beyond liver biomarkers, various research indicates that increasing liver fibrosis assessed through both magnetic resonance elastography (MRE) and transient elastography (TE) correlates with CVD risk and could enhance CVD risk assessments in MASLD patients. Mangla *et al.* found in a patient population of asymptomatic T2D individuals that increased liver fibrosis (assessed by MRE ≥ 3.62) was associated with more elevated CVD risk assessed with CAC scores[95]. However, MRE is not universally available and other techniques may be used to assess liver fibrosis.

NEW EVIDENCE: EMPHASIS ON LIVER-RELATED PARAMETERS AND OPPORTUNITIES FOR SPECIFIC CARDIOVASCULAR RISK ASSESSMENT IN MASLD

The guidelines from the American Gastroenterological Association (AGA) / American Association for the Study of Liver Diseases (AASLD) propose a three-step screening approach for advanced fibrosis[69,96]. Initially, FIB-4 or NFS scoring is recommended[97], followed by liver stiffness measurement (LSM). These initial steps aim to rule out advanced fibrosis, with thresholds set at FIB-4 < 1.3 or NFS < -1.455 and LSM < 8 kPa. The final step confirms advanced fibrosis using either magnetic resonance elastography (MRE) or liver biopsy, particularly in intermediate to high-risk patients.

While it is well recognized that patients with advanced fibrosis (≥ F3) are at a heightened risk of CVD[60,98-106], previous research on MASLD populations has associated this risk with any degree of fibrosis (≥ F1)[107-110] or significant fibrosis (≥ F2)[111-115]. For instance, a study by Wu *et al.* on asymptomatic MASLD patients diagnosed with MRI-PDFF demonstrated that the presence of any fibrosis (assessed by TE > 6.1 kPa) is the strongest predictor of subclinical atherosclerosis in MASLD[108]. Similarly, Park *et al.* reported that significant fibrosis (assessed by MRE ≥ 2.97) in MASLD is associated with CVD risk regardless of their FRS[113].

Moreover, a meta-analysis comprising 12 studies and 4,725 MASLD patients without prior CVD, focusing on elastography (TE and MRE) for fibrosis assessment, found that any degree of fibrosis was linked to subclinical atherosclerosis[13]. The pooled odds ratio (OR) was 1.64 (95%CI: 1.22-2.20) for ≥ F1, increasing with the degree of fibrosis to 2.22 (95%CI: 1.37-3.62) for ≥ F2, and to 3.42 (95%CI: 1.81-6.46) for ≥ F3. These findings underscore the importance of considering all levels of fibrosis in assessing CVD risk in MASLD patients, as even mild fibrosis appears to be associated with an increased risk of subclinical atherosclerosis.

In summary, recent investigations emphasize the critical importance of identifying patients at early disease stages, encompassing not only advanced fibrosis but also milder stages. These findings highlight the limitations of solely focusing on advanced fibrosis while broadening the scope of CVD risk assessments in MASLD. While FIB-4 < 1.3 and NFS < -1.455 demonstrate good performance in excluding advanced fibrosis[116,117], aligning with the primary goal of current guidelines for fibrosis assessment in the MASLD population, they exhibit relatively poor performance in ruling out significant fibrosis[117-119]. This presents a notable challenge, with special reference to patients classified as low-risk, who represent up to 80% of individuals with MASLD[120].

Conversely, recent studies with extensive sample sizes and population-based designs, typically enrolling individuals deemed to be at lower risk for advanced fibrosis, demonstrate that the extent of steatosis is associated with significantly increased CVD risk in MASLD. A meta-analysis of 19 studies involving 147,411 asymptomatic individuals, with a substantial proportion sourced from health screenings, revealed a significant association between higher liver fat content (LFC) and CVD risk in MASLD[12]. The pooled OR for subclinical atherosclerosis was 1.27 (95%CI: 1.13-1.41) in cases of mild steatosis, which significantly increased to 1.68 (95%CI: 1.41-2.00) in moderate to severe steatosis.

Furthermore, the longitudinal study by Pisto *et al.*, involving 988 Finnish participants, with a median follow-up of 17.6 years, demonstrated an elevated risk of future cardiovascular events with higher LFC (adjusted Hazard Ratio [aHR]: 1.74, 95%CI: 1.16-2.63)[121].

Similarly, a longitudinal study conducted in Korea, encompassing a large sample size of 7.8 million individuals without prior CVD over a median follow-up of 8 years, illustrated that high LFC as measured by the surrogate Fatty Liver Index (FLI) was associated with a higher risk of MACE (myocardial infarction and ischemic stroke) in MASLD, both with and without DM. The adjusted HR in MASLD grade 1 without DM was 1.23 (95%CI: 1.22-1.25), significantly increasing to 1.44 (95%CI: 1.42-1.47) in MASLD grade 2 without DM, and the adjusted HR was 1.10 (95%CI: 1.07-1.13) in grade 1 MASLD with DM, which significantly increased to 1.25 (95%CI: 1.22-1.29) in grade 2 MASLD with DM[122]. These findings offer robust evidence supporting the utilization of steatosis quantification for CVD risk assessment in MASLD.

It is imperative to exercise caution when quantifying liver fat in populations at high risk for advanced fibrosis. In nearly all studies conducted within such populations, the severity of steatosis has shown either a

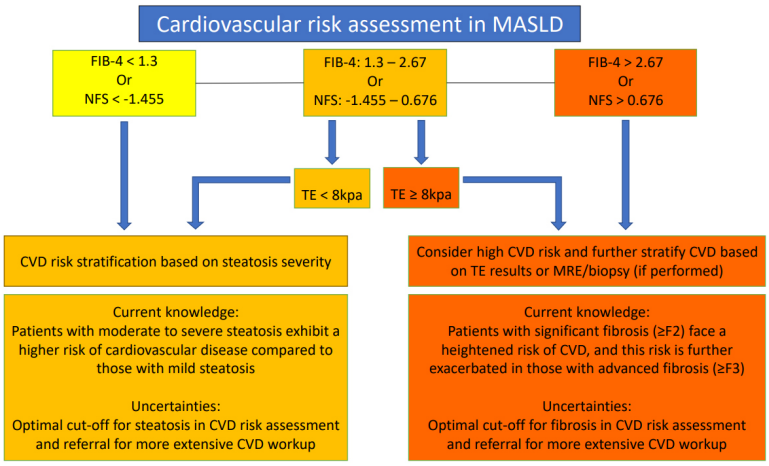

Figure 2. Proposed Algorithm for Cardiovascular Risk Assessments in MASLD. FIB-4: fibrosis-4; NFS: NAFLD fibrosis score; MASLD: Metabolic dysfunction-associated steatotic liver disease; TE: transient elastography; MRE: magnetic resonance elastography; CVD: cardiovascular disease.

non-significant or reverse association with CVD risk[100,103,112,113]. This underscores the significant confounding effect of advanced fibrosis on this association, potentially attributed to burnout MASH, where advanced fibrosis typically exhibits a reduction in the extent of steatosis, probably due to increased adiponectin serum levels[123,124]. Consequently, given that this strategy may mistakenly classify patients with advanced fibrosis as low-risk, it would be advisable to reserve this approach only to those patients in whom advanced fibrosis has reasonably been excluded (FIB-4 < 1.3, NFS < -1.455, or LSM < 8 kPa).

To date, an imaging-free scoring system for accurately quantifying steatosis remains unavailable. The most useful index for steatosis assessment, the FLI, is confounded by fibrosis and inflammation, does not precisely quantify steatosis and fails to take sex differences into account[125,126]. In contrast, Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) is considered to be the most accurate modality for quantifying liver fat[127]. However, its widespread application is hindered by cost and availability constraints and is, therefore, primarily suitable for clinical trials.

Despite these challenges, recent advancements in ultrasound technology offer a promising alternative for quantifying liver fat. Two previous meta-analyses shed light on the effectiveness of ultrasound in this regard. The first analysis, conducted by Hernaez *et al.* in 2011, encompassed 49 studies and demonstrated ultrasound's sensitivity of 62% for detecting mild steatosis (≥ 5% hepatic steatosis) and 84.8% for detecting moderate to severe steatosis (≥ 30% hepatic steatosis)[128]. Building upon this foundation, an updated meta-analysis by Ballestri *et al.* in 2021, focusing on studies published in the last decade (comprising 12 studies), revealed improved detection rates for mild steatosis (sensitivity 82%) and consistent results for moderate to severe steatosis (sensitivity 85%)[129]. These advancements likely stem from evolving techniques and increased operator awareness of hepatic steatosis[129]. Consequently, conventional ultrasound emerges as a cost-effective and widely applicable modality for quantifying liver fat.

In summary, liver-related parameters could enhance the discriminatory power of existing risk calculators for identifying more patients at high risk of CVD, ideally in a sequential manner, as they can address each other's limitations. Additionally, patients identified as at high risk for CVD using this approach could be referred for more extensive investigations, such as non-invasive markers of early cardiovascular disease, including coronary artery calcium score, carotid intima-media thickness, and arterial stiffness. These

markers have clear associations with long-term CVD events[130-134] and could guide clinicians in deciding whether to subject patients to more aggressive cardiometabolic risk reduction. However, uncertainties persist regarding patient selection for such referrals, as optimal cut-offs for liver-related parameters to effectively rule in or rule out CVD risk have not yet been determined, and the cost-effectiveness of such referrals has yet to be examined. Until optimal risk calculators and solid evidence are available, individual patients' personal histories may better guide clinicians in the decision-making process.

CONCLUSION

Our perspective article suggests that a sequential combination of FIB-4/NFS with imaging modalities for quantifying both liver fibrosis and steatosis enhances CVD risk assessments in MASLD [Figure 2]. Patients with FIB-4 > 1.3 or NFS > -1.455 should undergo more accurate assessments of fibrosis through TE, MRE, or biopsy, aligning with current guidelines for screening advanced fibrosis. Furthermore, among individuals classified as at low risk for advanced fibrosis (FIB-4 < 1.3, NFS < -1.455, or TE < 8 kPa), cardiovascular risk could be stratified based on the severity of steatosis. However, this proposed approach requires rigorous validation. Future studies should focus on the simultaneous use of liver biomarkers and imaging modalities with longitudinal designs to evaluate, in a sex-specific manner, the efficacy of the proposed approach and to determine optimal thresholds for both fibrosis and steatosis in CVD risk assessments.

DECLARATIONS

Authors' contributions

study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation and reviewed the initial drafts and approved the final version of the manuscript: Jamalinia M, Lonardo A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Amedeo Lonardo is the Editor-in-Chief of the journal *Metabolism and Target Organ Damage*. However, he was not involved in the selection of Reviewers nor in any editorial decisions regarding the present manuscript. Mohamad Jamalinia has declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol* 2022;7:851-61. DOI
2. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes

mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021;70:962-9. DOI PubMed

3. Lonardo A, Leoni S, Alswat KA, Fouad Y. History of nonalcoholic fatty liver disease. *Int J Mol Sci* 2020;21:5888. DOI PubMed PMC
4. Konyn P, Ahmed A, Kim D. Causes and risk profiles of mortality among individuals with nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2023;29:S43-57. DOI PubMed PMC
5. Kim D, Adejumo AC, Yoo ER, et al. Trends in mortality from extrahepatic complications in patients with chronic liver disease, from 2007 through 2017. *Gastroenterology* 2019;157:1055-66.e11. DOI
6. Duell PB, Welty FK, Miller M, et al; on behalf of the American Heart Association Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Lifestyle and Cardiometabolic Health; and Council on Peripheral Vascular Disease. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the american heart association. *Arterioscler Thromb Vasc Biol* 2022;42:e168-85. DOI PubMed
7. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:903-13. DOI
8. Jaruvongvanich V, Chenbhanich J, Sanguankeo A, Rattanawong P, Wijarnpreecha K, Upala S. Increased arterial stiffness in nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroen Hepat* 2017;29:e28-35. DOI
9. Wong MYZ, Yap JJL, Sultana R, Cheah M, Goh GBB, Yeo KK. Association between non-alcoholic fatty liver disease and subclinical atherosclerosis in Western and Asian cohorts: an updated meta-analysis. *Open Heart* 2021;8:e001850. DOI PubMed PMC
10. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *Circulation* 2019;140:e596-646. DOI PubMed PMC
11. 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 Gastroen Hepat* 2022;34:1277-84. DOI
12. 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
13. Jamalinia M, Zare F, Lankarani KB. Systematic review and meta-analysis: Association between liver fibrosis and subclinical atherosclerosis in nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2023;58:384-94. DOI PubMed
14. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020;73:202-9. DOI PubMed
15. Eslam M, Sanyal AJ, George J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020;158:1999-2014.e1. DOI
16. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. *Clin Gastroenterol Hepatol* 2021;19:2138- 47.e10. DOI PubMed
17. Sung K, Yoo TK, Lee MY, Byrne CD, Zheng M, Targher G. Comparative associations of nonalcoholic fatty liver disease and metabolic dysfunction-associated fatty liver disease with coronary artery calcification: a cross-sectional and longitudinal cohort study. *ATVB* 2023;43:482-91. DOI
18. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol* 2023;79:1542-56. DOI PubMed PMC
19. Moon JH, Jeong S, Jang H, Koo BK, Kim W. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. *eClinicalMedicine* 2023;65:102292. DOI PubMed PMC
20. Choe HJ, Moon JH, Kim W, Koo BK, Cho NH. Steatotic liver disease predicts cardiovascular disease and advanced liver fibrosis: a community-dwelling cohort study with 20-year follow-up. *Metabolism* 2024;153:155800. DOI PubMed
21. Kim D, Wijarnpreecha K, Cholankeril G, Ahmed A. Steatotic liver disease-associated all-cause/cause-specific mortality in the United States. *Aliment Pharmacol Ther* 2024;60:33-42. DOI PubMed
22. Tamaki N, Kimura T, Wakabayashi S, et al. Long-term clinical outcomes in steatotic liver disease and incidence of liver-related events, cardiovascular events and all-cause mortality. *Aliment Pharmacol Ther* 2024;60:61-9. DOI
23. Kim D, Wijarnpreecha K, Cholankeril G, Ahmed A. Metabolic dysfunction-associated steatotic liver disease and all-cause/cause-specific mortality among adults in the United States. *J Hepatol* 2024;80:e79-81. DOI PubMed
24. Ng CH, Chan KE, Ou KQ, et al. IDDF2022-ABS-0132 Mafld and nafld in lean individuals. A prospective analysis of 12,505 lean individuals. *Gut* 2022;71:A50. DOI
25. De A, Bhagat N, Mehta M, Taneja S, Duseja A. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with NAFLD. *J Hepatol* 2024;80:e61-2. DOI PubMed
26. Ramírez-Mejía MM, Jiménez-Gutiérrez C, Eslam M, George J, Méndez-Sánchez N. Breaking new ground: MASLD vs. MAFLD-which holds the key for risk stratification? *Hepatol Int* 2024;18:168-78. DOI PubMed
27. Wijarnpreecha K, Li F, Lundin SK, et al. Higher mortality among lean patients with non-alcoholic fatty liver disease despite fewer metabolic comorbidities. *Aliment Pharmacol Ther* 2023;57:1014-27. DOI PubMed PMC
28. Arvind A, Henson JB, Osganian SA, et al. Risk of cardiovascular disease in individuals with nonobese nonalcoholic fatty liver disease. *Hepatol Commun* 2022;6:309-19. DOI PubMed PMC
29. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020;5:739-52. DOI PubMed

30. Nso N, Mergen D, Ikram M, et al. Cardiovascular morbidity and mortality in lean vs. non-lean MASLD: A comprehensive meta-analysis. *Curr Prob Cardiology* 2024;49:102569. DOI
31. Kang MK, Song J, Loomba R, et al. Comparative associations of MASLD and MAFLD with the presence and severity of coronary artery calcification. *Res Sq* 2024;rs.3:rs-3979461. DOI PubMed PMC
32. Chan KE, Ong EYH, Chung CH, et al. Longitudinal outcomes associated with metabolic dysfunction-associated steatotic liver disease: a meta-analysis of 129 studies. *Clin Gastroenterol H* 2024;22:488-98.e14. DOI
33. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut* 2024;73:691-702. DOI PubMed
34. Durak H, Çetin M, Emlek N, et al. FIB-4 liver fibrosis index correlates with aortic valve sclerosis in non-alcoholic population. *Echocardiography* 2024;41:e15732. DOI
35. Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. *Diabetes Obes Metab* 2022;24:28-43. DOI PubMed
36. Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2018;15:425-39. DOI PubMed
37. 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
38. Kumar J, Mohsin S, Hasan M, et al. Cardiovascular outcomes post bariatric surgery in patients with metabolic dysfunction-associated steatotic liver disease - a systematic review and meta-analysis. *Clin Res Hepatol Gas* 2024;48:102261. DOI
39. Wang G, Huang Y, Yang H, Lin H, Zhou S, Qian J. Impacts of bariatric surgery on adverse liver outcomes: a systematic review and meta-analysis. *Surg Obes Relat Dis* 2023;19:717-26. DOI
40. Solomon A, Negrea MO, Cipăian CR, et al. Interactions between metabolic syndrome, MASLD, and arterial stiffening: a single-center cross-sectional study. *Healthcare* 2023;11:2696. DOI PubMed PMC
41. Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? *J Hepatol* 2018;68:335-52. DOI PubMed
42. Brunner KT, Pedley A, Massaro JM, Hoffmann U, Benjamin EJ, Long MT. Increasing liver fat is associated with progression of cardiovascular risk factors. *Liver Int* 2020;40:1339-43. DOI PubMed PMC
43. Brunner KT, Pedley A, Massaro JM, Hoffmann U, Benjamin EJ, Long MT. Increasing liver fat is associated with incident cardiovascular risk factors. *Clin Gastroenterol Hepatol* 2020;18:1884-6. DOI PubMed PMC
44. Srinivas AN, Suresh D, Santhekadur PK, Suvarna D, Kumar DP. Extracellular vesicles as inflammatory drivers in NAFLD. *Front Immunol* 2021;11:627424. DOI PubMed PMC
45. Chandrasekharan K, Alazawi W. Genetics of non-alcoholic fatty liver and cardiovascular disease: implications for therapy? *Front Pharmacol* 2020;10:1413. DOI PubMed PMC
46. Petermann-rocha F, Wirth MD, Boonpor J, et al. Associations between an inflammatory diet index and severe non-alcoholic fatty liver disease: a prospective study of 171,544 UK Biobank participants. *BMC Med* 2023;21:123. DOI PubMed PMC
47. Khan A, Ding Z, Ishaq M, et al. Understanding the effects of gut microbiota dysbiosis on nonalcoholic fatty liver disease and the possible probiotics role: recent updates. *Int J Biol Sci* 2021;17:818-33. DOI PubMed PMC
48. Lonardo A, Singal A, 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
49. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. *The Lancet* 2020;396:565-82. DOI PubMed PMC
50. Desai R, Alvi AT, Vasavada A, et al. Sex and racial disparities in non-alcoholic fatty liver disease-related cardiovascular events: national inpatient sample analysis (2019). *World J Cardiol* 2024;16:137-48. DOI PubMed PMC
51. Kammerlander AA, Lyass A, Mahoney TF, et al. Sex differences in the associations of visceral adipose tissue and cardiometabolic and cardiovascular disease risk: the Framingham heart study. *JAHA* 2021;10:e019968. DOI PubMed PMC
52. Polman R, Hurst JR, Uysal OF, Mandal S, Linz D, Simons S. Cardiovascular disease and risk in COPD: a state of the art review. *Expert Rev Cardiovasc Ther* 2024;22:177-91. DOI PubMed
53. Lonardo A, Beghe B, Fabbri LM. Chronic obstructive pulmonary disease (COPD) and metabolic fatty liver syndromes: a dangerous but neglected liaison. *Metab Target Organ Damage* 2022;2:6. DOI
54. Viglino D, Plazanet A, Bailly S, et al. Impact of non-alcoholic fatty liver disease on long-term cardiovascular events and death in chronic obstructive pulmonary disease. *Sci Rep* 2018;8:16559. DOI PubMed PMC
55. Lonardo A. Association of NAFLD/NASH, and MAFLD/MASLD with chronic kidney disease: an updated narrative review. *Metab Target Organ Damage* 2024;4:16. DOI
56. Miyamori D, Tanaka M, Sato T, et al. Coexistence of metabolic dysfunction-associated fatty liver disease and chronic kidney disease is a more potent risk factor for ischemic heart disease. *JAHA* 2023;12:e030269. DOI PubMed PMC
57. Loria P, Adinolfi LE, Bellentani S, et al; NAFLD Expert Committee of the Associazione Italiana per lo studio del Fegato. Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease. A decalogue from the Italian association for the study of the liver (AISF) expert committee. *Dig Liver Dis* 2010;42:272-82. DOI PubMed
58. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol* 2008;103:2263-71. DOI PubMed PMC

59. Söderberg C, Stål P, Askling J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. *Hepatology* 2010;51:595-602. DOI
60. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015;61:1547-54. DOI
61. Spahillari A, Mukamal K, Defilippi C, et al. The association of lean and fat mass with all-cause mortality in older adults: the cardiovascular health study. *Nutr Metab Cardiovas* 2016;26:1039-47. DOI PubMed PMC
62. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. *J Hepatol* 2016;65:589-600. DOI PubMed
63. 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
64. Li M, Wang H, Zhang X, Cai J, Li H. NAFLD: an emerging causal factor for cardiovascular disease. *Physiology* 2023;38:255-65. DOI
65. Li W, Sheridan D, McPherson S, Alazawi W; Collaborators. National study of NAFLD management identifies variation in delivery of care in the UK between 2019 to 2022. *JHEP Rep* 2023;5:100897. DOI PubMed PMC
66. Driessen S, Francque SM, Anker SD, et al. Metabolic dysfunction-associated steatotic liver disease and the heart. *Hepatology* 2023;Online ahead of print. DOI PubMed
67. Aller R, Fernández-Rodríguez C, lo Iacono O, et al. Documento de consenso. Manejo de la enfermedad hepática grasa no alcohólica (EHGNA). Guía de práctica clínica. *Gastroenterología y Hepatología* 2018;41:328-49. DOI
68. Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64:1388-402. DOI PubMed
69. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797-835. DOI PubMed PMC
70. Cusi K, Isaacs S, Barb D, et al. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings. *Endocrine Practice* 2022;28:528-62. DOI
71. Visseren FLJ, Mach F, Smulders YM, et al; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227-337. DOI PubMed
72. Ren Z, Wesselius A, Stehouwer CD, Brouwers MC. Cardiovascular implications of metabolic dysfunction-associated fatty liver disease. *Endocrin Metab Clin* 2023;52:459-68. DOI PubMed
73. Chiang CH, Huang CC, Chan WL, Chen JW, Leu HB. The severity of non-alcoholic fatty liver disease correlates with high sensitivity C-reactive protein value and is independently associated with increased cardiovascular risk in healthy population. *Clin Biochem* 2010;43:1399-404. DOI PubMed
74. Lonardo A, Ballestri S, Targher G, Loria P. Diagnosis and management of cardiovascular risk in nonalcoholic fatty liver disease. *Expert Rev Gastroent* 2015;9:629-50. DOI
75. Ichikawa K, Miyoshi T, Osawa K, et al. Prognostic value of non-alcoholic fatty liver disease for predicting cardiovascular events in patients with diabetes mellitus with suspected coronary artery disease: a prospective cohort study. *Cardiovasc Diabetol* 2021;20:8. DOI PubMed PMC
76. Kweon Y, Ko H, Kim A, et al. Prediction of cardiovascular risk using nonalcoholic fatty liver disease scoring systems. *Healthcare* 2021;9:899. DOI PubMed PMC
77. Tsou M, Chen J. Gender-based association of coronary artery calcification and framingham risk score with non-alcoholic fatty liver disease and abdominal obesity in taiwanese adults, a cross-sectional study. *Front Cardiovasc Med* 2022;9:803967. DOI PubMed PMC
78. Zhou H, Zhang C, Ni J, Han X. Prevalence of cardiovascular risk factors in non-menopausal and postmenopausal inpatients with type 2 diabetes mellitus in China. *BMC Endocr Disord* 2019;19:98. DOI PubMed PMC
79. Wang J, Lonardo A. Commentary: of women, liver, and heart. *Metab Target Organ Damage* 2023;3:14. DOI
80. 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
81. Kim Y, Han E, Lee JS, et al. Cardiovascular risk is elevated in lean subjects with nonalcoholic fatty liver disease. *Gut and Liver* 2022;16:290-9. DOI PubMed PMC
82. Han E, Lee Y, Kim YD, et al. Nonalcoholic fatty liver disease and sarcopenia are independently associated with cardiovascular risk. *Am J Gastroenterol* 2020;115:584-95. DOI
83. Zhang P, Dong X, Zhang W, et al. Metabolic-associated fatty liver disease and the risk of cardiovascular disease. *Clin Res Hepatol Gas* 2023;47:102063. DOI
84. Chun HS, Lee M, Lee JS, et al. Metabolic dysfunction associated fatty liver disease identifies subjects with cardiovascular risk better than non-alcoholic fatty liver disease. *Liver Int* 2023;43:608-25. DOI
85. Semmler G, Balcar L, Wernly S, et al. Insulin resistance and central obesity determine hepatic steatosis and explain cardiovascular risk in steatotic liver disease. *Front Endocrinol* 2023;14:1244405. DOI PubMed PMC

86. Martínez-arranz I, Bruzzone C, Noureddin M, et al. Metabolic subtypes of patients with NAFLD exhibit distinctive cardiovascular risk profiles. *Hepatology* 2022;76:1121-34. DOI PubMed PMC
87. 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 279013 individuals. *Eur Heart J* 2018;39:385-93. DOI
88. Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, St Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. *Liver Int* 2012;32:945-50. DOI PubMed PMC
89. Golabi P, Fukui N, Paik J, Sayiner M, Mishra A, Younossi ZM. Mortality risk detected by atherosclerotic cardiovascular disease score in patients with nonalcoholic fatty liver disease. *Hepatol Commun* 2019;3:1050-60. DOI PubMed PMC
90. Mellemkjær A, Kjær MB, Haldrup D, Grønbæk H, Thomsen KL. Management of cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease. *Eur J Intern Med* 2024;122:28-34. DOI PubMed
91. Lonardo A. Renaming NAFLD to MAFLD: could the LDE system assist in this transition? *J Clin Med* 2021;10:492. DOI PubMed PMC
92. Thiele M, Kamath PS, Graupera I, et al. Screening for liver fibrosis: lessons from colorectal and lung cancer screening. *Nat Rev Gastroenterol Hepatol* 2024;21:517-27. DOI
93. Niederseer D, Wernly S, Bachmayer S, et al. Diagnosis of non-alcoholic fatty liver disease (NAFLD) is independently associated with cardiovascular risk in a large austrian screening cohort. *J Clin Med* 2020;9:1065. DOI PubMed PMC
94. Simon TG, Kartoun U, Zheng H, et al. Model for end-stage liver disease Na Score predicts incident major cardiovascular events in patients with nonalcoholic fatty liver disease. *Hepatol Commun* 2017;1:429-38. DOI PubMed PMC
95. Mangla N, Ajmera VH, Caussy C, et al. Liver stiffness severity is associated with increased cardiovascular risk in patients with type 2 diabetes. *Clin Gastroenterol H* 2020;18:744-6.e1. DOI PubMed PMC
96. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:1657-69. DOI PubMed PMC
97. Sterling RK, Patel K, Duarte-Rojo A, et al. AASLD practice guideline on blood-based non-invasive liver disease assessments of hepatic fibrosis and steatosis. *Hepatology* 2024;Online ahead of print. DOI
98. 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
99. 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;155:443-457.e17. DOI
100. Cardoso CRL, Villela-nogueira CA, Leite NC, Salles GF. Prognostic impact of liver fibrosis and steatosis by transient elastography for cardiovascular and mortality outcomes in individuals with nonalcoholic fatty liver disease and type 2 diabetes: the Rio de Janeiro Cohort Study. *Cardiovasc Diabetol* 2021;20:193. DOI PubMed PMC
101. Shili-masmoudi S, Wong GL, Hiriart J, et al. Liver stiffness measurement predicts long-term survival and complications in non-alcoholic fatty liver disease. *Liver Int* 2020;40:581-9. DOI
102. 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
103. Arai T, Atsukawa M, Tsubota A, et al. Factors influencing subclinical atherosclerosis in patients with biopsy-proven nonalcoholic fatty liver disease. *PLoS ONE* 2019;14:e0224184. DOI PubMed PMC
104. Sonaglioni A, Cerini F, Nicolosi GL, Lombardo M, Rumi MG, Viganò M. Left ventricular strain predicts subclinical atherosclerosis in nonadvanced nonalcoholic fatty liver disease patients. *Eur J Gastroen Hepat* 2022;34:707-16. DOI
105. Anstee QM, Berentzen TL, Nitze LM, et al. Prognostic utility of fibrosis-4 index for risk of subsequent liver and cardiovascular events, and all-cause mortality in individuals with obesity and/or type 2 diabetes: a longitudinal cohort study. *Lancet Reg Health Eur* 2024;36:100780. DOI PubMed PMC
106. Baratta F, Pastori D, Angelico F, et al. Nonalcoholic fatty liver disease and fibrosis associated with increased risk of cardiovascular events in a prospective study. *Clin Gastroenterol H* 2020;18:2324-31.e4. DOI
107. Shao C, Ye J, Li F, et al. Early predictors of cardiovascular disease risk in nonalcoholic fatty liver disease: non-obese versus obese patients. *Dig Dis Sci* 2020;65:1850-60. DOI
108. Wu T, Ye J, Shao C, et al. The ability of lipoprotein (a) level to predict early carotid atherosclerosis is impaired in patients with advanced liver fibrosis related to metabolic-associated fatty liver disease. *Clin Transl Gastroenterol* 2022;13:e00504. DOI PubMed PMC
109. You SC, Kim KJ, Kim SU, et al. Hepatic fibrosis assessed using transient elastography independently associated with coronary artery calcification. *J Gastroenterol Hepatol* 2015;30:1536-42. DOI
110. Yu X, Song X, Tong Y, Wu L, Song Z. Usefulness of controlled attenuation parameter and liver stiffness measurement for detecting increased arterial stiffness in asymptomatic populations in China. *Medicine* 2020;99:e23360. DOI PubMed PMC
111. Hanafy AS, Abd-Elsalam S, Ahmed AF, Dawoud MM. Multifocal fatty liver disease, insulin resistance and carotid atherosclerosis: exploring the interrelated relationship. *J Ultrason* 2018;18:302-9. DOI PubMed PMC
112. Kim H, Koo BK, Joo SK, Kim W. Association of arterial stiffness with the histological severity of nonalcoholic fatty liver disease. *Hepatol Int* 2020;14:1048-56. DOI
113. Park JG, Jung J, Verma KK, et al. Liver stiffness by magnetic resonance elastography is associated with increased risk of cardiovascular disease in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2021;53:1030-7. DOI PubMed PMC

114. Tan EC, Tai MS, Chan W, Mahadeva S. Association between non-alcoholic fatty liver disease evaluated by transient elastography with extracranial carotid atherosclerosis in a multiethnic Asian community. *JGH Open* 2019;3:117-25. DOI PubMed PMC
115. 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 H* 2022;20:1171-1173.e2. DOI PubMed PMC
116. 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
117. Han S, Choi M, Lee B, et al. Accuracy of noninvasive scoring systems in assessing liver fibrosis in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gut Liver* 2022;16:952-63. DOI PubMed PMC
118. Younossi ZM, Stepanova M, Felix S, et al. The combination of the enhanced liver fibrosis and FIB-4 scores to determine significant fibrosis in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2023;57:1417-22. DOI
119. Gosalia D, Ratziu V, Stanicic F, et al. Accuracy of noninvasive diagnostic tests for the detection of significant and advanced fibrosis stages in nonalcoholic fatty liver disease: a systematic literature review of the US studies. *Diagnostics* 2022;12:2608. DOI PubMed PMC
120. Golabi P, Paik JM, Harring M, Younossi E, Kabbara K, Younossi ZM. Prevalence of high and moderate risk nonalcoholic fatty liver disease among adults in the United States, 1999-2016. *Clin Gastroenterol Hepatol* 2022;20:2838-2847.e7. DOI PubMed
121. Pisto P, Santaniemi M, Bloigu R, Ukkola O, Kesäniemi YA. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. *BMJ Open* 2014;4:e004973. DOI PubMed PMC
122. Kim K, Hong S, Han K, Park C. Association of non-alcoholic fatty liver disease with cardiovascular disease and all cause death in patients with type 2 diabetes mellitus: nationwide population based study. *BMJ* 2024;384:*e*076388. DOI PubMed PMC
123. Yoshioka Y, Hashimoto E, Yatsuji S, et al. Nonalcoholic steatohepatitis: cirrhosis, hepatocellular carcinoma, and burnt-out NASH. *J Gastroenterol* 2004;39:1215-8. DOI
124. Van der Poorten D, Samer CF, Ramezani-Moghadam M, et al. Hepatic fat loss in advanced nonalcoholic steatohepatitis: are alterations in serum adiponectin the cause? *Hepatology* 2013;57:2180-8. DOI
125. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V; the LIDO Study Group. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2014;40:1209-22. DOI PubMed
126. Lonardo A, Ballestri S, Bedogni G, Bellentani S, Tiribelli C. The fatty liver index (FLI) 15 years later: a reappraisal. *Metab Target Organ Damage* 2021;1:10. DOI
127. Park CC, Nguyen P, Hernandez C, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Gastroenterology* 2017;152:598-607.e2. DOI PubMed PMC
128. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology* 2011;54:1082-90. DOI PubMed PMC
129. Ballestri S, Mantovani A, Byrne CD, Lonardo A, Targher G. Diagnostic accuracy of ultrasonography for the detection of hepatic steatosis: an updated meta-analysis of observational studies. *Metab Target Organ Damage* 2021;1:7. DOI
130. Allan PL, Mowbray PI, Lee AJ, Fowkes FGR. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease: the Edinburgh artery study. *Stroke* 1997;28:348-53. DOI
131. Bakhshi H, Ambale-Venkatesh B, Yang X, et al. Progression of Coronary artery calcium and incident heart failure: the multi-ethnic study of atherosclerosis. *JAHA* 2017;6:e005253. DOI PubMed PMC
132. Fuchs A, Kühl JT, Sigvardsen PE, et al. Subclinical coronary atherosclerosis and risk for myocardial infarction in a danish cohort: a prospective observational cohort study. *Ann Intern Med* 2023;176:433-42. DOI
133. Geurts S, Brunborg C, Papageorgiou G, Ikram MA, Kavousi M. Subclinical measures of peripheral atherosclerosis and the risk of new-onset atrial fibrillation in the general population: the Rotterdam study. *JAHA* 2022;11:e023967. DOI PubMed PMC
134. Heffernan KS, Charry D, Xu J, Tanaka H, Churilla JR. Estimated pulse wave velocity and incident heart failure and its subtypes: Findings from the multi-ethnic study of atherosclerosis. *Am Heart J Plus* 2023;25:100238. DOI PubMed PMC