

Perspective

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

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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



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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: 1. overweight 2. T2DM 3. at least 2 metabolic abnormalities: increased WC increased BP elevated TG low HDL elevated FBS elevated HOMA-IR score elevated CRP | steatosis with the presence (or treatment of) any of the following: 1. overweight or increased WC 2. T2DM or prediabetes 3. increased BP 4. elevated TG 5. low HDL |

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

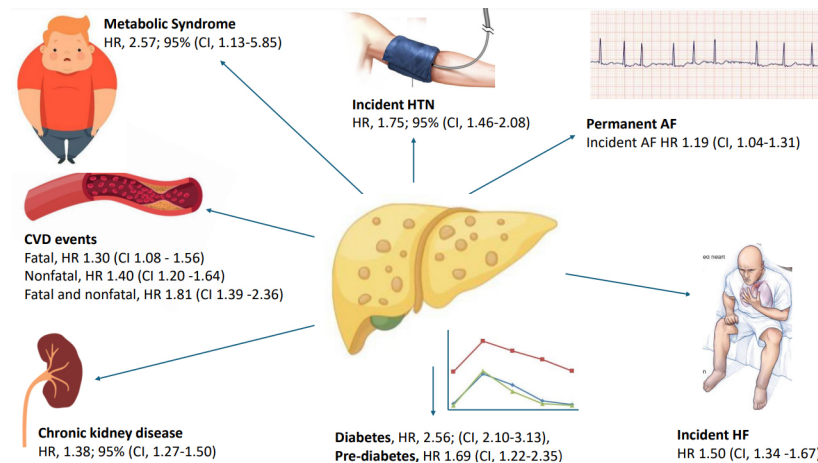


Figure 1. Spectrum of cardio-nephro-metabolic and vascular manifestations of MASLD^[32-36]. AF: atrial fibrillation; CVD: cardiovascular disease; HF: heart failure; HTN: arterial hypertension; MASLD: metabolic dysfunction-associated steatotic liver disease.

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 ($\geq F3$) are at a heightened risk of CVD^[60,98-106], previous research on MASLD populations has associated this risk with any degree of fibrosis ($\geq F1$)^[107-110] or significant fibrosis ($\geq F2$)^[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 $MRE \geq 2.97$) 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 $\geq F1$, increasing with the degree of fibrosis to 2.22 (95%CI: 1.37-3.62) for $\geq F2$, and to 3.42 (95%CI: 1.81-6.46) for $\geq F3$. 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

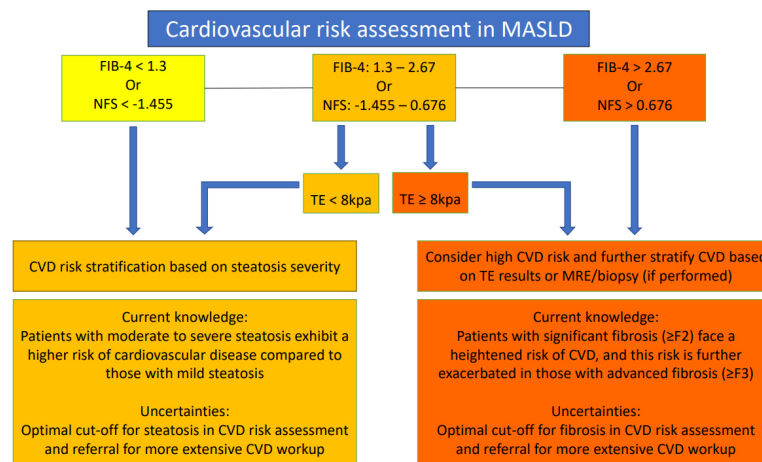


Figure 2. Proposed Algorithm for Cardiovascular Risk Assessments in MASLD. FIB-4: fibrosis-4; NFS: NAFLD fibrosis score; MASLD: Metabolic dysfunction-associated steatotic liver disease; TE: transient elastography; MRE: magnetic resonance elastography; CVD: cardiovascular disease.

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 ($\geq 5\%$ hepatic steatosis) and 84.8% for detecting moderate to severe steatosis ($\geq 30\%$ 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

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Not applicable.

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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.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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