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Metabolic Dysfunction–Associated Steatotic Liver Disease: An Underrated and Emerging Cardiovascular Risk Factor

ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide and is increasingly recognized as a major contributor to cardiovascular morbidity and mortality. Beyond liver involvement, MASLD represents a systemic metabolic disorder closely linked to cardiovascular disease (CVD), the leading cause of death in affected patients. This association persists independently of traditional cardiometabolic risk factors and is driven by multiple mechanisms, including insulin resistance, chronic low-grade inflammation, atherogenic dyslipidemia, endothelial dysfunction, and prothrombotic states. Disease severity, particularly liver fibrosis, appears to further increase cardiovascular risk. This review summarizes current evidence on the epidemiological and pathophysiological links between MASLD and CVD, including its role in atherosclerosis, coronary artery disease, and heart failure. Clinical implications for cardiovascular risk stratification, screening, and multidisciplinary management are also discussed, highlighting the need for integrated strategies to reduce both hepatic and cardiovascular complications.

Keywords: Cardiovascular disease, heart failure, liver fibrosis, metabolic dysfunction–associated steatotic liver disease, risk stratification

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) is now one of the most frequent chronic liver diseases worldwide and is consistently associated with an increased risk of overall and cardiovascular mortality, independently of traditional cardiometabolic risk factors.[1-4] Metabolic dysfunction–associated steatotic liver disease–related fibrosis, systemic inflammation, and metabolic dysfunction appear to act as both amplifiers and potential therapeutic targets for cardiovascular risk.[5,6]

Metabolic dysfunction–associated steatotic liver disease represents the largest subgroup within the broader spectrum of steatotic liver disease (SLD), encompassing most patients previously classified as non-alcoholic fatty liver disease (NAFLD) and emphasizing the central role of metabolic dysfunction.[1,2] The global spread of obesity, type 2 diabetes (T2D), and sedentary lifestyles has driven a parallel rise in MASLD, making it a key determinant of liver-related and extrahepatic morbidity, dominated by cardiovascular disease (CVD).[2,3] This narrative review summarizes current evidence linking MASLD to CVD, with a particular focus on fibrosis-related risk stratification and potential implications for cardiometabolic clinical practice. Importantly, MASLD is a heterogeneous condition, and accumulating evidence indicates that fibrosis stage, rather than steatosis alone, is the principal determinant of cardiovascular risk.

DEFINITION OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

Metabolic dysfunction–associated steatotic liver disease is defined by the presence of hepatic steatosis detected by imaging, non-invasive biomarkers, or histology, combined with at least 1 cardiometabolic risk factor such as overweight/

INVITED REVIEW

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obesity, T2D, or specific features of metabolic dysregulation.[1] Alcohol intake and other chronic liver diseases may coexist, but the defining feature is metabolic dysfunction as the central driver of steatosis, in contrast to purely alcohol- or virus-driven entities.

The MASLD concept is part of a broader nomenclature of SLD, which includes metabolic-associated steatohepatitis when there is histologic inflammation and hepatocellular injury.[1] The SLD framework includes distinct etiological subgroups, allowing a more precise classification of patients based on underlying drivers of steatosis. The updated classification also includes cryptogenic SLD, referring to SLD without a clearly identifiable etiology, possibly representing burnt-out metabolic disease. This new terminology aims to improve disease recognition in cardiometabolic practice and reduce stigma linked to the term "non-alcoholic." The classification of SLD according to the updated nomenclature is summarized in Table 1.

EPIDEMIOLOGY, PREVALENCE, AND INCIDENCE

Metabolic dysfunction–associated steatotic liver disease affects approximately 25%-30% of adults globally, with higher prevalence in regions with high obesity and diabetes burden.[2,7] Population-based cohorts show a strong age gradient and rapid increases in younger adults parallel to rising metabolic syndrome, suggesting that MASLD has become a major public health challenge.[7]

Incidence data from large cohorts indicate that new-onset MASLD tracks closely with weight gain, incident T2D, and decline in overall cardiovascular health indicators.[8] In many countries, MASLD is now the leading cause of chronic liver disease and a growing indication for liver transplantation and hepatocellular carcinoma, further amplifying its long-term impact.[3]

PATHOPHYSIOLOGICAL LINKS TO CARDIOVASCULAR RISK

Several intertwined mechanisms link MASLD to atherosclerosis and CVD beyond shared risk factors.[9,10] These interactions support the concept of a liver–heart axis in which hepatic dysfunction contributes directly to systemic cardiovascular risk. Patients exhibit persistent low-grade systemic inflammation, with elevated interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, which promote endothelial activation, plaque formation, and thrombosis.[9] Hepatic insulin resistance and altered lipid handling lead to atherogenic dyslipidemia [high triglycerides, small dense low-density lipoprotein (LDL), low high-density lipoprotein (HDL)] and procoagulant changes, further fueling cardiovascular risk.[5,10]

At the hepatic level, disturbances in lipid droplet biology and phosphatidylcholine content destabilize lipid storage, triggering organelle stress, mitochondrial dysfunction, and activation of stellate cells toward fibrosis.[10] Progressive fibrosis and hepatocellular injury amplify systemic oxidative stress, activate mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase–protein kinase B–mechanistic target of rapamycin (PI3K-Akt-mTOR) pathways, and promote a pro-inflammatory global state that accelerates

HIGHLIGHTS

- Liver fibrosis severity, assessed by fibrosis-4 index (FIB-4), is a major determinant of cardiovascular risk in metabolic dysfunction–associated steatotic liver disease (MASLD).
- Cardiovascular risk assessment in MASLD should move beyond steatosis alone and incorporate fibrosis-based stratification.
- Advanced fibrosis identifies MASLD patients at particularly high cardiovascular risk and mortality.
- Integrated cardiometabolic management may improve prevention strategies and clinical outcomes in MASLD.
- Emerging therapies targeting metabolic and fibrotic pathways may provide dual hepatic and cardiovascular benefits.

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Table 1. Classification of Steatotic Liver Disease

Category	Definition	Key Features
MASLD	Steatosis with ≥ 1 cardiometabolic risk factor	Obesity, T2D, metabolic dysregulation
MASH	MASLD with inflammation and hepatocellular injury	Ballooning, fibrosis progression
MetALD	MASLD with moderate alcohol intake	Mixed metabolic and alcohol-related drivers
ALD	Alcohol-related liver disease	High alcohol consumption
Other SLD	Less common causes	Genetic, drug-induced
Cryptogenic SLD	Steatotic liver disease without clearly identifiable etiology	Possible burnt-out metabolic disease

ALD, alcohol-related liver disease; MASH, metabolic-associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; SLD, steatotic liver disease; T2D, type 2 diabetes.

vascular damage and potential CVD.[5,9] The main mechanistic pathways linking MASLD and CVD are summarized in Figure 1.

CARDIOVASCULAR OUTCOMES: COHORTS AND REGISTERS

Not all MASLD stages confer the same cardiovascular risk, with advanced fibrosis consistently emerging as the strongest predictor of adverse outcomes. Large cohort studies and meta-analyses consistently show that MASLD is associated with higher rates of incident CVD, overall mortality, and cardiovascular mortality compared with individuals without SLD.[11-13] In a recent meta-analysis including over 3 million patients with MASLD, the hazard ratio for incident CVD was 1.33 versus non-MASLD controls, with a similar risk

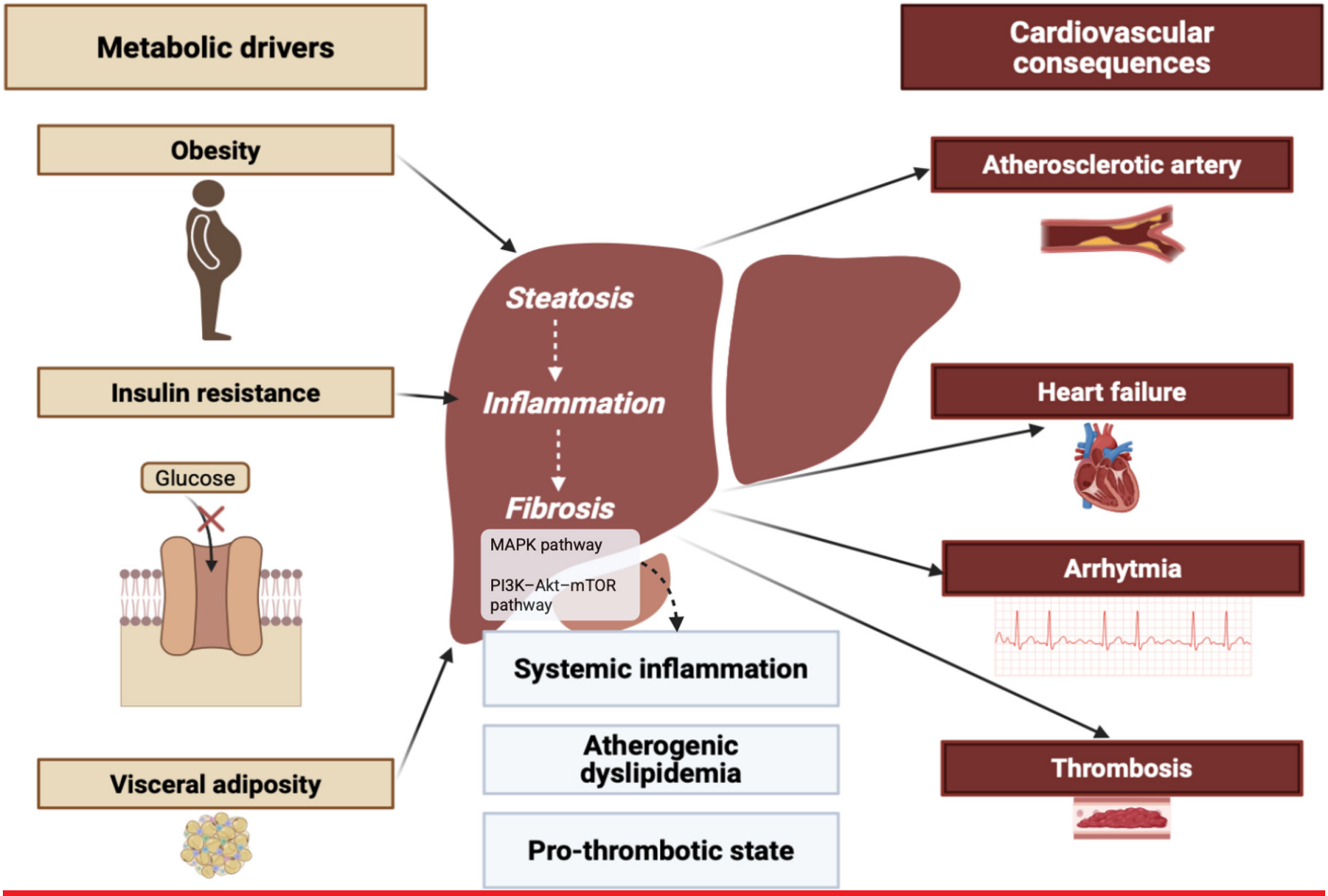

Figure 1. The liver–heart axis in metabolic dysfunction–associated steatotic liver disease (MASLD). Metabolic drivers such as obesity, insulin resistance, and visceral adiposity promote hepatic steatosis and progression toward inflammation and fibrosis. As liver disease advances, systemic abnormalities including low-grade inflammation, atherogenic dyslipidemia, and a prothrombotic milieu may develop and contribute to cardiovascular damage. These mechanisms help explain the association between MASLD and major cardiovascular outcomes such as atherosclerotic disease, heart failure, arrhythmias, and thrombotic events. The figure summarizes the bidirectional links between hepatic and cardiovascular dysfunction within the broader cardiometabolic context, including the activation of key signaling pathways such as MAPK and PI3K-Akt-mTOR.

of cardiovascular mortality, although subject to the inherent limitations of observational epidemiological studies.[11] More recent large-scale epidemiological analyses have further refined these estimates, highlighting the substantial burden of cardiovascular events in MASLD and suggesting evolving temporal trends, with some studies indicating a stabilization or modest decline in cardiovascular mortality despite increasing disease prevalence.[14]

Registries and population-based datasets reveal that patients with MASLD are more likely to die from cardiovascular causes than from liver-related complications.[12] These observations reinforce the view of MASLD as a systemic cardiometabolic condition rather than a liver-limited disease. Within MASLD, fibrosis severity assessed by non-invasive scores such as FIB-4 is strongly associated with all-cause and CV deaths, underscoring the prognostic importance of fibrotic remodeling.[15-17] Importantly, emerging evidence suggests that the association between MASLD and cardiovascular outcomes is largely driven by fibrosis severity, whereas simple steatosis appears to confer a more modest risk.

FIBROSIS, FIB-4, AND RISK STRATIFICATION

The FIB-4 index, combining age, aminotransferases, and platelet count, is widely used as a first-line tool to stage fibrosis in MASLD.[15-17] In individuals with MASLD, higher FIB-4 values are consistently associated with increased all-cause and cardiovascular mortality, even after adjustment for traditional risk factors.[15]

In cohorts of patients with heart failure (HF), elevated FIB-4 identifies a subgroup with higher mortality, suggesting that hepatic fibrosis is a marker of systemic disease severity and may add prognostic information beyond standard cardiac indices.[18] This dual liver–heart risk stratification can help target intensive preventive strategies in cardiometabolic clinics. These findings support a paradigm shift from a binary view of MASLD presence toward a fibrosis-based risk stratification approach, which may better identify patients at the highest cardiovascular risk.

Recent studies specifically conducted in MASLD populations further support the prognostic role of fibrosis severity in predicting mortality, with CVD representing a leading

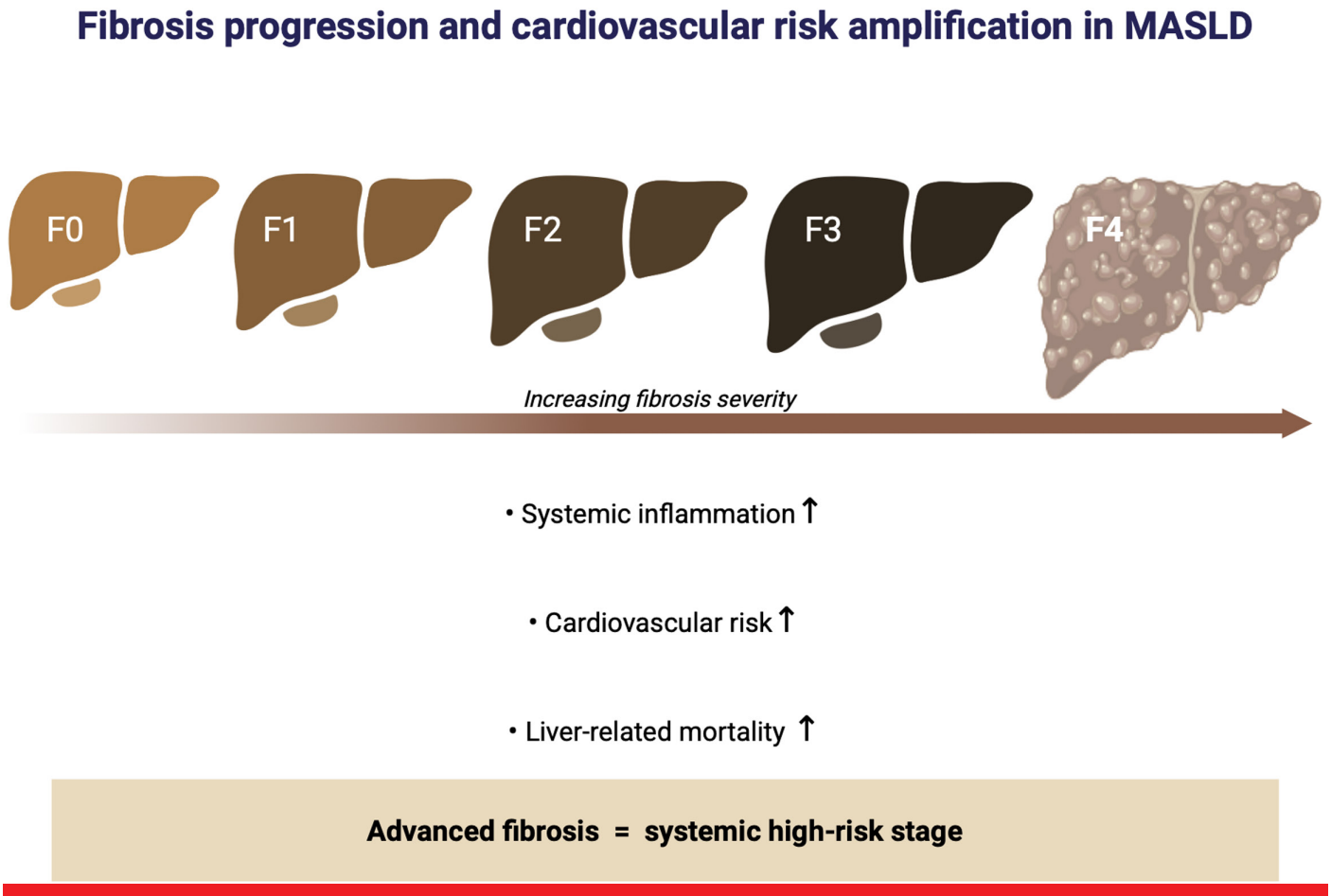

Figure 2. Fibrosis progression and cardiovascular risk amplification in metabolic dysfunction–associated steatotic liver disease. Progression of liver fibrosis from early stages (F0-F1) to advanced fibrosis (F3-F4) is associated with a gradual increase in systemic and clinical risk. As fibrosis advances, systemic inflammation, cardiovascular risk, and liver-related mortality progressively rise, supporting the concept that advanced fibrosis reflects a broader high-risk systemic condition rather than a purely liver-limited stage of disease, highlighting the marked difference in cardiovascular risk between simple steatosis and advanced fibrosis.

cause of death in this population.[14] The progressive increase in systemic and cardiovascular risk across fibrosis stages is schematically illustrated in Figure 2, highlighting the marked difference between simple steatosis and advanced fibrosis.

RANDOMIZED CLINICAL TRIALS AND PHARMACOLOGICAL INTERVENTIONS

Cardiovascular outcome trials primarily designed for diabetes, obesity, or lipid disorders have provided important indirect evidence in MASLD.[19,20] However, most available evidence derives from studies not specifically designed for MASLD populations. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve weight, glycemic control, and liver fat content. Importantly, landmark cardiovascular outcome trials such as landmark cardiovascular outcome trials, including LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), and SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity), have demonstrated significant reductions in major adverse cardiovascular events, supporting their role in cardiovascular risk reduction. In patients with MASLD, these agents may provide additional benefit by targeting shared metabolic and inflammatory pathways.[21-23]

Double agonists [GLP1-RAs and glucose-dependent insulinotropic polypeptide (GIP)] also represent a promising class but require dedicated studies to confirm their potential CV benefits in this field.[19]

Other drug classes with established cardiovascular benefit such as sodium–glucose cotransporter 2 (SGLT2) inhibitors and statins also improve key metabolic drivers of MASLD, as observational data suggest favorable hepatic and cardiovascular effects in this population, although dedicated MASLD-CV outcome trials remain currently limited.[20,24] Emerging agents targeting hepatic lipid metabolism, inflammation, and fibrosis, for example, fibroblast growth factor 21 (FGF21) analogues or thyroid hormone receptor-β agonists provide improvements in steatosis and histologic features, but their impact on cardiovascular events is not yet proven.[25,26] Importantly, the magnitude of cardiovascular risk reduction appears to be greater in patients with higher baseline fibrosis scores, suggesting that fibrosis-based stratification may help identify individuals deriving the greatest therapeutic benefit. This concept is supported by a post hoc analysis from FIDELITY, a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials, in which finerenone was associated with a 52% reduction in cardiovascular events in diabetic patients with higher fibrosis scores (>3.25), compared with a 24% reduction in those with lower scores (>1.3).[27] However, dedicated cardiovascular outcome trials specifically designed for MASLD populations are still lacking.

LIFESTYLE AND NON-PHARMACOLOGICAL TREATMENTS

Healthy lifestyle interventions focused on weight loss, dietary quality, and physical activities remain the cornerstone of MASLD management and are strongly linked to cardiovascular benefit.[28,29] Indeed, moderate-to-vigorous physical activities are associated with lower CVD risk in general populations, and similar relationships likely extend to individuals with MASLD given shared pathways in insulin resistance, blood pressure, and lipid profiles.[28]

Bariatric surgery and intensive sustained weight-loss programs may induce substantial regression of steatosis and fibrosis, which is typically accompanied by major improvements in cardiometabolic risk profile and reduction in cardiovascular events.[30] Nevertheless, access, patient selection, and long-term adherence to healthy lifestyle changes remain major implementation challenges in daily practice.

CURRENT GUIDELINES AND CLINICAL MANAGEMENT

Recent hepatology and cardiometabolic guidelines recommend systematic screening for MASLD in high-risk groups such as patients living with obesity, T2D, and metabolic syndrome.[31] Many patients with MASLD already fulfill criteria for high or very high cardiovascular risk according to current prevention guidelines because of the frequent coexistence of diabetes, obesity, dyslipidemia, and hypertension. In this setting, fibrosis-based stratification may provide incremental prognostic information beyond traditional cardiovascular risk factors. Non-invasive tests, including FIB-4 and elastography, are proposed to identify patients with advanced fibrosis who require referral and closer cardiovascular risk assessment.[31] FIB-4 thresholds (<1.3 low risk, 1.3-2.67 intermediate risk, >2.67 high risk, with a higher cut-off of <2.0 used to define low risk in patients older than 65 years) should guide clinical decision-making. From a practical perspective, a pragmatic clinical approach integrating fibrosis assessment and cardiometabolic risk management is proposed in Figure 3.

For cardiovascular prevention, guidelines emphasize intensive management of traditional risk factors in MASLD: optimization of blood pressure, LDL cholesterol lowering according to risk-based targets (e.g., <70 mg/dL in high-risk and <55 mg/dL in very high-risk patients), including statins, which are considered safe even in this setting.[31] Cardiovascular risk assessment in patients with MASLD may rely on established prediction tools such as Systematic Coronary Risk Evaluation 2 (SCORE2) or the Framingham Risk Score.[32,33] SCORE2, developed for European populations, may offer improved calibration, whereas Framingham remains widely used but may underestimate cardiovascular risk in individuals with metabolic dysfunction. There is growing support for integrating hepatologists, diabetologists, and cardiologists in multidisciplinary clinics to coordinate care and tailor preventive strategies.

GAPS IN EVIDENCE

Despite progress in knowledge, several important gaps persist.[4] Many observational links between MASLD and CVD are subject to confounding factors, and data dissecting independent effects of steatosis versus fibrosis, or disentangling MASLD from overlapping conditions such as HF and chronic kidney disease, remain limited.[34] In addition, composite cardiovascular endpoints are not uniformly defined

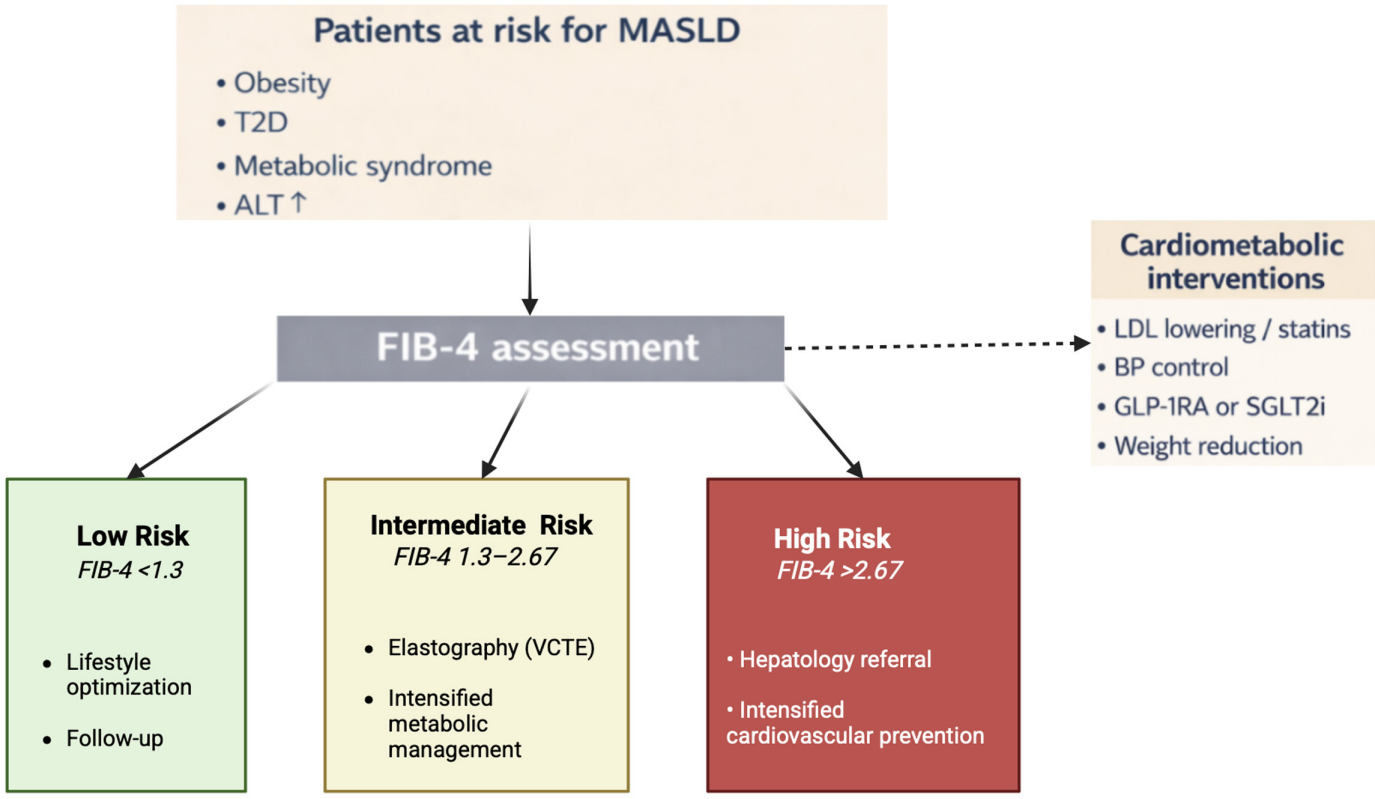

Figure 3. Suggested pragmatic approach for clinical risk stratification in patients with metabolic dysfunction–associated steatotic liver disease. Patients with metabolic risk factors or unexplained elevation of liver enzymes may be initially evaluated using the FIB-4 index as a simple non-invasive tool for fibrosis risk estimation. According to the estimated risk category, management may range from lifestyle optimization and follow-up to further non-invasive assessment or referral for specialist evaluation, together with appropriate cardiometabolic risk reduction strategies. FIB-4 thresholds (<1.3 low risk, 1.3-2.67 intermediate risk, >2.67 high risk, with a higher cut-off [<2.0] used to define low risk in patients older than 65 years) are incorporated to guide clinical decision-making.

across studies and may include heterogeneous combinations of myocardial infarction, stroke, HF, revascularization, and cardiovascular death. This variability may contribute to differences in effect estimates and partly explain inconsistencies across studies, particularly in the absence of systematic fibrosis stratification. Furthermore, most cardiovascular outcome trials have not been powered or stratified specifically for MASLD, making it difficult to provide definitive, disease-specific treatment guidelines. This limitation highlights the need to move from associative evidence toward integrated cardiovascular–hepatic risk models capable of guiding personalized prevention strategies.

Validated risk scores that integrate hepatic parameters (for example, FIB-4, elastography) with traditional cardiovascular risk engines are still under development, and the cost-effectiveness of broad MASLD screening in cardiology practice remains uncertain.[31] Data on MASLD in younger adults, women, and diverse ethnic groups are also less robust, which may limit the generalizability of current estimates and require dedicated studies.

FUTURE RESEARCH DIRECTIONS

Future research should be focused on large prospective cohorts with precise MASLD phenotyping (including fibrosis staging and genetic modifiers) and adjudicated cardiovascular outcomes to refine risk estimates. Randomized clinical trials specifically enrolling MASLD patients and powered for cardiovascular endpoints are needed to evaluate GLP-1-RAs, double agonists, SGLT2 inhibitors, lipid-lowering treatments, and emerging liver-targeted therapies in this population.[19,25,26]

Research into integrated care models that combine hepatology and cardiovascular prevention, as well as implementation studies testing screening strategies with FIB-4 and elastography in primary care and cardiology settings, could bridge current practice gaps.[31] Mechanistic investigations of

lipid droplet biology, inflammation, and fibrosis may uncover novel drug targets with dual hepatic and vascular benefits.

CONCLUSION

Metabolic dysfunction–associated steatotic liver disease has emerged as a highly prevalent liver manifestation of systemic metabolic dysfunction and a robust, independent marker of increased cardiovascular morbidity and mortality.[4,11] Early identification of high-risk patients, particularly those with advanced fibrosis, and intensive management of cardiometabolic risk factors, supported by promising pharmacologic developments such as GLP-1 RAs, represent key opportunities to reduce the growing burden of liver and cardiovascular complications in this population.[20] Overall, MASLD should be viewed as a systemic cardiometabolic disorder and a potential amplifier of cardiovascular risk rather than a purely hepatic condition. Importantly, cardiovascular risk assessment in MASLD should move beyond the mere presence of steatosis and prioritize fibrosis-based stratification to better identify patients at the highest risk and guide targeted preventive strategies.

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