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REVIEW

MASLD and cardiovascular disease: a state-of-the-art review

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease, is the most prevalent chronic liver disease worldwide, affecting more than 30% of adults and up to 70-90% of individuals with obesity or type 2 diabetes mellitus. Cardiovascular disease (CVD) represents the leading cause of mortality in this population. MASLD is increasingly recognized as an independent cardiovascular risk factor beyond traditional metabolic comorbidities. This narrative review summarizes epidemiologic, mechanistic, and clinical evidence linking MASLD with cardiovascular disease, with a focus on population-based cohort studies, imaging-based assessments of subclinical cardiovascular disease, and fibrosis-based risk stratification. Population-based cohorts, including the Framingham Heart Study and the Multi-Ethnic Study of Atherosclerosis, demonstrate that hepatic steatosis is associated with a 1.5-2.0-fold increased risk of incident cardiovascular events after adjustment for age, sex, body mass index, diabetes, and lipid levels. MASLD is characterized by insulin resistance, increased visceral adiposity, atherogenic dyslipidemia with elevated triglycerides, small dense low-density lipoprotein particles, and reduced high-density lipoprotein cholesterol. Patients exhibit systemic low-grade inflammation with elevated tumor necrosis factor-α, interleukin-6, and high-sensitivity C-reactive protein, alongside altered adipokine and hepatokine signaling, including reduced adiponectin and increased leptin, resistin, fetuin-A, and fibroblast growth factor 21. Imaging studies identify higher carotid intima-media thickness, increased coronary artery calcium scores, and early left ventricular diastolic dysfunction in patients with MASLD compared with controls. Fibrosis stage has emerged as the strongest hepatic predictor of cardiovascular outcomes. Individuals with advanced fibrosis have significantly higher rates of cardiovascular events and mortality compared with those without fibrosis, independent of traditional risk factors. Emerging data also implicate gut-liver axis dysfunction and increased intestinal permeability in amplifying systemic inflammation and vascular injury. MASLD is closely linked to cardiovascular disease through shared metabolic, inflammatory, and fibrotic pathways. Cardiovascular risk in MASLD is driven primarily by fibrosis severity rather than steatosis burden. Incorporation of liver disease assessment, particularly fibrosis evaluation, into cardiovascular risk stratification may improve identification of high-risk individuals and support integrated cardiometabolic care.

Key words: metabolic dysfunction-associated steatotic liver disease; cardiovascular disease; metabolic syndrome; state-of-the-art review.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now recognized as the most common chronic liver disease worldwide, affecting more than a quarter of the global population.[1] Previously referred to as nonalcoholic fatty liver disease (NAFLD), the terminology was recently updated to MASLD to better reflect the central role of metabolic dysfunction, rather than the exclusion of alcohol, in the development of hepatic steatosis. This change aligns with the understanding that MASLD is not just a liver-specific condition but a systemic metabolic disorder with widespread implications, especially for cardiovascular health.

The clinical spectrum of MASLD ranges from simple steatosis

to steatohepatitis, progressive fibrosis, cirrhosis, and, in some cases, hepatocellular carcinoma.[2] Despite the risk of liver-related complications, the leading cause of death among individuals with MASLD is cardiovascular disease (CVD).[3,4] Patients with MASLD are at increased risk for a broad range of cardiovascular conditions, including coronary artery disease, heart failure, arrhythmias, and stroke. This elevated risk persists even after adjusting for traditional risk factors such as diabetes, hypertension, and obesity, suggesting that MASLD contributes independently to cardiovascular pathology.

The mechanisms linking MASLD and CVD are complex and multifactorial. Insulin resistance, low-grade systemic inflammation, endothelial dysfunction, and atherogenic dyslipidemia all contribute to the development of both conditions.[5] Additionally, the liver in MASLD releases biologically active molecules such as inflammatory cytokines and hepatokines, which can negatively influence vascular function and metabolic homeostasis.[5] These shared pathophysiologic pathways underscore the close relationship between liver and cardiovascular health.

Fibrosis stage, rather than the degree of steatosis, has emerged as the most important hepatic predictor of cardiovascular outcomes.[6,7] Patients with more advanced fibrosis have higher cardiovascular morbidity and mortality, which has implications for risk stratification and management. However, MASLD often remains undiagnosed or underestimated in clinical settings, partly due to its asymptomatic nature and lack of routine screening in cardiometabolic care.[8]

This review advances the central thesis that MASLD is not merely a hepatic manifestation of metabolic dysfunction but a clinically meaningful cardiovascular risk enhancer, with liver fibrosis serving as a key determinant of cardiovascular outcomes. We argue that MASLD contributes independently to cardiovascular disease through shared metabolic, inflammatory, and endocrine pathways and that failure to incorporate liver disease severity into cardiovascular risk assessment represents a missed opportunity for early intervention. By synthesizing epidemiological evidence, mechanistic insights, and emerging diagnostic and therapeutic strategies, this review frames MASLD as a target for integrated cardiometabolic care rather than an isolated hepatic condition.

To ensure comprehensive and up-to-date coverage of the literature, this narrative review draws on a targeted search of PubMed and Google Scholar databases. Searches were conducted using combinations of keywords including “metabolic dysfunction-associated steatotic liver disease,” “MASLD,” “nonalcoholic fatty liver disease,” “cardiovascular disease,” “atherosclerosis,” “heart failure,” and “cardiovascular outcomes.” Priority was given to large population-based cohort studies, meta-analyses, randomized controlled trials, and major guidelines or consensus statements published between 2000 and 2025, with particular emphasis on recent studies that reflect contemporary definitions of MASLD. Reference lists of relevant articles were also screened to identify additional key publications.

Epidemiology and clinical relevance

MASLD currently affects approximately 25 to 30% of the global population.[9] In high-income countries, the prevalence is even greater, largely due to the parallel rise in obesity, sedentary lifestyles, and type 2 diabetes mellitus. Among individuals with obesity, the prevalence of MASLD may exceed 80%, while estimates suggest that individuals with type 2 diabetes have nearly 70% underlying hepatic steatosis.[10] Despite these high numbers, MASLD remains underdiagnosed in routine practice, in part due to the often silent course of the disease and limited awareness outside of hepatology settings.

Multiple population-based studies have demonstrated the epidemiological link between MASLD and CVD. Data from large cohorts such as the National Health and Nutrition Examination Survey (NHANES) in the United States, the United Kingdom Biobank, and several Asian registries consistently show that MASLD is associated with an increased risk of myocardial infarction, stroke, heart failure, and overall cardiovascular mortality.[11] One meta-analysis involving over 34,000 individuals found that MASLD conferred a 64% increased risk of fatal and nonfatal cardiovascular events, independent of traditional risk factors like age, hypertension, and hyperlipidemia.[12] Notably, CVD accounts for 40 to 50% of all deaths in MASLD patients, whereas liver-related deaths constitute a much smaller proportion.[13] This finding underscores the systemic nature of MASLD and the central role of cardiovascular complications in its clinical course.

Importantly, the severity of liver fibrosis, rather than steatosis alone, has emerged as the most powerful predictor of cardiovascular events. Advanced fibrosis (stages F3 to F4) has been associated with significantly higher risks of myocardial infarction, heart failure, and cardiac mortality.[14] These findings highlight the need for clinicians to not only recognize MASLD as a hepatic disorder but also to assess fibrosis severity in the context of broader cardiovascular risk.

While the epidemiological evidence linking MASLD to cardiovascular disease is consistent across populations, most data are derived from observational cohort studies, which limit causal inference. Many studies rely on imaging-based definitions of hepatic steatosis rather than histological assessments and may be subject to misclassification, particularly in lean individuals or those with early-stage disease. Residual confounding remains a concern, as MASLD frequently coexists with obesity, diabetes, and other cardiometabolic risk factors that may not be fully captured or adjusted for. In addition, variability in diagnostic criteria, follow-up duration, and outcome ascertainment across cohorts contributes to heterogeneity in reported effect sizes. Despite these limitations, the persistence of associations after multivariable adjustment and across diverse populations supports a robust link between MASLD and cardiovascular risk.

Pathophysiological mechanisms linking MASLD and cardiovascular disease

The association between MASLD and CVD is driven by a set of interconnected pathophysiological processes (Figures 1 and 2).[15] Central to this link are systemic metabolic abnormalities, including insulin resistance, visceral fat accumulation, chronic low-grade inflammation, and dyslipidemia.[15] These metabolic disturbances contribute not only to liver fat accumulation but also to the development of atherosclerosis, cardiac remodeling, and vascular dysfunction.

Insulin resistance plays a pivotal role in the pathogenesis of MASLD and its cardiovascular complications.[16] It promotes hepatic fat accumulation by increasing de novo lipogenesis and impairing the normal suppression of adipose tissue lipolysis, leading to elevated circulating free fatty acids.[17] These fatty acids are taken up by the liver and stored as triglycerides, contributing to hepatic steatosis. At the same time, insulin resistance in skeletal muscle and adipose tissue impairs glucose uptake and promotes hyperglycemia, both of which have been linked to endothelial dysfunction and increased oxidative stress and are key contributors to atherosclerosis.[18] Elevated hepatic glucose production further promotes hyperinsulinemia, creating a cycle of worsening insulin resistance and metabolic disturbance.

Patients with MASLD commonly exhibit an atherogenic lipid profile, including elevated triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol, and a predominance of small dense low-density lipoprotein (LDL) particles.[19] These small, dense LDL particles are more prone to oxidation and are strongly associated with plaque formation and instability. A large population-based study using data from the Framingham Heart Study[20] showed that individuals with hepatic steatosis had significantly higher levels of remnant lipoproteins, which are particularly atherogenic and associated with coronary artery disease risk independent of LDL cholesterol levels.

Chronic systemic inflammation is another key mechanism linking MASLD and CVD.[21] Lipotoxic hepatocytes and activated Kupffer cells release a range of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP).[22] These inflammatory mediators circulate systemically and contribute to endothelial injury, increased arterial stiffness, and promotion of foam cell formation in atherosclerotic plaques. Elevated CRP levels, commonly observed in MASLD, are a known independent predictor of cardiovascular events.[23] In an individual participant meta-analysis of over 160,000 individuals, high-sensitivity CRP was significantly associated with increased risk of myocardial infarction and stroke, highlighting the systemic impact of MASLD-related inflammation.[24]

In addition to cytokine-driven inflammation, MASLD is associated with adipose tissue dysfunction and an altered adipokine profile.[25] Levels of adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, are significantly reduced in MASLD and inversely correlate with both hepatic fat content and cardiovascular risk.[26] Conversely, levels of pro-inflammatory adipokines such as leptin and resistin are elevated. Leptin has been implicated in promoting vascular smooth muscle proliferation, oxidative stress, and myocardial hypertrophy.[27] This dysregulated adipokine signaling contributes to both hepatic and vascular inflammation, fostering a pro-atherogenic environment.

Emerging research has also highlighted the role of hepatokines, which are proteins secreted by the liver that influence systemic metabolism and vascular function.[28] Among these, fetuin-A has been shown to inhibit insulin receptor signaling and promote vascular calcification, while fibroblast growth factor 21 (FGF21), typically elevated in MASLD, reflects hepatic stress and correlates with both insulin resistance and subclin-

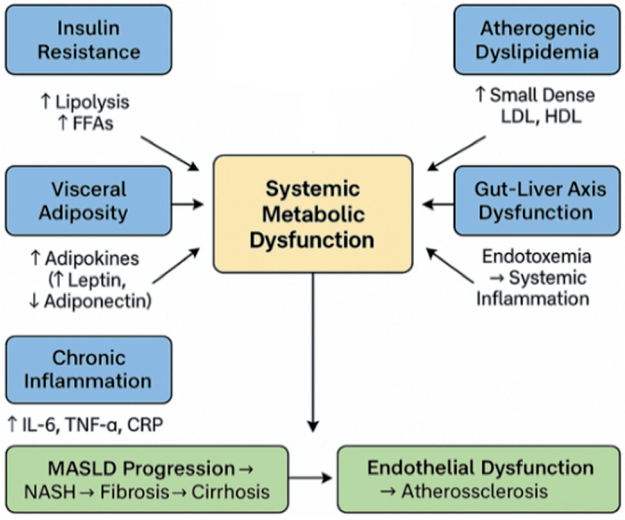

Figure 1. Mechanistic pathways linking MASLD to cardiovascular disease.

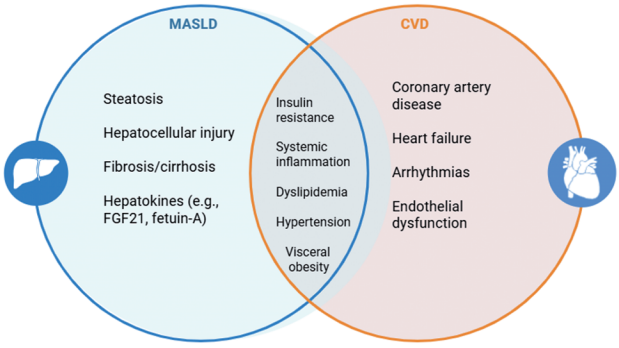

Figure 2. Clinical overlap between MASLD and cardiovascular disease.

ical atherosclerosis.[29] Moreover, selenoprotein P and angiopoietin-like protein 8 (ANGPTL8), also secreted by hepatocytes, have been linked to impaired lipid metabolism and endothelial dysfunction, although their precise role in human disease remains under investigation (Tables 1 and 2).[30]

The gut-liver axis represents another important pathway linking MASLD and cardiovascular disease. In MASLD, increased intestinal permeability allows the translocation of bacterial products such as lipopolysaccharide (LPS) into the portal circulation.[31] This triggers hepatic Toll-like receptor (TLR) signaling and amplifies local and systemic inflammation. In turn, this can exacerbate insulin resistance and promote atherogenesis. Alterations in gut microbiota composition, termed dysbiosis, have also been associated with MASLD progression and may influence cardiovascular risk via modulation of bile acid metabolism, short-chain fatty acid production, and systemic immune responses.[32,33]

There is also growing evidence from imaging and biomarker studies that MASLD is associated with early, subclinical cardiovascular changes. Studies using carotid ultrasound have shown increased carotid intima-media thickness (CIMT) in patients with MASLD, independent of other risk factors.[34] Cross-sectional data from the Dallas Heart Study and the Multi-Ethnic Study of Atherosclerosis (MESA) have confirmed higher coronary artery calcium (CAC) scores in individuals with hepatic steatosis, even in the absence of overt cardiovascular disease.[35,36] In addition, echocardiographic assessments have demonstrated impaired left ventricular diastolic function and increased left ventricular mass in MASLD patients, which are early signs of cardiac remodeling.

Advanced fibrosis, as assessed by non-invasive fibrosis scoring systems or liver biopsy, has emerged as a strong predictor of cardiovascular events in MASLD. A study using data from the NHANES III cohort found that liver stiffness measured by elastography correlated with higher rates of cardiovascular mortality.[37] Similarly, a large Swedish registry study reported that patients with biopsy-proven steatohepatitis and advanced fibrosis had significantly increased risks of major adverse cardiovascular events compared to those with simple steatosis.[38] Collectively, these data support the view that MASLD is not merely a hepatic manifestation of metabolic syndrome, but a condition that actively contributes to cardiovascular pathology through a range of mechanisms. This recognition has important clinical implications, particularly for cardiovascular risk stratification, as current models may underestimate risk in patients with MASLD. Greater awareness of the pathophysiological links between the liver and the cardiovascular system is essential for developing integrated care pathways and targeted interventions.

Mechanistic insights linking MASLD and cardiovascular disease are supported by experimental models, biomarker studies, and cross-sectional human data; however, several limitations warrant consideration. Many mechanistic studies are associative and rely on surrogate markers of inflammation, endothelial dysfunction, or subclinical atherosclerosis rather than hard cardiovascular endpoints. Human studies often involve selected populations and may not fully reflect disease heterogeneity or longitudinal risk. Furthermore, the relative contributions of individual pathways, including hepatokines,

Table 1. Key pathophysiological mechanisms linking MASLD and cardiovascular disease.

Mechanism	Details	Cardiovascular impact
Insulin resistance	Promotes hepatic fat accumulation via *de novo* lipogenesis; impairs glucose metabolism	Endothelial dysfunction, atherogenesis
Visceral adiposity	Source of pro-inflammatory cytokines and free fatty acids	Promotes systemic inflammation and plaque formation
Atherogenic dyslipidemia	Elevated triglycerides, small dense LDL, reduced HDL	Enhances plaque development and vascular injury
Chronic low-grade inflammation	Increased TNF-α, IL-6, CRP levels	Impairs endothelial function, increases arterial stiffness
Altered adipokines	↓ Adiponectin, ↑ leptin and resistin	Pro-inflammatory, pro-atherogenic effects
Hepatokines	Fetuin-A, FGF21 involved in glucose and lipid metabolism	Contribute to insulin resistance and cardiac remodeling
Gut-liver axis dysfunction	Increased intestinal permeability and bacterial endotoxin translocation	Amplifies hepatic and systemic inflammation

Table 2. Hepatic and cardiovascular biomarkers in MASLD.

Biomarker	Pathophysiological role	Association with CVD	Clinical utility
ALT, AST	Liver injury enzymes	Weak direct link with CVD	Not a reliable CVD predictor
FGF21	Hepatokine regulating glucose/lipid metabolism	Linked to atherosclerosis, cardiac stress	Emerging biomarker for metabolic dysfunction
CRP	Systemic inflammation marker	Strong predictor of cardiovascular events	Prognostic marker
Adiponectin	Anti-inflammatory adipokine	Inversely related to atherosclerosis	Reduced in MASLD and CVD
Fetuin-A	Pro-inflammatory hepatokine	Promotes insulin resistance	Potential dual MASLD-CVD biomarker

adipokines, and alterations in gut microbiota, remain incompletely defined, and causal relationships have yet to be confirmed in large interventional trials. These limitations highlight the need for prospective studies integrating mechanistic biomarkers with clinical outcomes.

Diagnostic considerations and risk stratification

Accurate identification and risk stratification of MASLD patients are essential to prevent both liver-related and cardiovascular complications. While hepatic steatosis can be detected through imaging techniques such as ultrasound, computed tomography, or magnetic resonance imaging, these modalities do not provide information about the fibrosis stage or cardiovascular risk.[39]

Noninvasive fibrosis assessment tools have become central to risk stratification in MASLD.[40] The Fibrosis-4 index, the NAFLD fibrosis score, and the AST-to-platelet ratio index are commonly used in clinical practice.[40] These scores combine routine laboratory values and clinical parameters to estimate the likelihood of advanced fibrosis. Importantly, several studies have shown that higher fibrosis scores are also associated with increased risk of cardiovascular events, independent of traditional risk calculators.[41] In the AMI cohort, high-risk FIB-4 and APRI scores independently predicted mortality regardless of T2DM status, while NFS only predicted mortality in T2DM patients. Following AMI, individuals stratified by FIB-4, APRI, and NFS as high-risk for liver fibrosis were associated with excess long-term mortality.[42]

Advanced imaging techniques such as vibration-controlled transient elastography and magnetic resonance elastography offer more precise quantification of liver stiffness and have been correlated with subclinical markers of atherosclerosis and arterial stiffness.[43] Their role in cardiovascular risk prediction is still evolving, but growing evidence supports their utility in comprehensive risk assessment for MASLD patients.

Standard cardiovascular risk calculators, such as the Framingham Risk Score, the pooled cohort atherosclerotic cardiovascular disease (ASCVD) equation, and the European SCORE2 algorithm, remain valuable tools in assessing cardiovascular risk. However, these tools may underestimate risk in individuals with MASLD, especially those with advanced fibrosis. In response to this gap, expert consensus has increasingly advocated for the inclusion of MASLD as a risk-enhancing factor. In 2021, a Delphi panel of hepatology and cardiology experts recommended that all patients with MASLD undergo formal cardiovascular risk evaluation, regardless of liver enzyme levels or metabolic syndrome status.[44] Despite these recommendations, cardiovascular risk screening is inconsistently applied in patients with MASLD. Many hepatologists lack access to cardiovascular diagnostics, and cardiologists often do not screen for liver disease, even in high-risk individuals. This underscores the need for integrated care models and shared clinical pathways.

Management strategies

The management of MASLD with coexisting CVD requires a holistic, multifaceted approach. Lifestyle modification is the cornerstone of therapy, with growing evidence supporting pharmacologic treatments that address both liver pathology and cardiovascular risk. Sustained weight loss remains the most effective intervention for MASLD. A reduction of 5% of total body weight can decrease hepatic steatosis, while losses of 7 to 10% have been associated with histological improvement in steatohepatitis and even regression of fibrosis.[45] These improvements in liver health are paralleled by reductions in blood pressure, insulin resistance, and dyslipidemia, translating into meaningful cardiovascular risk reduction. This aligns with recent global obesity guidelines that emphasize comprehensive cardiometabolic management.[46]

Dietary modification plays a crucial role in achieving and maintaining weight loss. The Mediterranean diet, rich in fruits, vegetables, whole grains, lean protein, and unsaturated fats, has been associated with improvements in liver fat content, glycemic control, and lipid profiles.[47] Regular physical activity, particularly a combination of aerobic and resistance exercise, enhances insulin sensitivity and cardiorespiratory fitness and helps preserve lean muscle mass. Importantly, exercise has been shown to reduce liver fat independent of weight loss, emphasizing its role as a therapeutic strategy.

Pharmacotherapy is often necessary in patients with MASLD and increased cardiovascular risk. Statins are first-line agents for lipid lowering and are underutilized in MASLD despite substantial evidence supporting their safety and efficacy. Multiple observational studies and randomized trials have shown that statins reduce cardiovascular events and may modestly improve liver enzyme levels and hepatic inflammation.[48] Concerns about hepatotoxicity have been largely dispelled, and current guidelines support the use of statins in MASLD patients with elevated low-density lipoprotein cholesterol or established cardiovascular disease.

Antidiabetic medications with cardioprotective properties are also being investigated for their effects on MASLD. Glucagon-like peptide-1 receptor agonists, such as liraglutide and semaglutide, promote weight loss, improve glycemic control, and have demonstrated cardiovascular benefit in high-risk patients. Recent trials have also shown that these agents reduce liver fat and improve markers of inflammation and fibrosis.[49] Sodium-glucose co-transporter-2 inhibitors, including empagliflozin and dapagliflozin, have been associated with reduced risk of heart failure and cardiovascular death[50,51] and are currently under study for their potential role in improving hepatic outcomes in MASLD.

New liver-specific therapies are on the horizon. Resmetirom, a thyroid hormone receptor beta agonist, has recently received regulatory approval for the treatment of steatohepatitis and shows promise in reducing atherogenic lipids and liver fat.[52] Agents such as obeticholic acid and pan-PPAR agonists, with already established safety profiles,[53,54] are undergoing clinical trials to further define their cardiovascular efficacy.

For patients with severe obesity and advanced MASLD, bariatric surgery can be a transformative intervention. Surgical weight loss results in substantial reductions in liver fat, reversal of fibrosis, and improved metabolic and cardiovascular outcomes. Long-term studies have shown decreased mortality from both liver and cardiovascular causes following bariatric procedures.[55]

Integrated care models and future directions

The intersection of MASLD and cardiovascular disease supports the view that MASLD functions as a cardiovascular risk enhancer rather than an isolated hepatic condition. Despite substantial epidemiological and mechanistic evidence linking MASLD to adverse cardiovascular outcomes, liver disease severity is not routinely incorporated into cardiovascular risk assessment, and cardiovascular screening remains inconsistently applied in patients with MASLD. This disconnect reflects ongoing fragmentation between hepatology and cardiovascular care.

Future research should address several key gaps. First, prospective cohort studies are needed to determine whether improvement in MASLD severity, particularly regression of liver fibrosis, is associated with meaningful reductions in cardiovascular events beyond traditional risk factor modification. Second, randomized controlled trials should evaluate whether integrating non-invasive fibrosis assessment tools, such as FIB-4, APRI, and elastography, into cardiovascular risk stratification improves clinical outcomes compared with standard risk models alone. Third, mechanistic studies linking hepatokines, adipokines, and gut microbiota profiles with longitudinal cardiovascular endpoints are required to clarify causal pathways and identify therapeutic targets.

From a clinical perspective, implementation studies are needed to define effective multidisciplinary care models that integrate hepatology, cardiology, and primary care. Such models should evaluate coordinated screening strategies, shared risk assessment frameworks, and streamlined referral pathways, particularly for patients with advanced fibrosis or high cardiovascular risk. Finally, clinical trials of emerging MASLD therapies should systematically include cardiovascular outcomes as prespecified endpoints to better define their cardiometabolic impact. Addressing these gaps will be essential for translating mechanistic insights into evidence-based, integrated care strategies aimed at reducing both liver-related and cardiovascular morbidity in patients with MASLD.

Conclusions

MASLD is a significant public health concern with consequences that involve not only the liver but also broader systemic conditions, especially cardiovascular disease. Cardiovascular disease is the leading cause of death in this population and often precedes liver-related complications. The pathophysiological interplay between hepatic steatosis and systemic metabolic dysfunction underscores the need for comprehensive, multidisciplinary care. Clinicians must recognize MASLD as a cardiovascular risk enhancer and prioritize early identification, fibrosis staging, and risk modification. With lifestyle interventions, pharmacologic therapies, and integrated care models, the burden of both liver and cardiovascular complications can be significantly reduced.

Contributions

All authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethical approval

Not applicable.

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