

# Metabolic dysfunction-associated steatotic liver disease and its associated health risks

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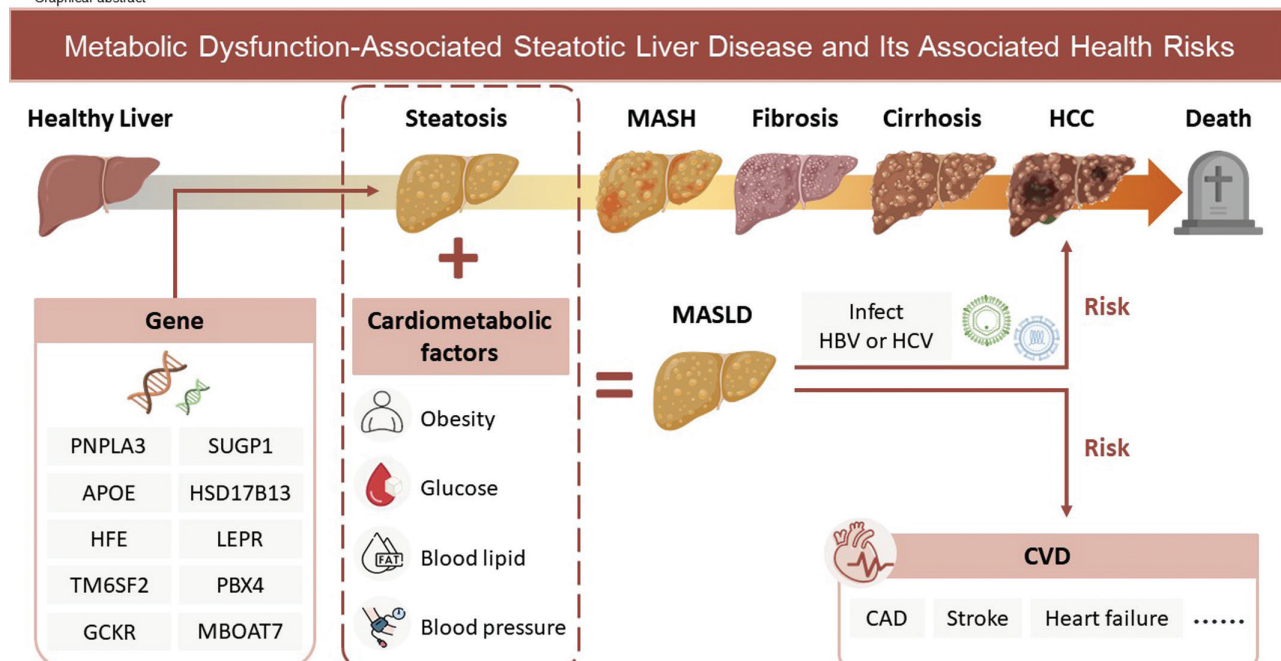
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## Abstract

This article synthesizes the current knowledge on the epidemiology of metabolic dysfunction-associated steatotic liver disease (MASLD), its associated risks, and its genetic determinants. The findings presented in this article can be used to develop clinical strategies to reduce MASLD's growing global burden. MASLD has become a major global health concern due to increasing rates of obesity, sedentary lifestyles, and metabolic disorders. MASLD is a leading cause of end-stage liver diseases, including cirrhosis and hepatocellular carcinoma (HCC), and MASLD also significantly increases the risk of cardiovascular disease (CVD), thereby exerting dual effects on liver and cardiovascular health. MASLD was once referred to as nonalcoholic fatty liver disease, and this change in nomenclature reflects a growing focus on its metabolic underpinnings, facilitating the more precise diagnosis and clinical management of this disease. Epidemiological studies have demonstrated that the prevalence of MASLD is increasing worldwide, although the prevalence varies across regions and populations. Noninvasive diagnostic tools such as ultrasound and fatty liver indices along with biomarkers such as alanine aminotransferase (ALT) are crucial for early detection and risk stratification. Genetic research has identified key gene variants, including *PNPLA3* (rs738409) and *TM6SF2* (rs58542926), that influence MASLD susceptibility and progression, and these findings have created opportunities for improving precision medicine with respect to treating MASLD. Research has revealed an association between MASLD and major adverse cardiovascular events and increased mortality, which highlights the importance of integrating cardiovascular risk management into treatment strategies for MASLD. Future research should focus on advancing noninvasive diagnostics, leveraging genetic insights to provide tailored care, and implementing population-specific interventions to address regional variations.

**Keywords:** Epidemiology; Liver disease; Noncommunicable diseases; Obesity

Graphical abstract



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**Lay summary:** Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern linked to obesity, sedentary lifestyles, and metabolic disorders. Previously known as nonalcoholic fatty liver disease (NAFLD), the updated term emphasizes its metabolic causes, improving diagnosis and management. MASLD increases the risk of severe liver diseases like cirrhosis and liver cancer, as well as cardiovascular disease. Its prevalence is rising worldwide, though it varies across populations. Early detection using noninvasive tests, such as ultrasound and blood biomarkers, is crucial for identifying at-risk individuals. Genetic factors, including *PNPLA3* and *TM6SF2* variants, influence MASLD progression, offering opportunities for personalized treatment. Given its impact on liver and heart health, integrating cardiovascular risk management into MASLD care is essential. Future research should enhance noninvasive diagnostics, apply genetic insights for tailored treatments, and develop population-specific prevention strategies to reduce the growing burden of MASLD.

## 1. INTRODUCTION

Fatty liver disease is closely linked to the global obesity epidemic, and it has become a critical public health concern. The prevalence of fatty liver disease has increased, with this increase being the result of economic progress, urbanization, and changes in dietary and lifestyle habits. Fatty liver disease substantially contributes to the development of advanced liver diseases, including cirrhosis and hepatocellular carcinoma (HCC), resulting in a substantial healthcare burden. Historically, chronic hepatitis B and C (CHB and CHC, respectively) infections were considered to be the leading causes of cirrhosis and HCC. However, successful public health initiatives—such as neonatal hepatitis B vaccination programs and efforts toward expanding the availability of highly effective direct antiviral agents for hepatitis C—have considerably reduced the prevalence of chronic viral hepatitis. As a result, the influence of CHB and CHC has lessened, and fatty liver disease is beginning to emerge as the primary contributor to end-stage liver disease.

The present review synthesized the epidemiological trends of metabolic dysfunction-associated steatotic liver disease (MASLD), updates on its nomenclature, and current findings regarding MASLD, focusing on the importance of early diagnosis, lifestyle modifications, and preventive strategies. Understanding the evolving landscape of MASLD is essential for developing effective public health interventions and optimizing the clinical management of MASLD.

## 2. NOMENCLATURE OF STEATOTIC LIVER DISEASE

Although the nomenclature for steatotic liver disease (SLD) is continually evolving, the term “MASLD” has become widespread because it is associated with liver-related complications, such as cirrhosis and HCC.<sup>1,2</sup> MASLD was previously referred to as nonalcoholic fatty liver disease (NAFLD) or metabolic

dysfunction-associated fatty liver disease (MAFLD). However, the term MASLD has become the preferred term for this disease because it more accurately reflects the fact that metabolic dysfunction underlies the disease. Furthermore, replacing MAFLD with MASLD avoids the potential stigma associated with the term “fatty” and provides greater clarity with respect to the role of alcohol consumption in the classification of the disease. According to research, liver steatosis is currently categorized into three primary subtypes<sup>3</sup>:

- MASLD: predominantly caused by metabolic dysfunction.
- MASLD with excessive alcohol consumption (MetALD): caused by a combination of alcohol consumption and metabolic dysfunction.
- Alcohol-related liver disease (ALD): primarily caused by excessive alcohol consumption.

The term “MASLD” has been adopted in an effort to categorize highly homogeneous patient populations with diverse liver disease etiologies to facilitate identification of biomarkers and enable more targeted clinical trials to be designed. This change in terminology was implemented with a focus on enhancing diagnostic precision, improving risk stratification, and facilitating the implementation of tailored therapeutic approaches for individuals with different underlying etiologies. Although the definition of and term for the disease has been changed, the clinical characteristics of patients classified as having NAFLD, MAFLD, and MASLD are fairly consistent.<sup>4</sup> A study demonstrated that 89.2% of individuals with intrahepatic triglyceride content >5% satisfied the diagnostic criteria for all three of these classifications, which demonstrates that the definitions of the three classifications do not notably differ.<sup>5</sup> Furthermore, the natural history of end-stage liver disease appears to be similar across these three categorizations,<sup>6</sup> which further demonstrates the practical overlap of the classifications despite the terminology and definitions of the disease being refined.

Table 1 provides a summary of the definitions for NAFLD, MAFLD, and MASLD and the timeline of terminological changes for this disease.<sup>3,7,8</sup> NAFLD was first defined in 1980 as the presence of steatohepatitis in the absence of excessive alcohol consumption; NAFLD was considered to be associated with obesity, diabetes, or gallstones. To address its limitations, the term MAFLD was introduced to more clearly highlight metabolic dysfunction as the primary driver of the disease; the new term and its definition encompassed chronic hepatitis B, CCHB, and CHC. However, the definition of MAFLD did not account for alcohol consumption, and the phrase MAFLD included the term “fatty,” which may carry stigma. In consideration of this, the term MASLD was proposed. The term MASLD and its updated definition enabled more inclusive and precise classification; within this definition, SLD was considered to occur in individuals with at least one cardiometabolic risk factor, and alcohol intake was considered in the categorization of SLD subtypes. However, it does not explicitly refer to the presence of chronic viral hepatitis, which is known to increase the risks of cirrhosis and HCC. The changes that have occurred in the terminology used to discuss SLD have been made with a focus on enhancing diagnostic precision and risk stratification in clinical practice.

## 3. EPIDEMIOLOGY OF SLD

The prevalence of fatty liver disease is strongly linked to the global obesity pandemic; overweight and obesity are key causes of the disease. According to the 2017 Global Health Observatory data from the World Health Organization, the global prevalence rate of overweight among adults is 39.7% in women and 38.5%

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Table 1 Summary of the definitions of NAFLD, MAFLD, and MASLD				
Steatosis term	Year	Alcohol consumption	Metabolic risk factors	Chronic liver disease
NAFLD <sup>7</sup>	1986	≤20 g/d for women ≤30 g/d for men	Not addressed	Excluded
MAFLD <sup>8</sup>	2020	Not addressed	1. BMI ≥25 kg/m <sup>2</sup> in White people or BMI ≥23 kg/m <sup>2</sup> in Asian people 2. Type 2 diabetes mellitus 3. At least 2 metabolic risk abnormalities <ul style="list-style-type: none"><li>• Waist circumference ≥102/88 cm in White men and women or ≥90/80 cm in Asian men and women</li><li>• Prediabetes (fasting glucose levels of 100–125 mg/dL, 2-h post-load glucose levels of 140–199 mg/dL, or HbA1c 5.7%–6.4%)</li><li>• Blood pressure ≥130/85 mmHg or specific drug treatment</li><li>• Plasma triglycerides ≥150 mg/dL or specific drug treatment</li><li>• Plasma HDL-cholesterol &lt;40 mg/dL for men and &lt;50 mg/dL for women or specific drug treatment</li><li>• Homeostasis model assessment of insulin resistance score ≥2.5</li><li>• Plasma high-sensitivity C-reactive protein level &gt;2 mg/L</li></ul> At least 1 of the following 5 criteria: <ul style="list-style-type: none"><li>• BMI ≥25 kg/m<sup>2</sup> in White people or BMI ≥23 kg/m<sup>2</sup> in Asian people, waist circumference &gt;94 cm for men and 80 cm for women</li><li>• Fasting glucose level of ≥100 mg/dL, 2-h post-load glucose level of ≥140 mg/dL, HbA1c ≥5.7%, type 2 diabetes, or treatment for diabetes</li><li>• Blood pressure ≥130/85 mmHg or specific drug treatment</li><li>• Plasma triglycerides ≥150 mg/dL or specific drug treatment</li><li>• Plasma HDL-cholesterol &lt;40 mg/dL for men and &lt;50 mg/dL for women or specific drug treatment</li></ul>	<ul style="list-style-type: none"><li>• ALD</li><li>• Viral infection (HIV, HBV, and HCV)</li><li>• Drug-induced liver injury</li><li>• Autoimmune hepatitis</li><li>• Inherited liver disorders</li><li>• Other known liver diseases</li></ul>
MASLD <sup>3</sup>	2023	≤20 g/day for women ≤30 g/day for men 20–50 g/day for women 30–60 g/day for men >50 g/day for women >60 g/day for men	Not clearly defined	Not clearly defined

ALD = alcohol-associated liver disease; BMI = body mass index; MAFLD = metabolic dysfunction-associated fatty liver disease; MASLD = metabolic dysfunction-associated steatotic liver disease; MetALD = MASLD and increased alcohol intake; NAFLD = nonalcoholic fatty liver disease.

in men.<sup>9</sup> Over the past two decades, a notable increase in body mass index (BMI) has been observed worldwide, which has raised serious concerns. Studies in China have reported that the average BMI among Chinese individuals increased from 21.9 to 23.5 kg/m<sup>2</sup>, with a parallel increase occurring in the prevalence of fatty liver disease.<sup>10</sup> In addition, a meta-analysis of 237 studies estimated the global prevalence rates of fatty liver disease, and the results indicated that fatty liver disease affects 29.6% (95% CI, 28.1–31.2) of the population. The study revealed that the prevalence rate has markedly risen with time, increasing from 25.3% in 1999 to 2005 to 33.9% in 2012 to 2017.<sup>11</sup> According to the projections from modeling studies, the prevalence rate of fatty liver disease is likely to increase from 21.8% (95% CI, 18.6–25.0) in 2019 to 23.2% (95% CI, 19.8–26.7) in 2030.<sup>12</sup>

Estimates of the prevalence rates of SLD often vary with the diagnostic method. A study reported that when abdominal ultrasound was used, among adults undergoing health check-ups, the prevalence rate of fatty liver disease was approximately 46.1%.<sup>13</sup> A community-based study reported a prevalence rate ranging from 50.6% when transient elastography was used to 58.6% when ultrasound was used.<sup>14</sup> Notably, although obesity rates are generally lower in Asian than in Western populations, fatty liver disease remains prevalent in Asia, even among non-obese individuals (~18%).<sup>15</sup> This discrepancy is partly attributable to the unique risk factors, such as higher visceral fat content and lower muscle mass, and the higher risks of hypertension and diabetes in Asian individuals.<sup>16</sup>

Obesity is the greatest risk factor for fatty liver disease. Among overweight or obese adults, the overall prevalence rate for this disease is approximately 50.7% (95% CI, 46.9–54.5), with this rate remaining consistent regardless of the diagnostic method used.<sup>17</sup> Metabolic syndrome, which is characterized by the presence of obesity, diabetes, hypertension, and central obesity (ie, increased waist circumference), is associated with a significantly higher likelihood of developing fatty liver disease, and it is a crucial clinical indicator for referral and diagnosis.<sup>1</sup> Research has reported that among Asian people, unhealthy lifestyle factors can increase the risk of fatty liver disease. Smoking (3.8%–22.6%) and high consumption of carbonated beverages (22.6%–62.2%) are key contributors to the risk of fatty liver disease. Notably, <30% of individuals meet physical activity guidelines, with many reporting sedentary behavior exceeding 42 hours per week.<sup>18</sup>

Dietary patterns characterized by a low intake of vegetables, fruits, and vitamin C are common among individuals with fatty liver disease, particularly in regions such as Hong Kong.<sup>19</sup> Collectively, the aforementioned results indicate that sedentary behavior, inadequate physical activity, a high-calorie diet, and Western dietary habits are closely associated with the growing prevalence of fatty liver disease.

4. MASLD AND ASSOCIATED RISK OF END-STAGE LIVER DISEASE

The course of MASLD involves progression from simple steatosis to fibrosis and, in some cases, HCC, even in the absence of cirrhosis. Clinical evidence indicates that >35% of patients with MASLD-related HCC do not have cirrhosis.<sup>20</sup> A significantly higher proportion of patients with MASLD were reported to have HCC than that of those with other liver diseases, indicating MASLD is a major risk factor for HCC in patients without cirrhosis.<sup>21</sup> Notably, MASLD often coexists with metabolic abnormalities such as obesity, diabetes, and dyslipidemia, which may increase the risk of hepatocarcinogenesis.<sup>22</sup>

MASLD significantly increases the risks of advanced liver diseases, including cirrhosis and HCC. Table 1 provides a detailed



summary of the studies that have evaluated these risks. Key findings from large, diverse cohorts have revealed significantly increased risks of cirrhosis and HCC in patients with MASLD or its progressive form (ie, metabolic dysfunction-associated steatohepatitis) compared with those in nonaffected individuals. A large European cohort study of 18 million participants reported hazard ratio (HRs) of 5.83 for cirrhosis and 3.15 for HCC among individuals with NAFLD. Among participants with NASH, the HRs were higher; that is, they were 22.67 for cirrhosis and 8.02 for HCC.<sup>23</sup> A Swedish cohort study with a 26-year follow-up demonstrated that biopsy-proven NAFLD was associated with increased liver-related mortality.<sup>24</sup> A meta-analysis<sup>25</sup> of 54 studies involving 26 738 patients examined the progression and regression rates of NAFLD stages over a median follow-up of 3.5 to 4.7 years. The incidence of steatohepatitis progression (7.4/100 person-years) was higher than the incidence of its regression (5.1/100 person-years). In addition, the analysis revealed that fibrosis progressed at similar rates in baseline stages but regressed more frequently in advanced stages. These findings highlight the dynamic nature of SLD progression and indicate that early intervention is crucial in preventing disease progression.

Research has also indicated that the use of noninvasive diagnostic methods, such as ultrasound and assessment of persistent elevation of alanine aminotransferase (ALT) levels, can facilitate early detection of SLD. Elevated ALT levels are strongly associated with an increased risk of HCC<sup>26,27</sup>; thus, ALT is a valuable marker for identifying high-risk patients.<sup>28</sup> A prospective cohort study reported HRs of 3.51 for cirrhosis and 1.91 for HCC among patients with NAFLD with elevated ALT levels, indicating the utility of ALT as a surrogate for steatohepatitis.<sup>11</sup> Studies on MASLD have also reported a twofold increase in HCC risk in patients with persistent elevation of ALT levels after adjustment for confounders.<sup>29,30</sup> Furthermore, research identified persistent ALT elevation and the fibrosis stage as critical predictors of adverse outcomes in MASLD. Specifically, Kanwal et al<sup>27</sup> reported a 7.62-fold increase in HCC risk in patients with NAFLD with elevated ALT levels. Notably, differences across ethnicities and regions along with differences in diagnostic methods can influence estimates of the risk of HCC.

## 5. MASLD SUBTYPES AND ASSOCIATED RISK OF HCC

Distinct risks of progression have been observed across the subtypes of SLD. A prospective cohort study with a 16-year follow-up that involved 332 175 individuals reported HRs of 1.30 (95% CI, 1.21-1.39) for cirrhosis in patients with MASLD, 1.72 (95% CI, 1.48-2.00) for cirrhosis in patients with MetALD, and 2.82 (95% CI, 2.54-3.13) for cirrhosis in patients with ALD. The HRs for HCC were 1.31 (95% CI, 1.16-1.47) in patients with MASLD, 1.83 (95% CI, 1.43-2.34) in patients with MetALD, and 1.52 (95% CI, 1.24-1.86) in patients with ALD. These findings indicate that the risks of disease progression vary across SLD subtypes.<sup>31</sup> Additional studies have confirmed that ALD is associated with the highest risk of cirrhosis, followed by MetALD and MASLD. However, although a general consensus has been reached regarding the relative risk (RR) of cirrhosis in different SLD subtypes, the RRs of HCC across these subtypes remain unclear.<sup>32</sup> For example, a Korean cohort study identified MetALD as the subtype with the highest risk of HCC.<sup>33</sup> Other nationwide studies have indicated that ALD is associated with the highest risk.<sup>32,34</sup> These discrepancies highlight the need for further research to clarify the relationship between SLD subtypes and HCC progression.

## 6. MASLD AND ASSOCIATED RISK OF CARDIOVASCULAR DISEASES

Several studies have revealed a robust association between MASLD and cardiovascular disease (CVD).<sup>35</sup> Notably, large cohort studies have consistently reported that patients with MASLD exhibit increased risks of major adverse cardiovascular events, including heart failure (HF), myocardial infarction (MI), ischemic stroke (IS), and atrial fibrillation (AF).<sup>36-38</sup> The increased risk of CVD in patients with MASLD is attributable to shared pathophysiological mechanisms between the diseases, including systemic inflammation, endothelial dysfunction, insulin resistance, and oxidative stress.<sup>36,39</sup> These mechanisms promote the development of atherosclerosis and cardiomyopathies, which significantly contribute to a high incidence of CVD and high mortality in patients with MASLD.<sup>40</sup>

Evidence suggests that compared with the general population, individuals with MASLD exhibit not only a higher likelihood of cardiovascular events but also a twofold higher likelihood of CVD-related mortality.<sup>40</sup> A study identified CVD as the leading cause of mortality in patients with MASLD, with this finding indicating a critical need for effective management of cardiovascular risk in this patient population.<sup>41</sup> Regular screening of cardiovascular events and preventive measures should be implemented to address the concern of cardiovascular risk in patients with MASLD. Early identification and proactive management of cardiovascular risk factors—such as hypertension, dyslipidemia, and diabetes—are essential to preventing disease progression and improving survival outcomes in patients with MASLD.

Table 2 provides a comprehensive summary of the evidence regarding MASLD and CVD across diverse populations, definitions of steatosis, and diagnostic methods. The studies that have provided this evidence have involved sample sizes ranging from tens of thousands to millions and have highlighted the risks of various cardiovascular outcomes, including MI, IS, HF, AF, coronary artery disease (CAD), and cardiovascular mortality, associated with SLD. Diagnostic tools such as the fatty liver index (FLI), ultrasound, liver enzymes, and biopsy were used in the studies. The key findings revealed significant associations of MASLD with composite cardiovascular events, including MI, stroke, HF, AF, CAD, and cardiovascular mortality.<sup>35,42</sup> In a Korean cohort, MASLD and related subtypes were noted to be associated with increased cardiovascular risks, with HRs ranging from 1.28 to 1.39.<sup>35</sup> Through longitudinal analyses, Chinese studies have demonstrated increased risks of HF (HR: 1.40, 95% CI, 1.30-1.50)<sup>43</sup> and AF (HR: 1.99, 95% CI, 1.39-2.83) in patients with MAFLD.<sup>44</sup> Additionally, a study conducted in the United Kingdom reported increased risks of MI (HR: 1.35, 95% CI, 1.29-1.41) and stroke (HR: 1.26, 95% CI, 1.18-1.33) in patients with MAFLD.<sup>45</sup>

A Japanese study reported a significantly high risk of CAD in patients with MASLD.<sup>46</sup> Furthermore, a global meta-analysis<sup>47</sup> revealed that NAFLD was associated with increased risks of angina (HR: 1.45, 95% CI, 1.17-1.79), coronary artery calcification (CAC >0; RR: 1.39, 95% CI, 1.15-1.69), and calcified plaques (HR: 1.55, 95% CI, 1.05-2.27), although no significant associations were observed between NAFLD and CAC >100 or the MI. Additionally, a Swedish study<sup>48</sup> highlighted additional cardiovascular risks in patients with MASLD, including risks of ischemic heart disease (HR: 1.64, 95% CI, 1.54-1.75), congestive HF (HR: 1.75, 95% CI, 1.63-1.87), and CV mortality (HR: 1.37, 95% CI, 1.27-1.48). These findings highlight that fatty liver disease is associated with high cardiovascular risk and reinforce that cardiovascular risk assessment are crucial for patients with MASLD.

Liver stiffness has increasingly been recognized as a biomarker linking hepatic and cardiovascular health. A large

Table 2 Evidence from prospective studies on risk of end-stage liver diseases associated with steatotic liver disease			
Authors, year	Diagnosis/definition of steatosis	Number of participants	Hazard ratio (95% CI)
Ekstedt et al <sup>24</sup>	Biopsy	N = 2515 NAFLD: 229	Death from cirrhosis: NAFLD: 3.20 (1.05-9.81) Death from HCC: NAFLD: 6.55 (2.14-20.03) HCC: NAFLD: 7.62 (5.76-10.09) Cirrhosis: NAFLD/NASH: 4.73 (2.43-9.19) NAFLD: 5.83 (1.87-18.13) NASH: 22.67 (5.96-86.23) HCC: NAFLD/NASH: 3.51 (1.72-7.16) NAFLD: 3.15 (1.16-8.56) NASH: 8.02 (4.08-15.77) HCC: NAFLD: 2.41 (1.39-4.17) HCC: MAFLD: 1.96 (1.00-3.86) HCC: MAFLD with other LD: 0.98 (0.70-1.36) MAFLD without other LD: 1.84 (1.09-3.11)
Kanwal et al <sup>27</sup>	Persistent ALT elevation (≥6 mo)	N = 593 414 NAFLD: 296 707	
Alexander et al <sup>23</sup>	ICD code/ Read code/ IPC Dutch	N = 18 782 281 NAFLD/NASH: 136 703 NAFLD: 93 469 NASH: 2712	
Ji et al <sup>26</sup>	Ultrasound/ultrasound plus hepatic steatosis index	N = 1241 NAFLD: 317	
van Kleef et al <sup>30</sup>	Biopsy	N = 1076 MAFLD: 296	
Song et al <sup>29</sup>	Ultrasound	N = 73 691 MAFLD: 29 976	

ALT = alanine aminotransferase; BMI = body mass index; HCC = hepatocellular carcinoma; HSD = Health Search Database; ICD = International Classification of Disease; IPCI = Integrated Primary Care Information; NAFLD = nonalcoholic fatty liver disease; NASH = steatohepatitis; SIDIAP = Information System for the Development of Research in Primary Care; THIN = Health Information Network

community-based cohort study revealed that elevated liver stiffness (≥8.0 kPa) was associated with increased mortality, particularly in individuals with HF; this suggests that cardiac dysfunction contributes to liver stiffness and poor outcomes.<sup>49</sup> Additionally, a study involving hospitalized patients with acute decompensated HF revealed that liver stiffness was frequently elevated in these patients and tended to decrease with clinical improvement, indicating the presence of a dynamic relationship between liver congestion and liver stiffness.<sup>50</sup> Furthermore, research indicated that in individuals with biopsy-proven NAFLD, advanced fibrosis stages (stages 3-4) were an independent predictor of incident cardiovascular events; the study indicated that in addition to traditional risk scores, hepatic fibrosis can be used for cardiovascular risk stratification.<sup>51</sup> Collectively, these findings indicate the complex interplay between liver stiffness and CVD, emphasizing the need for integrated assessment strategies for at-risk populations.

7. INTERPLAY BETWEEN MASLD AND CHRONIC VIRAL HEPATITIS

Investigation of the interplay between MASLD and chronic viral hepatitis, particularly CHB and CHC, is critical, and findings from such investigations would have crucial clinical implications. MASLD has become increasingly prevalent among patients with chronic viral hepatitis, and MASLD influences disease progression, treatment outcomes, and long-term survival in these patients.

In untreated patients with HBeAg-negative CHB, MASLD was reported to be associated with an increased likelihood of hepatitis B surface antigen (HBsAg) seroclearance and seroconversion.<sup>52</sup> This suggests the presence of an interaction between metabolic dysfunction and immune control of HBV infection. Furthermore, a study indicated that metabolic abnormalities in patients with CHB contribute to worse outcomes for liver disease because individuals with concurrent MASLD exhibit high dose-dependent risks of cirrhosis and cirrhotic complications.<sup>53</sup> Notably, the additional presence of new-onset diabetes mellitus increases these risks, whereas hepatic steatosis may exert protective effects against these risks. Additionally, among patients with SLD and CHB, the cumulative metabolic burden of the conditions results in significant increases in the risks of all-cause, liver disease-related, and cardiovascular mortality.<sup>54</sup> New-onset diabetes, hypertension, and weight gain further increase these risks. These findings indicate that proactive metabolic risk assessment and continuous monitoring are required to optimize disease management.

In patients with CHC, HCV eradication leads to metabolic changes. However, its effect on MASLD remains uncertain. A nationwide study of 5840 patients with CHC who were treated with direct-acting antivirals revealed significant reductions in HbA1c and BMI after viral clearance.<sup>55</sup> However, the prevalence of MASLD mostly remained unchanged, with BMI being the primary determinant of MASLD resolution. Furthermore, cardiometabolic risk factors, including increased BMI and HbA1c, were independently associated with the development of MASLD after HCV clearance. Another study involving patients with CHC who achieved sustained virologic responses discovered that MASLD was linked to a two-fold increased risk of de novo HCC<sup>56</sup>; mediation analysis in that study confirmed that MASLD is a key contributor to the effects of cardiometabolic dysfunction on the development of HCC. These findings demonstrate the need for continual metabolic risk surveillance, proactive lifestyle modification, and careful HCC monitoring in patients with CHC after viral eradication.

**Table 3**  
Cardiovascular risk associated with steatotic liver disease

Author, year	Number of participants	Definition of steatosis	Cardiovascular outcomes	Associated risk
Wu et al <sup>42</sup>	N = 164 494	Ultrasound, liver biopsy, CT images, or liver enzyme	Overall mortality, CVD mortality, and incident CVD, CAD, hypertension, and atherosclerosis	Coronary artery disease, HR: 2.31 (95% CI, 1.46-3.65) Atherosclerosis, HR: 1.37 (95% CI, 1.10-1.72)
Alexander et al <sup>43</sup>	Italy (n = 1 542 672) The Netherlands (n = 2 225 925)	ICD code, Read code, ICD Dutch	Fatal or nonfatal acute myocardial infarction and ischemic or unspecified stroke	Acute myocardial infarction, HR: 1.01 (95% CI, 0.91-1.12) Stroke, HR: 1.04 (95% CI, 0.99-1.09)
Yoneda et al <sup>46</sup>	Spain (n = 5 488 397) UK (n = 12 695 046) N = 2 452 949	FLI $\geq 60$	Cerebral infarction, coronary artery event, and cardiovascular event (cerebral infarction + coronary artery event)	Cerebral infarction, HR: 1.33 (95% CI, 1.04-1.68) Coronary artery disease, HR: 2.43 (95% CI, 2.29-2.58) Cardiovascular disease, HR: 2.33 (95% CI, 2.19-2.46)
Chen et al <sup>45</sup>	NAFLD: 2 215 707 MAFLD: 237 242 N = 325 129	FLI $\geq 60$	Myocardial infarction and stroke	Myocardial infarction, HR: 1.35 (95% CI, 1.29-1.41) Stroke, HR: 1.26 (95% CI, 1.18-1.33) HR: 1.99 (95% CI, 1.39-2.83)
Lei et al <sup>44</sup>	N = 54 832	Ultrasound	Atrial fibrillation	OW-MAFLD, HR: 1.16 (95% CI, 1.15-1.18)
Lee et al <sup>42</sup>	N = 8 412 730	FLI $\geq 30$	Composite cardiovascular disease events: including myocardial infarction, ischemic stroke, heart failure, or cardiovascular disease-related death	lean-MAFLD, HR: 1.23 (95% CI, 1.20-1.27) DM-MAFLD, HR: 1.82 (95% CI, 1.80-1.85)
Simon et al <sup>48</sup>	N = 13 498	Liver biopsy	MACE outcomes, that is, IHD, stroke, CHF, or CV mortality	IHD, HR: 1.64 (95% CI, 1.54-1.75) CHF, HR: 1.75 (95% CI, 1.63-1.87) Stroke, HR: 1.58 (95% CI, 1.46-1.71) CV mortality, HR: 1.37 (95% CI, 1.27-1.48) HR: 1.40 (95% CI, 1.30-1.50)
Wei et al <sup>43</sup>	N = 98 685	Ultrasound	Heart failure	MASLD, HR: 1.39 (95% CI, 1.30-1.50)
Lee et al <sup>45</sup>	N = 9 775 066	FLI $\geq 30$	Composite of cardiovascular events, including myocardial infarction, ischemic stroke, heart failure, and cardiovascular death	MetALD, HR: 1.28 (95% CI, 1.26-1.30)
Abosheataishaa et al <sup>47</sup>	N = 5 610 990	Liver enzymes	Angina, CAD, CAC, MI, and calcified coronary plaques	MASLD with other combined etiology, HR: 1.30 (95% CI, 1.26-1.34) Angina, HR: 1.45 (95% CI, 1.17-1.79) CAD, HR: 1.21 (95% CI, 1.07-1.38) CAC $>0$ , HR: 1.39 (95% CI, 1.15-1.69) Calcified coronary plaques, HR: 1.55 (95% CI, 1.05-2.27) No significant association identified between NAFLD and CAC $>100$ or MI

CT images = computed tomography images; DM = diabetes mellitus; FLI = fatty liver index; HR = hazard ratio; MAFLD = metabolic dysfunction-associated fatty liver disease; MASLD = metabolic dysfunction-associated steatotic liver disease; MetALD = MASLD with increased alcohol intake; NAFLD = nonalcoholic fatty liver disease; OW = overweight/obese; ICD = International Classification of Disease; ICD = Integrated Primary Care Information.

Overall, the literature indicates that complex interactions occur between MASLD and chronic viral hepatitis, with these interactions influencing disease progression, treatment outcomes, and long-term prognosis. The burden of metabolic dysfunction in patients with viral hepatitis is increasing, and metabolic risk assessments, lifestyle interventions, and long-term surveillance strategies must be implemented to improve patient outcomes and to reduce liver disease-related morbidity and mortality.

8. GENETIC VARIANTS ASSOCIATED WITH MASLD

Genetic predisposition plays a critical role in the pathogenesis and progression of MASLD (Table 4). A heritability study revealed a significant genetic component in the development of SLD. The study reported a heritability estimate of 38.6% ( $h^2 = 0.386, p < 0.05$ ) for NAFLD, which indicates that genetic factors play crucial roles in patient susceptibility to MASLD.<sup>57</sup>

Advancements in genome-wide association studies have facilitated the identification of numerous genetic variants in MASLD. One of the most well-established variants in MASLD is *PNPLA3* (rs738409), which is strongly associated with hepatic fat accumulation and fibrosis development across diverse patient populations.<sup>58</sup> Schwimmer et al<sup>57</sup> were the first to demonstrate the association between *PNPLA3* and hepatic TG content in a multiethnic cohort; they did so using proton magnetic resonance spectroscopy (H-MRS). A subsequent study confirmed this association and reported an increased RR (RR: 1.83, 95% CI, 1.69-1.98) for European populations.<sup>59</sup> This polymorphism is notable because of its robust influence on disease severity.

Additional genetic variants linked to an increased risk of MASLD include *TM6SF2* (rs58542926), which affects lipid metabolism, and *GCKR* (rs1260326), which influences glucose homeostasis. Other genetic variants contributing to an increased

risk include *APOE* (rs429358), *SUGP1* (rs8107974), *LEPR* (rs12077210), and *PBX4* (rs10500212).<sup>59,60</sup> Protective genetic variants have also been identified. These include *HSD17B13* (rs13118664 and rs9992651), which reduces hepatic inflammation and fibrosis development (HR: 0.74, 95% CI, 0.67-0.82),<sup>59</sup> and *MBOAT7* (rs641738), which is implicated in lipid remodeling (HR: 1.20, 95% CI, 1.05-1.37).<sup>60</sup> Furthermore, in a Chinese cohort study of individuals aged >65 years, *SAMM50* (rs738491)<sup>61</sup> was associated with an increased risk of SLD (HR: 1.22, 95% CI, 1.01-1.47). Table 3 provides a detailed summary of these findings, providing information regarding the discovery and validation cohorts, the definition of steatosis, and RRs.

Collectively, these results reveal the substantial contribution of genetic factors to the pathogenesis of MASLD. Identification of high-risk individuals on the basis of their genetic profiles can enable earlier intervention and targeted therapy. Moreover, insights into the mechanistic roles of the aforementioned genetic variants can be used to identify novel biomarkers and develop therapies to improve clinical outcomes in patients with MASLD.

9. NONINVASIVE TESTS FOR MASLD

Early diagnosis and accurate staging of fibrosis are essential in the management of MASLD. Although liver biopsy remains the gold standard, its invasiveness and associated risks limit its widespread use. Thus, noninvasive tests (NITs) should be developed as alternative diagnostic tools. NITs can be broadly categorized into serum-based biomarker and imaging-based tests. Such tests are safer and more accessible options for assessing fibrosis.

Serum-based NITs include assessments to obtain commonly used fibrosis scores such as the fibrosis-4 (FIB-4) score,<sup>64,65</sup> NAFLD fibrosis score,<sup>66</sup> and steatosis-associated fibrosis

Table 4  
Genetic variants linked to steatotic liver disease

Author, year	Gene	SNP	Relative risk (95% CI)	Numbers in discovery	Numbers in validation	Comments
Romeo et al <sup>58</sup>	<i>APOE</i>	rs429358	0.88 (0.84-0.92)	N = 32 941	NA	<ul style="list-style-type: none"><li>Cases were detected by a liver proton density fat fraction (WL-PDFF) ≥5%</li><li>European</li></ul>
	<i>HFE</i>	rs1800562	1.25 (1.19-1.31)	Case: 6623		
	<i>TM6SF2</i>	rs58542926	1.40 (1.36-1.44)	Control: 26 318		
Schwimmer et al <sup>57</sup>	<i>PNPLA3</i>	rs738409	NA	N = 2111	NA	<ul style="list-style-type: none"><li>The first study identified <i>PNPLA3</i> associated with hepatic TG content</li><li>Multiethnic participant</li><li>TG content was measured as a continuous variable by using H-MRS</li></ul>
Mancina et al <sup>61</sup>	<i>SAMM50</i>	rs738491	1.22 (1.01-1.47)	Case: 590 Control: 463	NA	<ul style="list-style-type: none"><li>For Chinese patients aged &gt;65 years, cases were identified through abdominal ultrasonography</li></ul>
Anstee et al <sup>60</sup>	<i>MBOAT7</i>	rs641738	1.20 (1.05-1.37)	N = 2736	N = 1149	<ul style="list-style-type: none"><li>Discovery cohort involved multiethnic participants</li><li>TG content was considered, and diagnoses were made using H-MRS</li><li>Validation was conducted with 3 cohorts in Europe</li></ul>
Sun et al <sup>59</sup>	<i>PNPLA3</i>	rs738409	1.83 (1.69-1.98)	N = 19 264	N = 2079	<ul style="list-style-type: none"><li>Participants in the discovery cohort</li><li>Patients were recruited from European tertiary centers</li><li>Cases were diagnosed using ALT, gamma GT, abdominal ultrasonography, and liver biopsy</li></ul>
	<i>GCKR</i>	rs1260326	1.28 (1.19-1.38)	Case: 1483	Case: 559	
	<i>TM6SF2</i>	rs58542926	1.61 (1.40-1.85)	Control: 17 781	Control: 1520	
	<i>SUGP1</i>	rs8107974	1.63 (1.42-1.87)			
	<i>HSD17B13</i>	rs13118664	0.74 (0.67-0.82)			
		rs9992651	0.74 (0.67-0.83)			
	<i>LEPR</i>	rs12077210	1.48 (1.29-1.71)			
	<i>PBX4</i>	rs10500212	1.55 (1.37-1.75)			

ALT = alanine aminotransferase; gamma GT = gamma-glutamyl transpeptidase; H-MRS = proton magnetic resonance spectroscopy; TG = triglyceride; WL-PDFF = whole-liver proton density fat fraction.



estimator score.<sup>67,68</sup> These scores are obtained through analysis of routinely assessed clinical and biochemical parameters, such as age, BMI, diabetes status, AST, ALT, platelet count, and globulin levels, and are used to estimate fibrosis risk. Additionally, the enhanced liver fibrosis<sup>69,70</sup> test can be used to directly measure fibrogenesis markers, although its specificity may be lower in populations with a low prevalence of fibrosis. Imaging-based NITs, including vibration-controlled transient elastography<sup>71</sup> and magnetic resonance elastography,<sup>72,73</sup> can be used to conduct quantitative assessments of liver stiffness, and the findings of these tests can help with fibrosis staging and risk stratification. The integration of NITs into clinical practice may enable early detection of fibrosis, facilitate treatment decision-making, and reduce reliance on liver biopsy, thereby improving overall disease management.

## 10. CONCLUSIONS AND FUTURE PERSPECTIVES

MASLD is a global health challenge caused by a growing prevalence of obesity and metabolic disorders. Currently, it is a leading cause of end-stage liver diseases, such as cirrhosis and HCC, and MASLD is strongly associated with increased CVD-related morbidity and mortality. Early diagnosis, risk stratification, and integrative management strategies are crucial to addressing both liver-related and cardiovascular complications in patients with MASLD. Future research efforts in this area should focus on improving noninvasive diagnostic tools, integrating cardiovascular risk management into MASLD care, and developing precision medicine approaches based on genetic and biomarker research. Population-specific interventions that account for regional and ethnic variations in risk factors should also be developed. Adopting a multifaceted strategy can reduce the effect of MASLD on global health.

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