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Review Article

Lean MAFLD: A Hepatocentric Phenotype with Systemic Manifestations

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Abstract

The prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) continues to increase worldwide, partly because of rising rates of obesity and metabolic syndrome. However, a substantial proportion of patients with MAFLD are neither overweight nor obese and are classified as having lean MAFLD. The increasingly recognized phenotype of lean MAFLD challenges the traditional paradigm linking obesity to metabolic risk. Despite a normal body mass index (BMI), lean MAFLD is associated with substantial metabolic dysfunction and a range of extrahepatic manifestations. Evidence from systematic reviews and meta-analyses including more than 10 million individuals indicates that patients with lean MAFLD have metabolic profiles comparable to those of overweight or obese patients with MAFLD, including insulin resistance, dyslipidemia, and hypertension. Importantly, although cardiovascular and cancer-related mortality appear broadly similar across BMI categories, liver-related mortality is generally higher in lean individuals, suggesting disticnt hepatocentric vulnerability. Variation in all-cause mortality estimates is influenced by disease severity, study design, and ethnicity. Important mechanistic factors include genetic susceptibility, sarcopenia, and visceral adiposity. These findings support comprehensive metabolic and hepatic assessment in lean MAFLD beyond BMI-based risk classification. This review examines lean MAFLD as a hepatocentric phenotype with systemic effects beyond BMI.

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Introduction

Nonalcoholic fatty liver disease can occur in individuals with a normal body mass index (BMI) but heterogeneous metabolic risk, challenging established paradigms. Metabolic dysfunction-associated fatty liver disease (MAFLD) is considered a more appropriate definition than nonalcoholic fatty liver disease, as it explicitly associates metabolic dysfunction with fatty liver disease. This redefinition challenges and reshapes our understanding of the disease.[1]

The prevalence of MAFLD continues to increase worldwide, partly because of rising rates of obesity and metabolic syndrome. However, a substantial proportion of patients with MAFLD are neither overweight nor obese and are classified as lean MAFLD. Lean MAFLD is more prevalent in Asian populations but increasingly recognized worldwide.[2,3] Once considered benign, lean MAFLD is now recognized as conferring substantial metabolic and hepatic risk, challenging long-standing assumptions about the relationship between adiposity and disease severity. Recognition of lean MAFLD has important implications for research and clinical practice. Conventional BMI-based screening approaches may miss at-risk individuals, thereby delaying diagnosis and treatment. Furthermore, the pathophysiology of lean MAFLD may differ from that of obesity-associated disease, requiring a more comprehensive approach to risk assessment and therapeutic management.[4] Accordingly, this review examines lean MAFLD as a hepatocentric phenotype with systemic manifestations, with emphasis on epidemiology, mechanisms, extrahepatic outcomes, mortality, and clinical implications.

Methods and evidence base

This narrative review summarizes findings from relevant systematic reviews and meta-analyses. Diagnosis of MAFLD requires hepatic steatosis—identified by histology, imaging, or noninvasive biomarkers—together with at least one of the following three criteria: overweight or obesity, type 2 diabetes mellitus (T2DM), or metabolic dysregulation.[5] Unlike nonalcoholic fatty liver disease, MAFLD does not require the exclusion of other chronic liver diseases or alcohol consumption. Conversely, lean individuals with fatty liver who have none of the metabolic abnormalities specified in the MAFLD criteria would not meet the definition of MAFLD. The studies

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reviewed generally defined lean MAFLD using BMI thresholds of < 25 kg/m^2 for non-Asian populations and < 23 kg/m^2 for Asian populations, consistent with international consensus criteria.[5]

The pooled studies included populations from Asia, Europe, and North America, with sample sizes ranging from tens of thousands to more than 10 million individuals. Outcomes included metabolic characteristics, extrahepatic manifestations, and mortality, providing a broad overview of the clinical burden associated with lean MAFLD.

Epidemiology and global distribution

The prevalence of lean MAFLD varies widely among populations because of differences in diagnostic criteria, lifestyle, and ethnicity. In the general population, prevalence estimates range from 1.9% to 5.4%. Pooled studies indicate that approximately 12.3% of patients with MAFLD are lean; however, estimates range from 1.9% in Korean cohorts to 16.5% in cohorts from Taiwan, China.[6] A recent meta-analysis identified more than 90 studies (n = 10,576,383) from 24 countries or regions. Among individuals with MAFLD, 19.2% (95% confidence interval [CI], 15.9–23.0) were lean and 40.8% (95% CI, 36.6–45.1) were non-obese. The proportion of non-obese MAFLD in the general population ranged from ≤ 25% in some countries, such as Malaysia and Pakistan, to > 50% in others, such as Austria, Mexico, and Sweden. In the overall population, including individuals with and without MAFLD, the prevalence was 12.1% (95% CI, 9.3–15.6) for non-obese MAFLD and 5.1% (95% CI, 3.7–7.0) for lean MAFLD. Among individuals with non-obese or lean MAFLD, 39.0% (95% CI, 24.1–56.3) had metabolic dysfunction-associated steatohepatitis, 29.2% (95% CI, 21.9–37.9) had significant fibrosis (stage ≥ 2), and 3.2% (95% CI, 1.5–5.7) had cirrhosis. Rates per 1,000 person-years were 12.1 (95% CI, 0.5–38.8) for all-cause mortality, 4.1 (95% CI, 1.9–7.1) for liver-related mortality, 4.0 (95% CI, 0.1–14.9) for cardiovascular mortality, 12.6 (95% CI, 8.2–22.7) for incident diabetes, and 56.1 (95% CI, 38.5–77.0) for incident hypertension. Most analyses showed substantial heterogeneity.[7] These differences highlight the importance of applying geographic- and ethnicity-specific BMI thresholds when estimating disease burden. Genetic susceptibility and differences in body composition, including greater visceral adiposity at lower BMI, may contribute to the higher prevalence in Asian populations.[8]

Clinical and metabolic phenotype

Lean MAFLD challenges the long-standing assumption that hepatic steatosis is primarily associated with obesity. It has emerged as a distinct and underrecognized clinical entity affecting individuals with a normal BMI but conferring risks of cardiovascular disease, hepatocellular carcinoma, and liver-related mortality similar to those associated with obesity-related MAFLD. The absence of overweight or obesity can complicate recognition and expose limitations in current BMI-based screening frameworks. Lean MAFLD is characterized by a paradoxical metabolic profile in which individuals with a normal BMI exhibit features commonly associated with obesity-related metabolic dysfunction, including elevated inflammatory markers, dyslipidemia, insulin resistance, and impaired glucose tolerance. Several metabolic markers are similar between lean and non-lean MAFLD, suggesting that body weight alone does not determine the severity of metabolic dysfunction.[4,9,10]

Adipose tissue dysfunction and systemic inflammation may exacerbate steatohepatitis and fibrosis. Insulin resistance, oxidative stress, inflammatory signaling, and alterations in the gut–liver axis contribute to the complex pathophysiology of lean MAFLD. Disease progression is influenced by both environmental factors and genetic susceptibility.[8]

Compared with metabolically healthy lean individuals, those with lean MAFLD have substantially less favorable metabolic profiles, including higher fasting glucose and glycated hemoglobin levels, as well as adverse lipid profiles. This finding supports the concept that lean MAFLD is metabolically detrimental despite a normal BMI.[11]

Body composition and pathophysiology

A major difference in body composition between obese and non-obese patients with MAFLD is the distribution of adipose tissue. Patients with obesity typically have excess visceral and subcutaneous adiposity, which increases BMI and the risk of dyslipidemia, insulin resistance, and other metabolic disorders. In contrast, individuals with lean MAFLD may have less subcutaneous adipose tissue but still exhibit disproportionate visceral adiposity and ectopic hepatic fat deposition, indicating a distinct metabolic phenotype that confers risk of fatty liver despite a lower BMI. Increased waist circumference and adverse lipid levels are important risk factors for MAFLD in lean individuals.[10,12]

Patients with lean MAFLD have distinct body-composition characteristics. Despite lower BMI and waist circumference than those of non-lean MAFLD, they may have relatively greater visceral adiposity. Body-composition analyses have also reported lower fat tissue index, lean tissue index, and total body water in lean MAFLD than in non-lean MAFLD.[11]

Recent studies indicate that lean individuals with larger waist circumferences are more likely to develop atherosclerosis, T2DM, and hepatic fibrosis. In addition, liver biopsies from individuals with lean MAFLD have shown greater hepatocyte ballooning and inflammation than biopsies from patients with obesity-associated MAFLD.[13]

Skeletal muscle, which accounts for 40%–50% of adult lean body mass and functions as both a locomotor and metabolic organ, plays a central role in energy metabolism. Sarcopenia is now recognized as a progressive degenerative condition associated with metabolic syndrome, liver disease, cardiovascular disease, and T2DM. It was traditionally considered an age-related syndrome characterized by loss of muscle mass, strength, and physical performance but is also associated with disorders driven by systemic inflammation and insulin resistance. Sarcopenia is a key feature of lean MAFLD. A meta-analysis found a higher prevalence of sarcopenia among patients with lean MAFLD and proposed that it may contribute to increased liver-related mortality. Figure 1 illustrates the interconnected genetic, metabolic, and organ-axis mechanisms that may contribute to lean MAFLD despite a normal BMI. These pathways converge on hepatic inflammation, oxidative stress, hepatocyte injury, and fibrosis, potentially contributing to hepatocellular carcinoma and increased liver-related mortality. The liver–muscle, liver–heart, and liver–kidney axes emphasize bidirectional interactions between hepatic metabolic dysfunction and extrahepatic disease. Altered gut microbiota, oxidative stress, inflammatory signaling, and dysregulation of the renin–angiotensin–aldosterone system are shared pathways linking MAFLD and chronic kidney disease (CKD). Metabolic dysfunction and atherogenic dyslipidemia contribute to cardiovascular disease, whereas persistent hepatic inflammation and fibrosis may facilitate hepatocarcinogenesis.

The liver and skeletal muscle are closely linked through the metabolism of ammonia, glucose, and amino acids. Pa-

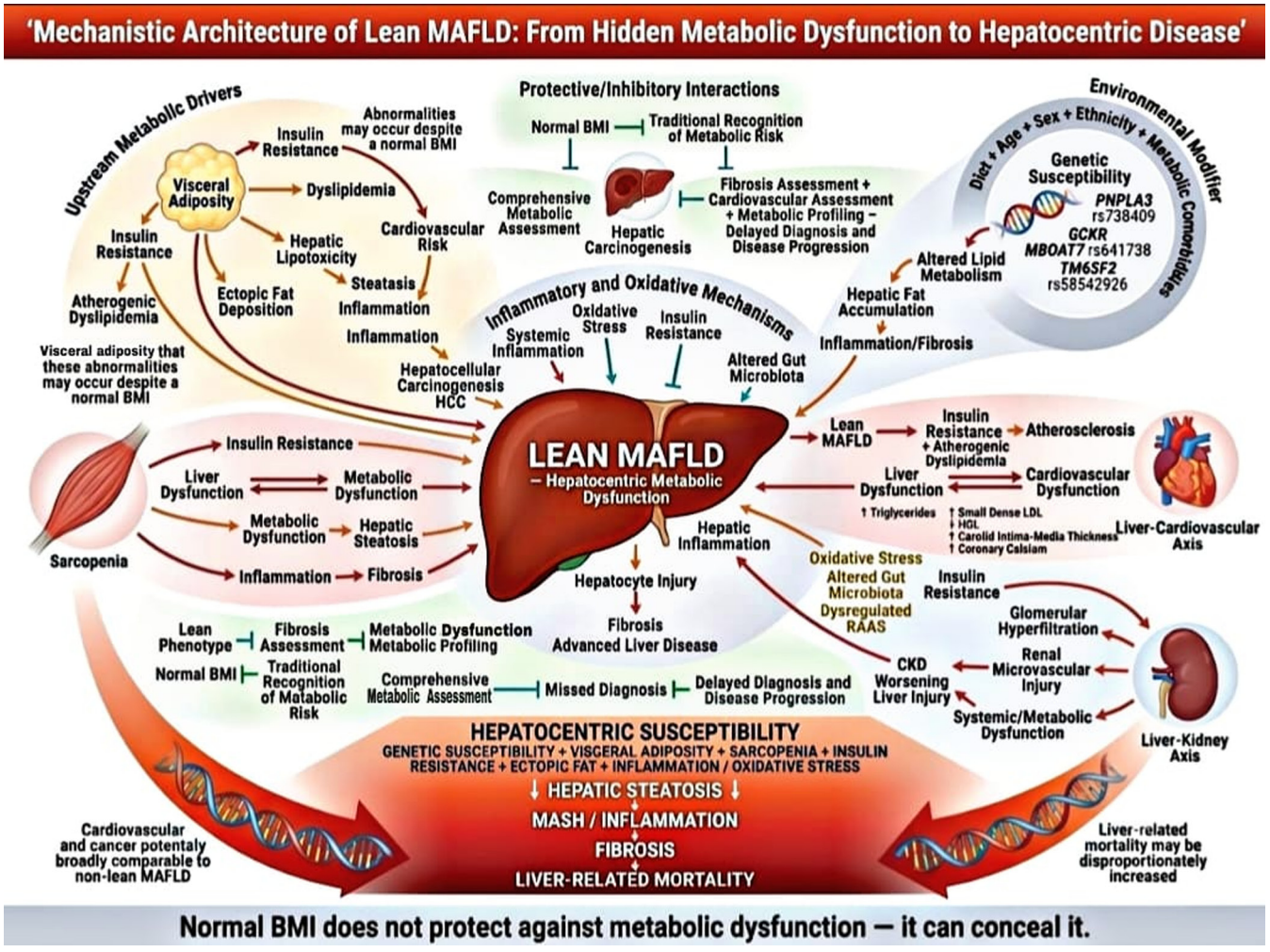


Fig. 1. Mechanistic architecture of lean MAFLD: Stimulatory and inhibitory interactions underlying a hepatocentric phenotype. Blue: Upstream Metabolic Drivers; Red: Central Hepatocentric Mechanisms; Purple: Systemic Organ Axes & Outcomes; Solid Black Arrow: Direct causal pathway; Dashed Arrow: Modifying/indirect effect. BMI, body mass index; CKD, chronic kidney disease; *GCKR*, glucokinase regulator; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; *MBOAT7*, membrane-bound O-acyltransferase domain-containing 7; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; RAAS, renin–angiotensin–aldosterone system; *TM6SF2*, transmembrane 6 superfamily member 2.

tients with MAFLD and sarcopenia are approximately twice as likely to develop metabolic dysfunction-associated steatohepatitis (MASH) and severe fibrosis, independent of obesity and insulin resistance. Sarcopenia is particularly prevalent among patients with lean MAFLD. The prevalence of sarcopenia was significantly higher among patients with MASH than among healthy individuals (35.0% vs. 8.7%).[14,15]

Distinct changes in body composition and molecular pathways contribute to lean MAFLD. Compared with obesity-associated MAFLD, lean MAFLD is characterized by relatively limited subcutaneous adiposity but disproportionate visceral adiposity and ectopic hepatic fat accumulation despite a normal BMI. Increased waist circumference, rather than body weight alone, may better reflect adverse metabolic risk in these individuals. A bidirectional liver–skeletal muscle axis links sarcopenia with insulin resistance, impaired glucose metabolism, chronic inflammation, and progressive steatohepatitis, thereby increasing the likelihood of MASH and advanced fibrosis. Genetic susceptibility, including variants in *PNPLA3*, *TM6SF2*, *GCKR*, and *MBOAT7*, together with emerging biomarkers such as circulating miR-122, may further influence disease susceptibility and progression. Studies have examined genes involved in lipid and glucose metabolism, hepatic iron accumulation, cholesterol metabolism, and epigenetic regulation in relation to MAFLD pathogenesis. Associations between the *PNPLA3* rs738409 variant and MAFLD risk have been replicated across populations. Variants in *GCKR*, *MBOAT7* rs641738, and *TM6SF2* rs58542926 have also been associated with susceptibility to MAFLD. Circulating miR-122 is elevated in MASH, supporting its potential as a diagnostic or prognostic biomarker.[16]

The effects of genetic variants may differ according to patient characteristics and environmental exposures. Therefore, age, sex, BMI, comorbidities such as T2DM, and dietary factors should be considered when comparing patient and control groups. Liver biopsy is invasive but remains the reference standard for diagnosing and staging steatohepatitis and fibrosis. Identifying genetic variants associated with MAFLD may facilitate the development of noninvasive biomarkers for disease prediction, diagnosis, and prognostic monitoring.[16,17]

Table 1. Cardiovascular outcomes

Study	Lean MAFLD finding	Non-lean MAFLD finding	Risk estimate (lean vs. non-lean)	Statistical significance
Mark C C Cheah *et al.*, 2025[6].	2.53 per 1,000 person-years (95% CI, 0.65–9.96)	2.07 per 1,000 person-years (95% CI, 0.80–5.39)	OR = 1.91 (95% CI, 0.02–142.76)	*P* = 0.58
Q. Ye *et al.*, 2020[7].	4.0 per 1,000 person-years (95% CI, 0.1–14.9)	NR	NR	NR
Ping Miao *et al.*, 2025[9].	Similar risk	Reference group	HR = 0.92 (95% CI, 0.65–1.30)	NS
Steven H. Young *et al.*, 2020[12].	Lower odds vs. obese MAFLD	Reference group	28% lower mortality	NR
Jane Ha *et al.*, 2022[20].	NR	Reference group	RR = 1.12 (95% CI, 0.66–1.90)	NS
Shaomin Huang *et al.*, 2023[22].	7.7 per 1,000 person-years (95% CI, 6.4–9.2)	NR	NR	NR
Matheus Souza *et al.*, 2024[21].	Similar CV outcomes	Reference group	NR	NR
Gerard Stupecki *et al.*, 2025[23].	Lower risk of severe events but higher mortality	Reference group	50% increased mortality risk	NR

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; RR, risk ratio; NR, not reported; NS, not significant.

Extrahepatic manifestations

Cardiovascular disease

Cardiovascular disease remains the leading cause of death worldwide and among individuals with MAFLD. Its prevalence is expected to increase with urbanization, population aging, and lifestyle changes, particularly in low- and middle-income countries. Numerous cohort and observational studies have demonstrated a bidirectional association between MAFLD and cardiovascular disease, suggesting shared mechanisms.[18] Heart failure and liver disease also have a well-established bidirectional relationship: heart failure can cause congestive hepatopathy, whereas advanced liver disease may cause cirrhotic cardiomyopathy. Several studies have shown that diastolic dysfunction may be associated with fibrosis severity. Recent evidence further suggests that MAFLD may increase the risk of heart failure with preserved ejection fraction even without advanced fibrosis.[19]

Population-based cohorts, including the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study, have shown that hepatic steatosis is associated with a 1.5- to 2.0-fold higher risk of incident cardiovascular events after adjustment for age, sex, BMI, diabetes, and cholesterol levels (Table 1).[6,7,9,12,20,22,23,31] MAFLD is also characterized by insulin resistance and atherogenic dyslipidemia. Imaging studies have shown greater carotid intima-media thickness, higher coronary artery calcium scores, and early left ventricular diastolic dysfunction in patients with MAFLD.[24]

An increased flux of free fatty acids from hepatic fat accumulation promotes systemic inflammation through cytokine release and oxidative stress, thereby worsening insulin resistance and dyslipidemia. The resulting atherogenic environment promotes endothelial dysfunction, plaque formation, and a prothrombotic state, increasing plaque instability and cardiovascular risk. Lipotoxic spillover, genetic variants, and gut dysbiosis are additional emerging factors that support the liver–heart axis as a potential therapeutic target.[25]

A recent large-scale study found that patients with lean MAFLD had worse liver-related outcomes and a higher risk of all-cause mortality, a similar risk of hepatocellular carcinoma and extrahepatic malignancy, and a lower risk of cardiovascular disease than patients with non-lean MAFLD.[26]

Metabolic complications

The global burden of T2DM and MAFLD imposes substantial public health costs and challenges. An estimated 529 million people worldwide had T2DM in 2021, representing 10.5% of the adult population, and the number is projected to increase to more than 1.31 billion by 2050. Furthermore, a substantial proportion of people with T2DM remain undiagnosed, and approximately 50% of those diagnosed have suboptimal metabolic control. For example, one-third of affected individuals in Latin America are untreated, and 52%–72% have suboptimal glycemic control.[27,28]

T2DM and MAFLD interact bidirectionally. T2DM is a major risk factor for MAFLD. A recent meta-analysis of 156 studies, and a pooled analysis of 1,832,125 patients found that 65% of people with T2DM had MAFLD and 31.5% had MASH. More advanced forms of MAFLD were also common in this population, with estimated prevalences of 15% for advanced fibrosis. Conversely, MAFLD is a major risk factor for incident T2DM. A meta-analysis of 33 studies estimated this risk at a hazard ratio of 2.2 (95% CI, 1.98–2.43; Table 2).[1,6,7,22,29] The risk was higher in the presence of steatosis or advanced fibrosis (F2–F4; hazard ratio = 2.69).[30–32]

Because of their similar metabolic burden, patients with lean MAFLD may have a risk of serious extrahepatic outcomes comparable to that of non-lean MAFLD. However, patients with lean MAFLD are more likely to die from liver-related causes.[6,20]

Renal dysfunction

Patients with MAFLD are more likely to develop CKD than those without MAFLD, and the risk is higher among those with MASH or fibrosis. Insulin resistance may cause glomerular hyperfiltration and renal microvascular injury. Increased activity of the renin–angiotensin–aldosterone system causes

Table 2. Metabolic outcomes

Manifestation	Study	Lean MAFLD finding	Risk estimate (lean vs. non-lean)
Diabetes incidence	Mark C C Cheah *et al.*, 2025[6]	Not specified	OR = 1.19 (95% CI, 0.44–3.24), *P* = 0.67
Diabetes incidence	K. Chan *et al.*, 2022[1]	NR	OR = 3.80 (95% CI, 2.65–5.43)
Diabetes prevalence	A. Tang *et al.*, 2022[29]	19.56% (95% CI, 15.28–24.69%)	45.70% in obese MAFLD (95% CI, 35.01–56.80%), *P* < 0.01
Diabetes incidence	Q. Ye *et al.*, 2020[7]	12.6 per 1,000 person-years (95% CI, 8.0–18.3)	NR
Diabetes incidence	S. Huang *et al.*, 2023[22]	13.7 per 1,000 person-years (95% CI, 8.2–22.7)	NR
Hypertension incidence	K. Chan *et al.*, 2022[1]	NR	OR = 2.63 (95% CI, 1.85–3.74)
Hypertension incidence	Q. Ye *et al.*, 2020[7]	56.1 per 1,000 person-years (95% CI, 38.5–77.0)	NR
Hypertension incidence	S. Huang *et al.*, 2023[22]	56.1 per 1,000 person-years (95% CI, 40.2–77.9)	NR

CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; NR, not reported.

glomerular hypertension, accelerating albuminuria and the development of CKD. Increased inflammatory signaling may accelerate renal fibrosis and nephron loss.[29,33]

The mechanisms linking MAFLD and CKD remain incompletely understood. The association may be bidirectional: CKD may accelerate liver injury, as occurs in T2DM. Common pathophysiologic pathways include oxidative stress, altered gut microbiota, and dysregulation of the renin–angiotensin system. Current evidence suggests that MAFLD may not simply be a consequence of CKD but also contribute to its onset and progression.[29,34]

Renal function should be evaluated and monitored in all patients with MAFLD. A meta-analysis by Musso *et al.* recommended screening patients with MAFLD for CKD, even in the absence of other risk factors.[33]

Malignancy

Lean MAFLD has complex implications for cancer. Individuals with lean MAFLD have been reported to have a higher incidence of hepatocellular carcinoma, although total cancer mortality appears similar between lean and non-lean MAFLD. These findings suggest that mechanisms beyond obesity may contribute to hepatocarcinogenesis.[35]

A recent systematic review and meta-analysis found that lean individuals with MAFLD had a higher risk of specific gastrointestinal cancers, including pancreatic, colorectal, and liver cancers (Table 3).[6,9,22,23] These findings suggest that lean and non-lean phenotypes may have distinct prognostic profiles and support evaluation of tailored cancer-prevention strategies. However, causality cannot be inferred because the included studies were observational. Further research is needed to clarify the association between lean MAFLD and gastrointestinal cancer risk.[21]

Skin manifestations

MAFLD is more prevalent among individuals with psoriasis, a chronic autoimmune inflammatory skin disorder, and this association varies with psoriasis severity. However, whether psoriasis is more prevalent among patients with MAFLD remains uncertain. It is also unclear whether the association is attributable to psoriasis itself or to treatments such as methotrexate. Hirsutism, keratosis, and acanthosis nigricans are additional dermatologic manifestations associated with underlying insulin resistance in MAFLD.[36]

Psoriasis and other cutaneous manifestations are increasingly associated with MAFLD, suggesting shared metabolic dysfunction and systemic inflammation. Kaya and Yilmaz reported that the prevalence of psoriasis ranged from 2% to 3% in the general population and from 3%–14.2% among patients with MAFLD.[37] The severity of cutaneous manifestations has also been associated with the severity of liver fibrosis. These findings support consideration of skin examination in the clinical assessment of patients with MAFLD.[38]

Table 3. Cancer outcomes

Study	Lean MAFLD finding	Non-lean MAFLD finding	Risk estimate (lean vs. non-lean)	Statistical significance
Mark C C Cheah *et al.*, 2025[6]	3.42 per 1,000 person-years (95% CI, 3.33–3.51)	3.15 per 1,000 person-years (95% CI, 1.21–8.19)	OR = 1.99 (95% CI, 0.29–13.52)	*P* = 0.13
P Miao *et al.*, 2025[9]	Comparable risk	Reference group	HR = 1.20 (95% CI, 0.90–1.60)	NS
S Huang *et al.*, 2023[22]	25.7 per 1,000 person-years (95% CI, 20.3–32.4)	NR	NR	NR
G Stupecki *et al.*, 2025[23]	Comparable extrahepatic cancer risk	Reference group	NR	NR

CI, confidence interval; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; NS, not significant; NR, not reported.

Table 4. All-cause mortality

Study	Lean MAFLD finding	Non-lean MAFLD finding	Risk estimate (lean vs. non-lean)	Statistical significance
Mark C C Cheah *et al.*, 2025[6]	10.08 per 1,000 person-years (95% CI, 9.93–10.23)	8.94 per 1,000 person-years (95% CI, 4.08–19.57)	OR = 1.92 (95% CI, 0.01–220.57)	P = 0.33
Q. Ye *et al.*, 2020[7]	12.1 per 1,000 person-years (95% CI, 0.5–38.8)	NR	NR	NR
P Miao *et al.*, 2025[9]	Higher risk vs. high BMI	Reference group	HR = 1.34 (95% CI, 1.23–1.47)	NR
J Ha *et al.*, 2022[20]	NR	Reference group	RR = 1.09 (95% CI, 0.66–1.90)	NS
S Huang *et al.*, 2023[22]	13.3 per 1,000 person-years (95% CI, 6.7–26.1)	Reference group	RR = 1.39 (95% CI, 1.08–1.82)	I^2 = 43%

CI, confidence interval; HR, hazard ratio; I^2, heterogeneity statistic; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; RR, risk ratio; NS, not significant; NR, not reported.

Mortality outcomes

All-cause mortality

Patients with lean MAFLD may have a higher risk of all-cause mortality than patients with non-lean MAFLD (Table 4). Therefore, BMI alone should not determine whether patients with MAFLD receive continued monitoring and treatment. A recent meta-analysis included 12 studies (n = 26,329), 7 of which (n = 7,924) evaluated the risk of all-cause mortality in lean versus non-lean patients with MAFLD. Patients with lean MAFLD had a higher risk of death than those with non-lean MAFLD (risk ratio = 1.39; 95% CI, 1.08–1.82; I^2 = 43%). Among patients with lean MAFLD, rates per 1,000 person-years were 13.3 (95% CI, 6.7–26.1) for all-cause mortality, 7.7 (95% CI, 6.4–9.2) for cardiovascular mortality, and 3.6 (95% CI, 1.0–11.7) for liver-related mortality. Incidence rates per 1,000 person-years were 25.7 (95% CI, 20.3–32.4) for cancer and 13.7 (95% CI, 8.2–22.7) for diabetes.[6,7,9,20,22]

A hepatocentric model of Lean MAFLD

This conceptual model may help explain the apparent paradox of similar metabolic profiles but differing mortality outcomes between lean and non-lean MAFLD. Lean MAFLD may represent a hepatocentric phenotype in which metabolic burden and mortality patterns are partially decoupled. Despite comparable cardiovascular risk, metabolic dysfunction in this phenotype may manifest predominantly as hepatic injury, thereby increasing liver-related mortality.[6]

Clinical implications

Recognition of lean MAFLD has important implications for clinical practice. Lean MAFLD challenges the traditional obesity-centered paradigm of fatty liver disease. Although affected individuals have a normal BMI, they may have substantial hepatic steatosis driven by occult metabolic dysfunction rather than excess body weight. Insulin resistance, chronic low-grade inflammation, dyslipidemia, impaired glucose tolerance, and elevated fasting glucose may converge to promote hepatic fat accumulation despite an apparently healthy body habitus. Importantly, lean MAFLD is associated with outcomes comparable to those of obesity-associated MAFLD, including increased risks of cardiovascular disease, hepatocellular carcinoma, progressive liver fibrosis, and liver-related mortality.

A normal BMI should not be reassuring in patients with hepatic steatosis or metabolic dysfunction. Comprehensive assessment should include cardiovascular risk stratification, fibrosis assessment, and metabolic profiling. Because of the increased risk of liver-related mortality, patients with lean MAFLD may require closer surveillance for disease progression.

Refining the MAFLD criteria, particularly by incorporating indicators of insulin resistance such as the homeostatic model assessment of insulin resistance, may improve early metabolic risk detection and disease stratification in lean populations.[39] This phenotype should be considered when developing treatment and follow-up strategies.[40]

Diagnosis of lean MAFLD is often delayed because normal aminotransferase levels do not exclude clinically significant fibrosis, BMI may underestimate risk, and the validity of non-invasive scores for detecting steatosis in lean individuals has not been established. Lower waist circumference and BMI in lean individuals may contribute to underdiagnosis or overestimation of the contribution of conventional metabolic risk factors.[41] A systematic approach should include assessment of body composition, fibrosis risk stratification, confirmation of steatosis, and exclusion of secondary causes.[42]

Most available data were derived from tertiary care centers, which may overrepresent advanced disease and limit generalizability to the overall population. Many studies used cross-sectional designs and conventional ultrasonography, limiting causal inference and potentially underestimating mild steatosis. Differences in BMI thresholds between Western and Asian populations also impede direct comparisons. Conversely, the transition from an exclusion-based definition of nonalcoholic fatty liver disease to positive metabolic criteria for MAFLD or metabolic dysfunction-associated steatotic liver disease (MASLD, updated in 2023) allows inclusion of patients with metabolic dysfunction despite concurrent alcohol use or viral liver disease. In addition, large global epidemiologic cohorts and meta-analyses including millions of individuals provide substantial statistical power to estimate prevalence and mortality outcomes.

Regarding pharmacotherapy for lean MAFLD patients; most participants in pivotal studies were overweight or obese, so the applicability of resmetirom and semaglutide to lean MAFLD populations is yet unknown, they could not be excluded but were under-represented.[43,44] Resmetirom may be suitable for selected lean individuals with sarcopenia or a low BMI because it is generally weight neutral and its efficacy does not primarily depend on weight loss.[42] Semaglutide may benefit lean individuals with increased cardiometabolic risk, T2DM, or insulin resistance. However, its weight-reducing effects may be undesirable in those with sarcopenia, low

muscle mass, or a low BMI; these patients may benefit from resistance exercise. Further research is needed to determine the efficacy and safety of resmetirom and semaglutide specifically in patients with lean MAFLD.[42]

Future research priorities

Future research should prioritize prospective cohort studies that apply consistent definitions of lean MAFLD and provide long-term follow-up. Mechanistic studies are needed to clarify interactions among visceral adiposity, sarcopenia, and genetic factors. Risk-prediction models incorporating non-BMI indicators of metabolic health should be developed to improve patient classification and guide targeted therapy.

Conclusions

Lean MAFLD is an important but underrecognized clinical condition characterized by substantial metabolic dysfunction and extrahepatic disease burden despite a normal BMI. Although cardiovascular and cancer outcomes are often similar to those of non-lean MAFLD, liver-related mortality is generally higher, supporting a hepatocentric disease model. These findings challenge conventional BMI-based paradigms and highlight the need for comprehensive risk assessment and management strategies in individuals with lean MAFLD.

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Conflict of interest

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Author contributions

Drafting the manuscript (AAH, AME, ME, AAZ, YMF), figure preparation (RS, OM, EMA, YMF), and critical revision of the manuscript (AAH, RS, EMA, OM, AAZ, ME, AME, YMF). All authors made a significant contribution to this study and approved the final manuscript.

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