Lean Metabolic-Associated Fatty Liver Disease

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KEYWORDS

• MAFLD • Lean MAFLD • Hepatic and extrahepatic MAFLD complications
• Lean MAFLD mortality

KEY POINTS

- Lean metabolic-associated fatty liver disease (MAFLD) is a distinct clinical entity that carries similar complication rates to overweight/obese MAFLD.
- Most studies addressing lean MAFLD have been performed as a subgroup analysis of larger data sets.
- More work needs to be performed in lean MAFLD to better understand the pathophysiology and response to management strategies.

INTRODUCTION

Fatty liver infiltration has been recognized for centuries. Early work by Ludwig and colleagues[1] resulted in a report examining the histologic similarities between alcohol-related liver disease and liver disease in the absence of a history of alcohol use, and thus the term nonalcoholic fatty liver disease (NAFLD) was born. Since that time, significant work has been undertaken to determine the pathophysiologic manifestations and clinical associations of this disorder, which differ from that of alcohol-related liver disease. However, the term NAFLD has persisted despite its inadequacies in describing the disease and its diagnostic characteristics.[2]

A nomenclature change for fatty liver disease was proposed in 2020 to replace NAFLD with a term that better reflects the known pathophysiology.[3] The international consensus used a 2-stage Delphi method and suggested the name metabolic (dysfunction) -associated fatty liver disease (MAFLD) and subsequently proposed a

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simple set of criteria for diagnosis. Since the proposed change, there have been more than 1000 original articles referencing the name, inspiring a new wave of study into this field.

An aspect of MAFLD that has developed significantly since the introduction of the new classification has been studies on the clinical phenotype of lean MAFLD.[4] Reports before the introduction of MAFLD have shown that lean NAFLD is phenotypically different from overweight/obese NAFLD. Interestingly, individuals with normal weight with hepatic steatosis under the definition of NAFLD had similar outcomes as individuals who were overweight or obese, which may have been confounded by selection bias, underestimation of alcohol intake, and unaccounted weight changes over time.[6] Since the introduction of MAFLD into the diagnostic terminology, there have been several studies that have examined the associated pathophysiologic features and end-organ complications that accompany lean MAFLD.

DEFINITION OF LEAN METABOLIC-ASSOCIATED FATTY LIVER DISEASE

With the introduction of MAFLD into the medical nomenclature in 2020, simple diagnostic criteria were proposed.[3] Using the requisite hepatic steatosis of $\geq$5% that makes up an NAFLD diagnosis, 3 nonexclusive diagnostic phenotypes were reported. The first MAFLD phenotype consisted of patients with an underlying diagnosis of type 2 diabetes who may or may not be of healthy body weight by body mass index (BMI) criteria. The second phenotype uses definitions of overweight/obesity by ethnic-specific BMI classifications, namely a BMI of 25 to 29.9 kg/m^2 for overweight and BMI of $\geq$30 kg/m^2 for obese individuals of European ancestry and a BMI of 23.0 to 24.9 kg/m^2 for overweight and BMI of $\geq$25 kg/m^2 for obesity in individuals of Asian descent. The third MAFLD phenotype consists of patients who are of healthy weight by ethnic-specific BMI criteria but who have metabolic dysregulatory factors that are part of the operational definition of metabolic syndrome. For a diagnosis of MAFLD using this criterion, an individual needs 2 of 7 risk factors. The risk factors include waist circumference, blood pressure, plasma triglycerides, plasma HDL-cholesterol, prediabetes, homeostasis model assessment of insulin resistance score, and plasma high-sensitivity C-reactive protein. Individuals require 1 of the 3 different phenotypes coupled with hepatic steatosis of $\geq$5% for a diagnosis of MAFLD.[3] A unique aspect of the MAFLD criteria is that it provides an operational definition of what the disease is, rather than what it is not. Stemming from this, MAFLD can coexist with any other liver disease and contribute to its clinical manifestations and natural history. **Fig. 1** shows the graphical representation of MAFLD definition.

Although a definition of lean MAFLD was proposed in the initial diagnostic criteria as normal/lean weight with at least 2 metabolic dysregulatory risk factors, its utilization seemingly excludes patients of normal weight with diabetes and MAFLD.[3] The definition of lean MAFLD in this article uses either the first (if a patient is of health body weight with type 2 diabetes) or the third metabolic dysregulatory phenotype but not the second. Although commonly referred to as lean MAFLD, a more appropriate term would be that of MAFLD in lean/healthy-weight individuals.

PREVALENCE

Because of the short period of time between the introduction of MAFLD into the medical compendium and this publication, there have been limited data on the global prevalence of lean MAFLD.[4] Because of the high concordance between the diagnosis of NAFLD and MAFLD, previous studies have used this information to estimate the global

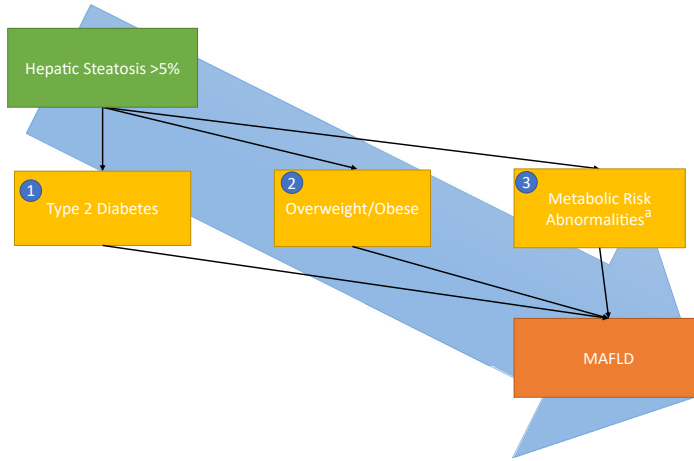

Fig. 1. Diagnostic criterion for MAFLD.[a]Metabolic risk abnormalities – 2 out of 7: Waist circumference >102/88 in Caucasian men and women, (or >90/80cm in Asian men or women). Blood pressure >130/85mmHg or specific drug treatment. Plasma triglycerides >150mg/dL (>1.70mmol/L) or specific drug treatment. Plasma HDL-cholesterol <40mg/dl (<1.0mmol/L) for men and <50mg/dl (<1.3mmol/L) for women or specific drug treatment. Prediabetes (i.e. fasting glucose levels 100-125mg/dL (5.6-6.9mmol/L) or 2-hour post-load glucose levels 140-199mg/dL (7.8-11.0mmol/L) of HbA1c of 5.7-6.4% (39-47mmol/mol). Homeostasis model assessment of insulin resistance score >2.5. Plasma high-sensitivity C-reactive protein level >2mg/L.

prevalence of MAFLD. In a study by Ye and colleagues,[5] a meta-analysis was conducted using 10,530,308 patients from 84 studies to estimate the global prevalence of lean NAFLD. In that study, lean NAFLD prevalence in the general population was 5.1%, with a prevalence of 19.2% in the global NAFLD population.

In another study by Chan and colleagues,[7] a meta-analysis and systematic review of 3,320,108 individuals were performed. Although it attempted to tabulate the global prevalence of MAFLD, owing to a lack of available data, there was limited insight into the prevalence of lean MAFLD. In a pooled analysis of 7106 patients from the 3,320,108 patients that the study reviewed, the prevalence of lean MAFLD was 5.4% of the general population. Although this is similar in numbers to previous studies, this estimate may be flawed particularly because of the geographic disparity of lean MAFLD demonstrated in the lean studies.

Several reports have attempted to examine the prevalence of MAFLD in order to identify the prevalence of lean MAFLD.[4,6–15] These studies have led to a wide range of lean MAFLD prevalence estimates ranging from 3.1% to 7.9% in the general population, and between 3.0% and 35.0% for prevalence within the wider MAFLD population. There are significant ethnic disparities in the reported prevalence and incidence owing to the wider uptake of MAFLD terminology among Asian countries, with less reported data from the West.[4,6–15] At this time, the prevalence and incidence of lean MAFLD appear to be similar to that of lean NAFLD; however, significantly more data in this area are required to establish a better global and ethnic estimation of the burden of this disease. It should also be noted that most studies have not determined the prevalence of lean MAFLD in patients with a coexistent secondary liver disease, which may be significantly underestimated in areas of high prevalence of chronic liver disease, such as alcohol-related liver disease.

PATHOPHYSIOLOGIC CHARACTERISTICS

Although little is known about lean MAFLD clinicopathologic characteristics, there have been several recent studies that have examined the clinical features of the condition and its metabolic and nonmetabolic associations (**Table 1**).

Disease Associations

For lean MAFLD, several articles have assessed its clinicopathologic associations compared with MAFLD groups and healthy controls. Unfortunately, because of the heterogeneity of these studies, particularly in view of the ethnic disparities in lean MAFLD, there are limited data, and that data appear at times to be conflicting.

In a recent study by Chan and colleagues[7] from the pooled analysis of 7100 patients with a prevalence of lean MAFLD of 5.4%, the associated clinicopathologic features were determined. Compared with healthy controls, patients with lean MAFLD were significantly older (mean difference [MD], 2.22; $P = .0001$), were more frequent in men (odds ratio [OR], 1.68; $P = .0003$), and were related to metabolic complications, such as hypertension (OR, 2.63; $P<.0001$) and type 2 diabetes (OR, 3.80; $P<.0001$). Although the correlation between type 2 diabetes and hypertension coincides with the determination of lean MAFLD as per the diagnostic criterion, the higher prevalence in older and male patients appears to be significant when compared with healthy controls in the largest study addressing this issue to date.

Cheng and colleagues[16] investigated 394 patients diagnosed with MAFLD, of which 65 (16.5%) were defined as lean MAFLD. This study compared individuals with lean MAFLD with healthy controls, and individuals with lean MAFLD with nonlean MAFLD. Factors that were independently associated with MAFLD in lean subjects were BMI (OR, 1.5; $P = .011$), waist circumference (OR, 1.1; $P = .010$), and hypertension (OR, 3.7; $P = .032$). Comparison between lean and nonlean MAFLD showed that the lean phenotype was associated with older age (61.1 years vs 57.5 years), female sex (69.2% vs 42.9%), higher high-density lipoprotein (47.8 mg/dL vs 42.0 mg/dL; $P<.001$), but lower waist circumference (76.8 cm vs 90.34 cm $\pm$ 8.75 cm; $P<.001$), diastolic blood pressure (75.5 mm Hg vs 79.47 mm Hg; $P = .008$), serum triglycerides (116.8 mg/dL vs 143.33 mg/dL; $P = .015$), and alanine aminotransferase levels (33.8 U/L vs 42.38 U/L; $P = .001$). Variables that were significant on binary logistic regression were age (1.4; $P = .040$) and waist circumference (OR, 0.81 95%; $P<.001$).[7]

Several extrahepatic complications have been associated in the wider MAFLD population, including chronic kidney disease, breast cancer, colorectal cancer, polycystic ovarian syndrome, and cardiac arrhythmias; these data are not readily available for the lean MAFLD subgroup.[17–19] Further research thus needs to be performed to assess for disease associations that are associated with lean MAFLD. At this stage, the literature on lean MAFLD is in its infancy, and further prospective evidence will further elaborate on clinicopathologic features.

Liver Fibrosis

Individuals with lean MAFLD have conflicting evidence when it comes to levels of fibrosis and noninvasive liver fibrosis scores. The main scoring systems that have been used in the NAFLD literature are the NAFLD fibrosis score (NFS) and the Fibrosis-index 4 (FIB-4). These systems have been extensively validated in NAFLD populations, and recent evidence in the wider MAFLD population suggests that these scores work as well to exclude significant fibrosis.[20]

Younes and colleagues[21] examined 1339 biopsy-proven MAFLD subjects of white ethnicity from 4 countries and showed that the prevalence of lean MAFLD was

Table 1
Clinicopathologic features of lean metabolic-associated fatty liver disease

Study		Patients	Results
Lin et al,[28] 2021	Total MAFLD Lean MAFLD	341 28	Compared with all MAFLD, lean MAFLD were: • Older age, 60.7 ± 9.2 y vs 55.8 ± 10.2 y (P = .015) • Higher prevalence of diabetes 67.9% vs 28.8% (P<.001) • Lower serum ALT 33.2 ± 15.7 vs 48.1 ± 38.9 (P = .048) • Lower BMI 21.4 ± 1.4 vs 27.1 ± 3.0 (P<.001)
Zeng et al,[15] 2022	Total MAFLD Lean MAFLD	3340 1171	Compared with all MAFLD, lean diabetic MAFLD had a higher prevalence of advanced fibrosis (14.7%)
Yu et al,[13] 2022	Lean MAFLD Lean NAFLD	531 816	Compared with lean NAFLD, lean MAFLD were: • Older age, higher weight circumference, and high prevalence of diabetes (P<.001) • Higher AST (35.39 ± 18.97 vs 32.19 ± 11.41; P = .0034) • High FPG (5.84 ± 1.77 vs 5.50 ± 1.48; P = .030)
Yuan et al,[14] 2022	Total MAFLD Lean MAFLD	49,734 724	Compared with all MAFLD, lean MAFLD had a higher female predominance (62.43% vs 47.30%; P<.001)
Ordonez-Vazquez et al,[6] 2022	Lean MAFLD Lean NAFLD	118 273	Compared with lean NAFLD, lean MAFLD had: • Older age (OR, 1.42; 95% CI, 1.02–1.97; P = .036) • Higher fasting glucose (OR, 1.80; 95% CI, 1.30–2.48; P<.0001) • Higher triglycerides (OR, 1.52; 95% CI, 1.12–2.08; P = .007) • Higher waist circumference (OR, 2.04; 95% CI, 1.47–2.83; P<.0001)
Chan et al,[7] 2022	Total patients Lean MAFLD	7100 381	Compared with general population, lean MAFLD had: • Older age (MD, 2.22; 95% CI, 1.09–3.336; P = .0001) • Male predominance (OR, 1.68; 95% CI, 1.27–2.21; P = .0003) • Higher prevalence of diabetes (OR, 3.80; 95% CI, 1.74–2.38; P<.001)

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Table 1
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Study		Patients	Results
Cheng et al,[16] 2021	Total MAFLD Lean MAFLD	329 65	Compared with all MAFLD, lean MAFLD had: • Older age (61.1 ± 8.01 y vs 57.5 ± 10.57 y; *P* = .001) • Female predominance (69.2% vs 42.9%; *P*<.001) • Higher HDL (47.81 mg/dL ± 11.45 mg/dL vs 42.02 mg/dL ± 11.83 mg/dL; *P*<.001) • Lower waist circumference (76.86 cm ± 5.27 cm vs 90.34 cm ± 8.75 cm; *P*<.001) • Lower diastolic blood pressure (75.51 mm Hg ± 9.80 mm Hg vs 79.47 mm Hg ± 11.13 mm Hg; *P* = .008) • Lower serum triglycerides (116.80 mg/dL ± 66.14 mg/dL vs 143.33 mg/dL ± 82.65 mg/dL; *P* = .015) • Lower ALT (33.77U/L ± 16.50 U/L vs 42.38U/L ± 27.36U/L; *P* = .001)

14.4% out of the total population of MAFLD. When reviewed in detail, patients with lean MAFLD had less severe disease with lower prevalence of metabolic syndrome (54.1% vs 71.2%; $P<.001$), lower proportions with advanced fibrosis (10.1% vs 25.2%; $P<.001$), and a lower prevalence of type 2 diabetes (9.2% vs 31.4%; $P<.001$).

In a more recent study by Eren and colleagues,[22] the accuracy of FIB-4 and NFS was assessed against liver biopsies in patients with MAFLD stratified by BMI. In lean MAFLD, the area under the receiver operating curve failed to discriminate patients with advanced fibrosis using FIB-4 ($P = .352$) and NFS ($P = .511$), and they suggested that new noninvasive markers for advanced fibrosis were needed for lean MAFLD. Unfortunately, there are issues with this blanket statement that are not addressed in the article. There were only 4 patients with lean MAFLD who had advanced fibrosis on biopsy out of a total of 37 patients. Although this study is otherwise reasonable, it is clearly not powered to provide reliable data to answer the question.

From established evidence regarding noninvasive fibrosis markers in lean NAFLD patients and the overlap of lean NAFLD and lean MAFLD, it would appear that FIB-4 and NFS should have reasonable ability to exclude advanced fibrosis in the latter population.[23,24] The conflicting evidence regarding noninvasive biomarkers' ability to discriminate advanced fibrosis from nonadvanced fibrosis in the lean MAFLD population has not been adequately addressed in the literature at this time.

Genetics

The contribution of genetic variation to pathogenic liver fat infiltration has been an area of keen research interest. Although genetic variants have an impact on fatty liver disease, the exact pathophysiologic mechanisms underpinning the higher prevalence of liver fat in these patients have not been fully elucidated. The change in nomenclature has been a driver to reexamine the genetic variants and their association with MAFLD. Further to this, the subgroup of lean MAFLD has been examined to determine the weight that these known genetic variants have on the underlying disease process, and on hepatic and extrahepatic complications.

In the study performed by Younes and colleagues,[21] genetic analysis was performed on the genetic variant *PNPLA3* I1448M. The study showed no differences in the *PNPLA3* I148M ($P = .57$) between patients with lean MAFLD and patients with nonlean MAFLD.[21] Similarly, another study by Liu and colleagues[25] examined for outcomes of MAFLD in terms of liver cancer, cirrhosis, other liver disease, cardiovascular disease, renal diseases, and other cancers from the UK BioBank coupled with the genetic variants previously reported for NAFLD. A subgroup analysis was performed on patients with lean MAFLD and showed that they had higher rates of hepatocellular carcinoma (hazard ratio [HR], 3.23), cirrhosis (HR, 11.73), other liver disease (HR, 4.46), cardiovascular disease (HR, 1.37), renal disease (HR, 1.53), and other cancers (HR, 1.18).

Interestingly, the genetic variants had an increased impact in MAFLD on the abovementioned complications but did not have an associated effect on patients with lean MAFLD.[25] Although this suggests some interesting pathophysiologic nuances surrounding the lean MAFLD phenotype, there were several issues that limit its applicability to practice. First, because of lack of imaging data, hepatic steatosis was implied by noninvasive biomarkers using the fatty liver index. Although this has been used in previous studies and shown to have relatively good sensitivity, it is not part of the usual diagnostic pathway for MAFLD. Second, the aforementioned complications were assessed on the basis of patients' ICD codes, rather than review of the patients or formal interrogation of the medical notes.

Although genetic variations do appear to have a place in the wider MAFLD population, currently their impact on lean MAFLD appears to be conflicting. The investigators of the previous studies have suggested that genetic variations appear to play a greater role in peripheral fat accumulation and that may influence their impact on both the hepatic and the extrahepatic complications of lean MAFLD. From previous studies examining NAFLD, there is a suggestion that genetic factors may have an effect; however, this is less pronounced in the absence of environmental factors, such as a sedentary lifestyle or poor diet.[26] At this time, there is a lack of evidence on genetic factors and their impact on lean MAFLD, and further research is required.

Dual Causes

One of the most significant features of the MAFLD definition is the removal of exclusion of coexisting liver diseases that was a prerequisite for an NAFLD diagnosis. This has allowed individuals to assess comorbid MAFLD with other liver diseases, such as viral hepatitis and autoimmune disease, and the relevant associations and complications of dual cause liver disease.

Al-Omary and colleagues[27] studied patients admitted to 2 tertiary institutions who underwent a liver biopsy for MAFLD and chronic hepatitis C. In the review period, there were 437 patients with MAFLD and 321 patients with dual MAFLD and chronic hepatitis C.[27] This study demonstrated that dual MAFLD and chronic hepatitis C had higher rates of advanced fibrosis over those with chronic hepatitis C alone (32.7% vs 14.2%; $P<.001$), A subgroup analysis of those with chronic hepatitis C was performed comparing patients with lean MAFLD with overweight/obese MAFLD and diabetic MAFLD, with comparable rates of advanced fibrosis (30.0% vs 31.9% vs 42.9%; $P = .352$).[27] This demonstrates that the overall rates of advanced fibrosis are higher with dual causes when combined with MAFLD and affect those with lean as well as overweight/obese individuals.

A recent study by Lin and colleagues[28] reviewed patients with chronic hepatitis B with Barcelona Clinic Liver Cancer (BCLC) 0/A hepatocellular carcinoma undergoing hepatic resection for presence of MAFLD. Of the 812 patients who underwent hepatic resection, 369 had MAFLD, with 28 satisfying the criteria for lean MAFLD. In multivariate analysis, lean MAFLD was associated with a higher risk of hepatocellular carcinoma recurrence when compared with nonlean MAFLD (HR, 2.03; $P = .020$) independent of other predictive risk factors.

Although these findings are useful and highlight the contributory effect of lean MAFLD on viral hepatitis, further work is required to establish disease synergisms in healthy-weight individuals.

Associated Complications and Prognosis

As with the aforementioned areas in lean MAFLD, the level of evidence surrounding prognosis is scarce and misleading. Because of the relatively novel nature of the nomenclature, currently all the data are retrospective from previously collected databases. Because of this, there are critical data flaws in most of the studies presented, which hamper their direct applicability to patient care.

Several complications have been highlighted as associations with lean MAFLD in recent reports. In a study by Fukunaga and colleagues,[29] 9100 patients who underwent esophagogastroduodendoscopy and ultrasonography were reviewed and placed into MAFLD and non-MAFLD groups. MAFLD was diagnosed in 26.5% of patients in the study. Interestingly, stratification analysis showed that the cumulative incidence of reflux esophagitis was significantly higher in lean MAFLD when compared

with the nonlean MAFLD group (HR, 1.33). On logistic regression, visceral adiposity was the only independent metabolic risk factor for reflux esophagitis (HR, 2.83; $P = .0457$) in the lean MAFLD group.

In another study by Bessho and colleagues,[30] 977 patients with a previous diagnosis of NAFLD were evaluated for subclinical atherosclerosis using cardiac computed tomographic scans, brachial-ankle pulse-wave velocity, and carotid artery ultrasound as part of health checkup. Using these previously collected data, patients were reclassified into MAFLD criteria as overweight/obese, type 2 diabetic, or lean MAFLD. Overall, there were high rates of subclinical atherosclerosis across these groups. In particular, it showed that lean MAFLD had a positive coronary artery calcification score of greater than 0 (OR, 2.26; $P = .006$) and greater than 100 (OR, 3.48; $P<.001$), and carotid intimal thickness $\geq$1.1 (OR, 3.77; $P<.001$), all of which had higher OR than individuals who were diagnosed with overweight/obese MAFLD. Of particular note, those with lean MAFLD did not have increased brachial ankle pulse wave velocity greater than 1400, whereas those with diabetic MAFLD and overweight/obese MAFLD did.

A recent study be Peng and colleagues[31] examined the effects of MAFLD subgroups on left ventricular diastolic function and cardiac morphology. Of the 171 patients with MAFLD, 31 had lean MAFLD. Although both diabetic MAFLD and overweight/obese MAFLD had evidence of left ventricular diastolic dysfunction and cardiac remodeling, lean patients did not demonstrate any association. This is interesting, as there appears to be a different cardiovascular pathophysiologic pathway that the lean MAFLD phenotype exhibits when compared with diabetic and overweight/obese patients with MAFLD, although confirmation in other larger cohorts is warranted.

In a study by Lee and colleagues,[12] 8,412,730 participants in a nationwide health screening database were categorized into overweight/obese MAFLD, diabetic MAFLD, and lean MAFLD. The health screening substituted the fatty liver index for imaging demonstration of hepatic steatosis. Using this health screening at baseline, patients were followed up for a median of 10 years, and data were examined for incident cardiovascular disease risk, development of liver cancer, liver transplantation, and all-cause mortality. Of the total number of participants, 3,087,640 (36.7%) were given a diagnosis of MAFLD, with 2,424,086 (78.5%) classified as overweight MAFLD, 490,793 (16.0%) classified as diabetic MAFLD, and 170,761 (5.5%) classified as lean MAFLD.

Using overweight MAFLD as the control, lean MAFLD had the second highest increased risk when compared with diabetic MAFLD in cardiovascular disease events (HR, 1.41 vs HR, 2.16), liver cancer (HR, 1.52 vs HR, 2.42) and liver transplantation (HR, 1.93 vs HR, 1.98), but higher all-cause mortality (HR, 2.40 vs HR, 2.32). In addition, cardiovascular disease events increased significantly in lean MAFLD in the presence of advanced liver fibrosis compared with no advanced liver fibrosis (HR, 1.15 vs HR, 1.04). The investigators suggested that these results indicate that the fibrotic burden is a driver of cardiovascular disease risk, and this burden may be the driver for differences in liver-related outcomes.[12] Unfortunately, it is unclear from the data if there is an increased burden of other comorbidities affecting patients with lean MAFLD, which lead to their overall higher all-cause mortality, or whether lean MAFLD is the driver.

Further to the study by Younes and colleagues[21] mentioned above, the 1339 biopsy-proven patients with MAFLD were followed up for a median of 7.8 years. Although these individuals appeared to have less severe disease at baseline, their prognosis appears to be similar. There was no statistically significant difference

between lean MAFLD and nonlean MAFLD in terms of liver-related events (4.7% vs 7.7%; $P = .37$) and survival ($P = .069$), although survival did trend toward significance. Despite this more favorable baseline metabolic profile in lean MAFLD, these patients experience both hepatic and extrahepatic complications of the disease, including hepatocellular carcinoma and cardiovascular disease.

In a study by Chen and colleagues,[32] patients from the NHANES III database were analyzed for mortality based on the specific MAFLD phenotype. This showed that lean MAFLD had increased mortality when compared with healthy subjects (HR, 1.4 95%; $P<.001$), which continued to be statistically significant when adjusted for major confounders. Although this study defined lean MAFLD as individuals without diabetes and who were not overweight or obese, and adjusted for metabolic conditions associated with the diagnosis of MAFLD, the increased mortality risk continued to be significant.

A study by Dao and colleagues[8] using the widely cited NHANES III, which has arguably the best long-term data for fatty liver disease, combined lean and overweight patients into a nonobese MAFLD category versus obese MAFLD. Patients with lean MAFLD made up 15% of the nonobese MAFLD category, with an overall prevalence of 7.2% in the total MAFLD population. The investigators showed that nonobese patients with MAFLD had a higher 20-year cumulative incidence for all-cause mortality compared with obese MAFLD (33.2% vs 28.8%; $P = .0137$). In this study, FIB-4 1.3 to 2.67, FIB-4 >2.67, and cardiovascular disease were the strongest risk factors associated with increased mortality (HR, 2.73; $P<.001$; HR, 3.69; $P<.001$; HR, 3.19; $P<.001$, respectively). Although the combination of lean and overweight into a nonobese category limits the applicability of the results in terms of the lean MAFLD population and must be interpreted with caution, there appears to be higher incidence rates of mortality in this phenotype.

Semmler and colleagues[33] reported on patients undergoing colorectal cancer screening. Of the 4718 patients, 221 (4.7%) fulfilled criteria for lean MAFLD. During a median follow-up of 7.5 years, 8.6% of patients with lean MAFLD died compared with 2.7% of patients with lean NAFLD and 5.6% of healthy controls. The main drivers of increased death in these patients were attributed to age and components of the metabolic syndrome. Unfortunately, there were some limitations in this study that decreased its utility in prescribing it to the lean MAFLD population. First, as part of the trial design, other coexisting liver diseases and alcohol consumption were excluded. Unlike NAFLD, MAFLD needs not exclude concomitant liver diseases, which limits the utilization of this study to the real-world lean MAFLD population. The second is that components of the metabolic syndrome cannot be used in an adjustment model for MAFLD, as they are used to formulate the MAFLD diagnosis. Removing these components invalidates the diagnosis of MAFLD, and the resultant assessment using adjustment modeling was assessing steatosis (**Fig. 2**).

TREATMENTS

The mainstay of treatment of lean MAFLD at this time is the same as for nonlean MAFLD. Lifestyle modifications centering on diet and exercise form the bedrock of management for this chronic disease. Although this has been proven to be effective among the lean NAFLD population to decrease hepatic steatosis, there has yet to be a study performed that addresses the lean MAFLD population to examine the effectiveness of these interventions, as also the long-term outcomes.

Currently there are no approved drug therapies available for MAFLD, although there are clinical trials ongoing with encouraging results.[34] Because the majority of patients

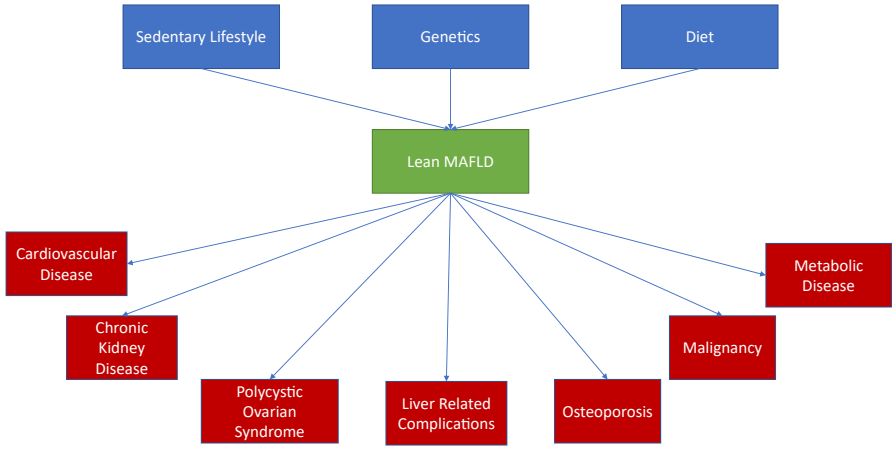

Fig. 2. Risk factors for, and complications of, lean MAFLD.

in these trials will be overweight/obese, the data may not specifically apply to the lean population. Hence, a key goal once the initial clinical trials have been completed is to undertake studies in other MAFLD subgroups, including those that are lean.

RESEARCH

At this time, there is limited published research into lean MAFLD as a standalone entity. Despite similar outcomes, and what appears to be a somewhat different pathophysiologic pathway to disease, the majority of studies have addressed lean MAFLD through subgroup analysis of data. Current research has been hampered by a lack of a standardized definition of lean MAFLD, which has led to further

Box 1
Open research questions on lean metabolic-associated fatty liver disease

Definition
- What is the standardized definition of lean MAFLD?
- Do diabetic patients with MAFLD of healthy weight fall within the criteria of lean MAFLD?
- Is BMI an appropriate measure to define lean MAFLD among ethnic groups?

Prevalence
- What is the global prevalence of lean MAFLD?
- What are the ethnic variations in lean MAFLD?

Pathophysiology
- What are the pathophysiologic differences between lean and nonlean MAFLD?
- What are the features that correspond with higher rates of hepatic and extrahepatic complications in lean MAFLD?
- Do noninvasive liver fibrosis scores in lean MAFLD correspond to that in the nonlean MAFLD population? If not, what noninvasive markers are needed to be developed that will allow clinicians to exclude significant fibrosis?
- Does lean MAFLD have the same levels of hepatic and extrahepatic complications when compared with the wider MAFLD population?

Treatment
- How effective are lifestyle interventions for lean MAFLD?
- How effective will pharmacotherapies be for lean MAFLD?

heterogeneity in published data. In addition, the utilization of nonobese MAFLD to encompass both lean and overweight MAFLD has hampered the generalizability of the published data.

Although the MAFLD diagnostic criterion has provided individuals with the ability to succinctly diagnose MAFLD in the community, there have been a number of maladaptive interpretations of lean MAFLD. Many studies have applied a stepwise strategy for MAFLD diagnosis, first identifying patients with type 2 diabetes followed by those who are overweight or obese, and then finally those with metabolic dysregulatory risk factors. Using this stepwise model, they have designated patients with diabetes MAFLD, overweight/obese MAFLD, and then lean MAFLD to represent those who only have metabolic dysregulatory risk factors. The diagnostic criterion was not intended to validate only 1 MAFLD phenotype at a time while discarding the others.[3] Thus, patients who have more than 1 MAFLD phenotype could potentially have additional risks of hepatic and extrahepatic complications and respond differently to management strategies and potential treatments. It is imperative that this be addressed sufficiently to provide enough granular detail regarding these patients, as subsets of MAFLD may need adjustments in screening, follow-up, and management based upon their disease cause (**Box 1**).

SUMMARY

Lean MAFLD is a clinical entity with similar rates of hepatic and extrahepatic complications to the wider MAFLD population. Because of the lower incidence of lean MAFLD, further research is needed to understand the prevalence, underlying pathophysiology, and management strategies applicable to this population of patients.

CLINICS CARE POINTS

- Metabolically unhealthy individuals can have "normal" weight and suffer from metabolic-associated fatty liver disease.
- Lean metabolic-associated fatty liver disease should be considered in patients with liver derangements or steatosis $\geq$5% on imaging.
- With the new diagnostic criterion for metabolic-associated fatty liver disease, dual liver causes can be considered.
- Patients with lean metabolic-associated fatty liver disease should be assessed for extrahepatic complications, including cardiovascular and chronic kidney disease.
- Current management strategies for lean metabolic-associated fatty liver disease are diet and exercise, although there is limited evidence for their effectiveness.

DISCLOSURE

The authors have nothing to disclose.

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