JAMA | Review

Metabolic Dysfunction–Associated Steatotic Liver Disease in Adults
A Review

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IMPORTANCE Metabolic dysfunction–associated steatotic liver disease (MASLD) includes a range of liver conditions, progressing from isolated steatosis (characterized by fat accumulation in the liver without inflammation) to metabolic dysfunction–associated steatohepatitis (MASH), which involves fat accumulation and inflammation in the liver. The presence of MASLD is associated with increased morbidity and mortality due to liver-related complications, hepatocellular carcinoma, cardiovascular disease, and certain extrahepatic cancers.

OBSERVATIONS The most common chronic liver disease worldwide, MASLD affects approximately 30% to 40% of the general adult population globally (with varying prevalence across continents), including approximately 60% to 70% of individuals with type 2 diabetes and approximately 70% to 80% of those with obesity. It is typically diagnosed based on an ultrasonographic finding of hepatic steatosis, along with at least 1 of 5 features of the metabolic syndrome (abdominal overweight or obesity, prediabetes or type 2 diabetes, hypertension, elevated level of plasma triglycerides, and low level of high-density lipoprotein cholesterol) for women who consume less than 140 g/wk of alcohol (<2 standard drinks/d) and for men who consume less than 210 g/wk (<3 standard drinks/d) and have no other known causes of steatosis such as use of a particular medication (eg, corticosteroids, tamoxifen, or methotrexate), hepatitis C, or iron overload. Other risk factors for MASLD include older age (≥50 years) and male sex (male:female ratio approximately 2). The Fibrosis-4 index (a scoring system incorporating age, serum levels of aspartate aminotransferase and alanine aminotransferase, and platelet count) and vibration-controlled transient elastography (a noninvasive imaging technique) are commonly used to stage hepatic fibrosis in patients with MASLD. Cardiovascular disease is the leading cause of death, followed by certain extrahepatic cancers (primarily gastrointestinal, breast, and gynecologic cancer) and liver-related complications, including cirrhosis, hepatic decompensation (ascites, hepatic encephalopathy, or variceal bleeding), and hepatocellular carcinoma. First-line treatment of MASLD involves behavioral modifications (including hypocaloric low-carbohydrate and low-fat diets, physical exercise, and avoidance of alcohol) and management of type 2 diabetes, obesity, hypertension, and hyperlipidemia. Bariatric surgery should be considered for patients with MASLD and a body mass index greater than 35. Resmetirom (a liver-directed, thyroid hormone receptor β-selective agonist) and subcutaneous semaglutide (a glucagon-like peptide-1 receptor agonist) are conditionally approved by the US Food and Drug Administration (FDA) for the treatment of adults with MASH who have moderate to advanced fibrosis.

CONCLUSIONS A highly prevalent condition among adults worldwide, MASLD is associated with liver-related complications, hepatocellular carcinoma, cardiovascular disease, and certain extrahepatic cancers. First-line treatment includes behavioral modifications, including a weight-reducing diet, physical exercise, and avoidance of alcohol. Resmetirom and semaglutide are conditionally FDA-approved medications for the treatment of adults with MASH and moderate to advanced fibrosis.

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Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease, includes pathological conditions ranging from isolated hepatic steatosis to metabolic dysfunction–associated steatohepatitis (MASH) and cirrhosis, which can progress to hepatocellular carcinoma.[1,2] The diagnosis of MASLD is based on detection of hepatic steatosis (usually with abdominal ultrasonographic findings) in combination with at least 1 of 5 clinical traits of the metabolic syndrome in individuals without significant alcohol consumption and no other known causes of hepatic steatosis.[3]

The most common chronic liver disease worldwide, MASLD affects approximately 30% to 40% of the general adult population, including approximately 60% to 70% of individuals with type 2 diabetes and approximately 70% to 80% of those with obesity.[4-6] Worldwide, MASLD is an increasingly important contributor to liver-related and extrahepatic morbidity and mortality.[7,8] Cardiovascular disease and extrahepatic cancer–related deaths are the leading causes of death in individuals with MASLD, whereas liver-related complications account for approximately 10% of deaths.[9-12]

However, because the risk of liver-related complications rises with increased severity of hepatic fibrosis, liver-related and cardiovascular disease–related deaths are the predominant causes of mortality in individuals with MASLD-related cirrhosis.[11,12] This Review summarizes the pathogenesis, epidemiology, diagnosis, treatment, and prognosis of MASLD (**Box**).

Box. Commonly Asked Questions About Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)

How Is MASLD Diagnosed?

The diagnosis of MASLD is made based on detection of hepatic steatosis (typically with ultrasonography) combined with at least 1 of 5 typical features of the metabolic syndrome (abdominal overweight or obesity, prediabetes or type 2 diabetes, hypertension, increased level of plasma triglycerides, or low level of high-density lipoprotein cholesterol) for women who consume less than 140 g/wk of alcohol (<2 standard drinks/d) and for men who consume less than 210 g/wk of alcohol (<3 standard drinks/d) and do not have other known causes of hepatic steatosis.

How Is Hepatic Fibrosis Assessed and Staged?

Severity of liver fibrosis should be noninvasively assessed in individuals with imaging-detected hepatic steatosis; in those with prediabetes or type 2 diabetes, obesity, or 2 or more cardiometabolic risk factors (such as level of triglycerides ≥150 mg/dL [to convert to mmol/L, multiply by 0.0113] or waist circumference ≥94 cm in men and ≥80 cm in women); and in those with persistently elevated serum levels of aspartate aminotransferase and alanine aminotransferase. The Fibrosis-4 index is a noninvasive prediction tool (performed by primary care clinicians) to assess for risk of MASLD-related advanced liver fibrosis. Vibration-controlled transient elastography (performed by hepatologists) and the enhanced liver fibrosis test are 2 other commonly used tools to noninvasively stage liver fibrosis. If noninvasive testing is inconclusive, a liver biopsy can be performed to diagnose and stage MASLD.

How Is MASLD Treated?

First-line treatment for MASLD involves a weight-reducing diet, increased physical activity, alcohol avoidance, and effective management of type 2 diabetes, hyperlipidemia, and hypertension. Bariatric surgery may be considered for selected patients with MASLD and obesity who have a body mass index greater than 35 (calculated as weight in kilograms divided by height in meters squared). Resmetirom (a liver-directed, thyroid hormone receptor β-selective agonist; 80 or 100 mg/d) and semaglutide (a glucagon-like peptide-1 receptor agonist; 2.4 mg/wk) are conditionally approved by the US Food and Drug Administration for the treatment of adults with noncirrhotic metabolic dysfunction–associated steatohepatitis and moderate to advanced fibrosis.

Methods

A PubMed search was performed for English-language articles related to the epidemiology, pathogenesis, diagnosis, prognosis, and treatment of MASLD in adults aged 18 years or older published between January 1, 2000, and August 31, 2025. The search terms included *metabolic dysfunction–associated steatotic liver disease*, *MASLD*, *metabolic dysfunction–associated steatohepatitis*, *MASH*, *nonalcoholic fatty liver disease*, *nonalcoholic steatohepatitis*, and *NASH*. Of 10 154 retrieved articles, 99 were included. There were 46 observational studies, 15 randomized clinical trials, 16 systematic reviews or meta-analyses, 15 reviews, and 7 guidelines or position statements. If available, absolute data were reported from the included studies.

Pathogenesis

Hepatic steatosis occurs due to (1) increased hepatic uptake of free fatty acids (mainly from food and increased release from adipose tissue lipolysis); (2) increased de novo hepatic lipogenesis (also associated with high dietary intake of glucose and fructose[13]); (3) decreased hepatic fatty acid oxidation; and (4) reduced hepatic export of triglycerides into very low–density lipoproteins.[14] Systemic insulin resistance, which is common among patients with MASLD,[15] triggers lipolysis in adipose tissue (releasing larger amounts of free fatty acids) and hepatic de novo lipogenesis.

Lipotoxicity, characterized by the accumulation of various lipids in the liver (such as triglycerides, free cholesterol, saturated fatty acids, and ceramide), leads to inflammation, cellular dysfunction, and cell death and is an important factor contributing to MASH.[16] Multiple other factors (ie, metabolic and dietary factors, genetics, and the gut microbiome) also likely contribute to the development of MASH.[17]

Proteobacteria and various bacteria-derived components (such as endotoxin or peptidoglycans) are increased in both feces and the liver, and may be involved in the development of MASLD by promoting hepatic inflammation.[18-20] Various dietary factors (such as a high-fat diet and excessive intake of glucose or fructose) may promote low-grade inflammation in multiple organs, including the liver, kidneys, heart, and blood vessels.[20-22] In addition, excess adipose tissue promotes systemic low-grade inflammation through increased release of multiple proinflammatory cytokines and recruitment and activation of immune cells (especially macrophages) within the adipose tissue, which can lead to the progression of MASLD.[23]

Epidemiology

Currently, up to 30% to 40% of adults have MASLD worldwide.[24] Based on a systematic review[9] of 92 population-based studies from

1990 to 2019, the highest prevalence of ultrasound-detected MASLD was observed in Latin America (44.4%) and the lowest was in Western Europe (25.1%). By 2040, the global prevalence of MASLD among adults is projected to exceed 55% due to worldwide increases in obesity and the metabolic syndrome.[24]

The Global Burden of Disease Study (from 2010 to 2021)[25] reported increasing rates and trends in prevalence, annual incidence, and disability-adjusted life-years for MASLD across 204 countries. Globally in 2021, the age-standardized prevalence of MASLD was 15 018 per 100 000 population (95% uncertainty interval, 13 756-16 361) and the annual incidence was 608 per 100 000 population (95% uncertainty interval, 599-618). The prevalence of MASLD was higher in men than in women (15 731 vs 14 310 per 100 000 population), and the prevalence peaked at 45 to 49 years of age for men and at 50 to 54 years for women.[25] The largest increases in age-standardized prevalence estimates from 2010 to 2021 occurred in China (16.9%), Sudan (13.3%), and India (13.2%).[25] Age-standardized mortality attributable to MASLD also increased in the US from 2006 to 2023 (from 0.25 to 1.27 per 100 000 population).[26] The highest average annual percentage change in age-standardized mortality was observed among people older than aged 65 years (average annual percentage change, 15.3% [95% CI, 14.4%-16.3%]), among residents of rural areas (13.5% [95% CI, 10.7%-16.3%]), among non-Hispanic White individuals (11.1% [95% CI, 9.5%-12.8%]), and among Hispanic individuals (10.7% [95% CI, 9.1%-12.3%]).[26]

The worldwide prevalence of MASLD is substantially higher among individuals with other metabolic diseases (such as obesity or type 2 diabetes).[4-6] In a systematic review and meta-analysis[5] of 123 cohort studies (involving 2.2 million individuals with type 2 diabetes), the global pooled prevalence from 1990 to 2021 of MASLD (based on ultrasonographic findings) was 65.3% (95% CI, 62.3%-68.2%). Among these patients with type 2 diabetes, the prevalence of MASLD was highest in Eastern Europe (80.6% [95% CI, 75.7%-84.7%]) and the Middle East (71.2% [95% CI, 62.2%-78.8%]) and lowest in Africa (53.1% [95% CI, 26.0%-78.4%]).[5] Among individuals with type 2 diabetes who had liver biopsy data (12 studies including 2733 patients with type 2 diabetes), the global histological prevalence of MASH was 66.4% (95% CI, 56.6%-75.0%).[5] Stage F2 hepatic fibrosis (histologically defined as perisinusoidal and portal or periportal fibrosis) was present in 40.8% (95% CI, 24.2%-59.7%) of patients, and 15.5% (95% CI, 6.9%-30.9%) had advanced fibrosis (defined as stage F3 or F4).[5] The liver fibrosis scale and stages are defined later in this article.

Risk Factors

The most important clinical risk factors for MASLD are abdominal overweight or obesity (defined as a body mass index [BMI; calculated as weight in kilograms divided by height in meters squared] ≥23 for Asian individuals and ≥25 for White individuals and a waist circumference of ≥80 cm for women and ≥94 cm for men), insulin resistance (usually estimated by the homeostatic model assessment of insulin resistance score >2.5), and prediabetes or type 2 diabetes.[27-30]

The risk of developing MASLD and progressing to MASH increases with the number of metabolic syndrome features, including abdominal obesity, hypertension (defined as systolic/diastolic blood pressure ≥130/85 mm Hg in the context of MASLD or use of antihypertensive medication), hypertriglyceridemia (fasting level of triglycerides ≥150 mg/dL [to convert to mmol/L, multiply by 0.0113] or use of lipid-lowering medication), low level of high-density lipoprotein (HDL) cholesterol (<40 mg/dL for men and <50 mg/dL for women [to convert to mmol/L, multiply by 0.0259]), and elevated blood glucose level (fasting glucose level ≥100 mg/dL [to convert to mmol/L, multiply by 0.0555], hemoglobin A_{1c} level ≥5.7%, or use of antihyperglycemic medication).[31] In addition to male sex and older age, postmenopausal status (primarily due to estrogen deficiency) and certain genetic variants (in the *PNPLA3* and *TM6SF2* genes) may also contribute to the development and progression of MASLD.[27-30,32]

Behavioral factors such as a sedentary lifestyle, smoking, and high intake of fructose (principally from sugar-sweetened beverages ≥1 serving/d), alcohol consumption (>140 g/wk [>2 standard drinks/d] for women and >210 g/wk [>3 standard drinks/d] for men; a standard drink is equivalent to approximately 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits), and high-calorie diets (especially those high in saturated fats, sugars, and processed foods) also increase the risk of MASLD.[27-30]

Metabolic Dysfunction and Alcohol-Related Liver Disease

Metabolic dysfunction and alcohol-related liver disease represents a separate category of individuals in whom the etiology of liver disease is both the metabolic syndrome and alcohol intake. This category is defined as higher weekly amounts of alcohol consumption (140-350 g/wk for women and 210-420 g/wk for men) compared with the lower weekly amounts of alcohol consumption associated with MASLD indicated below. Alcohol intake above these levels is usually classified as alcohol-associated liver disease.[3] Therefore, accurate assessment of alcohol use (determined from the patient history) is necessary to correctly classify steatotic liver disease subtypes; however, this classification may be affected by underreporting.

Clinical Presentation

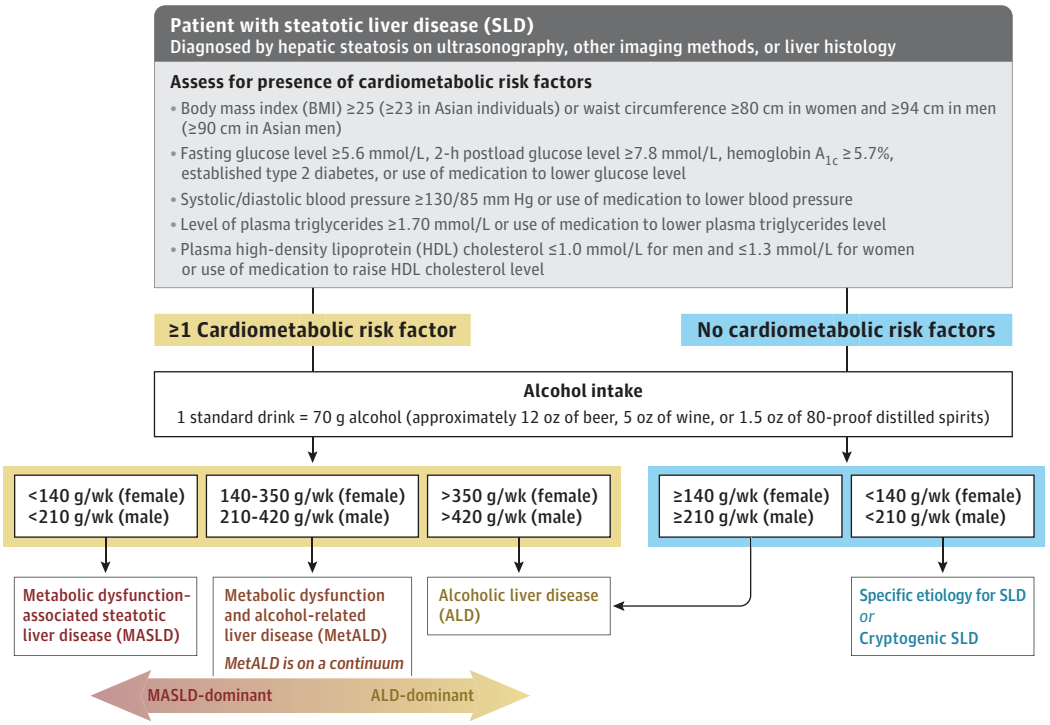
Patients with MASLD are usually asymptomatic during precirrhotic stages,[33,34] although some may experience fatigue, malaise, or right upper quadrant abdominal discomfort. Based on physical examination, about 50% to 60% of patients with MASLD have mild to moderate hepatomegaly. Less than 5% of patients have splenomegaly,[33,34] and more than 80% are classified by BMI as overweight or obese, 60% to 70% have atherogenic dyslipidemia (typically characterized by high plasma level of triglycerides and low level of HDL cholesterol), approximately 60% have prediabetes or type 2 diabetes, and up to 50% have hypertension.[19,35]

The presence of MASLD is often identified incidentally by detection of hepatic steatosis on abdominal ultrasonographic findings when ultrasonography is performed for other reasons or because of mild to moderate increases in serum aminotransferase levels, mainly due to elevations in serum alanine aminotransferase (ALT) levels. However, up to two-thirds of patients with MASLD, including those with advanced fibrosis or cirrhosis, have normal serum aminotransferase levels; serum ALT levels do not correlate well with the histological severity of MASLD.[33,34]

Assessment and Diagnosis

The diagnosis of MASLD is made based on detection of hepatic steatosis (typically with ultrasonographic findings) combined

Figure 1. Flowchart Showing the Classification and Subclassification of Steatotic Liver Disease



Individuals without metabolic risk factors and no identifiable causes are considered to have cryptogenic SLD. Those with cryptogenic SLD may be reexamined over time or be recategorized in the future, pending developments in the understanding of disease pathophysiology. Other known causes of SLD include drug-induced liver injury, iron overload, monogenic disorders such as lysosomal acid lipase deficiency, hypobetalipoproteinemia, Wilson disease, inborn errors of metabolism, and other liver diseases (such as genotype 3 hepatitis C virus infection, autoimmune hepatitis), celiac disease, malnutrition, or HIV infection. BMI is calculated as weight in kilograms divided by height in meters squared. To convert glucose to mg/dL, divide by 0.0555; HDL cholesterol to mg/dL, divide by 0.0259; and triglycerides to mg/dL, divide by 0.0113.

with at least 1 of 5 typical features of the metabolic syndrome (abdominal overweight or obesity, prediabetes or type 2 diabetes, hypertension, increased plasma level of triglycerides, or low level of HDL cholesterol) for women who consume less than 140 g/wk of alcohol (<2 standard drinks/d) and for men who consume less than 210 g/wk (<3 standard drinks/d) and do not have other known causes of hepatic steatosis, including use of certain medications (such as corticosteroids, methotrexate, or tamoxifen), hepatitis C virus infection, iron overload, celiac disease, HIV, malnutrition, Wilson disease, lysosomal acid lipase deficiency, hypobetalipoproteinemia, or inborn errors of metabolism[3] (**Figure 1**).

Imaging Studies

Although hepatic steatosis may be incidentally identified with abdominal computed tomography or magnetic resonance imaging, abdominal ultrasonography is the first-line imaging test for the diagnosis of hepatic steatosis, which is characterized by the qualitative assessment of increased hepatic echogenicity (compared with the renal cortex), decreased visibility of intrahepatic vessels, and impaired visualization of the diaphragm and deeper liver tissue. Ultrasonography, which is widely available and affordable, has a sensitivity of 80% to 89% and a specificity of 87% to 90% for detecting moderate to severe steatosis.[34,36-38] However, the sensitivity of ultrasonography is less than 50% for detecting mild steatosis (hepatic fat content <20%).[39] For detection of any degree of hepatic steatosis, magnetic resonance imaging–proton density fat fraction has a sensitivity of 77% to 92% and a specificity of 87% to 94% and the range is 95% to 98% for both the sensitivity and specificity of magnetic resonance spectroscopy.[40] However, these 2 imaging techniques are primarily used in clinical trials and are only available at specialized centers.

The controlled attenuation parameter (CAP), which measures the attenuation of ultrasound waves passing through the liver, is another noninvasive method for assessing hepatic steatosis. It is typically performed in conjunction with vibration-controlled transient elastography (an imaging method usually performed by hepatologists) to measure liver stiffness based on the speed of ultrasound pulses passing through the liver. CAP values of 248 dB/m or greater are considered diagnostic for hepatic steatosis, and higher CAP values indicate more severe steatosis.[34,37,38] Compared with conventional ultrasonography, CAP has a similar sensitivity and a slightly higher specificity (approximately 90%) for detecting hepatic steatosis.[34,37,38]

Liver Biopsy and Liver Fibrosis Stage

Liver biopsy is the criterion standard for diagnosing MASH and staging hepatic fibrosis, but it is an invasive procedure that is costly and is associated with acute bleeding in rare cases (approximately <2%).[41] Although typically not used to diagnose MASLD, liver

biopsy is useful for the diagnosis and management of patients with liver conditions of unknown etiology and in those with MASLD and coexisting liver diseases (such as autoimmune hepatitis or viral hepatitis).[42] Based on liver biopsy histology, liver fibrosis is scored using a 5-stage scale: F0 (absence of fibrosis), F1 (perisinusoidal or portal fibrosis), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis), and F4 (cirrhosis).

Noninvasive Assessment of Hepatic Fibrosis Severity

The 2 most commonly used noninvasive tests to evaluate fibrosis severity in individuals with MASLD are the Fibrosis-4 (FIB-4) index and the enhanced liver fibrosis (ELF) test. The FIB-4 index equation (includes age, serum ALT level, serum aspartate aminotransferase level, and platelet count) provides an estimate of the risk of advanced liver fibrosis as low (score <1.30), indeterminate (score of 1.30-2.67), or high (score >2.67). An FIB-4 index of less than 1.3 has a negative predictive value of 85% to 90% for detecting advanced liver fibrosis. The ELF test uses 3 serum biomarkers of fibrosis (tissue inhibitor of metalloproteinase 1, type III procollagen amino terminal peptide, and hyaluronic acid), which are associated with liver extracellular matrix metabolism, to provide a score reflecting fibrosis severity. The ELF test has a sensitivity of approximately 98% for detecting advanced liver fibrosis.[43]

Another noninvasive test, the Agile 3+ score (based on a combination of measured liver stiffness via vibration-controlled transient elastography with aspartate aminotransferase:ALT ratio, platelet count, diabetes status, sex, and age), has been shown to better identify advanced fibrosis in patients with MASLD than the FIB-4 index or the measurement of liver stiffness alone.[44,45] In addition, the single or serial use of the Agile 3+ score accurately predicted long-term liver-related events in a multinational cohort of 16 603 patients with MASLD followed up for a median of 51.7 months (IQR, 25.2-85.2 months), making it a suitable alternative to liver biopsy in clinical practice and in clinical trials of MASH.[46]

Other less frequently used serum biomarkers and imaging techniques for identifying individuals with MASH and fibrosis stage of F2 or higher[47-49] are summarized in eTable 1 in the Supplement.

Screening for MASLD

Guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver (EASL), the European Association for the Study of Obesity, and the American Diabetes Association do not recommend universal screening for MASLD.[50-55] Instead, the guidelines from these organizations strongly recommend a 2-tier testing approach to screening for advanced liver fibrosis in high-risk populations for MASLD (such as individuals with prediabetes or type 2 diabetes, those with obesity or ≥2 metabolic risk factors, and those with an incidental finding of imaging-detected hepatic steatosis or persistently elevated serum aminotransferase levels).[50-55]

The first step of this 2-tier screening approach involves calculation of the FIB-4 index, which is usually performed by primary care clinicians (**Figure 2**). Patients with an FIB-4 index greater than 1.3 should undergo either vibration-controlled transient elastography to measure liver stiffness or another noninvasive test (such as the ELF test). Patients with a liver stiffness measurement greater than 8.0 kPa or an ELF test score greater than 9.8 should be referred to a hepatologist for further evaluation.[50-55]

Development of Advanced Fibrosis, Cirrhosis, and Hepatocellular Carcinoma

Approximately 15% to 40% of patients with isolated hepatic steatosis progress to MASH.[56] Fibrosis progression typically occurs slowly; estimated progression is about 1 liver fibrosis stage over approximately 14 years for patients with isolated steatosis and 1 liver fibrosis stage over approximately 7 years for those with MASH.[57] More advanced stages of liver fibrosis are the strongest risk factor for progression to cirrhosis and hepatic decompensation[40] (**Figure 3**).

In a systematic review and meta-analysis[56] of 54 studies involving 26 738 patients with histologically confirmed MASLD, 2% to 3% of patients with isolated steatosis developed advanced fibrosis (determined by histology) over 15 to 20 years, and about 25% to 30% of patients with MASH developed advanced fibrosis (defined as histological fibrosis stage ≥F3) within 8 to 10 years. In a study of patients with biopsy-confirmed MASH, progression to cirrhosis occurred over 2 years in 22% (48/217) of patients with fibrosis stage F3.[58] Cirrhosis is associated with hepatic decompensation events (such as ascites, hepatic encephalopathy, and variceal bleeding) that occur at rates of about 10% annually.[9,59,60] In addition, up to nearly 2.5% of patients with cirrhosis develop incident hepatocellular carcinoma annually.[9,59]

Treatment

The primary goals of MASLD treatment are to induce resolution of MASH and to prevent progression of liver fibrosis and long-term liver-related events (such as new-onset cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related death).[10,55,61] Effective management of metabolic comorbidities (obesity, type 2 diabetes, hyperlipidemia, and hypertension) is also important to decrease the progression risk for MASLD, chronic kidney disease (stage ≥3), heart failure, and certain types of extrahepatic cancer.[8]

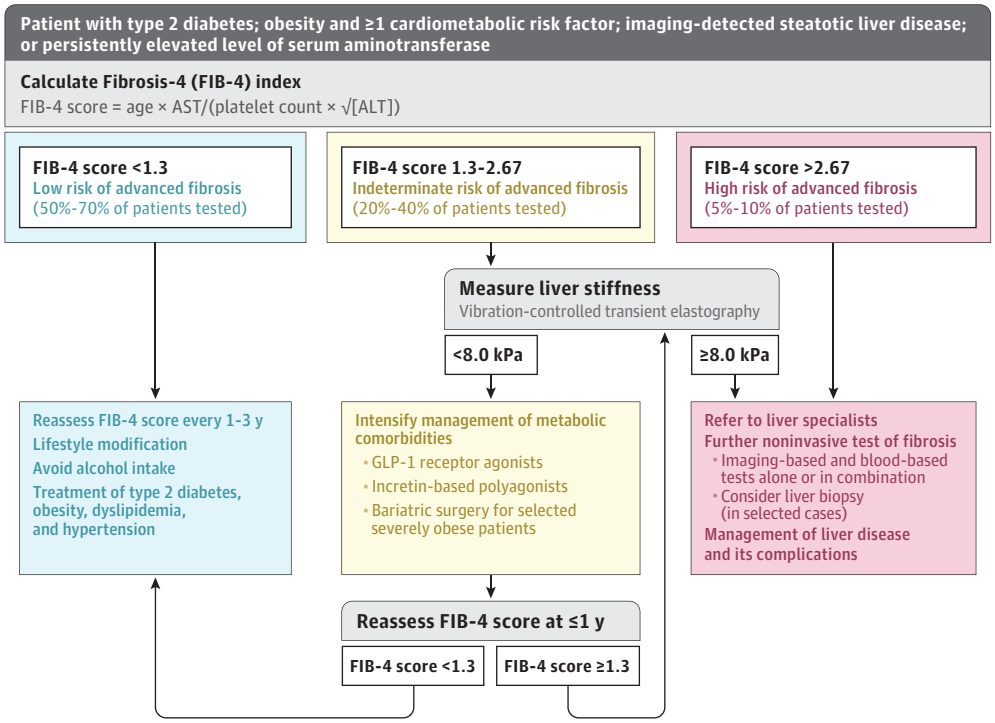
Behavioral Modifications

Behavioral modifications are the first-line treatment for MASLD. A prospective study with paired liver biopsy results (involving 293 adult patients with MASH followed up for 52 weeks) reported lifestyle-induced weight loss of 7% to 10% improved MASH and liver fibrosis, and a weight loss of 5% decreased hepatic steatosis.[62] Improvement by more than 30% in histological hepatic steatosis was reported in 76% of patients with weight loss of 7% to 10% compared with 35% of patients with weight loss of less than 5% ($P < .001$); resolution of MASH was more common in the group with weight loss of 7% to 10% (64% vs 10% in the group with weight loss of <5%; $P < .001$). Patients with weight loss of 10% or greater showed more improved resolution of MASH vs patients with weight loss of less than 5% (90% vs 10%, respectively; $P < .001$) and more patients showed a reduction in liver fibrosis at 52 weeks (45% vs 16%; $P < .001$).[62]

Dietary Modifications

Low-carbohydrate and low-fat hypocaloric diets have shown similar effectiveness in reducing liver fat and related biomarkers (such as serum aminotransferase levels) in patients with MASLD.[63,64] The EASL guidelines[50] recommend a Mediterranean-type diet with high intake of fruits, vegetables, whole grains, fish, and olive oil and limiting ultraprocessed foods, saturated fats, and refined sugars to

Figure 2. Diagnostic Framework for Detection of Advanced Liver Fibrosis in Individuals at High Risk



This diagnostic framework, which is structured around a 3-tier testing process (each serving a specific purpose), has been validated.[50,51] The FIB-4 index (first-line test) is a reliable and accurate test that helps rule out advanced fibrosis, with a high negative predictive value, thereby reducing the need for further testing. The FIB-4 index should be performed by primary care clinicians. Vibration-controlled transient elastography (second-line test) is used to noninvasively measure liver stiffness; alternatively, a blood test is used to obtain the enhanced liver fibrosis score in certain countries (such as the UK). These more expensive, specialized noninvasive tests aim to identify patients at high risk of advanced fibrosis and are usually performed by specialists (eg, hepatologists). Hepatologists perform third-line testing to confirm the presence of advanced fibrosis and develop a treatment plan. Confirmation of the diagnosis by hepatologists may require additional noninvasive imaging–based or blood-based tests of liver fibrosis (alone or in combination) or a liver biopsy, especially if the results from the noninvasive tests are inconsistent (or discordant). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GLP-1, glucagon-like peptide-1.

manage MASLD. Long-term dietary adherence is important and may improve when individual preferences are considered along with clinical, cultural, and economic factors.

Physical Activity

The EASL guidelines[50] strongly recommend regular physical activity (preferably consisting of ≥150 min/wk of moderate-intensity aerobic exercise or 75-150 min/wk of vigorous-intensity exercise) to reduce hepatic steatosis in individuals with MASLD.[65] Evidence from well-designed trials is needed to assess the long-term effects of physical activity on liver-related events.

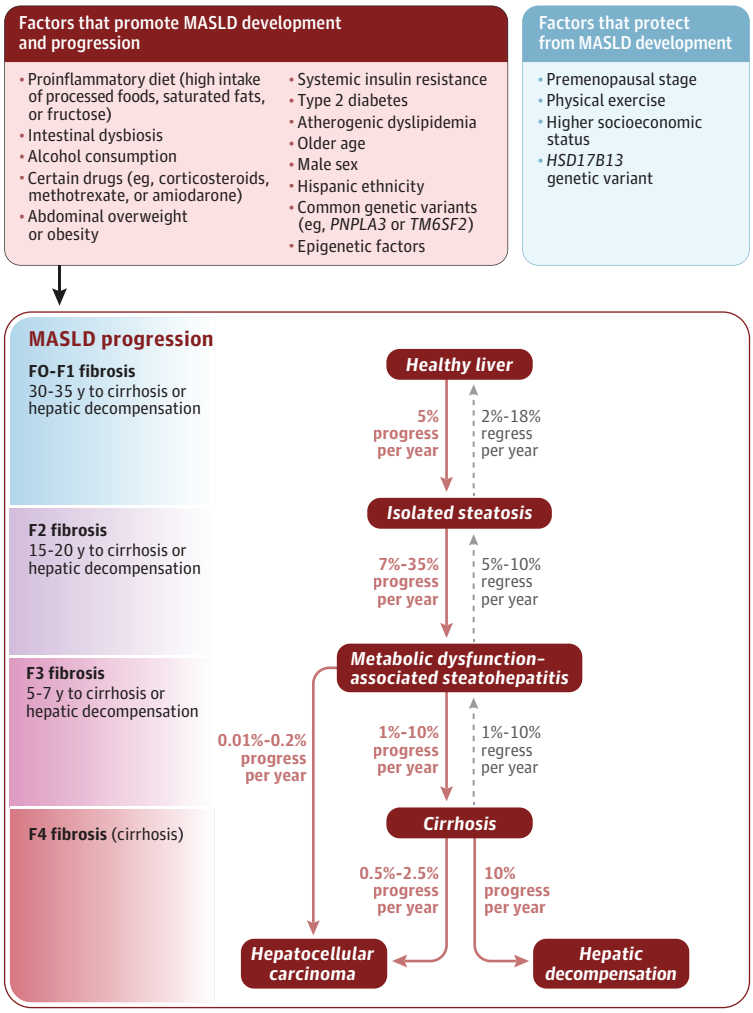
Medications

Two pharmacotherapies (resmetirom and semaglutide) are conditionally approved by the US Food and Drug Administration (FDA) for the treatment of adults with noncirrhotic MASH and moderate to severe fibrosis (stages F2-F3) (**Table**).[66,67] To date, no randomized clinical trials have compared the combined effects of semaglutide and resmetirom for the treatment of MASH and moderate to advanced fibrosis.

Resmetirom | Resmetirom is a liver-directed, thyroid hormone receptor β-selective agonist, which was conditionally approved by the FDA on March 14, 2024, and by the European Medicines Agency on August 19, 2025, for the treatment of adults with MASH and moderate to advanced fibrosis. A phase 3 trial involving 966 patients with obesity and biopsy-confirmed MASH (fibrosis stages F1-F3) reported that resmetirom (80 mg/d or 100 mg/d for 52 weeks) resulted in histological resolution of MASH without worsening of fibrosis in the 80-mg resmetirom group (25.9%) and in the 100-mg resmetirom group (29.9%) compared with the placebo group (9.7%); $P < .001$ for both comparisons with placebo.[66] Improvement of liver fibrosis by at least 1 stage (without worsening of MASH) was achieved in 24.2% of patients in the 80-mg resmetirom group and in 25.9% of patients in the 100-mg resmetirom group compared with 14.2% of patients in the placebo group ($P < .001$).[66]

At week 52, treatment with 100 mg of resmetirom reduced serum ALT levels (between-group difference for 100 mg of resmetirom vs placebo, −26% [95% CI, −34% to −18%]; $P < .001$), achieved a measured reduction in liver stiffness of 25% or greater (49% for resmetirom vs 29% for placebo; $P < .001$), and significantly improved ($P < .001$) circulating levels of plasma low-density lipoprotein cholesterol (between-group difference, −16% [95% CI, −20% to −13%]), triglycerides (between-group difference, −19% [95% CI, −28% to −10%]), and lipoprotein(a) (between-group difference, −35% [95% CI, −43% to −27%]), which may confer cardiovascular

Figure 3. Pathogenesis and Progression of Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)



Among the possible genetic factors, some genetic polymorphisms are significantly associated with increased susceptibility to MASLD, such as the *PNPLA3* I148M variant and the *TM6SF2* E167K variant, which influence hepatic lipid droplet metabolism, lipoprotein secretion, and inflammation. Female sex (prior to postmenopausal status), hormonal factors (eg, estrogen levels), and specific genetic polymorphisms (eg, *HSD17B13* genetic variant) can beneficially influence the development and progression of MASLD. The stage of liver fibrosis is the strongest prognostic factor for long-term, liver-related morbidity and mortality.

benefits.[66] There was no significant difference in weight loss at week 52 (−1.8% for the 100 mg of resmetirom group vs −0.9% for the placebo group), indicating that the hepatoprotective effects of resmetirom were not due to weight loss.[66]

Semaglutide | On August 15, 2025, the FDA conditionally approved the glucagon-like peptide-1 receptor agonist semaglutide (2.4 mg/wk) for the treatment of MASH and moderate to advanced fibrosis based on a phase 3, placebo-controlled trial that included 800 patients with obesity and biopsy-confirmed MASH with fibrosis stage F2 or F3.[67] Histological resolution of MASH without worsening of fibrosis occurred in 62.9% of patients in the semaglutide group (2.4 mg/wk for 72 weeks) vs 34.3% of patients in the placebo group ($P < .001$). In addition, improvement by at least 1 fibrosis stage without worsening of MASH occurred in 36.8% of patients in the semaglutide group vs 22.4% of patients in the placebo group ($P < .001$).

At week 72, patients taking semaglutide had greater weight loss compared with placebo (−10.5% vs −2%, respectively; $P < .001$), improvements in plasma lipid levels (lower levels of plasma total cholesterol and triglycerides and higher HDL cholesterol level), reductions in mean serum ALT levels (−52% vs −8%; $P < .001$), and a higher likelihood of achieving a reduction of 25% or greater in the measurement of liver stiffness from baseline (60% vs 35%; $P < .001$).[67]

Bariatric Surgery

Bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy) should be considered for individuals with MASLD and obesity (BMI >35), especially in those without improvement from behavioral modifications or from the use of medications on imaging-detected hepatic steatosis and liver fibrosis.[68-70] A bariatric surgery cohort that included 180 patients with severe obesity (mean BMI, 48.1) and biopsy-proven MASH reported histological resolution of MASH (in 84% of patients) and reductions in liver fibrosis (in 70% of patients) at 5-year follow-up.[68]

In an observational study that included 1158 adults with confirmed histological diagnosis of MASH and liver fibrosis (stages F1-F3), patients who underwent bariatric surgery had a lower 10-year cumulative incidence rate of liver-related adverse events (eg, progression to cirrhosis, hepatocellular carcinoma, requiring a liver transplant, or liver-related mortality) compared with those who did not undergo bariatric surgery (2.3% [95% CI, 0%-4.6%] vs 8.5% [95% CI, 5.5%-11.4%]; adjusted hazard ratio [HR], 0.12

Table. Pharmacological Therapies Conditionally Approved by the US Food and Drug Administration for the Treatment of Adults With Noncirrhotic MASH and Moderate to Severe Fibrosis

Phase 3 trial name	Drug name (type)	Population	Group comparison	Primary outcomes	Secondary outcomes	Adverse events and other information
MAESTRO-NASH[66]	Resmetirom (liver-directed, thyroid hormone receptor β-selective agonist)	Patients with biopsy-confirmed MASH and liver fibrosis stage[a] F1b, F2, or F3 (N = 966)	Resmetirom (80 mg/d or 100 mg/d) vs placebo for 52 wk	MASH resolution with stable or improving fibrosis: • Resmetirom (80 mg/d): 25.9% (n = 316) • Resmetirom (100 mg/d): 29.2% (n = 321) • Placebo: 9.7% (n = 318) Improvement in fibrosis by ≥1 stage without worsening of MASH: • Resmetirom (80 mg/d): 24.9% • Resmetirom (100 mg/d): 25.9% • Placebo: 14.2% For comparisons with each dose of resmetirom vs placebo, $P < .001$	Change from baseline in plasma LDL cholesterol level: • Resmetirom (80 mg/d): lowered by 13.6% • Resmetirom (100 mg/d): lowered by 16.3% • Placebo: increased by 0.1% For comparisons with each dose of resmetirom vs placebo, $P < .001$	Resmetirom was well tolerated: • Diarrhea: 27%-33% vs 15% with placebo • Nausea: 19%-22% vs 12% with placebo Resmetirom was not associated with serious adverse events or liver toxicity Resmetirom was associated with significant reductions in: • Liver fat content (measured with an MRI) • Liver stiffness • Noninvasive fibrosis biomarkers • Serum ALT levels • Plasma lipid profile (in addition to lowering LDL cholesterol levels) No significant effects of resmetirom on body weight or insulin resistance (estimated by HOMA-IR)
ESSENCE[67]	Semaglutide (GLP-1 receptor agonist)	Patients with biopsy-confirmed MASH and liver fibrosis stage[a] F2 or F3 (N = 1197)	Semaglutide (2.4 mg/wk) vs placebo for 72 wk	MASH resolution without worsening of fibrosis: • Semaglutide: 62.9% (n = 534) • Placebo: 34.3% (n = 266) Improvement in fibrosis by ≥1 stage without worsening of MASH: • Semaglutide: 36.8% • Placebo: 22.4% For comparison of semaglutide vs placebo, $P < .001$	Change in body weight: • Semaglutide: decreased by 10.5% • Placebo: decreased by 2% Percentage of patients with resolution of MASH and reduction in liver fibrosis: • Semaglutide: 32.7% • Placebo: 16.1% For comparison of semaglutide vs placebo, $P < .001$	Semaglutide was well tolerated: • Diarrhea: 27% vs 12% with placebo • Constipation: 22% vs 18% with placebo • Nausea: 36% vs 13% with placebo • Vomiting: 18% vs 5% with placebo Semaglutide was not associated with serious adverse events or liver toxicity Semaglutide was associated with significant reductions in: • Liver stiffness • Noninvasive fibrosis biomarkers • Serum ALT levels • Plasma lipid profile • Insulin resistance (estimated by HOMA-IR) • Hemoglobin A_{1c} level

Abbreviations: ALT, alanine aminotransferase; GLP-1, glucagon-like peptide-1; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; MASH, metabolic dysfunction–associated steatohepatitis; MRI, magnetic resonance imaging.

[a] The 5-stage scale for liver fibrosis ranges from F0 (absence of fibrosis), F1 (perisinusoidal or portal fibrosis), F1b (moderate fibrosis, pericentral area only), F2 (perisinusoidal and portal or periportal fibrosis), F3 (septal and bridging fibrosis), to F4 (cirrhosis).

[95% CI, 0.02-0.63]; *P* = .01).[69] The 10-year cumulative incidence rates of cardiovascular disease events (defined as a composite of coronary artery events, cerebrovascular events, heart failure, or cardiovascular disease death) were also lower in the bariatric surgery group (8.5% [95% CI, 5.5%-11.4%] vs 15.7% [95% CI, 11.3%-19.8%] in those who did not undergo surgery; adjusted HR, 0.30 [95% CI, 0.12-0.72]; *P* = .007).[69]

Prognosis

A 2020 systematic review and meta-analysis[71] of 13 longitudinal studies, involving 4428 patients with biopsy-proven MASLD (65% of whom had MASH), reported that the unadjusted risk of adverse health outcomes increased with increasing stage of fibrosis (stage F0 [no fibrosis] vs F4) for liver-related events (HR, 12.8 [95% CI, 6.8-23.8]), liver-related mortality (HR, 11.1 [95% CI, 4.1-29.8]), liver transplant (HR, 5.42 [95% CI, 1.05-27.9]), and all-cause mortality (HR, 3.42 [95% CI, 2.6-4.5]). The HRs did not differ significantly after adjustment for age and sex.[71]

An analysis[72] including 4925 patients with MASLD (2135 with a histological diagnosis and 2790 diagnosed by vibration-controlled transient elastography) reported that the 5-year probability was 0.2% for liver-related events and was 3.0% for extrahepatic events (including cardiovascular disease–related outcomes and extrahepatic cancer–related outcomes) in patients with stage F0 or F1, 2.0% and 3.8%, respectively, in patients with stage F2, and 9.7% and 6.4% in patients with stage F3 or F4.

Recent cohort studies also reported that individuals with MASLD have significantly higher all-cause mortality rates than matched controls.[12,73-75] A nationwide, registry-based cohort study from Sweden that identified patients based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* codes for MASLD (n = 13 099) and control individuals from the general population (n = 118 884) matched for age, sex, municipality, and calendar year reported higher incidence rates (over a median follow-up of approximately 5 years) for all-cause mortality in patients with MASLD (20.4 [95% CI, 19.5-21.5] per 1000 person-years) vs control individuals (11.1 [95% CI, 10.8-11.3] per 1000 person-years; HR, 1.85 [95% CI, 1.74-1.96]), higher cardiovascular disease-related mortality (5.3 [95% CI, 4.8-5.8] per 1000 person-years vs 3.5 [95% CI, 3.4-3.7], respectively; HR, 1.54 [95% CI, 1.38-1.72]), and higher non–hepatocellular carcinoma cancer–related mortality (5.7 [95% CI, 5.2-6.2] per 1000 person-years vs 3.5 [95% CI, 3.4-3.7]; HR, 1.47 [95% CI, 1.32-1.63]).[12]

Another retrospective cohort study[11] of 366 433 US adults with imaging-detected steatotic liver disease at the Veterans Health Administration (2010-2021) reported that the leading causes of death in patients with noncirrhotic MASLD were cardiovascular disease and extrahepatic cancer (10-year cumulative incidence of 8.1% and 7.5%, respectively). Conversely, among patients with MASLD-related cirrhosis, the 10-year cumulative incidence of liver-related death was 9.2% and the incidence of cardiovascular disease–related death was 17.3%.[11]

A systematic review and meta-analysis[76] of 36 longitudinal studies, including 5.8 million middle-aged individuals (mean age, 53 years [SD, 7 years]), reported that MASLD was associated with an increased risk of fatal or nonfatal cardiovascular disease events (pooled random-effects HR, 1.45 [95% CI, 1.31-1.61]) over a median follow-up of 6.5 years (IQR, 5-10 years). The risk of cardiovascular disease events increased across the severity of MASLD, especially by the stage of fibrosis (pooled random-effects HR, 2.50 [95% CI, 1.68-3.72]).

Furthermore, meta-analyses[77-79] have reported that MASLD is significantly associated with a higher risk of developing heart failure (pooled HR, 1.50 [95% CI, 1.34-1.67] from an analysis[77] that included 11 cohort studies with 11.2 million participants who were followed up for a median of 10 years [IQR, 8-14 years]), a higher risk of developing chronic kidney disease stage 3 or higher (pooled HR, 1.43 [95% CI, 1.33-1.54] from an analysis[78] that included 13 cohort studies with 1.2 million individuals who were followed up for a median of 9.7 years [IQR, 5-10 years]), and a higher risk of developing new-onset atrial fibrillation (pooled HR, 1.20 [95% CI, 1.10-1.32] from an analysis[79] that included 16 cohort studies with aggregate data for 19.5 million individuals who were followed up for a median of 7.2 years [IQR, 3.6-9.5 years]). A meta-analysis of 33 cohort studies (including 501 022 individuals followed up for a median of 5 years [IQR, 4-19 years]) showed that MASLD is associated with an approximately 2-fold increased risk of developing incident type 2 diabetes (pooled HR, 2.19 [95% CI, 1.93-2.48]), and this risk markedly increases across the severity of liver fibrosis (pooled HR, 3.42 [95% CI, 2.29-5.11]).[80]

Another meta-analysis[81] of 10 cohort studies (including 182 202 individuals over a median follow-up of 5.8 years [IQR, 4-8 years]; there were 8485 incident cases of extrahepatic cancer) found that MASLD is also associated with a higher risk of developing certain types of gastrointestinal cancer (esophageal: HR, 1.93 [95% CI, 1.19-3.12]; stomach: HR, 1.81 [95% CI, 1.19-2.75]; pancreatic: HR, 1.84 [95% CI, 1.23-2.74]; and colorectal: HR, 1.64 [95% CI, 1.24-2.19]) and a higher risk of developing breast cancer (HR, 1.39 [95% CI, 1.13-1.71]) and gynecologic malignancies (HR, 1.62 [95% CI, 1.13-2.32]).

Future Directions

Phase 3, randomized, placebo-controlled trials are ongoing for tirzepatide and other dual- or triple-incretin receptor agonists,[82-86] gliflozins,[87] pan-peroxisome proliferator–activated receptor agonists (ie, lanifibranor),[88] and fibroblast growth factor 21 analogs[89-91] (eTable 2 in the Supplement). Other investigational approaches include fatty acid synthase inhibitors (NCT04906421) and genetic target–based therapies (such as antisense oligonucleotides targeting the *PNPLA3* genetic variant).[92]

Blood-based biomarkers of fibrosis and vibration-controlled transient elastography will likely be used more frequently to monitor liver disease progression and regression, predict long-term liver-related events, and assess treatment responses, especially with the availability of semaglutide and resmetirom for the treatment of MASH and liver fibrosis.[93-95] In addition, polygenic risk scores,[96,97] metabolic signatures,[98] and microbiome signatures[99] may help identify patients with MASLD who have distinct disease trajectories and responses to treatment.

Limitations

This Review has several limitations. First, some relevant publications may have been missed. Second, the quality of evidence was not formally assessed. Third, this Review focused on MASLD in adults and did not include information about MASLD in children and adolescents.

Conclusions

A highly prevalent condition among adults worldwide, MASLD is associated with liver-related complications, hepatocellular carcinoma, cardiovascular disease, and certain extrahepatic cancers. First-line treatment includes behavioral modifications, including a weight-reducing diet, physical exercise, and avoidance of alcohol. Resmetirom and semaglutide are conditionally FDA-approved medications for the treatment of adults with MASH and moderate to advanced fibrosis.

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REFERENCES

1. Israelsen M, Francque S, Tsochatzis EA, Krag A. Steatotic liver disease. *Lancet*. 2024;404(10464):1761-1778. doi:10.1016/S0140-6736(24)01811-7

2. Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. *Trends Endocrinol Metab*. 2024;35(8):697-707. doi:10.1016/j.tem.2024.02.007

3. Rinella ME, Lazarus JV, Ratziu V, et al; NAFLD Nomenclature Consensus Group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79(6):1542-1556. doi:10.1016/j.jhep.2023.06.003

4. Wong VWS, Ekstedt M, Wong GLH, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol*. 2023;79(3):842-852. doi:10.1016/j.jhep.2023.04.036

5. Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol*. 2024;22(10):1999-2010.e8. doi:10.1016/j.cgh.2024.03.006

6. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2023;8(1):20-30. doi:10.1016/S2468-1253(22)00317-X

7. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62(1)(suppl):S47-S64. doi:10.1016/j.jhep.2014.12.012

8. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *Lancet Gastroenterol Hepatol*. 2021;6(7):578-588. doi:10.1016/S2468-1253(21)00020-0

9. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77(4):1335-1347. doi:10.1097/HEP.0000000000000004

10. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. *Gut*. 2024;73(4):691-702. doi:10.1136/gutjnl-2023-330595

11. Ochoa-Allemant P, Hubbard RA, Kaplan DE, Serper M. Cause-specific mortality in patients with steatotic liver disease in the United States. *J Hepatol*. 2025;83(4):860-869. doi:10.1016/j.jhep.2025.05.013

12. Issa G, Shang Y, Strandberg R, Hagström H, Wester A. Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease in Sweden. *J Hepatol*. 2025;83(3):643-651. doi:10.1016/j.jhep.2025.03.001

13. Huang DQ, Wong VWS, Rinella ME, et al. Metabolic dysfunction–associated steatotic liver disease in adults. *Nat Rev Dis Primers*. 2025;11(1):14. doi:10.1038/s41572-025-00599-1

14. Carli F, Della Pepa G, Sabatini S, Vidal Puig A, Gastaldelli A. Lipid metabolism in MASLD and MASH: from mechanism to the clinic. *JHEP Rep*. 2024;6(12):101185. doi:10.1016/j.jhepr.2024.101185

15. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med*. 1999;107(5):450-455. doi:10.1016/S0002-9343(99)00271-5

16. Iturbe-Rey S, Maccali C, Arrese M, et al. Lipotoxicity-driven metabolic dysfunction–associated steatotic liver disease (MASLD). *Atherosclerosis*. 2025;400:119053. doi:10.1016/j.atherosclerosis.2024.119053

17. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology*. 2010;52(5):1836-1846. doi:10.1002/hep.24001

18. Carpino G, Del Ben M, Pastori D, et al. Increased liver localization of lipopolysaccharides in human and experimental NAFLD. *Hepatology*. 2020;72(2):470-485. doi:10.1002/hep.31056

19. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;42(1):44-52. doi:10.1002/hep.20734

20. Adolph TE, Tilg H. Western diets and chronic diseases. *Nat Med*. 2024;30(8):2133-2147. doi:10.1038/s41591-024-03165-6

21. Kawano Y, Edwards M, Huang Y, et al. Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome. *Cell*. 2022;185(19):3501-3519.e20. doi:10.1016/j.cell.2022.08.005

22. Todoric J, Di Caro G, Reibe S, et al. Fructose stimulated de novo lipogenesis is promoted by inflammation. *Nat Metab*. 2020;2(10):1034-1045. doi:10.1038/s42255-020-0261-2

23. du Plessis J, van Pelt J, Korf H, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(3):635-48.e14. doi:10.1053/j.gastro.2015.05.044

24. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction–associated steatotic liver disease. *Clin Mol Hepatol*. 2025;31(suppl):S32-S50. doi:10.3350/cmh.2024.0431

25. Feng G, Targher G, Byrne CD, et al. Global burden of metabolic dysfunction–associated steatotic liver disease, 2010 to 2021. *JHEP Rep*. 2024;7(3):101271. doi:10.1016/j.jhepr.2024.101271

26. Zhang X, Linden S, Levesley CR, et al. Projected trends in metabolic dysfunction–associated steatotic liver disease mortality through 2040. *JAMA Netw Open*. 2025;8(6):e2516367. doi:10.1001/jamanetworkopen.2025.16367

27. Byrne CD, Armandi A, Pellegrinelli V, Vidal-Puig A, Bugianesi E. Metabolic dysfunction–associated steatotic liver disease: a condition of heterogeneous metabolic risk factors, mechanisms and comorbidities requiring holistic treatment. *Nat Rev Gastroenterol Hepatol*. 2025;22(5):314-328. doi:10.1038/s41575-025-01045-z

28. Hagström H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction–associated steatotic liver disease.

Lancet Gastroenterol Hepatol. 2024;9(10):944-956. doi:10.1016/S2468-1253(24)00193-6

29. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol*. 2019;7(4):313-324. doi:10.1016/S2213-8587(18)30154-2

30. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction–associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. *Lancet Diabetes Endocrinol*. 2025;13(2):134-148. doi:10.1016/S2213-8587(24)00318-8

31. Cuthbertson DJ, Kennedy OJ, Bilson J, et al. Impact of metabolic dysfunction severity in steatotic liver disease and its interaction with liver fibrosis on all-cause mortality and multiple hepatic and extra-hepatic outcomes. *Metab Clin Exp*. 2025;170:156306. doi:10.1016/j.metabol.2025.156306

32. Petta S, Armandi A, Bugianesi E. Impact of PNPLA3 I148M on clinical outcomes in patients with MASLD. *Liver Int*. 2025;45(3):e16133. doi:10.1111/liv.16133

33. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002;346(16):1221-1231. doi:10.1056/NEJMra011775

34. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA*. 2015;313(22):2263-2273. doi:10.1001/jama.2015.5370

35. Lonardo A, Nascimbeni F, Targher G, et al; Italian Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. *Dig Liver Dis*. 2017;49(5):471-483. doi:10.1016/j.dld.2017.01.147

36. Byrne CD, Patel J, Scorletti E, Targher G. Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. *BMJ*. 2018;362:k2734. doi:10.1136/bmj.k2734

37. Anstee QM, Castera L, Loomba R. Impact of non-invasive biomarkers on hepatology practice: past, present and future. *J Hepatol*. 2022;76(6):1362-1378. doi:10.1016/j.jhep.2022.03.026

38. Tamaki N, Ajmera V, Loomba R. Non-invasive methods for imaging hepatic steatosis and their clinical importance in NAFLD. *Nat Rev Endocrinol*. 2022;18(1):55-66. doi:10.1038/s41574-021-00584-0

39. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. *Hepatology*. 2011;54(3):1082-1090. doi:10.1002/hep.24452

40. Zhang YX, Feng YP, You CL, Zhang LY. The diagnostic value of MRI-PDFF in hepatic steatosis of patients with metabolic dysfunction–associated steatotic liver disease: a systematic review and meta-analysis. *BMC Gastroenterol*. 2025;25(1):451. doi:10.1186/s12876-025-04017-4

41. Filingeri V, Francioso S, Sforza D, Santopaolo F, Oddi FM, Tisone G. A retrospective analysis of 1.011 percutaneous liver biopsies performed in patients with liver transplantation or liver disease: ultrasonography can reduce complications? *Eur Rev Med Pharmacol Sci*. 2016;20(17):3609-3617.

42. Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut*. 2020;69(8):1382-1403. doi:10.1136/gutjnl-2020-321299

43. Younossi ZM, Felix S, Jeffers T, et al. Performance of the enhanced liver fibrosis test to estimate advanced fibrosis among patients with nonalcoholic fatty liver disease. *JAMA Netw Open*. 2021;4(9):e2123923. doi:10.1001/jamanetworkopen.2021.23923

44. Dalbeni A, Lombardi R, Henrique M, et al. Diagnostic accuracy of AGILE 3+ score for advanced fibrosis in patients with NAFLD: a systematic review and meta-analysis. *Hepatology*. 2024;79(5):1107-1116. doi:10.1097/HEP.0000000000000694

45. Sanyal AJ, Foucquier J, Younossi ZM, et al. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. *J Hepatol*. 2023;78(2):247-259. doi:10.1016/j.jhep.2022.10.034

46. Lin H, Lee HW, Yip TCF, et al; VCTE-Prognosis Study Group. Vibration-controlled transient elastography scores to predict liver-related events in steatotic liver disease. *JAMA*. 2024;331(15):1287-1297. doi:10.1001/jama.2024.1447

47. Tincopa MA, Loomba R. Non-invasive diagnosis and monitoring of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Lancet Gastroenterol Hepatol*. 2023;8(7):660-670. doi:10.1016/S2468-1253(23)00066-3

48. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(5):1264-1281.e4. doi:10.1053/j.gastro.2018.12.036

49. Ajmera V, Loomba R. Imaging biomarkers of NAFLD, NASH, and fibrosis. *Mol Metab*. 2021;50:101167. doi:10.1016/j.molmet.2021.101167

50. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction–associated steatotic liver disease (MASLD). *J Hepatol*. 2024;81(3):492-542. doi:10.1016/j.jhep.2024.04.031

51. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797-1835. doi:10.1097/HEP.0000000000000323

52. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2021;161(5):1657-1669. doi:10.1053/j.gastro.2021.07.049

53. Ajmera V, Tesfai K, Sandoval E, et al. Validation of AGA clinical care pathway and AASLD practice guidance for nonalcoholic fatty liver disease in a prospective cohort of patients with type 2 diabetes. *Hepatology*. 2024;79(5):1098-1106. doi:10.1097/HEP.0000000000000635

54. Cusi K, Abdelmalek MF, Apovian CM, et al. Metabolic dysfunction–associated steatotic liver disease (MASLD) in people with diabetes: the need for screening and early intervention: a consensus report of the American Diabetes Association. *Diabetes Care*. 2025;48(7):1057-1082. doi:10.2337/dci24-0094

55. Leung PB, Davis AM, Kumar S. Diagnosis and management of nonalcoholic fatty liver disease. *JAMA*. 2023;330(17):1687-1688. doi:10.1001/jama.2023.17935

56. Le P, Payne JY, Zhang L, et al. Disease state transition probabilities across the spectrum of NAFLD: a systematic review and meta-analysis of paired biopsy or imaging studies. *Clin Gastroenterol Hepatol*. 2023;21(5):1154-1168. doi:10.1016/j.cgh.2022.07.033

57. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13(4):643-654.e1. doi:10.1016/j.cgh.2014.04.014

58. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology*. 2019;70(6):1913-1927. doi:10.1002/hep.30664

59. Pennisi G, Di Maria G, Enea M, et al. A Markov model unveiling the impact of resmetirom on the natural history of masld patients: a systematic review and meta-analysis. *Liver Int*. 2025;45(4):e70056. doi:10.1111/liv.70056

60. Sanyal AJ, Anstee QM, Trauner M, et al. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology*. 2022;75(5):1235-1246. doi:10.1002/hep.32204

61. Gries JJ, Lazarus JV, Brennan PN, et al. Interdisciplinary perspectives on the co-management of metabolic dysfunction–associated steatotic liver disease and coronary artery disease. *Lancet Gastroenterol Hepatol*. 2025;10(1):82-94. doi:10.1016/S2468-1253(24)00310-8

62. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367-378.e5. doi:10.1053/j.gastro.2015.04.005

63. Ahn J, Jun DW, Lee HY, Moon JH. Critical appraisal for low-carbohydrate diet in nonalcoholic fatty liver disease: review and meta-analyses. *Clin Nutr*. 2019;38(5):2023-2030. doi:10.1016/j.clnu.2018.09.022

64. Holmer M, Lindqvist C, Petersson S, et al. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet: a randomised controlled trial. *JHEP Rep*. 2021;3(3):100256. doi:10.1016/j.jhepr.2021.100256

65. Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs resistance exercise in non-alcoholic fatty liver disease: a systematic review. *J Hepatol*. 2017;66(1):142-152. doi:10.1016/j.jhep.2016.08.023

66. Harrison SA, Bedossa P, Guy CD, et al; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med*. 2024;390(6):497-509. doi:10.1056/NEJMoa2309000

67. Sanyal AJ, Newsome PN, Kliers I, et al; ESSENCE Study Group. Phase 3 trial of semaglutide in metabolic dysfunction–associated steatohepatitis. *N Engl J Med*. 2025;392(21):2089-2099. doi:10.1056/NEJMoa2413258

68. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of

fibrosis. *Gastroenterology*. 2020;159(4):1290-1301.e5. doi:10.1053/j.gastro.2020.06.006

69. Aminian A, Al-Kurd A, Wilson R, Bena J, Fayazzadeh H, Singh T, et al. Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. *JAMA*. 2021;326(20):2031-2042. doi:10.1001/jama.2021.19569

70. Hwang J, Hwang H, Shin H, et al. Bariatric intervention improves metabolic dysfunction–associated steatohepatitis in patients with obesity: a systematic review and meta-analysis. *Clin Mol Hepatol*. 2024;30(3):561-576. doi:10.3350/cmh.2023.0384

71. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology*. 2020;158(6):1611-1625.e12. doi:10.1053/j.gastro.2020.01.043

72. Pennisi G, Enea M, Romero-Gomez M, et al. Liver-related and extrahepatic events in patients with non-alcoholic fatty liver disease: a retrospective competing risks analysis. *Aliment Pharmacol Ther*. 2022;55(5):604-615. doi:10.1111/apt.16763

73. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. *Gut*. 2021;70(7):1375-1382. doi:10.1136/gutjnl-2020-322786

74. Feng Q, Izzi-Engbeaya CN, Beaney T, Smith AG, Manousou P, Woodward M. Extrahepatic disease clusters and mortality in people with steatotic liver diseases: a prospective analysis of 64,749 females and 113,587 males in the UK Biobank. *BMC Med*. 2025;23(1):450. doi:10.1186/s12916-025-04288-4

75. Park J, Chung GE, Yu SJ, et al. All-cause and disease-specific mortality in young adults with MASLD: a nationwide cohort study. *JHEP Rep*. 2025;7(9):101477. doi:10.1016/j.jhepr.2025.101477

76. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6(11):903-913. doi:10.1016/S2468-1253(21)00308-3

77. Mantovani A, Petracca G, Csermely A, et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. *Gut*. 2022;72(2):372-380. doi:10.1136/gutjnl-2022-327672

78. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. *Gut*. 2022;71(1):156-162. doi:10.1136/gutjnl-2020-323082

79. Mantovani A, Morandin R, Sani E, et al. MASLD is associated with an increased long-term risk of atrial fibrillation: an updated systematic review and meta-analysis. *Liver Int*. 2025;45(1):e16128. doi:10.1111/liv.16218

80. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut*. 2021;70(5):962-969. doi:10.1136/gutjnl-2020-322572

81. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. *Gut*. 2022;71(4):778-788. doi:10.1136/gutjnl-2021-324191

82. Loomba R, Hartman ML, Lawitz EJ, et al; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med*. 2024;391(4):299-310. doi:10.1056/NEJMoa2401943

83. Sanyal AJ, Bedossa P, Fraessdorf M, et al; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med*. 2024;391(4):311-319. doi:10.1056/NEJMoa2401755

84. Romero-Gómez M, Lawitz E, Shankar RR, et al; MK-6024 P001 Study Group. A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2023;79(4):888-897. doi:10.1016/j.jhep.2023.05.013

85. Harrison SA, Browne SK, Suschak JJ, et al. Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: a randomized, double-blind, placebo-controlled study. *J Hepatol*. 2025;82(1):7-17. doi:10.1016/j.jhep.2024.07.006

86. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction–associated steatotic liver disease: a randomized phase 2a trial. *Nat Med*. 2024;30(7):2037-2048. doi:10.1038/s41591-024-03018-2

87. Lin J, Huang Y, Xu B, et al. Effect of dapagliflozin on metabolic dysfunction–associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. *BMJ*. 2025;389:e083735. doi:10.1136/bmj-2024-083735

88. Francque SM, Bedossa P, Ratziu V, et al; NATIVE Study Group. A randomized, controlled trial of the Pan-PPAR agonist lanifibranor in NASH. *N Engl J Med*. 2021;385(17):1547-1558. doi:10.1056/NEJMoa2036205

89. Harrison SA, Frias JP, Neff G, et al; HARMONY Study Group. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1080-1093. doi:10.1016/S2468-1253(23)00272-8

90. Noureddin M, Rinella ME, Chalasani NP, et al. Efruxifermin in compensated liver cirrhosis caused by MASH. *N Engl J Med*. 2025;392(24):2413-2424. doi:10.1056/NEJMoa2502242

91. Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *N Engl J Med*. 2023;389(11):998-1008. doi:10.1056/NEJMoa2304286

92. Fabbrini E, Rady B, Koshkina A, et al. Phase 1 trials of PNPLA3 siRNA in I148M homozygous patients with MAFLD. *N Engl J Med*. 2024;391(5):475-476. doi:10.1056/NEJMc2402341

93. Tilg H, Byrne CD, Targher G. NASH drug treatment development: challenges and lessons. *Lancet Gastroenterol Hepatol*. 2023;8(10):943-954. doi:10.1016/S2468-1253(23)00159-0

94. Targher G, Mantovani A, Byrne CD, Tilg H. Recent advances in incretin-based therapy for MASLD: from single to dual or triple incretin receptor agonists. *Gut*. 2024;74(3):487-497. doi:10.1136/gutjnl-2024-334023

95. Feng G, Wong VWS, Targher G, Byrne CD, Zheng MH. Non-invasive tests of fibrosis in the management of MASLD: revolutionising diagnosis, progression and regression monitoring. *Gut*. 2025;74(10):1741-1750. doi:10.1136/gutjnl-2025-335542

96. Raverdy V, Tavaglione F, Chatelain E, et al. Data-driven cluster analysis identifies distinct types of metabolic dysfunction–associated steatotic liver disease. *Nat Med*. 2024;30(12):3624-3633. doi:10.1038/s41591-024-03283-1

97. Jamialahmadi O, De Vincentis A, Tavaglione F, et al. Partitioned polygenic risk scores identify distinct types of metabolic dysfunction–associated steatotic liver disease. *Nat Med*. 2024;30(12):3614-3623. doi:10.1038/s41591-024-03284-0

98. Sanyal AJ, Williams SA, Lavine JE, et al. Defining the serum proteomic signature of hepatic steatosis, inflammation, ballooning and fibrosis in non-alcoholic fatty liver disease. *J Hepatol*. 2023;78(4):693-703. doi:10.1016/j.jhep.2022.11.029

99. Loomba R, Seguritan V, Li W, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. *Cell Metab*. 2017;25(5):1054-1062.e5. doi:10.1016/j.cmet.2017.04.001