

Management Strategies for Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)

HIGHLIGHTS

- › Pathophysiology and Natural History of MASLD and Metabolic Dysfunction–Associated Steatohepatitis (MASH)
- › The Central Role of Noninvasive Tests
- › New and Developmental Treatments

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Management Strategies for Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] provides managed care audiences with an overview of metabolic dysfunction–associated steatotic liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH), emphasizing the importance of early diagnosis using noninvasive tests, rising prevalence, associated comorbidities, and potential management strategies in at-risk patients.

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Management Strategies for Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)

Naim Alkhoury, MD, FAASLD; and Mazen Nouredin, MD, MHSc

A Note on Nomenclature of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

The naming convention of *nonalcoholic steatohepatitis (NASH)* was first established in 1980¹; since then, several alternative names for NASH have been proposed. From 2020 to 2022, a comprehensive and inclusive Delphi consensus process led to the adoption of new steatotic liver disease nomenclature. Thus, the terms *metabolic dysfunction–associated steatotic liver disease (MASLD)* and *metabolic dysfunction–associated steatohepatitis (MASH)* are now used.² Subsequent analyses have demonstrated that patients described with the new nomenclature are relatively indistinguishable from those classified using the former *nonalcoholic fatty liver disease (NAFLD)* nomenclature.^{2–4} Thus, the findings of studies reported over 3 decades that describe patient characteristics, treatment, and outcomes for NAFLD still apply when using the MASLD nomenclature. For these reasons, in this review, the terms MASLD and MASH will be used.

Background

MASLD is characterized by hepatic steatosis that is confirmed by imaging or histology in the setting of at least 1 metabolic risk factor in the absence of significant alcohol consumption (**Figure 1**).^{5–11} Disease severity within MASLD covers a spectrum from MASL with little or no inflammation or hepatocyte injury to MASH, at-risk MASH (defined as MASH with significant fibrosis), or MASH cirrhosis.^{5–11} MASH represents the progressive form of MASLD; it is defined by hepatic steatosis, lobular inflammation, and ballooning degeneration (hepatocellular injury) in a characteristic histologic pattern.^{5–11}

A formal diagnosis of MASH can only be confirmed through liver biopsy.^{5,7,12} However, this procedure is less commonly used in real-world clinical practice due to its invasive nature, procedure-related limitations, and potential for serious complications.^{13–20} As such, the diagnosis of suspected MASH in most patients is based upon clinical, laboratory, and imaging data that are collectively referred to as results of noninvasive tests (NITs) with appropriate exclusion of other liver conditions.²¹ Risk stratification among patients with MASH can be performed noninvasively according to

ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) is characterized by hepatic steatosis that is confirmed by imaging or histology in the setting of at least 1 metabolic risk factor in the absence of significant alcohol consumption. Nonalcoholic steatohepatitis, or NASH, was recently renamed metabolic dysfunction–associated steatohepatitis (MASH); it represents the progressive form of MASLD. MASH is defined by hepatic steatosis, lobular inflammation, and ballooning degeneration (hepatocellular injury) in a characteristic histologic pattern. Multiple pathophysiologic mechanisms underlie the development of MASLD, and multiple factors (eg, metabolic, hormonal, genetic, nutritional, and epigenetic components) are related to liver injury. MASH has a prevalence in the United States of 1% to 6%, and it is expected to rise in the next decade. Individuals living with MASH frequently suffer from comorbidities such as type 2 diabetes and cardiovascular disease. Several guidelines have been published to support the timely diagnosis of MASH that incorporate noninvasive tests that obviate the need for liver biopsy. Multiple MASH treatment options are in various stages of development. The THR- β agonist resmetirom, approved by FDA in March 2024, offers a liver-directed treatment for those patients living with moderate to severe fibrosis without cirrhosis. Considering the progressive nature of the disease and the availability of a treatment that can be initiated early to halt MASH progression, patients who have risk factors for MASH should urgently be encouraged to visit their health care providers for MASH screening.

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For author information and disclosures, see end of text.

patient characteristics such as the number of metabolic risk factors (eg, obesity, type 2 diabetes [T2D], hypertension, and dyslipidemia), age, platelet count, the results of various proprietary tests, and the output of algorithms.

Epidemiology of MASLD and MASH

MASLD is the most common chronic liver disease in the United States, affecting an estimated 31% of the nation’s adult population.²² The precise epidemiology of MASH—particularly the population of patients with clinically significant liver fibrosis (fibrosis stage 2/3 [F2/3])—is difficult to determine due to uncertainty in risk stratification, differences in diagnostic methods used to identify the condition (ie, liver biopsy or imaging- or biomarker-based NITs), and disparities in the definition of the disease.^{23,24}

Harrison and colleagues prospectively assessed the prevalence and severity of MASLD and MASH among 664 asymptomatic middle-aged Americans.²⁵ Patients were evaluated using results of NITs and liver biopsies to obtain point estimates of the prevalence and severity of MASLD/MASH. The prevalence of MASLD was 38% (95% CI, 34%-41%), and the prevalence of MASH was 14% (95% CI, 12%-17%). No patient had cirrhosis on biopsy; however, significant fibrosis (\geq F2) was present in 5.9% (95% CI, 4%-8%) of patients, and bridging fibrosis (F3) was revealed in 1.6% (95% CI, 1%-3%).²⁵

However, the estimated prevalence of MASH in the United States (1%-6%) is projected to increase substantially over the next decade.²⁶⁻³³

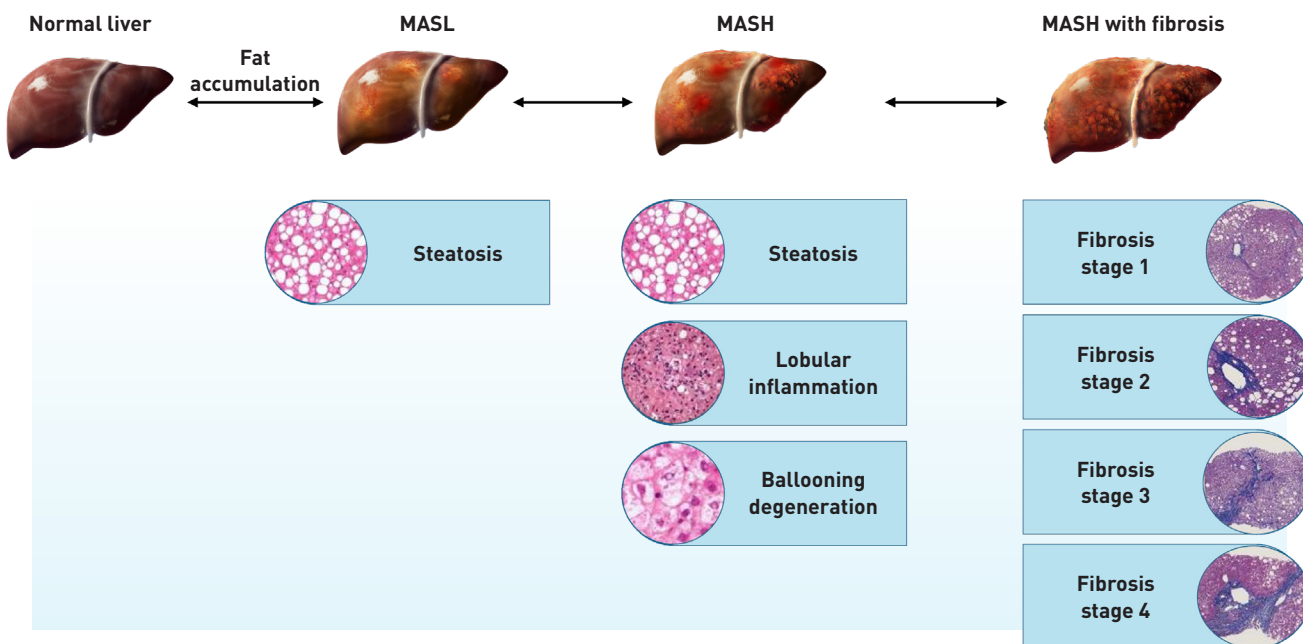
MASH is more common in patients with T2D or metabolic syndrome. There may be an 18-fold higher risk of MASH among people with diabetes.²⁹ For people living with obesity, the global prevalence of MASLD is 70% to 80% and rises to 90% for those living with morbid obesity. Of the 18.2 million people living in the United States with T2D and MASLD, 6.4 million individuals have MASH.³⁰

Men may be slightly more likely to develop MASH than are women; however, women experience a late peak in MASH diagnosis postmenopause.³² Both MASLD and MASH are more common among Hispanic individuals than among those belonging to other ethnic groups; MASLD is diagnosed in 58% of Hispanic patients and 45% of White patients, and MASH is diagnosed in 19% and 10% of patients in these groups, respectively.³¹ The presence of the *PNPLA3*G* allele may contribute to the higher prevalence of advanced MASLD among Hispanic individuals.³²

Pathophysiology and Natural History of MASLD and MASH

Multiple pathophysiologic mechanisms underlie the development of MASLD with multiple factors (eg, metabolic, hormonal, genetic, nutritional, and epigenetic components) related to liver injury.^{6,12,34}

FIGURE 1. MASLD Progression⁵⁻¹¹



MASH, metabolic dysfunction-associated steatohepatitis; MASL, metabolic dysfunction-associated steatotic liver; MASLD, metabolic dysfunction-associated steatotic liver disease.

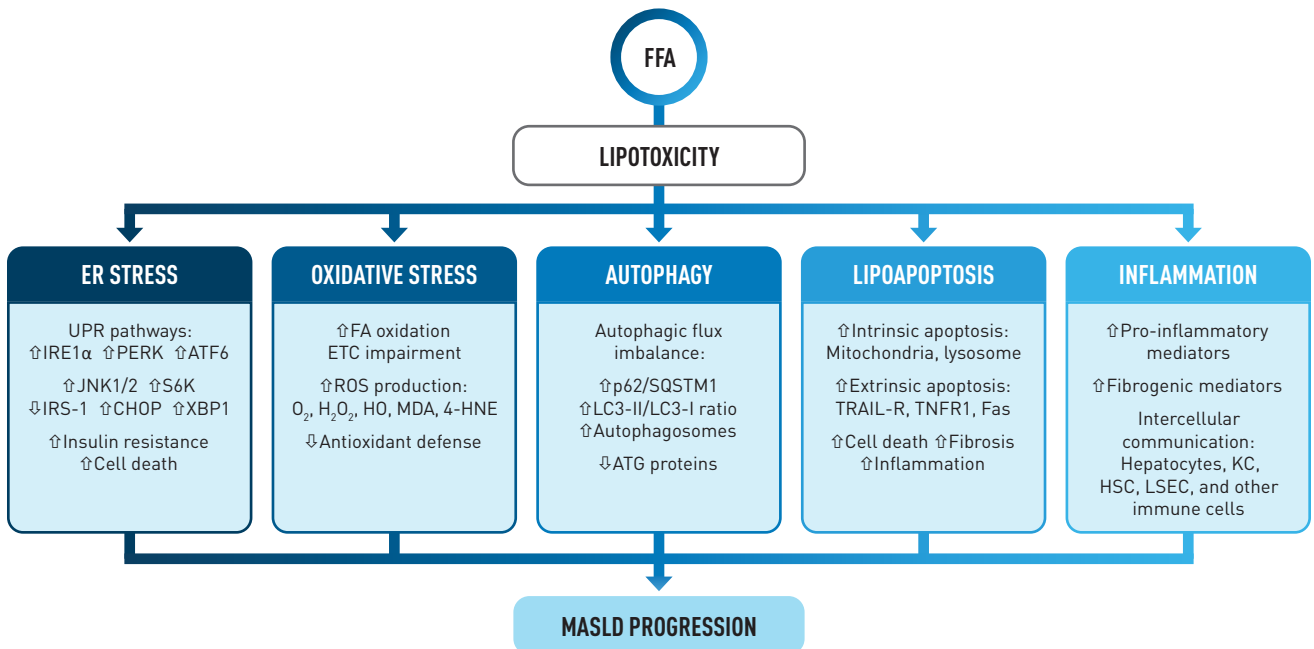
Hepatic fatty acid exposure and systemic insulin resistance resulting from dietary, genetic, and metabolic factors lead to hepatocyte lipotoxic injury and stress, which may contribute to mitochondrial dysfunction in MASLD.^{6,35} Impaired thyroid hormone signaling in hepatocytes worsens hepatic lipotoxicity and drives progression of MASLD to MASH with liver fibrosis.³⁶ Mitochondrial dysfunction in the liver leads to the generation of reactive oxygen species and hepatocellular oxidative injury, which contribute to necroptosis and downstream inflammation.^{6,35} Adipocytes release nonesterified fatty acids as a result of impaired insulin responsiveness, leading to lipid accumulation in the liver. In MASLD, de novo lipogenesis is also increased, contributing to the oversupply of free fatty acids in hepatocytes. Together, the increased supply of exogenous and endogenous free fatty acids leads to lipotoxic stress.

Fatty acids can be eliminated by the formation of triglyceride and its export into the blood as very low-density lipoprotein or by mitochondrial β -oxidation. Thyroid hormone is a regulator of mitochondrial biogenesis and oxidative capacity; however, in the setting of MASLD, conversion of thyroxine (the inactive form of thyroid hormone) to triiodothyronine (T_3) (the active form) is inadequate, and the MASLD liver is in a state of relative hypothyroidism. This can be counteracted by drugs that activate the thyroid hormone receptor (THR). The predominant THR in the liver is the

β isoform; THR- β agonism results in an increase in fat metabolism through mitochondrial β -oxidation, a reduction in fatty acids and other lipotoxic lipids such as ceramides, and an increase in cholesterol clearance.

There is an increase in inflammatory cytokines and an accumulation of hepatic triglycerides as dysfunctional adipose tissue causes the release of nonesterified fatty acids.³⁶ This perpetuates a cycle of oxidative stress, further inflammation, and eventual fibrogenesis.⁶ Endoplasmic reticulum (ER) stress is also a component of lipotoxic liver injury.³⁵ Stress in the ER brings on changes in signaling to a repair response to reestablish homeostasis; however, prolonged ER stress reduces the ability of hepatocytes to restore homeostasis.³⁵ Eventually, prolonged ER stress leads hepatocytes to undergo apoptosis and begins the wound-healing signaling cascade that is hallmarked by inflammation, vascular remodeling, fibrogenesis, and sequestering of immature hepatocytes.²⁷ Kupffer cell cytokine production also contributes to the development of fibrosis in the liver, playing a central role in activating stellate cells to initiate and perpetuate fibrogenesis.³⁷ Further, some individuals may be prone to the development of MASH due to genetic abnormalities, and they may not present with obesity and insulin resistance.^{6,37} The metabolic factors contributing to the progression of MASLD to MASH are described in **Figure 2**.^{6,12,34-36}

FIGURE 2. Metabolic Factors Contributing to Progression of MASLD^{6,12,34-36}



ER, endoplasmic reticulum; ETC, electron transport chain; FA, fatty acid; FFA, free fatty acid; H_2O , water; H_2O_2 , hydrogen peroxide; HO, hydroxyl radical; HSC, hepatic stellate cell; KC, Kupffer cell; LSEC, liver sinusoidal endothelial cell; MASLD, metabolic dysfunction-associated steatotic liver disease; MDA, malondialdehyde; ROS, reactive oxygen species; UPR, unfolded protein response.

Clinical Presentation and Diagnosis

MASLD represents a spectrum of liver diseases characterized by hepatic steatosis in the setting of at least 1 metabolic risk factor.^{5,6} Current guidelines from Europe, Japan, and the US define MASLD as the presence of hepatic steatosis (> 5% of hepatocytes show evidence of steatosis) confirmed by imaging or histology in the absence of significant alcohol consumption.⁵⁻¹¹ Diagnosis of MASLD requires that excessive alcohol consumption is ruled out as a contributor of fibrosis.⁵ Levels of alcohol consumption considered to be excessive in this context are less than 30 g/d for men or less than 20 g/d for women.²³

MASH is a hepatic disease, yet patients with MASLD/MASH typically present with obesity as defined by excessive body mass index (BMI) and/or other components of the metabolic syndrome.¹² On assessing patients at risk, care providers should also look for physical indicators of advanced liver disease including hepatomegaly or splenomegaly (enlarged liver or spleen, respectively), ascites, muscle loss, or signs of insulin resistance such as acanthosis nigricans (ie, darkening of skin in folds and creases).^{5,12} Routine screening for MASLD based on the presence of metabolic factors or T2D is currently recommended by the World Gastroenterology Organisation (WGO); Italian, Japanese, United Kingdom, and European guidelines; and recommendations by the American Association of Clinical Endocrinology (AACE), American Association for the Study of Liver Diseases (AASLD), and the American Gastroenterological Association (AGA) (Table 1).^{7,8,23,24,38}

The Central Role of Noninvasive Tests

Liver biopsy is the classic tool used in the diagnosis of MASLD/MASH, although it has limited practicality in routine clinical care due to its invasive nature, associated risks, and reader variability.³⁹ Accordingly, the current guidance extensively incorporates the use of NITs as markers for identification, determination of severity, monitoring, and establishment of prognosis of patients with MASLD/MASH (Table 2).^{7,24,38,40-56}

NITs include testing of blood-based biomarkers (the liver enzymes aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ -glutamyl transferase [GGT]).⁵⁷ In addition, the enhanced liver fibrosis (ELF) test (Siemens Healthineers USA) is a proprietary blood test to assess liver fibrosis using measures of hyaluronic acid, P3NP, and TIMP-1.⁵⁸ The ELF test has approval in the US for prognostic use; it has received FDA breakthrough device designation for diagnostic use,⁵⁸ and it has high sensitivity and specificity for detecting clinically advanced liver fibrosis and good prognostic value in predicting liver-related events and mortality in patients with chronic liver disease.

Other tests in development and not yet available in the clinic include the ProC3 test, which is an enzyme-linked immunosorbent assay (ELISA) that measures the cleavage of propeptide collagen

fragments released during active fibrogenesis.⁵⁹ In addition, the NIS2+ (GENFIT) test uses 2 biomarkers (miR-34a-5p and YKL-40); it has been used more extensively in conjunction with clinical trials of MASH treatments.⁶⁰ Further, the FIB-4 score is a relatively inexpensive, easy to use, and validated tool that employs age, platelet counts, and ALT and AST measurements as parameters to identify patients with advanced fibrosis; it is featured in European Association for the Study of the Liver (EASL), AACE, AASLD, and AGA guidelines/guidance for the diagnosis of NASH/MASH because of its ease of calculation and minimal cost.^{7,8,23,24} Its limitations include diagnostic cutoff ranges that may not be reliable in relevant populations (eg, patients with T2D),⁶¹ lack of accuracy in both younger (age, < 35 years) and elderly patients,⁴⁰ and limited data for monitoring disease evolution and treatment response. It also depends upon variations in liver enzymes that may be attributable to other causes.

The most common imaging method for identifying patients with hepatic steatosis is conventional ultrasound, which is widely available, inexpensive, and well established. It has inherent limitations including poor sensitivity, overestimation of steatosis (especially in patients with obesity), imprecision in quantifying steatosis, and high operator variability and reproducibility.^{7,62,63} Because of these limitations, routine ultrasound examination is not part of the current diagnostic algorithms for patients with suspected MASLD.

FibroScan (Echosens) is a noninvasive elastography test that uses vibration-controlled transient elastography (VCTE) for liver stiffness measurement (LSM) as a surrogate for fibrosis and controlled attenuation parameter (CAP) to assess hepatic steatosis.⁶⁴ Other ultrasound-based technologies for assessing liver stiffness and fibrosis staging include visual transient elastography, sound touch elastography, and sound touch quantification. The LSM performs similarly to biopsy in predicting liver-related events.⁶⁵

After the FIB-4 screen, elastography is the preferred imaging method; it may be used alone or in conjunction with blood tests for increased diagnostic specificity.⁶⁶ Drawbacks include decreased accuracy in severely obese individuals, limited insurance coverage and data for monitoring patients with MASLD, and the lack of discrete cutoffs for individual fibrosis stages. Magnetic resonance elastography (MRE) uses MRI and a low-frequency mechanical vibrating pad to assess liver stiffness as an indirect measure of fibrosis.^{41,67} LSM by MRE may be used alone or in combination with blood tests for increased diagnostic specificity.^{42,43}

MRE is considered the most accurate measure of LSM in MASLD.⁴⁴ Current guidelines recommend considering MRE when LSM by VCTE/FibroScan and FIB-4 are indeterminate due to relatively higher cost and lower availability as compared with those of ultrasound-based technologies. Currently, there are at least 650 machines in the US, and 1200 machines are expected to be available by the end of 2024.

(CONTINUED ON PAGE S166)

TABLE 1. Summary of Guidelines and Guidances for the Diagnosis of MASLD/MASH^{7,8,23,24,38}

	WGO (2014) ⁸	AGA (2021) ²⁴	AACE (2022) ³⁸	AASLD (2023) ²³	EASL-EASD-EASO (2024) ⁷
MASLD definition	Fat accumulation in the liver exceeding 5% of its weight	N/A	<ul style="list-style-type: none"> Hepatic steatosis in >5% of hepatocytes in the absence of significant ongoing or recent alcohol consumption and other known causes of liver disease (MASLD) ≥5% hepatic steatosis with inflammation and hepatocyte injury (ballooning), with or without fibrosis (MASH) 	<ul style="list-style-type: none"> ≥ 5% of hepatocytes display macrovesicular steatosis in the absence of a readily identified alternative cause of steatosis (eg, medications, starvation, monogenic disorders) in people who drink little or no alcohol Macrovesicular hepatic steatosis may be accompanied by: <ul style="list-style-type: none"> » mild inflammation (NAFL); » presence of inflammation and cellular injury (ballooning), with or without fibrosis (MASH); and/or » bands of fibrous septa leading to the formation of cirrhotic nodules (cirrhosis). 	Steatosis in >5% of hepatocytes, or CAP ≥248 dB/m
Alcohol threshold value	Women, < 20 g/d; men, <30 g/d	Women, < 14 drinks/wk; men, <21 drinks/wk	Previous 2 y: Women, <196 g/wk; men, <294 g/wk	Women, < 20 g/d; men, <30 g/d	Women, < 20 g/d; men, <30 g/d
High-risk comorbidities	<ul style="list-style-type: none"> Central obesity T2D Dyslipidemia MetS Altered liver enzyme levels Fatty liver on ultrasound 	<ul style="list-style-type: none"> T2D Hypertension Hypertriglyceridemia Reduced serum HDL-C level Central obesity Raised fasting plasma glucose 	<ul style="list-style-type: none"> Obesity Insulin resistance T2D Dyslipidemia Hypertension MetS 	<ul style="list-style-type: none"> Obesity T2D Hypertension Dyslipidemia Obstructive sleep apnea CVD CKD Hypothyroidism Hypogonadism Growth hormone deficiency Polycystic ovarian syndrome 	<ul style="list-style-type: none"> T2D Obesity and ≥1 additional metabolic risk factor Consistently elevated liver enzymes
High-risk patient screening recommended	Yes	Yes	Yes	Yes	Yes
Screening methods	<ul style="list-style-type: none"> Ultrasound Liver enzyme tests 	<ul style="list-style-type: none"> FIB-4 Liver function tests Blood count Ultrasound (not in patients with high pretest MASLD probability) 	<ul style="list-style-type: none"> FIB-4 VCTE SWE MRE 	<ul style="list-style-type: none"> FIB-4 VTE ELF 	Screen for MASLD with liver fibrosis in individuals with ≥1 risk factors or in case of incidental finding of steatosis

(continued)

TABLE 1. (Continued) Summary of Guidelines and Guidances for the Diagnosis of MASLD/MASH^{7,8,23,24,38}

	WGO (2014) ⁸	AGA (2021) ²⁴	AACE (2022) ³⁸	AASLD (2023) ²³	EASL-EASD-EASO (2024) ⁷
Diagnosis of MASLD	<ul style="list-style-type: none"> Assess liver and pancreatic function. Test for hepatic viruses, and assess eventual MetS. If risk factors are present, evaluate for liver disease; if not, treat MetS and follow up in 6 mo. 	<ul style="list-style-type: none"> Carry out history and laboratory tests if individual has ≥ 2 metabolic risk factors, T2D, or steatosis on any imaging modality or elevated aminotransferase levels. If test results indicate MASLD without excessive alcohol intake history and no presence of other forms of liver disease, use FIB-4 to test for fibrosis. Stratify patients into low, indeterminate, and high risk of advanced fibrosis based on FIB-4 and/or LSM. 	<ul style="list-style-type: none"> Use FIB-4 to assess risk of MASLD with fibrosis. Order LSM (by TE) or ELF test for high-risk patients with indeterminate (1.3-2.67) or high (>2.67) FIB-4. Use VCTE, SWE, or MRE to stage risk of fibrosis. 	<ul style="list-style-type: none"> Assess patients for hepatic steatosis if they have metabolic risk factors for MASLD or are identified as having fatty liver by imaging in the absence of other hepatic steatosis etiologies using FIB-4. <ul style="list-style-type: none"> If FIB-4 <1.3, patients are unlikely to have fibrosis; they can be managed in primary care. If FIB-4 is 1.3-2.67, use VCTE or ELF as secondary risk assessment. If FIB-4 >2.67, consider referral to GE/hepatology care. 	<p>Screen for MASLD with liver fibrosis in individuals with ≥ 1 risk factors or in case of incidental finding of steatosis</p>
Diagnosis of MASH	<ul style="list-style-type: none"> If there are signs of cirrhosis or liver enzyme alterations after 6 months of observation and MetS treatment, consider liver biopsy. 	<ul style="list-style-type: none"> Low risk of advanced fibrosis: FIB-4, <1.3; LSM, <8.0 kPa by TE; or liver biopsy fibrosis stage F0-F1 Indeterminate risk of advanced fibrosis: FIB-4, 1.3-2.67; and/or LSM, 8.0-12.0 kPa on TE; and patients who are unable or unwilling to obtain a liver biopsy High risk of advanced fibrosis: FIB-4, >2.67; LSM, >12.0 kPa by TE; or liver biopsy shows clinically significant liver fibrosis 	<ul style="list-style-type: none"> Consider liver biopsy if: <ul style="list-style-type: none"> FIB-4, 1.3-2.67; or LSM, 8-12 kPa; or ELF, 7.7-9.8; and/or <ul style="list-style-type: none"> FIB-4, >2.67; LSM, >12 kPa; or ELF, >9.8; and/or ALT or AST levels are persistently elevated. 	<ul style="list-style-type: none"> Patients with FIB-4 of 1.3-2.67 referred to GE/hepatology care following secondary risk assessment, or FIB-4, >2.67: <ul style="list-style-type: none"> Consider additional stratification with MRE/corrected T1. Consider liver biopsy if indeterminate imaging or biomarker tests, diagnostic uncertainty, and/or persistently high ALT and AST are noted. 	<ul style="list-style-type: none"> A stepwise approach using blood-based scores and imaging techniques is suitable to identify advanced fibrosis Patients with FIB-4 ≥ 2.67 referred to hepatology. Patients with FIB-4 of 1.3-2.67: VCTE (or alternative test [eg, MRE, SWE, ELF, with adapted thresholds]) recommended; VCTE ≥ 8.0 kPa referral to hepatology; VCTE <8.0 kPa intensified management of comorbidities and reassess FIB-4 at ≤ 1 year; FIB-4 ≥ 1.3, VCTE (or alternative test [eg, MRE, SWE, ELF, with adapted thresholds]) recommended, if ≥ 8.0 kPa, refer to hepatology. If FIB-4 <1.3, reassess FIB-4 every 1-3 years.

(continued)

TABLE 1. (Continued) Summary of Guidelines and Guidances for the Diagnosis of MASLD/MASH^{7,8,23,24,38}

	WGO (2014) ⁸	AGA (2021) ²⁴	AACE (2022) ³⁸	AASLD (2023) ²³	EASL-EASD-EASO (2024) ⁷
Role of imaging	<ul style="list-style-type: none"> • Ultrasound as first line in the assessment of fatty liver, suspected MASLD • Abdominal CT can be performed if ultrasound is not informative. 	<ul style="list-style-type: none"> • Abdominal ultrasound is commonly used to diagnose hepatic steatosis with high accuracy for detecting moderate and severe steatosis, but it has suboptimal sensitivity for mild steatosis. • In patients with a high pretest probability of MASLD, moving directly to risk stratification is reasonable without an abdominal ultrasound to diagnose hepatic steatosis. • LSM as assessed by VCTE can be used depending on initial FIB-4. 	<ul style="list-style-type: none"> • H-MRS and MRI-PDFF are the most accurate and sensitive imaging techniques to diagnose hepatic steatosis, but their use is reserved for clinical trials. • Liver ultrasound is not recommended for diagnosis. • TE can be used to quantify liver fat (CAP) and fibrosis (VCTE). • MRE should be ordered primarily by specialists in selected persons to diagnose liver fibrosis, although it is expensive, and it does not replace liver biopsy for MASH diagnosis. 	<ul style="list-style-type: none"> • Identification of hepatic steatosis: ultrasound; FibroScan CAP; MRI-PDFF <ul style="list-style-type: none"> » MRI-PDFF is superior to CAP in the diagnosis and quantification of liver fat; this advantage is tempered by cost, patient acceptance, and the disadvantage of not being a point-of-care technique. • Detection of advanced fibrosis: VCT, ARFI, SWE, MRE (FIB-4 is preferred technique over imaging) • Diagnosis of cirrhosis: VCTE, MRE. MRE is more sensitive than is VCTE in the detection of fibrosis stage ≥ 2. 	VCTE: LSM; MRI-MRE; VCTE: CAP; MRI-PDFF
Role of biopsy	<ul style="list-style-type: none"> • Liver biopsy to rule out other diseases and to determine grade and stage of disease • Cannot reliably distinguish MASH from alcoholic steatohepatitis • Performed in every patient with suspected advanced liver disease who does not improve with lifestyle modification 	<ul style="list-style-type: none"> • Liver biopsy provides helpful information; it should be considered for cases in which there is diagnostic doubt (eg, in patients with indeterminate, unreliable, or conflicting noninvasive assessments; as part of phase 2 or 3 clinical trials) 	<ul style="list-style-type: none"> • Liver biopsy is considered the reference standard for MASH diagnosis. 	<ul style="list-style-type: none"> • Liver biopsy should be considered when there is diagnostic uncertainty (eg, discordant or indeterminate NIT results or persistently high ALT and AST level). 	None

AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis score; FIB-4, fibrosis-4 score; GE, gastroenterology; HDL-C, high-density lipoprotein cholesterol; H-MRS, proton magnetic resonance spectroscopy; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetS, metabolic syndrome; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; N/A, not available; NAFL, nonalcoholic fatty liver; NIT, noninvasive test; SWE, shear wave elastography; T2D, type 2 diabetes; TE, transient elastography; VCTE, vibration-controlled transient elastography; VTE, visual transient elastography; WGO, World Gastroenterology Organisation.

(CONTINUED FROM PAGE S162)

MRI-based proton density fat fraction (MRI-PDFF) is a test used to quantify hepatic steatosis more precisely than can FibroScan CAP; it is commonly used in therapeutic trials.⁴⁵ MRI-PDFF is highly sensitive.⁴⁶ It offers a precise quantification of steatosis by using proprietary software available on any MRI equipment, and it is considered the gold standard in the clinical-trial setting; a 30% decrease in liver fat measured by MRI-PDFF can predict histological improvement and MASH resolution.⁴⁷ MRI-PDFF is predominantly used in clinical trials; its role in clinical practice, however, is uncertain, largely because the amount of liver fat does not correlate well with disease severity and outcomes.

Finally, various instruments that combine blood and imaging tests are used at varying degrees in the clinic. These include the FibroScan-AST (FAST) score (Echosens),^{48,49} the MRI/AST (MAST) score,⁴³ and the MRE and FIB-4 (MEFIB) index.⁴²

There are many guidelines/guidances available, and each differs somewhat from the others in its recommendations regarding screening for and diagnosis of MASH—there is no single or specific noninvasive approach that is commonly used. Further, the approaches used to develop the guidelines/guidances and the purposes of these documents may differ. For example, the AASLD guidance focuses on advances in MASLD with respect to noninvasive risk stratification and therapeutics; it is not a formal guideline in that it was not developed using a standardized framework, so the document provides actionable statements as opposed to formal recommendations.²³ In contrast, the ACE guidance provides formal recommendations for the diagnosis and management of MASLD in endocrinology and primary care practices; it was developed using a standardized framework for practical evidence-based guidelines.³⁸ The AGA Clinical Care Pathway, developed by a multidisciplinary panel of experts, focuses on the screening, diagnosis, and treatment of MASLD; it is intended to facilitate value-based, efficient, and safe care that is consistent with evidence-based guidelines in any setting in which management of MASLD is provided.²⁴

Patients who have risk factors for MASH (eg, obesity, T2D, hyperlipidemia, hypertriglyceridemia, and hypertension) should be encouraged to visit their health care providers (HCPs) for a MASH screening.⁵⁰ MASH is usually discovered incidentally during clinical testing performed for unrelated health reasons.⁵⁰ Patients with MASH may be asymptomatic or have nonspecific symptoms with normal liver chemistries; however, in advanced cases, patients may feel pain or discomfort in their upper right abdomen and concomitant fatigue.^{50,51}

Signs and symptoms of the metabolic syndrome may serve as an indicator of MASH in the clinical setting as well; these include increases in abdominal obesity (waist circumference: men, > 40 inches; women, > 35 inches), triglyceride level (≥ 150 mg/dL), high-density lipoprotein cholesterol (HDL-C) level (men, < 45 mg/dL;

women, < 50 mg/dL), blood pressure measurement ($\geq 130/85$ mm Hg), and fasting glucose level (≥ 110 mg/dL).^{12,52}

In the real-world setting, a work-up for MASH may be conducted after abnormal laboratory results indicating liver injury (ie, AST, ALT, GGT) or incidental findings of hepatic steatosis on abdominal imaging are recorded; however, some patients with at-risk MASH may have normal liver enzyme levels.^{12,53}

Common Comorbidities Associated With MASH

MASH is more common in patients with obesity and with T2D, but it can also occur in the absence of obesity and diabetes. Conversely, MASH is not present in all people with obesity and T2D. However, frequent comorbidities among people with MASLD and MASH include T2D, obesity, hyperlipidemia, hypertriglyceridemia, hypertension, and metabolic syndrome (**Table 3**).²² The most prevalent comorbidity in people with MASLD is hyperlipidemia (elevated cholesterol and/or triglyceride level).²² The most prevalent comorbidity among people with MASH is hypertriglyceridemia.²² Components of the metabolic syndrome generally were more prevalent among people with MASH than among those with MASLD.²²

The presence of comorbidities including T2D, cardiovascular disease (CVD), and cirrhosis also increases the risk of death among patients with MASH.¹⁴ In an analysis of real-world outcomes among 28,576 patients with MASH in the US using Optum's Clinformatics Data Mart Database (October 2015 to December 2022), the risk of all-cause death was nearly 5 times higher among patients with cirrhosis (HR, 4.68; 95% CI, 4.29-5.12) than among those without cirrhosis after adjustment for several baseline characteristics and comorbidities.¹⁴ The adjusted risk of all-cause death is increased with male sex (HR, 1.20; 95% CI, 1.12-1.29) and baseline T2D (HR, 1.78; 95% CI, 1.65-1.92) or CVD (HR, 1.58; 95% CI, 1.40-1.78).¹⁴ Among patients without cirrhosis at baseline, 23.1% experienced a composite clinical outcome of all-cause death or a significant hepatic event (including cirrhosis, decompensation, or liver transplant) over follow-up (mean: patients without cirrhosis, 3.2 years; patients with cirrhosis, 2.5 years), and the risk of progressing to this outcome increased with baseline T2D (HR, 1.28; 95% CI, 1.20-1.37), CVD (HR, 1.28; 95% CI, 1.19-1.38), or obesity (HR, 1.07; 95% CI, 1.00-1.15).¹⁴

The leading cause of mortality in patients with MASH is CVD, independent of other metabolic comorbidities.⁶⁸ In an observational, longitudinal study conducted using National Health and Nutrition Examination Survey data (1988-1994) linked to National Death Index mortality outcomes (through 2019), the major drivers of mortality among patients with high-risk MASLD were CVD, cancer, and other-cause (likely liver-related) complications. Notably, the contribution of CVD increased with age.⁶⁹

CV complications including atherosclerotic CVD (ASCVD) may result from visceral adiposity, atherogenic dyslipidemia (low HDL-C level; elevated levels of triglycerides and small-dense low density

TABLE 2. Summary of NITS^{7,24,38,40-56}

Test	Type	Cutoffs	When used	Strengths	Limitations	Management following indeterminate results
ELF	Proprietary blood test to assess liver fibrosis through measurement of HA, P3NP, and TIMP-1	<ul style="list-style-type: none"> High-risk: ELF, > 9.8 Indeterminate-risk: ELF, 7.7-9.8 Low-risk: ELF, < 7.7 Rules out advanced fibrosis: ELF, < 9.8 	<ul style="list-style-type: none"> With other blood tests for screening patient prior to FibroScan In patients shown to have indeterminate risk on FIB-4 in cases where FibroScan is not available 	<ul style="list-style-type: none"> Better automaticity High reproducibility Proven diagnostic performance 	<ul style="list-style-type: none"> Discrepancy between cutoffs in guidelines and test reports; Siemens cites ELF of 9.8-11.3 as mid-risk Insurance coverage in the US 	
MRE	Imaging to assess liver stiffness as an indirect measure of fibrosis	MRE ≥ 3.3 kPa and FIB-4 score ≥ 1.6 ruled in stage 2 or higher fibrosis with a positive predictive value of 97.1%	<ul style="list-style-type: none"> Uncommon use in place of FibroScan Used to support diagnosis after referral to specialist 	Higher diagnostic accuracy than FibroScan	<ul style="list-style-type: none"> Higher cost and lower availability Unclear if can replace biopsy 	
MRI-PDFF	Imaging technique for quantifying steatosis	Relative decline of ≈30% is associated with higher odds of histologic response. ⁷	Role in diagnosis paradigm is evolving; it is mostly used in clinical trials.	Most accurate NIT for quantifying steatosis	<ul style="list-style-type: none"> Lack of correlation between steatosis severity and outcomes Cost 	
Liver enzymes	Serum biomarkers	Persistently elevated levels indicate liver inflammation and steatosis.	Patients with persistently elevated liver enzyme levels should be further screened for MASH.	Relatively inexpensive	Plasma liver aminotransferase levels can be unreliable and normal in many cases of MASLD.	—
FIB-4	Serum biomarkers	<ul style="list-style-type: none"> FIB-4, high-risk: >2.67 FIB-4, indeterminate: 1.3-2.67 FIB-4, low-risk: < 1.3 	Preferred initial test to assess the risk of MASLD with liver fibrosis	Best diagnostic accuracy is for advanced fibrosis.	Less accurate in patients aged < 35 years and ≥ 65 years	High-risk patients require further workup with an LSM or ELF test.
Conventional ultrasound	Imaging	—	Not included in evaluation of MASLD in current guidances	—	—	—
FibroScan	Imaging	<ul style="list-style-type: none"> Excludes advanced fibrosis, < 6.5; excludes cirrhosis, < 12.1 CAP for steatosis, > 275 dB/m 	Preferred assessment for evaluating risk of fibrosis following FIB-4 screening	Efficacious for assessing steatosis and estimating the extent of fibrosis	Results can be affected by several factors, and cutoff values for fibrosis vary by cause (eg, abnormal glucose metabolism, obesity).	High-risk patients require further workup with an LSM or ELF test.
LiverMultiScan	Imaging	<ul style="list-style-type: none"> Excludes at-risk MASH, < 800 msec Rules in the presence of at-risk MASH, > 875 msec 	Role in diagnostic paradigm needs further validation.	Efficacious for assessing changes in liver fibroinflammation	Currently used mainly in clinical trials	—

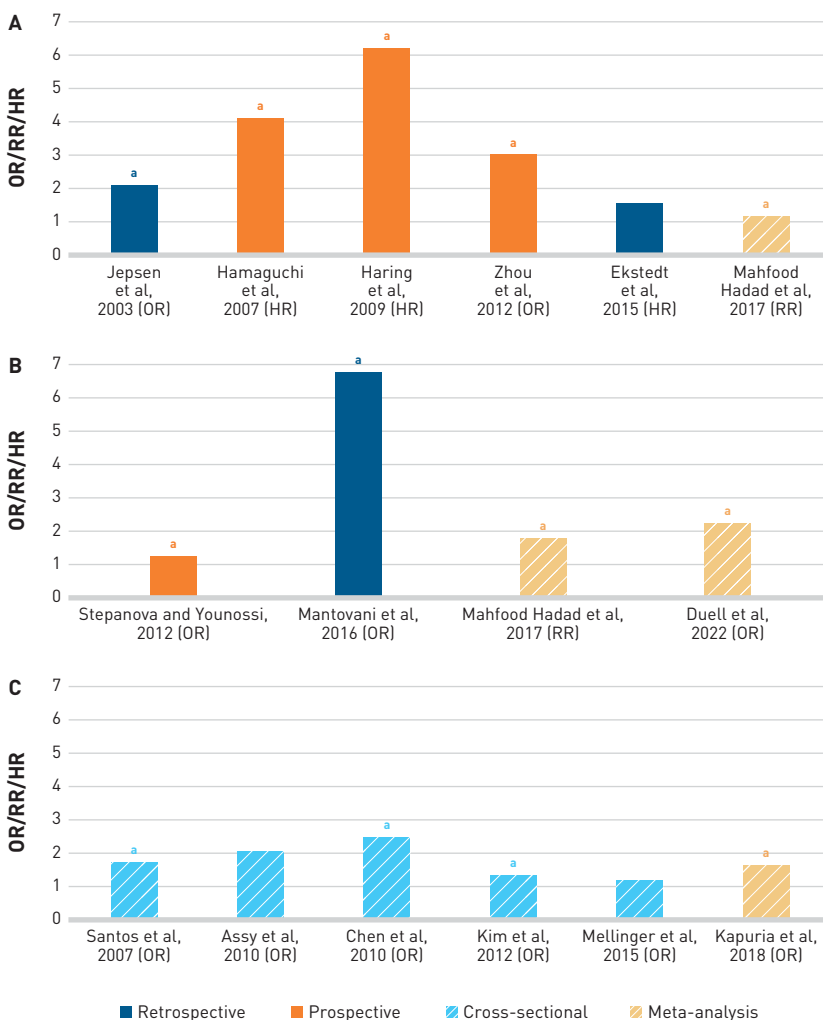
CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis score; FIB-4, fibrosis-4 score; HA, hyaluronic acid; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NIT, noninvasive test; P3NP, amino-terminal propeptide of type 3 procollagen.

TABLE 3. Common Metabolic and Cardiovascular Comorbidities With MASLD and MASH²²

Comorbidity	MASLD, % [95% CI]	MASH, % [95% CI]
Type 2 diabetes	22 (18-27)	44 (30-58)
Hyperlipidemia	69 (50-83)	72 (55-85)
Hypertriglyceridemia	40 (31-50)	83 (37-98)
Hypertension	39 (33-45)	68 (56-79)
Metabolic syndrome	45 (35-55)	71 (55-83)

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

FIGURE 3. Summary of Studies Evaluating the Association Between MASLD and ASCVD Risk⁷⁰⁻⁸⁴



A) Studies evaluating impact on CVD mortality in patients with MASLD compared with control subjects after adjustment for risk factor covariates; B) Studies evaluating impact of CVD events in patients with MASLD; C) Studies evaluating impact on coronary calcification in patients with MASLD compared with control subjects after adjustment for risk factor covariates.

*Ultrasound was used for MASLD diagnosis.

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; RR, relative risk.

lipoprotein cholesterol [LDL-C]), and insulin resistance with or without hyperglycemia.⁶⁹ Absolute reductions in LDL-C levels correlate with fewer major CV events, especially among patients with elevated aminotransferase levels.¹⁴

The American Heart Association has issued a scientific statement that includes a summary of study results involving the association between MASLD and ASCVD risk.⁷⁰ The statement demonstrates that in several trials, MASLD is an underappreciated and independent risk factor for ASCVD even after adjustment for ASCVD risk factor covariates (Figure 3).⁷⁰⁻⁸⁴

Guideline- and Guidance-Based Approaches for Identification and Risk Stratification of MASH and Comorbidities

Guidelines and guidances on the overall management and risk stratification of MASLD and MASH were outlined most recently by the EASL/European Association for the Study of Diabetes/European Association for the Study of Obesity in 2024, as well as by the AASLD and AACE; these are summarized in Table 4.^{7,23,24,38} Additionally, the AGA has published guidance on the clinical care pathway for the risk stratification and management of patients with MASLD. The pathway stratifies patients by their risk of advanced fibrosis. Low risk of advanced fibrosis is defined as an FIB-4 score below 1.3, LSM below 8.0 kPa by transient elastography (TE), or a liver biopsy fibrosis stage of F0 to F1. Indeterminate risk is defined as an FIB-4 score of at least 1.3 and up to 2.67 and/or an LSM between 8.0 and 12.0 kPa on TE. High risk is defined as an FIB-4 score above 2.67, LSM above 12.0 kPa by TE, or a liver biopsy that shows clinically significant liver fibrosis (F2-F4).²⁴ The AASLD guidance uses intermediate risk rather than indeterminate risk to denote FIB-4 scores of at least 1.3 and up to 2.67.²³

New and Developmental Treatments

MASH is increasingly recognized as a major public health concern, reflecting the global rise in obesity and metabolic syndrome. Characterized by hepatic steatosis,

TABLE 4. Treatment and Management Recommendations From Guidelines and Guidances^{7,23,24,38}

Guideline/Guidance	Treatment and management recommendations
EASL-EASD-ESO (2024) ⁷	<ul style="list-style-type: none"> • Prevention: prevent obesity, maintain healthy diet, promote regular physical activity, avoid smoking and alcohol. • In adults with MASLD with normal weight, 3%-5% weight reduction. Patients who are overweight or who have obesity, ≥5% weight loss for reduction in steatosis; 7%-10% weight reduction for MASH and fibrosis reduction; supportive measures include incretins and bariatric surgery. • In adults with MASLD, improving diet quality (similar to the Mediterranean dietary pattern), reducing the consumption of ultra-processed food (rich in sugars and saturated fat), increasing intake of whole foods. • In adults with MASLD, physical activity and exercise should be recommended to reduce steatosis and tailored to the individual's preference and ability (preferably >150 min/wk of moderate-intensity or 75 min/wk of vigorous-intensity physical activity). • Patients with MASH and cirrhosis: sarcopenia or decompensated cirrhosis, a high-protein diet and late-evening snack are recommended. For patients with compensated cirrhosis with obesity, weight reduction and high protein diet and exercise are recommended. • For patients with MASLD/MASH without cirrhosis (F0-F3), if locally approved, treatment with resmetirom is recommended in F2 and F3 fibrosis. • For MASLD/MASH with compensated cirrhosis (F4): check indication for liver transplantation in case of decompensation or hepatocellular carcinoma. • No MASH-targeted pharmacotherapy can currently be recommended for adults with MASH at the cirrhotic stage. • Preferred pharmacological options for treating comorbidities: <ul style="list-style-type: none"> » T2D: GLP1RA (eg semaglutide, liraglutide, dulaglutide) and coagonists (eg, tirzepatide); SGLT2 inhibitors (eg, empagliflozin, dapagliflozin); metformin (if glomerular filtration rate >30 mL/min); insulin (in case of DCC). » Dyslipidemia: statins » Obesity: GLP1RA (eg, semaglutide, liraglutide, dulaglutide) and coagonists (eg, tirzepatide); bariatric interventions (special caution in case of compensated cirrhosis)
AACE (2022) ³⁸	<ul style="list-style-type: none"> • Management of comorbidities (obesity, MetS, prediabetes, T2D, dyslipidemia, hypertension, CVD) based on current standards of care • Lifestyle changes targeting at least 5% (preferably ≥ 10%) weight loss, participation in structured weight loss program (when possible) • Pharmacotherapy targeted at weight loss (semaglutide, 2.4 mg/wk; liraglutide, 3 mg/d) may be considered as adjunctive therapy for patients with a BMI ≥ 27 and MASLD/MASH. Adjunctive pharmacotherapy targeted at weight loss must be considered for patients with obesity and MASLD/MASH. • Dietary changes to create an energy deficit (restriction of saturated fat, starch, and added sugar) and healthy eating patterns (eg, Mediterranean diet) should be adopted. • Physical activity to improve body composition and cardiometabolic health (eg, participation in a structured exercise program) should be maintained. • Pioglitazone, GLP-1 RAs, or SGLT2 inhibitors (no benefit to steatohepatitis) may be used in patients with T2D and biopsy-proven MASH or a high probability of MASH based on elevated liver enzyme levels and NIT results. • Metformin, acarbose, DPP4 inhibitors, and insulin may be given for treatment of hyperglycemia (but not steatohepatitis) in patients with MASLD/MASH and T2D. • Vitamin E may be used for patients with MASH and without T2D. • Bariatric surgery may be considered for patients with MASLD and BMI ≥ 30 (Asian patients, ≥27.5). Bariatric surgery is not recommended for patients with MASH and CC. • Use of endoscopic bariatric and metabolic therapies and orally ingested devices are not recommended for patients with MASLD.

(continued)

inflammation, and varying degrees of fibrosis, MASH can progress to cirrhosis, hepatocellular carcinoma (HCC), and liver-related death. Significant fibrosis (F2-F4) in patients with MASH marks a critical threshold beyond which the risk of adverse outcomes escalates sharply. Therefore, timely identification and treatment of MASH with significant fibrosis are imperative to prevent irreversible liver damage and improve patient prognosis.

The current management of MASH focuses on more indirect causes of MASH and includes lifestyle interventions such as modifications to physical activity and diet that target weight loss and improved CV fitness.^{23,24} Before March 2024, in the absence of an approved MASH treatment, only the drugs used for comorbidities associated with MASH were included in guidance documents.^{23,24} However, the evidence for off-label use of such products in patients with MASH is limited, and administration of these agents does not

provide benefits for all components of the disease (including no evidence of fibrosis improvement).^{23,24}

Resmetirom (Resmetirom (MGL-3196; Madrigal Pharmaceuticals) is the first and only medicine approved by the FDA for the treatment of adult patients with NASH (MASH) accompanied by liver fibrosis.⁸⁵ Resmetirom is a liver-directed, orally active, partial agonist for the THR with an approximately 28-fold selectivity for THR- β relative to THR- α compared to T₃.⁸⁵ Because resmetirom is a preferential THR- β agonist that has selective uptake into the liver, it avoids the systemic effects mediated by THR- α outside the liver.⁸⁵ THR- β stimulation in the liver improves mitochondrial function and lipid metabolism and reduces blood LDL-C, apolipoprotein B, and triglyceride levels.⁸⁵ Resmetirom was granted priority review, fast track, and breakthrough therapy designations by the FDA,^{86,87} and it was subsequently approved in conjunction with diet and

TABLE 4. (Continued) Treatment and Management Recommendations From Guidelines and Guidances^{7,23,24,38}

Guideline/Guidance	Treatment and management recommendations
AASLD (2023) ²³	<ul style="list-style-type: none"> • Patients with MASLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (eg, Mediterranean diet) should be encouraged due to their additional CV benefits. • Patients with MASLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss. • Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery, as it effectively resolves MASLD or MASH in most patients without cirrhosis and reduces mortality from CVD and malignancy. • Semaglutide can be considered for its approved indications (T2D/obesity) in patients with MASH, as it confers a CV benefit and improves MASH. • Pioglitazone improves MASH and can be considered for patients with MASH in the context of patients with T2D. • Vitamin E can be considered in select individuals as it improves MASH in some patients without T2D. • Metformin, ursodeoxycholic acid, DPP4 inhibitors, statins, and silymarin are well studied in MASH; they should not be used as a treatment for MASH, as they do not offer a meaningful histological benefit.
AGA (2021) ²⁴	<ul style="list-style-type: none"> • Low-risk patients should be managed using therapeutic lifestyle interventions; specific pharmacologic treatment targeting liver steatosis is not necessary. • High-risk patients should be managed by a multidisciplinary team who can monitor cirrhosis, HCC, and other cirrhosis-related complications. Aggressive lifestyle changes aimed at long-term weight loss are recommended for these patients; bariatric surgery should be considered for patients with clinically significant fibrosis and obesity with comorbidities. Following standards of care for managing T2D and CV risk factors is recommended in this patient population; when possible, preference should be given to medications that treat T2D and that have known efficacy in MASH (GLP-1 RAs and pioglitazone). • Patients at indeterminate risk should be given an individualized plan with a similar approach to that for managing patients at high risk of advanced fibrosis. Further efforts to confirm the stage of hepatic fibrosis, including the use of proprietary plasma biomarker tests or additional imaging-based fibrosis measurement, is recommended in some cases.

AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Disease; AGA, American Gastroenterological Association; BMI, body mass index; CC, compensated cirrhosis; CV, cardiovascular; CVD, cardiovascular disease; EASL, European Association for the Study of the Liver; GLP-1 RA, GLP1R agonist; HCC, hepatocellular carcinoma; MetS, metabolic syndrome; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NITs, noninvasive tests; T2D, type 2 diabetes.

exercise to treat adults with noncirrhotic nonalcoholic steatohepatitis (NASH/MASH) with moderate to advanced liver fibrosis (consistent with stages F2-F3 fibrosis).⁸⁵

MAESTRO-NASH (NCT03900429) is an ongoing (as of publication) phase 3 trial of adults with biopsy-confirmed MASH and fibrosis stages F1B, F2, or F3.⁸⁸ Patients were randomly assigned 1:1:1 to receive resmetirom, 80 or 100 mg, or placebo. The 2 primary end points at week 52 were NASH (MASH) resolution that included a reduction in the NAFLD activity score by at least 2 points with no worsening of fibrosis and a reduction in fibrosis by at least 1 stage with no worsening of the MASLD activity score. MASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the group given 80 mg of resmetirom, 29.9% of those in the group given 100 mg of resmetirom, and 9.7% of those in the group given placebo ($P < .001$ for both comparisons with placebo). Fibrosis improvement by at least 1 stage with no worsening of the NAFLD activity score was achieved in 24.2%, 25.9, and 14.2% of patients, respectively ($P < .001$ for both comparisons with placebo). These data formed the basis of support for the accelerated approval of resmetirom for use in this patient population. The MAESTRO-NASH study is continuing through 2026.⁸⁸

Treatments in Development

As of September 2023, multiple therapeutics with different mechanisms of action to treat MASH are being assessed in clinical trials (Table 5).⁸⁹

Symptoms and Disease Burden

Liver damage has a deleterious impact on an individual's quality of life (QOL) and general health status, with negative effects on QOL beginning early in the disease course. As MASH worsens, its symptoms—including anxiety, depression, fatigue, right upper quadrant pain, and impaired sleep, focus, and memory—often will hinder a patient's ability to work and perform standard day-to-day tasks.^{90,91}

As many as 80% of patients with MASH experience at least 1 other comorbidity. The most common comorbidities of MASH include obesity, CVD, and T2D, which lead to increased burden on patients and health systems.⁹²

Economically, use of health care resources by patients with MASH has a widespread impact—the annual direct health care costs exceed \$223 billion in the United States alone.⁹² With MASH prevalence increasing in the United States and globally, this economic burden is also expected to rise.⁹² On a per-patient basis, the direct costs of MASH (not including any comorbid, nonmedical, productivity, or societal costs) have been modeled at more than \$32,000 over a patient's lifetime, with costs increasing as the patient ages.⁹² There is also a correlation between the severity of disease as indicated by FIB-4 scores and the associated health care costs. In a claims-based, retrospective analysis of more than 6700 patients with MASH, there

was a mean increase from \$16,744 to \$34,667 between the lowest and highest FIB-4 cohorts. A 1-unit increase in FIB-4 scores corresponds to a 3.4% increase in mean total annual costs, emphasizing the financial burden associated with MASH severity.¹³

Patients with MASH experience higher hospitalization rates than do patients in the general population and those with T2D alone.⁹¹ The combination of MASH with comorbidities amplifies health care costs compared with expenditures for MASH or comorbidities alone, with MASH and T2D leading to a substantial 63% incremental increase in expenses.³⁰ With MASH likely to become the leading cause of advanced cirrhosis in coming decades, it is also predicted to become the leading cause of liver transplantation. Patients who undergo liver transplantation for MASH experience posttransplant hospitalization of up to 45 days. With an increasing number of liver transplantations attributable to MASH, the allocation of resources for this surgery will escalate.⁹²

Conclusion

Screening and diagnosis of MASLD and MASH evolved from primarily biopsy-based methods to incorporate the use of noninvasive techniques. This progression has been reflected in several consensus evidence-based guidelines as more evidence to support the use

TABLE 5. Phase 2 and 3 Clinical Trials to Assess MASH Treatments⁸⁹

Drug	Mechanism of action	Phase of study
Lanifibranor	Pan-PPAR agonist	3
Semaglutide	GLP-1 RA	3
Efruxifermin	FGF21 RA	3
Pegozafermin	FGF21 RA	3
Rencofilstat	Cyclophilin inhibitor	2
RXL065	Deuterium-modified thiazolidinedione	2
I0N224	DGAT2 inhibitor	2
Denifanstat	FASN inhibitor	2
Tirzepatide	GLP1-RA/GIP/GR RA	2
Survodutide	GLP1-RA/GIP/GR RA	2
Pemvidutide	GLP1-RA/GCG	2
Cotadutide	GLP1-RA/GIP/GR RA	2
GSK4532990	HSD17B13	2
Saroglitazar	PPAR α/γ agonist	2b
Icosabutate	Structurally engineered fatty acid	2
VK2809	THR- β agonist	2
Efinopegdutide	GLP1-RA/GIP/GR RA	2

GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GR, glucagon receptor; RA, receptor agonist; THR, thyroid hormone receptor.

of these techniques has been published.^{23,24} Some guidelines have provided additional detail on the use of biomarkers and other noninvasive approaches to stage disease severity, prognosis, and response to treatment.

Historically, the standard of care for managing MASH focused more on indirect causes of MASH and included lifestyle interventions such as modifications to physical activity and diet to promote weight loss.^{23,24} Until 2024, in the absence of a product approved by the FDA to treat NASH, pharmaceutical interventions to manage comorbidities also were recommended. However, the evidence for off-label use of such products in MASH is limited, and these agents do not provide benefits for all components of the disease (including no evidence of fibrosis improvement).^{23,24}

Delayed treatment of MASH with significant fibrosis can lead to a cascade of adverse clinical outcomes. Patients with significant fibrosis are at a higher risk of developing cirrhosis, which is often irreversible and associated with complications such as variceal bleeding, ascites, hepatic encephalopathy, and HCC. Furthermore, cirrhotic patients face increased morbidity and mortality, reduced QOL, and a greater burden on health care resources. The natural history of MASH underscores the critical window of opportunity to intervene before advanced fibrosis and cirrhosis develop. Early and aggressive treatment strategies can significantly alter disease trajectory, emphasizing the need for heightened clinical awareness and proactive management.

The substantial use of health care resources, economic burden, and overall impact on patients underscore the need for a metabolism- and liver-directed treatment that may attenuate the progression of liver disease. Accordingly, the approval of resmetirom in March 2024 holds promise as a treatment for patients with MASH and MASLD and continues the evolution of screening, diagnosis, and management of the condition. ■

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