



## Guideline

# Guideline for the Prevention and Treatment of Metabolic Dysfunction-associated Fatty Liver Disease (Version 2024)



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Received: August 28, 2024 | Revised: October 07, 2024 | Accepted: October 11, 2024 | Published online: November 04, 2024

## Abstract

With the rising epidemic of obesity, metabolic syndrome, and type 2 diabetes mellitus in China, metabolic dysfunction-associated non-alcoholic fatty liver disease has become the most prevalent chronic liver disease. This condition frequently occurs in Chinese patients with alcoholic liver disease and chronic hepatitis B. To address the impending public health crisis of non-alcoholic fatty liver disease and its underlying metabolic issues, the Chinese Society of Hepatology and the Chinese Medical Association convened a panel of clinical experts to revise and update the "Guideline of prevention and treatment of non-alcoholic fatty liver disease (2018, China)". The new edition, titled "Guideline for the prevention and treatment of metabolic dysfunction-associated fatty liver disease (Version 2024)", offers comprehensive recommendations on key clinical issues, including screening and monitoring, diagnosis and evaluation, treatment, and follow-up for metabolic dysfunction-associated fatty liver disease and metabolic dysfunction-associated steatotic liver disease.

**Keywords:** Non-alcoholic fatty liver disease; Metabolic dysfunction-associated fatty liver disease; Metabolic dysfunction-associated steatotic liver disease; Type 2 diabetes mellitus; Cardiovascular disease; Management; Guideline.

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Metabolic dysfunction-associated fatty liver disease is now the preferred English term and is used interchangeably with metabolic dysfunction-associated steatotic liver disease. Additionally, the guideline emphasizes the importance of multidisciplinary collaboration among hepatologists and other specialists to manage cardiometabolic disorders and liver disease effectively.

**Citation of this article:** Fan JG, Xu XY, Yang RX, Nan YM, Wei L, Jia JD, *et al.* Guideline for the Prevention and Treatment of Metabolic Dysfunction-associated Fatty Liver Disease (Version 2024). *J Clin Transl Hepatol* 2024. doi: 10.14218/JCTH.2024.00311.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic progressive liver condition resulting from over-nutrition and insulin resistance (IR) in genetically susceptible individuals. The spectrum of NAFLD ranges from non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH) to progressive fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).<sup>1-3</sup> The global prevalence and incidence of NAFLD are increasing alongside the epidemics of obesity and type 2 diabetes mellitus (T2DM), particularly in China.<sup>4-6</sup> Additionally, NAFLD has a reciprocal relationship with metabolic syndrome (MetS) and T2DM, contributing to the development of atherosclerotic cardiovascular disease (CVD), chronic kidney disease (CKD), hepatic decompensation, and both hepatic and non-hepatic malignancies.<sup>1-3,7,8</sup> Therefore, NAFLD has emerged as a significant public health issue worldwide, including in China.<sup>5,9</sup>

To standardize the screening, diagnosis, management,

**Table 1. Revised quality of evidence and grades of recommendation**

Evidence	Definitions
Quality of evidence	
High quality (A)	Further research is unlikely to change our confidence in the diagnosis or the assessment of efficacy.
Moderate quality (B)	The confidence in the observed values is moderate. The true values may be close to the observed values, but there is still a possibility of the two being different.
Low quality (C)	The confidence in observed values is limited. The true values may be different from the observed values.
Grades of recommendation	
Strong (1)	It is clearly demonstrated that the interventions do more good than harm, or do more harm than good.
Weak (2)	It is not clearly demonstrated that the interventions do more good or more harm. Evidence of both high and low quality shows that good and harm are comparable.

and follow-up of NAFLD patients, the Chinese Society of Hepatology and the Chinese Medical Association published the Guideline of prevention and treatment of non-alcoholic fatty liver disease (2018, China) (hereinafter referred to as 2018 guideline).<sup>2</sup> In 2020, an international panel of experts recommended renaming NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). The same year, the Asian Pacific Association for the Study of the Liver published clinical practice guidelines for the diagnosis and management of MAFLD.<sup>10–12</sup> However, in 2023, a multi-society Delphi consensus statement led by the American Association for the Study of Liver Diseases suggested the name and acronym metabolic dysfunction-associated steatotic liver disease (MASLD) to replace NAFLD.<sup>13</sup> In 2024, the European Association for the Study of the Liver (hereinafter referred to as EASL), the European Association for the Study of Diabetes (hereinafter referred to as EASD), and the European Association for the Study of Obesity (hereinafter referred to as EASO) published EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-associated Steatotic Liver Disease.<sup>3</sup> Regarding the renaming, the Chinese Society of Hepatology and the Chinese Medical Association actively expressed their expert committee's opinion,<sup>9</sup> emphasizing that the diagnosis and treatment of NAFLD should reflect the specific context in China. After extensive discussion, the expert committee recommended that both MAFLD and MASLD be translated as “代谢相关脂肪性肝病” in Chinese. Concurrently, the committee decided to revise and update the 2018 guideline to the “Guideline for the prevention and treatment of metabolic dysfunction-associated (non-alcoholic) fatty liver disease (Version 2024)” (hereinafter referred to as this guideline).<sup>14</sup>

The authors were invited by the Chinese Society of Hepatology and the Chinese Medical Association to develop this practice guideline document for managing patients with fatty liver disease (FLD). The recommendations are structured using a patient-intervention-comparison-outcome format and a modified Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system, informed by expert opinion and a review of current literature. The evidences supporting the recommendations are categorized into three levels: A, B, and C, while the recommendations themselves are grouped into two grades: 1 and 2 (Table 1). Although the terms MAFLD (2020) and MASLD (2023) have different working definitions, they largely overlap on major issues, with only minor differences. Therefore, this guideline proposes a modified diagnostic criterion for MAFLD/MASLD, with MAFLD being the preferred English term that

is interchangeable with MASLD.

The recommendations in this guideline aimed to assist clinicians in making informed decisions regarding the screening, diagnosis, management, follow-up, and monitoring of FLD. However, these recommendations should be tailored to the individual patient with MAFLD and their specific circumstances in routine clinical practice. Clinicians should consider the best clinical evidence, available medical resources, the patient's specific condition and preferences, and their knowledge and experience when developing diagnostic, therapeutic, and follow-up strategies. As research on MAFLD rapidly advances, this guideline should be continuously updated and refined based on ongoing developments in the field and clinical requirements.<sup>14</sup>

## Terminology and pathophysiology

### Terminology of FLD

FLD, or steatotic liver disease, is a heterogeneous group of diseases caused by various factors, including genetic susceptibility, epigenetic changes, diet, and lifestyle choices.<sup>1</sup> Advances in technology and clinical research have led to ongoing updates in the terminology, classification, and staging of FLD (Tables 2 and 3). Aside from alcohol-related liver disease (ALD), the original term NAFLD has been classified into MAFLD and cryptogenic FLD.<sup>11</sup> In clinical practice, it is not uncommon to encounter FLD with mixed etiologies, where two or more causes coexist. Furthermore, FLD can present alongside other types of liver disease, such as chronic hepatitis B (CHB) infection.<sup>12,13</sup>

### Pathophysiology of MAFLD

The liver plays a key role in regulating energy balance, as well as glucose and lipid metabolism in the body. A high-energy diet and sedentary lifestyle, along with conditions such as obesity, MetS, and T2DM, are major risk factors for MAFLD (Table 4). The ability of adipose tissue and the liver to handle excess nutrients influences the development and progression of MAFLD. Dysfunction in adipose tissue, along with IR and low-grade systemic inflammation, leads to increased synthesis of triglycerides (TG) and decreased oxidation and transport in hepatocytes, resulting in hepatic fat accumulation. Additional factors such as gut microbiota dysbiosis, glycolipid toxicity, and other mechanisms contribute to mitochondrial dysfunction, endoplasmic reticulum stress, lipid peroxidation damage, and hepatic inflammation. These processes activate

**Table 2. Clinical classification of fatty liver disease**

Terminology	Definition
Fatty liver disease	A group of heterogeneous diseases characterized by the presence of diffuse fatty liver on imaging technique or histological features of significant macrovesicular steatosis.
Metabolic dysfunction-associated fatty liver disease	Chronic metabolic stress-induced liver disease caused by over-nutrition and insulin resistance in genetically susceptible individuals.
Alcohol related-liver disease	Chronic progressive liver disease caused by long-term excessive alcohol consumption initially presents as simple fatty liver disease. With continued consumption, the disease advances to alcoholic hepatitis, liver fibrosis, and cirrhosis.
Secondary fatty liver disease	Macrovesicular steatosis caused by specific etiologies such as toxic/drug-induced liver disease (environmental factors, amiodarone, methotrexate, 5-fluorouracil, irinotecan, tamoxifen, glucocorticoids, etc.), nutrient deficiency, genotype 3 hepatitis C virus infection, Wilson disease, hypobetalipoproteinemia, congenital lipodystrophy, and celiac disease, etc.
Mixed etiology of fatty liver disease	Chronic liver diseases are caused by two or more coexisting factors that can lead to macrovesicular steatosis, in which the most common factors are obesity, type 2 diabetes mellitus, metabolic syndrome, and alcohol (ethanol) abuse.
Cryptogenic fatty liver disease	Idiopathic fatty liver disease, when no specific cause is detected, usually progresses to metabolic dysfunction-associated fatty liver disease. It's important to remain cautious about missing diagnosis of secondary fatty liver disease.
Special type of fatty liver disease	A group of acute liver diseases characterized by microvesicular steatosis, including acute fatty liver of pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), Reye's syndrome, Reye-like syndrome (liver damage induced by toxins or drugs such as carbon tetrachloride, sodium valproate, tetracycline, salicylate, phosphorus, etc.), alcoholic foamy degeneration, mitochondrial fatty acid oxidation gene defect, and acute hepatitis D.

stellate cells and ultimately cause metabolic dysfunction-associated steatohepatitis (MASH), liver fibrosis, cirrhosis, and even HCC.<sup>12,13,15</sup> Furthermore, hepatic fat accumulation and

steatohepatitis can contribute to the development of MetS and T2DM through mechanisms such as IR, disruptions in glucose and lipid metabolism, and oxidative stress, creating

**Table 3. Clinical classification of metabolic dysfunction-associated fatty liver disease**

Terminology	Definition
Metabolic dysfunction-associated simple fatty liver	Early stage of MAFLD. Hepatic steatosis identified by imaging techniques or ≥5% of macrovesicular steatosis by liver histology, with or without non-specific inflammation. The mild (S1), moderate (S2), and severe (S3) steatosis are defined that the percentage of hepatocyte steatosis is 5–33%, 34–66%, and ≥67% in view of hematoxylin and eosin stain under light microscope, respectively.
Metabolic dysfunction-associated steatohepatitis	MAFLD patients coexist with ≥5% of liver steatosis, lobular inflammation, and ballooned hepatocytes in liver histology. According to the fibrosis stage, it can be divided into early MASH (F0-1), fibrotic MASH (F2-3), and MASH cirrhosis (F4).
Metabolic dysfunction-associated liver fibrosis	MAFLD patients with biopsy-proven significant fibrosis (F2, F3) or NITs diagnosing advanced fibrosis (F3, F4), with or without elevated liver enzymes and histologic features of MASH.
Metabolic dysfunction-associated cirrhosis	MAFLD patients with cirrhosis are suggested by noninvasive tests or liver biopsy, with or without histologic features of MASH.

MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

**Table 4. The main risk factors for metabolic dysfunction-associated fatty liver disease**

Terminology	Definition
Obesity	A chronic metabolic endocrine disorder characterized by excessive accumulation of body fat and overweight. BMI is an important indicator of obesity. BMI 24.0–27.9 kg/m <sup>2</sup> is classified as overweight and ≥ 28 kg/m <sup>2</sup> as obesity.
Sarcopenic obesity	A state characterized by skeletal muscle mass loss and function decline, alongside excessive body fat, which BMI may underestimate or miss diagnose.
Type 2 diabetes mellitus	The most common type of diabetes characterized by elevated plasma glucose caused by hyperinsulinemia and insulin resistance. Diagnostic criteria include fasting plasma glucose ≥ 7.0 mmol/L, or 2-h postprandial plasma glucose ≥ 11.1 mmol/L, and glycated hemoglobin A1c ≥ 6.5%.
Metabolic syndrome	A cluster of conditions including three or more metabolic cardiovascular risk factors.

BMI, body mass index.

a vicious cycle.<sup>7,8</sup>

Genetic polymorphisms in proteins such as patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and glucokinase regulatory protein increase susceptibility to MAFLD/MASH, cirrhosis, and HCC.<sup>12,13</sup> Alcohol consumption also plays a role in the pathogenesis of MAFLD, acting as a trigger, risk factor, or co-pathogen. Both excessive alcohol intake and over-nutrition can induce metabolic disorders and synergistically damage the liver.<sup>12,13,16</sup> Even mild alcohol intake can increase the risk of hepatic oxidative stress, lipid peroxidation, and HCC in patients with MetS or fibrotic MAFLD.<sup>12,13,16</sup> Additionally, conditions such as sarcopenia, hypothyroidism, obstructive sleep apnea, polycystic ovary syndrome, and panhypopituitarism are also involved in the pathogenesis of MAFLD.<sup>2,4,7</sup>

## Epidemiology

NAFLD is the most common chronic liver disease worldwide and the primary cause of abnormal serum aminotransferases in individuals undergoing health check-ups. In China, it has surpassed CHB as the leading cause of chronic liver disease.<sup>5,6,11,14</sup> Retrospective analyses of epidemiological data show that over 95% of NAFLD patients meet the diagnostic criteria for MAFLD, allowing NAFLD data to be extrapolated to MAFLD.<sup>17</sup>

### Global epidemiology of NAFLD

The global prevalence of NAFLD is estimated at 32.4%, with a significantly higher rate in men than women (39.7% vs. 25.6%). Over the past two decades, the prevalence has risen significantly, reaching 37.8% since 2016.<sup>5</sup> The highest prevalence is found in Latin America (44.4%), followed by the Middle East and North Africa, South Asia, Southeast Asia, North America, and East Asia, with the lowest prevalence in Western Europe (25.1%).<sup>18</sup> Overweight and obese populations exhibit similar rates of NAFLD, non-alcoholic fatty liver, NASH, significant fibrosis ( $\geq F2$ ), and advanced fibrosis ( $\geq F3$ ), at 70.0% vs. 75.3%, 42.5% vs. 43.1%, 33.5% vs. 33.7%, 20.3% vs. 21.6%, and 6.7% vs. 6.9%, respectively.<sup>19</sup> Globally, 19.2% of NAFLD patients have a normal body mass index (BMI), classified as lean individuals, and 40.8% are non-obese. In the general population, 12.1% have non-obese NAFLD, and 5.1% have lean NAFLD. Among non-obese or lean NAFLD patients, 39.0% have NASH, 29.2% have significant fibrosis, and 3.2% have cirrhosis. Advanced age ( $>40$  years) and cardiometabolic risk factors are independently associated with liver fibrosis in NAFLD patients.<sup>20</sup>

Among patients with T2DM, the global prevalence of NAFLD, NASH, significant fibrosis, and advanced fibrosis was 65.0%, 31.6%, 35.5%, and 15.0%, respectively.<sup>21</sup> In a study of 501 patients with T2DM, 29 had cirrhosis (including two cases of HCC and one case of gallbladder cancer). Obesity and insulin use were independently associated with advanced fibrosis and cirrhosis in diabetic patients.<sup>22</sup> The prevalence of NAFLD in patients with type 1 diabetes is not higher than in the general population unless combined with obesity and MetS.<sup>7</sup> The pooled incidence of NAFLD in the Asian population is 46.1 per 1,000 person-year, with a higher rate in males than in females (53.1 vs. 33.7 per 1,000 person-year). Obese or overweight individuals have a threefold higher risk of developing NAFLD compared to non-obese or lean individuals (86.7 vs. 29.6 per 1,000 person-year, and 84.2 vs. 33.6 per 1,000 person-year). China shows the highest incidence (59.4 per 1,000 person-year) and the greatest increase in NAFLD prevalence worldwide.<sup>5,23</sup>

### Epidemiology of NAFLD in China

Over the past 20 years, the pooled prevalence of NAFLD among adults in China was 29.6%, with a higher rate in males (34.8%) than in females (23.5%).<sup>24</sup> Among obese individuals and those with T2DM, the prevalence of NAFLD was 66.2% and 51.8%, respectively. In Shanghai, the prevalence of NAFLD increased with BMI and waist circumference, even affecting 17.5% of adults with normal BMI and waist circumference (accounting for 11.1% of all NAFLD cases) and was associated with cardiometabolic risk factors.<sup>25</sup> In a 2012 study of adults aged 45 and older in the Chongming District of Shanghai, the prevalence of NAFLD and MAFLD (based on 2020 criteria) was 36.9% and 40.3%, respectively. Of those with NAFLD, 95.1% met the criteria for MAFLD. Among diabetic patients with NAFLD, 11.4% were diagnosed with advanced fibrosis based on non-invasive tests (NITs).<sup>26</sup> Although patients with chronic hepatitis B virus (HBV) infection generally have a lower prevalence of FLD compared to non-infected individuals, NAFLD is becoming more common in this population, largely driven by metabolic dysfunction.<sup>27</sup> Based on ultrasonic attenuation parameter (UAP) and liver stiffness measurement (LSM) data from transient elastography (TE) FibroTouch® performed on over 5.75 million adults during health check-ups in China between 2017 and 2022, the prevalence of FLD (UAP  $> 244$  dB/m), severe FLD (UAP  $> 296$  dB/m), advanced fibrosis (LSM  $> 10$  kPa), and cirrhosis (LSM  $> 13.5$  kPa) was 44.4%, 10.6%, 2.9%, and 0.87%, respectively. Common risk factors for FLD and fibrosis included male gender, obesity, diabetes mellitus, hypertension, dyslipidemia, MetS, elevated aminotransferase levels, and excessive alcohol consumption. Additionally, FLD, along with decreased serum albumin or blood platelet counts and HBV infection, was strongly associated with advanced fibrosis and cirrhosis.<sup>28</sup> It should be noted, however, that this study did not rely on a general population survey and did not differentiate the underlying causes of FLD.

**Recommendation 1:** MAFLD is the most common chronic progressive liver disease in China and should be a priority in screening and prevention efforts (B, 1).

**Recommendation 2:** High-risk populations, such as individuals with obesity (BMI  $\geq 28$  kg/m<sup>2</sup>), T2DM, MetS ( $\geq$ three cardiometabolic risk factors), or elevated serum aminotransferases without symptoms, should be screened for MAFLD and liver fibrosis (B, 1).

### Nature history

It is well-established that MetS and T2DM interact with FLD to mutually promote the development of multi-system metabolism-related chronic diseases.<sup>29</sup> The morbidity and mortality of patients with NAFLD are primarily associated with CVD and non-hepatic malignancies. Liver-related events—such as hepatic decompensation, HCC, liver transplantation, and liver-related death—are significantly increased only in patients with advanced fibrosis or cirrhosis.<sup>2,7,8</sup> Moreover, MetS is independently associated with an increased risk of all-cause mortality, as well as liver- and CVD-related mortality, in NAFLD patients. Interestingly, T2DM may have a more substantial impact on the outcomes of NAFLD patients than obesity.<sup>30,31</sup>

### Increased risk of hepatic decompensation and HCC

Compared to the general population, the pooled global all-cause mortality (15.44/1,000 person-year for NAFLD and 25.56/1,000 person-year for NASH), and liver-related mor-

tality (0.77/1,000 person-year for NAFLD and 11.77/1,000 person-year for NASH) increased by 1.05 and 1.94 times, respectively, in patients with NAFLD and NASH. Advanced fibrosis has a more significant effect on long-term prognosis than NASH, with approximately 40.8% of NASH patients showing fibrosis progression during follow-up.<sup>32</sup> In a median four-year follow-up of 1,773 patients with biopsy-proven NAFLD, all-cause mortality increased with fibrosis stage: 0.32, 0.89, and 1.76 deaths per 100 person-year at stages F0-F2, F3, and F4, respectively. Hepatic decompensation increased the all-cause mortality risk in NAFLD patients by 6.8 times, and the likelihood of complications such as ascites, esophageal variceal bleeding, hepatic encephalopathy, and HCC rises with fibrosis progression.<sup>33</sup>

The global pooled incidence of NAFLD-related HCC was 1.25 per 1,000 person-year, increasing to 14.46 per 1,000 person-year in patients with advanced fibrosis.<sup>34</sup> A study of U.S. veterans with NAFLD found that over a mean follow-up of nine years, the risk of developing cirrhosis and/or HCC increased with the number of MetS components, with T2DM being more strongly associated with HCC than with cirrhosis.<sup>31</sup> Although 30% to 50% of NASH-related HCC cases occur without underlying cirrhosis, the incidence of HCC in non-cirrhotic NASH patients is only 0.01% to 0.13%, compared to 0.5% to 2.6% in cirrhotic NASH patients. From 2012 to 2017, global mortality from cirrhosis and HCC increased by 11.4%, largely driven by NAFLD. During this period, the age-standardized death rate for cirrhosis and HCC due to NAFLD rose by 0.29% and 1.42%, respectively, accounting for 9% and 8% of deaths from cirrhosis and HCC.<sup>35</sup> However, the incidence of liver-related events in NAFLD patients was only 0.97 per 1,000 person-year, while the risk of CVD and non-hepatic malignancies was nine to sixteen times higher. Additionally, the risk of CKD in NAFLD patients aged 50 years and older was also higher than the risk of liver-related events.<sup>36</sup>

#### **Increased risk of cardiovascular-kidney-metabolic disease**

Cardiovascular-kidney-MetS is a systemic disease caused by the pathophysiological interactions between cardiometabolic risk factors, CKD, and CVD, with NAFLD playing a central role as a metabolic condition.<sup>37</sup> The incidence rates of MetS, T2DM, and CKD in NAFLD patients are higher than in the general population. NAFLD independently increases the risk of T2DM and CKD by 2.19 times and 1.43 times, respectively.<sup>38,39</sup> Compared to NAFLD patients with fibrosis stages F0-F2, those with stage F4 have a higher risk of developing T2DM (75.3 per 1,000 person-year vs. 44.5 per 1,000 person-year) and experiencing renal function deterioration (29.8 per 1,000 person-year vs. 9.7 per 1,000 person-year). In the meanwhile, T2DM and NAFLD synergistically increase the risk of developing CKD.<sup>33,40</sup>

NAFLD is also a critical early warning indicator of CVD, independently increasing the risk of coronary heart disease by 1.33 times and major cardiovascular events by 1.45 times. The pooled prevalence of clinical and subclinical coronary artery disease in NAFLD patients was 38.7% and 55.4%, respectively. NAFLD patients also face a significantly higher risk of heart failure and atrial fibrillation.<sup>41-43</sup> Additionally, the pooled prevalence of carotid atherosclerosis, ischemic stroke, and hemorrhagic stroke in NAFLD patients was 35.0%, 6.1%, and 2.2%, respectively. NAFLD increases the risk of carotid atherosclerosis by 3.2 times and stroke by 1.9 times.<sup>44</sup> The impact of NAFLD on incident CVD and all-cause mortality is even more pronounced in patients with T2DM and advanced fibrosis.<sup>45,46</sup> Genetic polymorphisms in *PNPLA3*, *TM6SF2*, and membrane-bound O-acyltransferase domain containing 7 (*MBOAT7*) in-

crease liver-related mortality in overweight or obese NAFLD patients but reduce their CVD-related mortality.<sup>47</sup>

#### **Increased risk of non-hepatic malignancies**

NAFLD, along with its associated metabolic inflammation, abnormal immune surveillance, and intestinal microbiota imbalance, contributes to carcinogenesis.<sup>48</sup> Globally, the incidence of non-hepatic malignancies in NAFLD patients (10.58 per 1,000 person-year) is eight times higher than that of HCC, with endometrial, breast, prostate, colorectal, and lung cancers being the most common.<sup>34</sup> The elevated risk of non-hepatic malignancies in NAFLD patients is independent of age, gender, smoking, obesity, diabetes, and fibrosis stage.<sup>34</sup> NAFLD also increases the risk of esophageal, gastric, pancreatic, and colorectal cancers by 1.5 to 2 times, and the risk of lung, breast, gynecological, and urinary system cancers by 1.2 to 1.5 times.<sup>49</sup> In the prospective cohort study of male adults in Kailuan, China, NAFLD was associated with an increased risk of total non-hepatic malignancies (hazard ratio [HR], 1.22), thyroid cancer (HR, 2.79), and lung cancer (HR, 1.23).<sup>50</sup>

#### **Metabolic dysfunction as a driver of the liver disease**

According to the Third National Health and Nutrition Examination Survey (NHANES III) in the U.S., the overall mortality rate among 12,878 patients with FLD was 30% over a median follow-up of 23 years. IR and cardiometabolic risk factors were associated with an increased risk of mortality in NAFLD patients. Coexisting ALD was the primary cause of increased liver-related mortality in patients with MAFLD (2020 criteria).<sup>30</sup> Fibrosis-4 index (FIB-4)  $\geq 2.67$  predicted liver-related mortality in both MAFLD (HR, 17.2) and NAFLD (HR, 9.3) patients. Liver-related mortality in MAFLD patients was nearly 50% higher than in NAFLD patients, and all-cause mortality in MAFLD patients increased by 17%, with the most significant rise in CVD-related mortality. Among subgroups, MAFLD+/NAFLD- patients had the most significant increase in all-cause mortality, while MAFLD-/NAFLD+ (cryptogenic FLD) patients had a lower mortality rate than the control group without FLD.<sup>30</sup> NAFLD patients with normal BMI had similar liver- and non-liver-related events to those with overweight and obesity. Metabolic dysfunction and advanced fibrosis were also associated with adverse outcomes in lean NAFLD patients.<sup>51,52</sup> Additionally, MetS and T2DM are significant risk factors for the progression of liver disease in patients with ALD and/or CHB infection.<sup>6,27,53</sup>

**Recommendation 3:** Patients with MAFLD should be screened and monitored for liver fibrosis (B, 1).

**Recommendation 4:** MAFLD patients with advanced fibrosis should be screened for HCC, and if cirrhosis is diagnosed, screening for esophageal varices and hepatic decompensation events should also be performed (B, 1).

**Recommendation 5:** Patients with MAFLD should be screened and monitored for MetS components (Table 5) and T2DM using fasting plasma glucose, hemoglobin A1c, and oral glucose tolerance tests, if necessary (B, 1).

**Recommendation 6:** Patients with MAFLD should be screened for CKD using estimated glomerular filtration rate and/or urine albumin, and the 10-year and lifetime CVD risk assessment model should be used to evaluate CVD risk in Chinese adults (B, 1).

**Recommendation 7:** MAFLD patients should adhere to age- and gender-stratified screening for common malignancies (C, 1).

**Table 5. Definitions of metabolic syndrome components**

Components	Definition
Overweight/obesity	BMI $\geq 24.0$ kg/m <sup>2</sup> , or waist circumference $\geq 90$ cm (male) and $\geq 85$ cm (female), or excessive body fat content and percentage.
Blood pressure	Blood pressure $\geq 130/85$ mmHg, or undergoing antihypertensive medication therapy.
Dysglycaemia or type 2 diabetes mellitus	Fasting plasma glucose $\geq 6.1$ mmol/L, or 2-h postprandial plasma glucose $\geq 7.8$ mmol/L, or HbA1c $\geq 5.7\%$ , or history of type 2 diabetes mellitus, or HOMA-IR $\geq 2.5$ .
Plasma TG	Plasma TG $\geq 1.70$ mmol/L, or undergoing lipid-lowering medication therapy.
HDL-cholesterol	Plasma HDL-cholesterol $\leq 1.0$ mmol/L (male) and $1.3$ mmol/L (female), or undergoing lipid-lowering medication therapy.

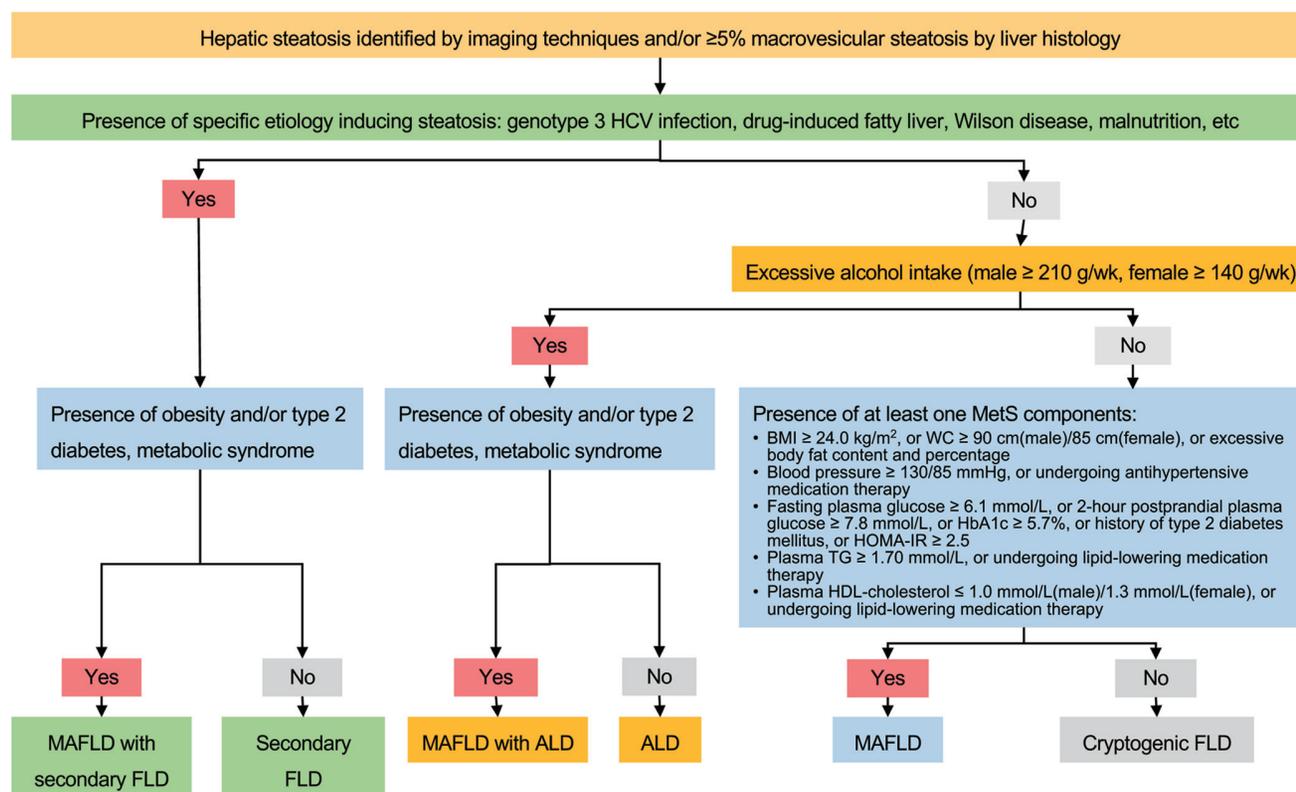
BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; TG, triglyceride; 1 mmHg = 0.133 kPa.

**Diagnosis and assessment**

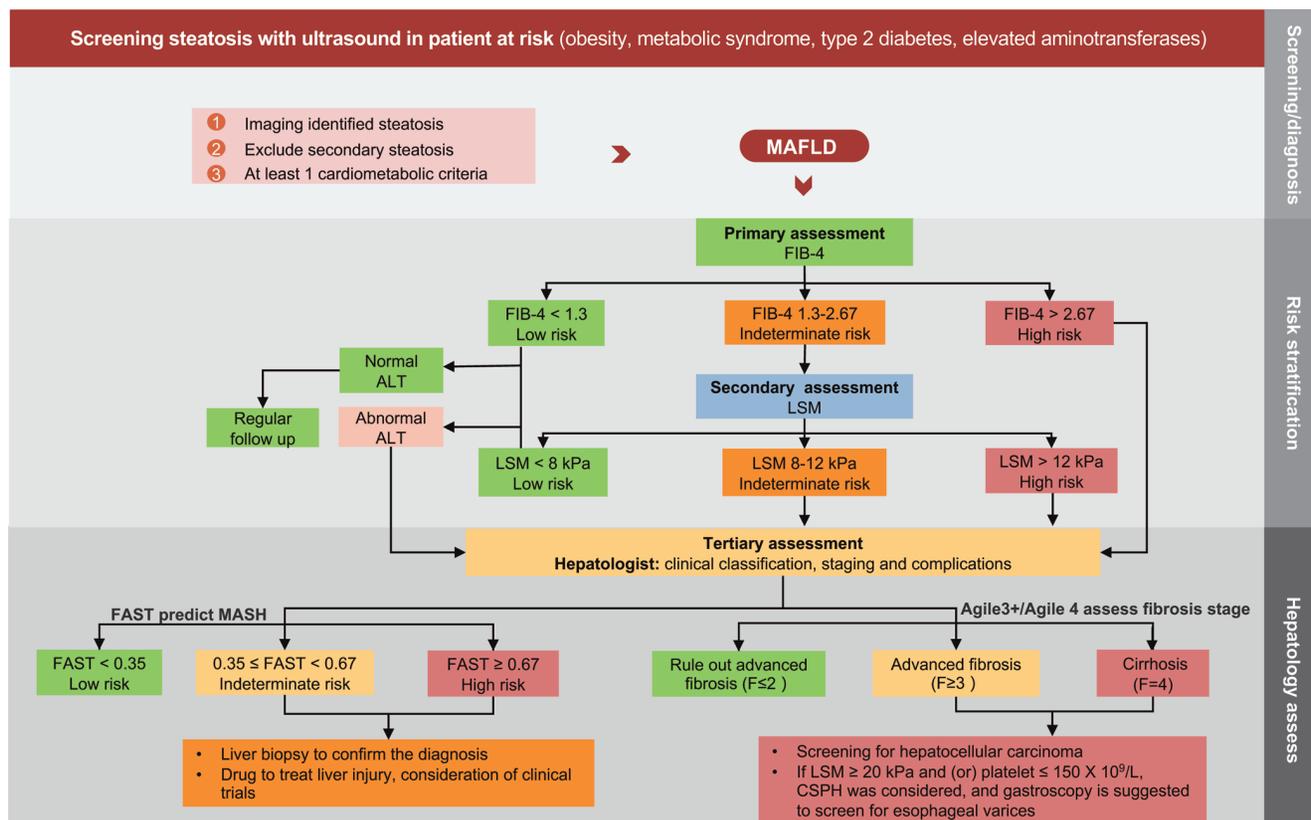
**Diagnosis of MAFLD alone and MAFLD with other liver disease**

The diagnosis of MAFLD alone requires evidence of diffuse fatty liver on imaging and/or histological confirmation of significant hepatic steatosis ( $\geq 5\%$  macrovesicular steatosis), at least one component of the MetS (Fig. 1, Table 5), and the exclusion of excessive alcohol consumption ( $\geq 210$  g/week in men and  $\geq 140$  g/week in women over the past 12 months) and other specific causes of FLD.<sup>1,2,13,14</sup> Routine blood tests and non-invasive assessments of hepatic steatosis and fibrosis are essential for suspected MAFLD cases. However, a liver biopsy is necessary for diagnosing MASH in MAFLD patients and for differential diagnosis in

certain cases or clinical trials (Fig. 2, Table 6).<sup>1,2,12,14</sup> In patients with ALD and other specific etiologies of FLD who have obesity, T2DM, or MetS, the coexistence of MAFLD (mixed etiology of FLD) should be considered.<sup>9-12</sup> Patients with other chronic liver diseases, such as CHB, chronic hepatitis C caused by non-genotype 3 hepatitis C virus infection, and primary biliary cholangitis, often have concomitant MAFLD, with CHB and MAFLD being the most common combination in China.<sup>2,12,27</sup> Additionally, MAFLD patients may be more susceptible to drug-induced liver injury.<sup>2</sup> A comprehensive analysis of a patient’s medical history, including medication history, laboratory data, and other specialized examinations, can assist in identifying the primary causes of liver injury in FLD patients with two or more etiologies, as well as in MAFLD patients combined



**Fig. 1. Etiological diagnosis flowchart of fatty liver disease.** HCV, hepatitis C virus; MetS, metabolic syndrome; MAFLD, metabolic dysfunction-associated fatty liver disease; FLD, fatty liver disease; ALD, alcoholic liver disease; BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides; HDL-cholesterol, high-density lipoprotein cholesterol; 1 mmHg = 0.133 kPa.



**Fig. 2. Screening, diagnosis and assessment of metabolic dysfunction-associated fatty liver disease.** ALT, alanine aminotransferase; FIB-4, fibrosis-4; LSM, liver stiffness measurement; FAST, Fibro scan-AST; MASH, metabolic dysfunction-associated steatohepatitis; CSPH, clinically significant portal hypertension.

with other types of liver diseases.

**Non-invasive assessment of hepatic steatosis**

Ultrasound is the most widely used imaging technique for

diagnosing significant hepatic steatosis, including diffuse and non-homogeneous steatosis.<sup>1,2,12,54</sup> The controlled attenuation parameter (CAP)/UAP, based on TE, has greater sensitivity in detecting hepatic steatosis compared to routine ultra-

**Table 6. Systematic assessment of patients suspected of metabolic dysfunction-associated fatty liver disease**

History	Smoking history, alcohol consumption history (including amount, pattern, and duration of use); diet and exercise habits; body weight and its change. History of hypertension, diabetes, dyslipidemia, hyperuricemia/gout, obstructive sleep apnea, polycystic ovary syndrome (for women), recent and current medications. Family history of obesity, fatty liver, diabetes, coronary artery disease, stroke, cirrhosis.
Physical examination	Height, body weight, waist circumference, arterial blood pressure, features of insulin resistance (e.g., dorsocervical fat pad, acanthosis nigricans). Features of advanced chronic liver disease (e.g., hepatomegaly and firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomas, palmar erythema, lower limb edema, and jaundice).
Laboratory tests	Complete blood count, high-sensitivity C-reactive protein, biochemical tests for the assessment of liver and renal function, lipid panel, fasting plasma glucose, insulin, glycated hemoglobin, and even oral glucose tolerance test; alpha-fetoprotein testing for patients with cirrhosis.
Additional tests	If there is no prior screening for hepatitis B and C, testing for hepatitis B surface antigen and hepatitis C antibodies will be recommended. Further analysis including HBV DNA and HCV RNA can be performed if necessary. Additional evaluation will be required if liver biochemistry parameters are significantly abnormal or if other causes of liver disease are suspected, such as testing for anti-nuclear antibodies and anti-smooth muscle antibodies (for autoimmune hepatitis), anti-mitochondrial antibodies (for primary biliary cholangitis), ceruloplasmin and 24-h urine copper (for Wilson disease), low-density lipoprotein, and apolipoprotein B (for hypobetalipoproteinemia). Ultrasonography (of the liver, gallbladder, pancreas, spleen, and kidneys) should be conducted, along with transient elastography recommended to assess liver fat content and fibrosis. Body composition analysis is recommended for individuals with normal BMI. Fundoscopy or carotid artery ultrasound can be performed to observe for signs of atherosclerosis, and if necessary, screening for coronary artery disease and stroke can be conducted through electrocardiography, cardiac dual-source CT, cranial MRI, etc.

HBV, Hepatitis B virus; HCV, Hepatitis C virus; BMI, Body mass index; CT, Computed tomography; MRI, magnetic resonance imaging.

**Table 7. Summary of non-invasive techniques and thresholds in the assessment of MAFLD**

Non-invasive techniques	Diagnostic thresholds
Assessment of steatosis grade	
CAP <sup>57</sup>	≥S1: 248 dB/m, ≥S2: 268 dB/m, and S3: 280 dB/m
UAP <sup>56</sup>	≥S1: 244 dB/m, ≥S2: 269 dB/m, and S3: 296 dB/m
MRI-PDFF <sup>58</sup>	≥S1: ≥5% and ≥S2: 10%
Assessment of fibrosis stage	
FIB-4 <sup>59,61</sup>	1.3 for rule-out and 2.67 for rule-in advanced fibrosis
NFS <sup>3</sup>	−1.455 for rule-out and 0.676 for rule-in advanced fibrosis
LSM <sup>1,3,61</sup>	8 kPa for rule-out and 12 kPa for rule-in advanced fibrosis
LSM <sup>60</sup>	10 kPa for rule-out and 15 kPa for rule-in cirrhosis
Agile 3+ <sup>62</sup>	0.451 for rule-out and 0.679 for rule-in advanced fibrosis
Agile 4 <sup>62</sup>	0.251 for rule-out and 0.565 for rule-in cirrhosis
Assessment of MASH with significant fibrosis (F2, F3)	
FAST <sup>63</sup>	0.35 for rule-out and 0.67 for rule-in
MAST <sup>65</sup>	0.165 for rule-out and 0.242 for rule-in
acFibroMASH index <sup>64</sup>	0.15 for rule-out and 0.39 for rule-in

CAP, controlled attenuation parameter; UAP, ultrasonic attenuation parameter; S1, mild steatosis (<10% hepatocytes); S2, moderate steatosis (10–30% hepatocytes); S3, severe steatosis (>30% hepatocytes); MRI-PDFF, magnetic resonance imaging proton density fat fraction; NFS, NAFLD fibrosis score; LSM, liver stiffness measurement; FAST, FibroScan-AST; MAST, MRI-AST.

sound. As a continuous variable, CAP/UAP can also monitor changes in liver fat content over time (Table 7).<sup>1,3,12,54–65</sup> Based on the CAP values measured by FibroScan<sup>®</sup> with M probe, the optimal cutoffs for significant hepatic steatosis (≥S1), moderate-to-severe steatosis (≥S2), and severe steatosis (S3) in patients with chronic liver diseases were 248 dB/m, 268 dB/m, and 280 dB/m, respectively.<sup>57</sup> CAP has been shown to be more accurate than ultrasound in diagnosing hepatic steatosis in CHB patients. However, its accuracy declines when the interquartile range exceeds 30 dB/m. Factors like obesity, skin-to-liver capsule distance > 25 mm, and the use of XL probes can also lead to overestimation of CAP values. Currently, no consensus exists on the ideal CAP cutoffs for diagnosing and grading hepatic steatosis.<sup>1,2,55,66,67</sup> FibroTouch<sup>®</sup> measurements of UAP provide results similar to CAP values from FibroScan<sup>®</sup>. In patients with chronic liver diseases, hepatic steatosis can be diagnosed based on UAP cutoffs by ≥ S1 (244 dB/m), ≥S2 (269 dB/m), and S3 (296 dB/m).<sup>56</sup> Quantitative ultrasound fat fraction may offer greater accuracy in diagnosing significant steatosis compared to CAP or UAP.<sup>68</sup> Magnetic resonance imaging proton density fat fraction (MRI-PDFF) provides an objective assessment of total liver fat content and is used in some clinical trials. MRI-PDFF ≥ 5% and 10% indicate significant and moderate-to-severe hepatic steatosis, respectively.<sup>58</sup> However, its high cost and limited availability restrict routine clinical practice.<sup>58,68</sup> Simple discriminant models based on anthropometric parameters, medical history, and common laboratory markers—such as the fatty liver index, hepatic steatosis index, NAFLD liver fat score, and TG-glucose-waist circumference index—are primarily used in epidemiological studies of FLD in the general population.<sup>69</sup>

#### **Non-invasive assessment of steatohepatitis and fibrosis**

Serum markers like alanine aminotransferase (ALT) and cy-

tokerin-18 M30 can indicate hepatocyte damage and apoptosis in patients with MAFLD. However, their accuracy is insufficient for diagnosing MASH.<sup>1,2,4,70</sup> Novel biomarkers, such as those derived from gut microbiota and their metabolites, are also unable to replace liver biopsy for MASH diagnosis.<sup>71,72</sup>

Fortunately, liver biopsy is usually unnecessary for staging fibrosis (Table 7). Thresholds such as the FIB-4 (<1.30 and >2.67) and the NAFLD Fibrosis Score (<−1.455 and >0.676) can be used to preliminarily assess the likelihood of advanced fibrosis in MAFLD patients. However, their accuracy is influenced by age (less reliable in patients under 35 or over 65 years old) and serum transaminase levels.<sup>59</sup> Other non-invasive fibrosis models, such as the Hepamet fibrosis score, enhanced liver fibrosis, and ADAPT algorithm, are rarely reported in China.<sup>54</sup> The LSM obtained by FibroScan<sup>®</sup> offers greater accuracy in diagnosing fibrosis compared to simple fibrosis scores such as FIB-4, but its accuracy can be affected by factors such as severe obesity, non-fasting state, elevated serum ALT, liver congestion, cholestasis, and severe hepatic steatosis.<sup>73,74</sup> LSM cut-off values of 8 kPa and 12 kPa are used to rule out and rule in advanced fibrosis/advanced chronic liver disease in MAFLD patients, respectively.<sup>1–3,75,76</sup> LSM cut-off values of 10 kPa and 15 kPa can be used to rule out and rule in cirrhosis.<sup>60</sup> A sequential or combined application of FIB-4 and LSM can improve fibrosis diagnostic accuracy. A combination using FIB-4 cut-off values (<1.3; ≥2.67) followed by LSM cut-off values (<8.0; ≥12.0 kPa) for ruling out or ruling in advanced fibrosis achieved sensitivity and specificity rates of 66% and 86%. Another combination of FIB-4 cut-off values (<1.3; ≥3.48) and LSM cut-off values (<8.0; ≥20.0 kPa) to rule out advanced fibrosis or rule in cirrhosis showed a sensitivity of 38% and specificity of 90%.<sup>61</sup>

Incorporating anthropometric indices, underlying metabolic diseases, laboratory biomarkers, and imaging data can further improve NITs for identifying steatohepatitis and fibrosis in MAFLD patients.<sup>77</sup> The Agile scoring system, which

combines gender, T2DM status, aspartate aminotransferase (AST)/ALT ratio, platelet count, and LSM by FibroScan<sup>®</sup>, enhances diagnostic performance for advanced fibrosis (Agile 3+) and cirrhosis (Agile 4) in patients with MAFLD. The cut-off values of Agile 3+ were 0.451 and 0.679 to rule out and rule in advanced fibrosis, respectively, while for Agile 4, the cut-offs were 0.251 and 0.565 to rule out and rule in cirrhosis.<sup>62</sup> A combined model incorporating FIB-4, high-density lipoprotein cholesterol, and LSM by FibroScan<sup>®</sup> can further improve diagnostic efficiency for advanced fibrosis in T2DM patients.<sup>78</sup> LSM assessed by FibroTouch<sup>®</sup> and shear wave elastography is likely comparable to FibroScan<sup>®</sup> for diagnosing advanced fibrosis and cirrhosis.<sup>79</sup> While the positive predictive value of magnetic resonance elastography (MRE) for diagnosing advanced fibrosis and cirrhosis in MAFLD patients is similar to that of FibroScan<sup>®</sup>, MRE has a higher negative predictive value.<sup>78</sup> However, there is limited data on MRE's use in fibrosis diagnosis in China.<sup>80</sup> Composite scores such as FAST (calculated from CAP, LSM via FibroScan<sup>®</sup>, and AST levels), MAST (based on LSM using MRE, MRI-PDFF, and AST), ME-FIB (combining LSM from MRE with FIB-4), and acFibro-MASH index (including serum creatinine, AST concentrations, and LSM by TE) may be helpful to diagnose suspected MASH with significant fibrosis and predict the risk of liver-related events.<sup>63-65,81</sup>

### Assessment of liver histology

Liver biopsy is the gold standard for classifying and staging MAFLD. It is essential for differentiating MASH from metabolic dysfunction-associated simple steatosis, and it may be necessary when there is diagnostic uncertainty regarding the fibrosis stage based on NITs. Biopsy specimens should undergo hematoxylin-eosin staining to evaluate morphological features, along with Sirius red or Masson's trichrome staining to assess fibrosis. The pathology report must clearly describe the degree and distribution of hepatic steatosis, hepatocyte ballooning, inflammation, and fibrosis. Additionally, the report should indicate the presence or absence of significant lesions, such as architectural distortion and pseudolobules of the liver.<sup>1,2,12,14</sup> The histological criteria for diagnosing hepatic steatosis in MAFLD specify significant steatosis ( $\geq 5\%$  of hepatocytes showing macrovesicular steatosis). The diagnosis of MASH requires the coexistence of steatosis, hepatocyte ballooning and inflammation. Compared to the NAFLD Activity Score (the unweighted sum of steatosis, lobular inflammation, and hepatocellular ballooning scores) proposed by the U.S. NASH Clinical Research Network, the SAF score (which combines steatosis, activity, and fibrosis scores) proposed by the European Fatty Liver Inhibition of Progression Pathology Consortium has improved interobserver variability in diagnosing MASH.<sup>1,2,6,12,14</sup> However, these scoring systems rely on semi-quantitative assessments of histological features of FLD and must be interpreted alongside clinical information for an accurate etiological diagnosis. Artificial intelligence and machine learning can enhance the consistency of pathologists' evaluations regarding MASH and fibrosis stage.<sup>82</sup>

When considering liver biopsy, the cost and associated risks must be weighed against the potential benefits, including clarifying etiology, elucidating pathogenesis, assessing prognosis, and guiding treatment for suspected MAFLD patients. Indications for liver biopsy in MAFLD patients include (1) Participation in clinical trials for new drug development in MASH and NITs; (2) Inconsistent results from two or more NITs when assessing fibrosis or discordance between NIT and clinical features; (3) Determination of the cause of elevat-

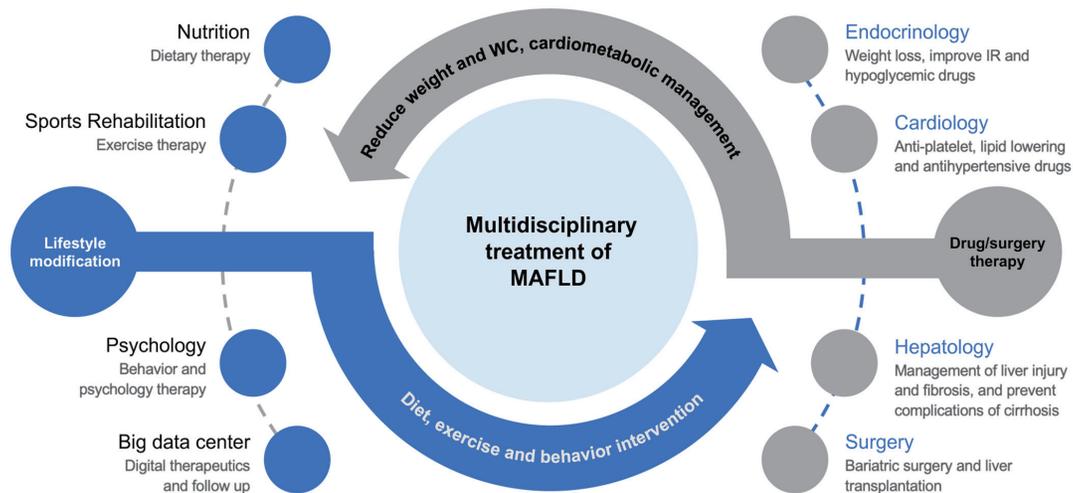
ed serum liver enzymes or advanced fibrosis when two or more liver injury factors coexist; (4) Endoscopic bariatric and metabolic surgery; and (5) Coexisting presence of atypical manifestations, such as significant elevation of blood immunoglobulins, high-titer positivity of autoantibodies, moderate to severe elevation of serum transaminases, or persistent abnormal serum transaminases after significant weight loss.<sup>1,2,6,12</sup>

### Assessment of liver-related complications

MAFLD patients diagnosed with advanced fibrosis or cirrhosis, whether through liver biopsy or NITs, should be screened and monitored for liver-related events, including HCC.<sup>83</sup> Therefore, MAFLD patients with FIB-4  $> 2.67$  and LSM by TE  $> 12$  kPa or Agile 3+  $\geq 0.679$  should be screened for HCC by serum alpha-fetoprotein and abdominal ultrasound. In cases of poor ultrasound quality or suspected liver cancer, further evaluation with computed tomography and/or magnetic resonance imaging is recommended.<sup>82</sup> For suspected intrahepatic cholangiocarcinoma, it is advised to test for serum carcinoembryonic antigen and carbohydrate antigen 199 as well. LSM by TE and blood platelet count in patients with advanced chronic liver disease can help predict clinically significant portal hypertension. Cirrhotic MAFLD patients with LSM  $\geq 20$  kPa and/or blood platelet count  $\leq 150 \times 10^9/L$  typically require endoscopic screening for esophageal varices.<sup>3,76</sup>

### Assessment of extrahepatic complications

Patients with suspected MAFLD should undergo routine measurements of height, body weight (to calculate BMI), waist circumference, and blood pressure. A thorough evaluation should include questions about smoking and alcohol consumption, diet and exercise habits, as well as a history of obesity, hypertension, diabetes, dyslipidemia, coronary artery disease, stroke, and any family history of cirrhosis or HCC. Special attention should be given to medications that may increase body weight or induce liver injury. MAFLD patients without a history of diabetes should be tested for fasting plasma glucose and hemoglobin A1c. For those with fasting plasma glucose levels between 6.1 and 6.9 mmol/L or hemoglobin A1c levels of 5.7% to 6.4%, an oral glucose tolerance test should be conducted to screen for T2DM. For patients with normal glucose metabolism, the homeostasis model assessment of insulin resistance (HOMA-IR) index can be calculated based on fasting plasma glucose and insulin levels. A lipid panel and biochemical tests for renal function can help screen for dyslipidemia, hyperuricemia, and CKD. MAFLD patients with a normal BMI should undergo body composition analysis to screen for sarcopenia and sarcopenic obesity.<sup>84</sup> Additionally, screening for atherosclerosis should be conducted using funduscopy or carotid artery ultrasound. Screening for CVD should be based on the 10-year and lifetime CVD risk assessment models for Chinese adults.<sup>85</sup> Screening for non-hepatic malignancies should be tailored according to the patient's age, gender, and other risk factors.<sup>1,2,6,12,14,84</sup> The independent roles of hypothyroidism, hypopituitarism, and polycystic ovary syndrome in the pathogenesis of MASH and fibrosis require further investigation; therefore, routine testing of thyroid function, androgens, and growth hormone is not recommended.<sup>6</sup> Furthermore, the accuracy of genetic risk variant testing is suboptimal for the prediction of liver disease severity and progression of MAFLD at the individual level.<sup>1,3</sup> Consequently, routine measurement of genetic risk profiles, such as *PNPLA3* p.I148M and *TM6SF2* p.E167K variants, is not recommended in clinical practice.



**Fig. 3. The multidisciplinary management for MAFLD.** MAFLD, metabolic dysfunction-associated fatty liver disease; IR, insulin resistance.

**Recommendation 8:** The diagnosis of MAFLD should meet the following three criteria: (1) Imaging techniques and/or liver biopsy confirming hepatic steatosis; (2) Presence of one or more components of MetS; (3) Exclusion of other potential etiologies of hepatic steatosis (B, 1).

**Recommendation 9:** In patients with ALD and/or fatty liver caused by other specific etiologies, the presence of obesity and/or T2DM, MetS should be considered as a potential coexistence of MAFLD (C, 1).

**Recommendation 10:** MAFLD can often coexist with other liver diseases, such as CHB infection (B, 1).

**Recommendation 11:** Ultrasonography is the preferred imaging technique for diagnosing hepatic steatosis and for screening and monitoring HCC (B, 1).

**Recommendation 12:** Transient elastography cut-off values of CAP/UAP (248/244 dB/m, 268/269 dB/m, and 280/296 dB/m for diagnosis of steatosis degree as  $\geq S1$ ,  $\geq S2$ , and  $S3$ , respectively) and LSM (8 kPa to rule out and 12 kPa to rule in advanced fibrosis) can be used for non-invasive assessments of hepatic steatosis and advanced fibrosis (B, 1).

**Recommendation 13:** MRI-PDFF can accurately assess hepatic fat content and its changes in some clinical trials of MAFLD (B, 1).

**Recommendation 14:** The FIB-4 score can serve as an initial tool to evaluate the risk of advanced fibrosis in MAFLD patients and high-risk populations. Individuals with  $FIB-4 \geq 1.3$  should undergo LSM by transient elastography for further risk stratification of fibrosis (B, 1).

**Recommendation 15:** MAFLD patients with  $FIB-4 \geq 1.3$  and  $LSM \geq 8$  kPa should undergo further diagnosis and assessment by hepatologists (B, 1).

**Recommendation 16:** MAFLD patients with inconsistent NIT results for fibrosis assessment and/or persistent elevation of serum aminotransferases should undergo further diagnosis and assessment by hepatologists (C, 1).

**Recommendation 17:** Indications for liver biopsy in suspected MAFLD patients include: the need for accurate assessment of MASH and fibrosis in clinical trials; differential diagnosis or identification of primary etiolo-

gy when two or more liver injury factors coexist; uncertain or inconsistent results from NITs for advanced fibrosis; bariatric surgery; and atypical presentations, such as moderate to severe elevation of transaminases or persistent abnormal transaminases after weight loss (B, 1).

**Recommendation 18:** Liver biopsy specimens require hematoxylin-eosin staining, as well as Sirius red or Masson's trichrome staining. Pathological results should be described using standardized scoring systems, such as the SAF and NAFLD Activity Score (C, 1).

**Recommendation 19:** The diagnosis of MASH should be based on the following two criteria: (1) Meeting clinical diagnostic criteria for MAFLD; (2) Presence of  $\geq 5\%$  macrovesicular steatosis with hepatocyte ballooning and lobular inflammation and/or portal inflammation (C, 1).

**Recommendation 20:** The diagnosis of metabolic dysfunction-associated liver fibrosis may be based on the following three criteria: (1) Liver biopsy-proven significant fibrosis (F2 and F3) and/or NITs diagnosing advanced fibrosis (F3 and F4); (2) Presence of one or more components of MetS; (3) Exclusion of other potential etiologies of liver fibrosis (C,1).

**Recommendation 21:** The diagnosis of metabolic dysfunction-associated cirrhosis/MAFLD-related cirrhosis may be based on the following three criteria: (1) Liver biopsy and/or NITs proven cirrhosis; (2) Past or present history of MAFLD; (3) Exclusion of other potential etiologies of liver cirrhosis (C,1).

**Recommendation 22:** For MAFLD patients with cirrhosis, endoscopic screening for esophageal varices can be determined based on platelet count and LSM obtained through transient elastography (C, 1).

## Treatment

The treatment of MAFLD requires a multidisciplinary approach, focusing on strategies that aim to reduce body weight and waist circumference, improve IR, prevent and manage MetS and T2DM, alleviate MASH, and reverse liver fibrosis (Fig. 3).<sup>1,2,6,7,12,86,87</sup> All patients across the spec-

trum of MAFLD require health education to modify unhealthy lifestyles, and further medication interventions are necessary when cardiometabolic diseases and liver injury coexist. Weight loss can improve metabolic dysfunction and liver injury in MAFLD patients in a dose-dependent manner. When selecting weight loss medications, lipid-lowering medications, antihypertensive medications, antidiabetic medications, and antiplatelet medications, it is essential to consider cardiovascular, renal, and hepatic benefits, while also paying attention to their role in preventing obesity-related malignancies. Even in patients with established cirrhosis, medication therapy for cardiometabolic risk factors and associated diseases should be emphasized. MAFLD patients who meet the appropriate surgical criteria may consider metabolic surgery and liver transplantation.<sup>1,2,6,7,12,14</sup>

### **Lifestyle modification**

Lifestyle modifications aimed at adjusting dietary patterns and increasing physical activity are the cornerstone of treating all forms of MAFLD.<sup>1,2,6,7,12,14,87–89</sup> In MAFLD patients with overweight or obesity, achieving greater weight loss yields more significant benefits for metabolism, cardiovascular health, and liver function in the long term. A gradual weight loss of 3% to 5% within one year may reverse hepatic steatosis; a loss of 7% to 10% can alleviate MASH; a loss exceeding 10% may reverse fibrosis; and a loss of 15% may even alleviate coexisting T2DM.<sup>90–92</sup> Moreover, MAFLD patients with a normal BMI should also aim for modest weight loss (3% to 5%) to address metabolic dysfunction and liver disease.<sup>93</sup> Lean individuals with MAFLD typically require a low-calorie, high-protein diet, and increased physical activity to prevent and treat underlying sarcopenic obesity.

**Dietary therapy:** A close association exists between high-energy-density or pro-inflammatory foods (rich in saturated fats, cholesterol, refined carbohydrates, sugar-sweetened beverages, and ultra-processed foods) and the prevalence of MAFLD. Conversely, diets adhering to the Healthy Diet Index, Dietary Approaches to Stop Hypertension, Mediterranean diet, and those high in antioxidant-rich foods (such as fresh fruits, green vegetables, whole grains, and foods rich in  $\omega$ -3 polyunsaturated fatty acids) are linked to a reduced risk of MAFLD. MAFLD patients are advised to focus on both controlling energy intake and adjusting their dietary patterns.<sup>87,94–96</sup> There is a dose-response relationship between energy restriction and improvements in body weight and liver function. Reducing daily energy intake by 500 to 1,000 kcal can facilitate gradual weight loss and decrease liver fat content, accompanied by improvements in IR and normalization of serum aminotransferase levels. Low-carbohydrate, low-fat, intermittent fasting, and Mediterranean diets can all promote weight loss while providing metabolic, cardiovascular, and hepatic benefits.<sup>97–100</sup> To facilitate implementation and long-term adherence, clinical nutritionists should develop personalized dietary plans based on the patient's comorbidities and preferences. Adequate water intake and limiting sodium (salt) intake to 2,300 mg or less per day are also essential. Currently, there is a lack of randomized controlled trials (RCTs) investigating the effectiveness of dietary interventions, functional foods, prebiotics, vitamin D, folic acid, and similar approaches in improving hepatic inflammation or fibrosis in MAFLD patients. The efficacy of the Jiangnan dietary pattern, akin to the Mediterranean diet, in Chinese patients with MAFLD remains to be studied.<sup>1,2,6,7,12,14,88,89</sup>

**Exercise therapy:** Gradually increasing physical activity can enhance skeletal muscle mass and function while independently reducing liver fat content.<sup>2,7,87,101</sup> Engaging in moderate-intensity aerobic exercise for three to five days per

week, accumulating over 135 mins, can improve cardiopulmonary function and decrease liver fat in MAFLD patients. When exercise duration exceeds 150 to 240 mins per week, moderate-intensity aerobic exercise additionally reduces body weight and waist circumference. High-intensity interval training (comprising one to five bouts of high-intensity exercise lasting 2 to 4 mins each, interspersed with 2 to 3 mins of low-intensity recovery exercise) for three to five days per week, can further reduce liver fat content and potentially enhance cardiopulmonary function.<sup>102</sup> Therefore, MAFLD patients are encouraged to engage in moderate-intensity aerobic exercise and/or high-intensity interval training. A dose-response relationship exists between exercise volume and reductions in liver fat content. For instance, brisk walking for 150 mins per week over three months can reduce liver MRI-PDFF by over 30% in MAFLD patients.<sup>103,104</sup> Combining dietary and exercise therapies proves more effective for MAFLD than either intervention alone, whereas exercise alone does not significantly improve liver inflammation and fibrosis.<sup>105–107</sup> Furthermore, there is insufficient evidence supporting resistance training as a standalone approach for reducing body weight and liver fat; it is currently recommended only for MAFLD patients with poor cardiopulmonary function or those unable to tolerate aerobic exercise.<sup>102</sup> Personalized exercise prescriptions tailored to patients' capabilities can enhance the safety and efficacy of physical activity for MAFLD.

**Behavioral therapy:** MAFLD patients should adopt an energy-deficit diet and avoid smoking, alcohol consumption, irregular eating patterns (such as skipping breakfast, late-night snacking, rapid eating, and consuming soft drinks), staying up late, and a sedentary lifestyle.<sup>87,88,108</sup> Consuming three or more cups of coffee (with or without caffeine) daily is associated with a reduced risk of advanced liver disease and HCC in MAFLD patients, while the hepatoprotective effects of green tea and black tea require further investigation.<sup>87</sup> Strategies are needed to overcome barriers to healthy lifestyles for MAFLD patients and to promote a multidisciplinary integrated care model that includes clinical nutritionists, exercise rehabilitation specialists, and psychological counselors to manage the dual challenges of cardiometabolic risk factors and liver disease. Digital therapies for MAFLD, facilitated by mobile health applications, could fundamentally assist in altering unhealthy lifestyles.<sup>1,6,12,14,109,110</sup>

### **Pharmacological therapy**

**Weight loss drugs:** Achieving a weight loss of over 5% within one year through intensive lifestyle modifications can be challenging for many patients. Therefore, patients with MAFLD and a BMI  $\geq$  28 kg/m<sup>2</sup> can be prescribed weight loss medications such as orlistat, liraglutide, and beaglutide. For obese patients with concomitant T2DM, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and metformin are preferred to manage both body weight and blood glucose levels.<sup>1,2,6,7,12,14,111–116</sup> However, the efficacy of these medications in improving MASH, particularly fibrosis, still requires confirmation through RCTs.<sup>2</sup> Furthermore, the use of medications for coexisting conditions that may contribute to weight gain should be avoided.

**Antidiabetic drugs:** MAFLD patients with prediabetes or T2DM should prioritize antidiabetic medications that offer potential hepatic benefits.<sup>1,2,6,7,12,14,117,118</sup> Metformin is the first-line treatment for preventing and managing T2DM in overweight or obese patients. Although it does not alleviate MASH, it may reduce the risk of HCC in patients with MAFLD.<sup>113</sup> Pioglitazone, a peroxisome proliferator-activated receptor  $\gamma$  agonist, has been shown to significantly improve

NAFLD activity scores and MASH in non-cirrhotic MASH patients with prediabetes or T2DM at doses of 30–45 mg/day. However, it requires constant monitoring for side effects such as weight gain, edema, worsening heart failure, and an increased risk of osteoporosis.<sup>118</sup> SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, can help reduce body weight, improve IR, and enhance cardiovascular and renal outcomes. They also prevent and treat heart failure, lower serum aminotransferase levels, and reduce liver fat content as assessed through imaging in MAFLD patients with T2DM. The primary adverse effects of these medications include genitourinary tract infections, hypovolemia, and osteoporosis.<sup>114–116</sup> Recent evidence suggests that incretin-based therapies may be superior to pioglitazone and SGLT-2 inhibitors for the treatment of MAFLD.<sup>119</sup> GLP-1 receptor agonists (e.g., liraglutide and semaglutide) are approved for the treatment of T2DM and obesity, which can reduce body weight and IR, lower CVD risk, delay CKD progression, and even prevent stroke. Two phase 2 trials showed semaglutide and liraglutide treatment resulted in hepatic histological benefits for patients with MASH.<sup>120,121</sup> However, semaglutide has not been shown to reverse fibrosis or resolve MASH in patients with compensated cirrhosis.<sup>122</sup> Additionally, the dual agonist of the glucose-dependent insulinotropic polypeptide and GLP-1 receptors (e.g., tirzepatide) and the dual agonist of glucagon and GLP-1 receptors (e.g., survodutide) are in development and have shown promising results in phase 2 trials.<sup>123,124</sup> Therefore, these newly developed dual agonists demonstrate better therapeutic effects than GLP-1 receptor agonists, warranting further investigation in phase 3 trials.<sup>125</sup> Currently, there is still a paucity of research data on the use of antidiabetic drugs in patients with MASH-related cirrhosis. Insulin remains the only safe option for patients with decompensated cirrhosis and acute-on-chronic liver failure (ACLF).<sup>118</sup> There is no evidence that insulin, acarbose, or dipeptidyl peptidase IV inhibitors have therapeutic effects on MAFLD.

**Lipid-lowering drugs:** For MAFLD patients with concomitant dyslipidemia, lipid-lowering drugs should be selected based on CVD risk stratification to maintain serum low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, TG, and apolipoprotein B at target levels.<sup>1,6,7,12,14,118</sup> Statins are the first-line agents for reducing CVD risk and are typically started at low doses; however, moderate to high doses may be necessary to achieve low-density lipoprotein cholesterol targets. In cases of statin intolerance or failure to reach lipid goals, adding or switching to ezetimibe or proprotein convertase subtilisin/kexin type-9 inhibitors is recommended.<sup>1,6,7,12,14</sup> Increasing evidences show that statins have good hepatic safety profiles and may slow liver disease progression, reduce portal vein pressure, and prolong survival in patients with compensated cirrhosis.<sup>1,6,7,12,14,126–128</sup> Recent results from a cohort study following 7,988 patients with MAFLD for a median of 4.6 years indicate that statin use is associated with a lower long-term risk of all-cause mortality, liver-related events, and fibrosis progression.<sup>129</sup> While statins, metformin, and aspirin can reduce the risk of HCC, only statins are independently associated with a decreased risk of HCC in patients with cirrhosis, MAFLD, and those treated concomitantly with aspirin or metformin.<sup>130</sup> Simvastatin can improve liver blood circulation and reduce portal vein pressure in patients with decompensated cirrhosis but should be used cautiously at low doses (20 mg/day).<sup>131</sup> However, there is currently a lack of histological evidence showing that statins improve MASH and fibrosis, so they should be used with caution or temporarily discontinued in patients with decompensated cirrhosis or ACLF.<sup>6,7,12</sup> Fibrates

do not provide cardiovascular benefits and are primarily used in MAFLD patients with serum TG levels > 5.6 mmol/L to reduce the risk of acute pancreatitis.<sup>1,6,7,12,14</sup>

Antihypertensive drugs: MAFLD patients with arterial hypertension should aim to maintain their blood pressure below 130/85 mmHg. The preferred medications are angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which can simultaneously reduce the risks of CVD, CKD, and their associated complications.<sup>1,6,7,12,132</sup> When blood pressure control is suboptimal, additional medications such as calcium channel blockers, non-selective beta-blockers (with carvedilol or propranolol being the primary choices for patients with clinically significant portal hypertension to prevent esophageal variceal bleeding), and thiazide diuretics may be added. A compound medication containing aspirin (81 mg), atorvastatin (20 mg), hydrochlorothiazide (12.5 mg), and either enalapril (5 mg) or valsartan (40 mg), taken once daily, has been shown to significantly reduce major cardiovascular events and CVD-related mortality in adults aged 40 to 75. This effect is even more pronounced in patients with MAFLD.<sup>133</sup> These commonly prescribed antihypertensive medications have good hepatic safety profiles, and ACEIs may help lower the risk of liver-related events in MAFLD patients.<sup>134</sup> Additionally, an RCT found that an 81 mg/day dose of aspirin significantly reduced liver fat content in MAFLD patients.<sup>135</sup>

**Therapeutic agents for MASH and fibrosis:** In non-diabetic and non-cirrhotic MASH patients, an 18-month course of antioxidant therapy using vitamin E (alpha-tocopherol, 800 IU/day) significantly improves hepatic steatosis and can alleviate MASH without worsening fibrosis. However, the potential risks of hemorrhagic stroke and prostate cancer limit its routine long-term use at a high dose.<sup>136,137</sup> Results from a multicenter RCT in China demonstrated that oral vitamin E at a dose of 300 mg daily was safe and resulted in significantly higher histological improvement (MASH remission without worsening fibrosis) in nondiabetic MASH patients.<sup>138,139</sup> Ursodeoxycholic acid, whether administered at conventional or high doses, can improve serum biochemical parameters of liver function but does not alleviate MASH. On the other hand, obeticholic acid, a farnesoid X receptor agonist, can reverse fibrosis, but adverse reactions such as pruritus and dyslipidemia hinder its approval for the treatment of MASH.<sup>140</sup> Preliminary results from RCTs of novel drugs, including the liver-directed thyroid hormone receptor beta-selective agonist (Resmetirom), pan-peroxisome proliferator-activated receptor agonists (Lanifibranor), fibroblast growth factor 21 analogs (Efruxifermin, Pegozafermin), and the dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist (tirzepatide), show promising results.<sup>141–146</sup> In March 2024, the U.S. Food and Drug Administration approved Resmetirom for treating non-cirrhotic MASH patients with significant fibrosis.<sup>147</sup> Patients with MASH and advanced fibrosis or cirrhosis should be encouraged to participate in RCTs.

Several widely used therapeutic agents for liver injury in China, including silymarin (Silybin), polyenylphosphatidylcholine, bicyclol, glycyrrhizic acid preparations (e.g., magnesium isoglycyrrhizinate, compound glycyrrhizin, diammonium glycyrrhizinate), and reduced glutathione, have been found to assist in improving liver biochemical parameters in patients with chronic liver diseases, including MAFLD. However, there is insufficient evidence supporting their histological benefits in MAFLD.<sup>1,2,12,14,148–150</sup> Currently, these therapeutic drugs for liver injury might be used in the following types of MAFLD patients: (1) Patients with liver biopsy-proven MASH and/or significant fibrosis; (2) Patients with persistently el-

evated liver enzymes or NITs suggesting a risk of advanced fibrosis; (3) Patients with concomitant drug-induced liver injury, autoimmune hepatitis, chronic viral hepatitis, or other types of liver injury. It is recommended to select one of these therapeutic agents for long-term treatment, in addition to comprehensive therapy, based on the type and severity of liver injury, as well as the efficacy and cost of the medication. If there is no significant reduction in serum aminotransferase levels after six months of treatment, alternative hepatoprotectants should be considered.

### **Surgical therapy**

**Bariatric surgery:** Obese patients and those with related metabolic disorders can undergo laparoscopic surgery to reduce body weight and treat metabolic disorders. Procedures such as gastric bypass, sleeve gastrectomy, duodenal switch surgery, and adjustable gastric banding have significant and lasting effects on weight loss in obese patients. These surgeries also lead to high remission rates of MetS and T2DM, along with decreased incidence and mortality of CVD and malignancies (including HCC).<sup>1,6,7,12,14,151</sup> Approximately 65% to 90% of patients undergoing bariatric surgery have MAFLD, with postoperative remission of MASH and reversion of fibrosis in about 75% and 70% of cases, respectively.<sup>1,6,152</sup> MAFLD patients with overweight or obese who meet the criteria for bariatric surgery and have no evidence of established cirrhosis can be considered for the treatment of MASH and fibrosis through bariatric surgery, particularly when BMI > 32.5 kg/m<sup>2</sup> and accompanied by T2DM. However, it is essential to be aware of potential perioperative complications, postoperative malnutrition, and the risk of alcohol abuse.<sup>1,6,12</sup> Currently, there is a lack of RCTs comparing different types of bariatric surgery with other interventions, making it challenging to accurately assess their advantages and disadvantages in treating MASH and related fibrosis. Endoscopic sleeve gastrectomy, intragastric balloon insertion, and other weight-loss techniques may hold potential for treating obesity and related diseases; however, they lack sufficient histological evidence of liver benefits and are therefore not recommended for fibrotic MASH.<sup>1,6,12</sup> The type, safety, and efficacy of bariatric surgery in patients with compensated cirrhosis remain to be clarified. Evaluation by a multidisciplinary team, including liver disease experts, is necessary to assess the benefits and risks associated with bariatric surgery. Additionally, surgeries on cirrhotic patients should be performed by experienced experts in hospitals with liver transplantation qualifications.<sup>1,6,12,152</sup> Studies have reported the safety and effectiveness of sleeve gastrectomy in treating severe obesity in patients with cirrhosis and clinically significant portal hypertension. After surgery, patients typically experience reductions in body weight, blood pressure, fasting plasma glucose, lipids, CAP, and LSM obtained through TE.<sup>153</sup> However, the risk of complications from bariatric surgery is notably high and severe in patients with decompensated cirrhosis.<sup>152,153</sup>

**Liver transplantation:** MASH-related cirrhosis, ACLF, and HCC are increasingly recognized as indications for liver transplantation worldwide,<sup>154</sup> including in China. Most patients with these conditions also have coexisting CHB or ALD (mixed etiologies of end-stage liver disease). The incidence of complications, overall survival rates, and graft survival rates in MASH patients undergoing liver transplantation are comparable to those of patients undergoing transplantation for other etiologies of liver diseases.<sup>1,6,12,155,156</sup> Extrahepatic complications can increase the risk of adverse outcomes following liver transplantation, with CVD being a significant contributor to postoperative mortality, particularly in patients

with a history of T2DM, CKD, and CVD.<sup>1,6,7,12,14</sup> Perioperative monitoring and postoperative follow-up for MASH patients undergoing liver transplantation require effective management of comorbidities such as MetS components and CVD, as well as careful use of immunosuppressive agents such as corticosteroids and calcineurin antagonists. Patients with dyslipidemia and/or a history of CVD should receive statin therapy and enhanced management of cardiometabolic risk factors post-transplantation.<sup>1,6,7,12,14</sup> Given that obesity is a significant risk factor for MASH recurrence after liver transplantation, combining liver transplantation with bariatric surgery may be considered for patients with severe obesity and end-stage liver disease.<sup>152</sup>

**Recommendation 23:** Patients with MAFLD require health education to promote lifestyle modifications. Structured dietary and exercise programs are the cornerstones of MAFLD treatment (B, 1).

**Recommendation 24:** For MAFLD patients who are overweight or obese, a weight reduction of at least 5% to 10% is crucial for treating metabolic disorders and liver disease. For patients with a normal BMI, a weight loss of 3% to 5% is sufficient (B, 1).

**Recommendation 25:** Patients with MAFLD should adhere to energy-deficit dietary therapy, limiting the intake of ultra-processed foods, high-saturated-fat foods, and high-sugar/fructose foods or beverages, while increasing consumption of high-fiber foods such as vegetables, whole grains, and foods rich in unsaturated fatty acids (C, 1).

**Recommendation 26:** Patients with MAFLD should engage in physical activity, aiming for moderate-intensity aerobic exercise for at least 150 mins per week and/or high-intensity interval training for three to five days per week over a period of more than three months (B, 1).

**Recommendation 27:** Patients with MAFLD should avoid unhealthy behaviors such as irregular eating, soft drink consumption, smoking, alcohol intake, and a sedentary lifestyle (C, 1).

**Recommendation 28:** Coexisting conditions in MAFLD patients, such as obesity, T2DM, dyslipidemia, hypertension, and CVD, should be managed in a standardized manner by appropriate specialists or general practitioners (C, 1).

**Recommendation 29:** MAFLD patients with a BMI ≥ 28 kg/m<sup>2</sup> may consider using weight loss medications, with a priority on incretin-based therapies for those with coexisting T2DM (B, 1).

**Recommendation 30:** For T2DM management in MAFLD patients, priority should be given to drugs with potential hepatic benefits, such as incretin-based therapies, SGLT-2 inhibitors, pioglitazone, and metformin (B, 1).

**Recommendation 31:** In patients with compensated MAFLD, statins are the preferred treatment for atherosclerotic dyslipidemia. However, statins should be discontinued in patients with decompensated cirrhosis or ACLF (C, 1).

**Recommendation 32:** For managing hypertension in MAFLD patients, the preferred medications are ACEIs or ARBs. In cases of clinically significant portal hypertension, non-selective beta-blockers can be used alone or in combination with ACEIs or ARBs (C, 1).

**Recommendation 33:** MAFLD patients with biopsy-proven MASH and fibrosis, or NITs indicating suspected

liver inflammation and/or fibrosis, can be treated with long-term liver injury therapeutic agents or be encouraged to participate in clinical trials (C, 1).

**Recommendation 34:** Non-cirrhotic MAFLD patients who meet the criteria for bariatric surgery may consider undergoing the surgery for the treatment of MASH and fibrosis (C, 2).

**Recommendation 35:** Patients with MAFLD-related decompensated cirrhosis, ACLF, or HCC should consider liver transplantation (B, 1).

**Recommendation 36:** MAFLD patients with advanced fibrosis and cirrhosis should strengthen management of body weight and plasma glucose levels. Medications such as statins, metformin, aspirin, and strategies for smoking cessation and alcohol abstinence may help reduce the risk of HCC (C, 1).

## Efficacy evaluation and follow-up

### Efficacy evaluation of the management

The treatment goals for MAFLD include reducing the risk of cardiovascular-renal-MetS, malignant tumors, and liver-related complications, while also improving patient-reported outcomes and quality of life. Efficacy evaluation encompasses various factors, including anthropometric indicators, blood biochemical analyses, the degree of liver steatosis, inflammation and fibrosis, adherence and adverse reactions to medication therapy, as well as patient satisfaction regarding quality of life and lifestyle changes, thereby continually refining treatment strategies and improving therapeutic effects during long-term follow-up.<sup>1,2,6,7,12,157-163</sup> Liver biopsy demonstrating remission of steatohepatitis and reversal of fibrosis are crucial treatment endpoints in clinical trials for fibrotic MASH. However, frequent liver biopsies for dynamic observation of histological changes are not feasible in routine clinical practice. In drug clinical trials, a decrease in serum ALT levels by more than 17 U/L, along with a reduction of more than 30% in liver MRI-PDFF compared to baseline, typically indicates hepatic histological improvement.<sup>1</sup>

Lifestyle interventions have better sustained effects in MAFLD patients with a normal BMI, often requiring only a subtle reduction in body weight. For MAFLD patients who achieve a weight loss of over 5% and maintain it for more than three months, it is essential to monitor for potential comorbidities, such as sarcopenia, T2DM, hyperthyroidism, and malignant tumors, especially if no improvement is observed in biochemical markers such as HOMA-IR and plasma glucose levels. If there is no decrease in serum aminotransferases, patients should be vigilant for other etiologies of liver injury, such as alcohol abuse, drug-induced hepatotoxicity, or concurrent liver diseases. Additionally, a decrease in serum aminotransferase levels and CAP/UAP, accompanied by an increase in LSM by TE during follow-up, may indicate ongoing liver disease progression.<sup>12,161</sup>

The coexistence of metabolic dysfunction and FLD may not impact the viral response to antiviral therapy in CHB patients with MAFLD. The remission rate and incidence of biopsy-proven MASH after 72 weeks of entecavir antiviral treatment are influenced by baseline overweight status and subtle changes in body weight in CHB patients.<sup>27,163,164</sup> Moreover, other liver diseases coexisting with MAFLD require active intervention, following the treatment principles outlined in relevant disease prevention and treatment guidelines. During follow-up, MAFLD patients should abstain

from alcohol or limit consumption to mild levels. For cases of MAFLD with coexisting ALD, prompt cessation of alcohol consumption and long-term abstinence are crucial for favorable outcomes.<sup>1,2,12</sup>

### Regular follow-up and monitoring

Given that MAFLD is a slowly progressive disease, clinicians should pay more attention to patients' lifestyles and regularly monitor their blood biochemical indicators, steatosis degree, and fibrosis stage. It is also vital to manage emerging comorbidities during long-term follow-up.<sup>1,2,6,7,12,14</sup> Regular assessments should include changes in body weight, waist circumference, and blood pressure, as well as dietary habits, physical activity levels, smoking, alcohol consumption, and medication adherence. Blood biochemical indicators, including liver and kidney function tests, blood lipid levels, and blood glucose, should be monitored every three to six months. Complete blood counts, along with upper abdominal and carotid ultrasounds, should be performed every six to twelve months. For patients without glucose metabolism abnormalities, insulin sensitivity should be monitored using HOMA-IR. Patients with a normal BMI should undergo annual body composition analyses to evaluate fat and skeletal muscle mass. Furthermore, FIB-4, CAP/UAP, and LSM by TE should be evaluated at least once annually. Baseline and follow-up changes in FIB-4, LSM by TE, and Agile scores can help monitor liver fibrosis and predict the risk of liver-related events.<sup>1,2,6,12,14,160-163</sup> An increase of 20% in LSM by TE during follow-up is associated with a 50% increase in the risk of liver decompensation and liver-related mortality in patients with compensated advanced MAFLD. Conversely, a 20% decrease in LSM reflects a reduced risk of liver-related events.<sup>160-163</sup> MAFLD patients with advanced fibrosis should undergo annual alpha-fetoprotein testing, and those diagnosed with established cirrhosis should also assess the risk of esophageal varices annually and closely monitor liver decompensation events.<sup>12</sup>

**Recommendation 37:** Follow-up indicators for MAFLD patients include assessing lifestyle changes, body weight, regular monitoring of blood pressure, blood biochemical indexes, hepatic steatosis degree, fibrosis stage, and extrahepatic comorbidities (C, 1).

**Recommendation 38:** If serum biochemical indicators, such as aminotransferases, do not improve after weight loss in patients with MAFLD, further investigation and management of the etiology are necessary (C, 1).

**Recommendation 39:** Histological resolution of steatohepatitis in MAFLD patients may be predicted by changes in non-invasive markers (e.g., serum ALT reduction by  $\geq 17$  U/L, MRI-PDFF relative reduction by  $\geq 30\%$ ) in the context of RCTs and depending on the mode of intervention (C, 2).

**Recommendation 40:** An increase in FIB-4 and LSM by TE during follow-up in MAFLD patients usually indicates liver disease progression and an increased risk for liver-related events (B, 1).

**Recommendation 41:** Treatment for other liver diseases coexisting with MAFLD should adhere to recommendations from relevant disease prevention and treatment guidelines (C, 1).

**Recommendation 42:** Patients with MAFLD, regardless of whether they have concomitant ALD, must reduce alcohol consumption and strive for abstinence whenever possible (C, 1).

### Summary, research agenda, and prospects

In summary, the screening, diagnosis, assessment, treatment, and follow-up of MAFLD necessitate the multidisciplinary involvement of hepatologists, endocrinologists, cardiologists, nutritionists, as well as primary care physicians and general practitioners.<sup>165</sup> Lifestyle modifications for weight management, including energy-deficit diets and exercise, are crucial for preventing and managing sarcopenic obesity and for improving cardiovascular, kidney, metabolic, and hepatic health. Medications such as GLP-1 receptor agonists, metformin, SGLT-2 inhibitors, statins, ACEIs/ARBs, and aspirin help prevent cardiometabolic diseases and related complications, with potential benefits for liver health. Liver-directed therapies are primarily used for MASH patients with significant fibrosis. Incretin-based therapy is currently effective in alleviating obesity and T2DM and should be recognized as an important component in the comprehensive prevention and treatment of MAFLD/MASH.<sup>125</sup>

Despite significant advances in clinical hepatology, many critical areas related to the management of MAFLD and its complications require further evidence to refine clinical practices. The research agenda and future prospects include: (1) As one of the most common causes of chronic progressive liver disease and a looming public health emergency in China, MAFLD urgently needs to be integrated into the national chronic disease management system.<sup>166-169</sup> (2) Follow-up cohorts of MAFLD patients with comprehensive clinical phenotypes and biological specimens should be established, utilizing multi-omics technologies for non-invasive assessment of MASH and fibrosis. This effort aims to develop and validate new indicators for the clinical classification of MAFLD and to predict long-term outcomes and treatment responses. (3) Large-sample, long-term, real-world observational studies and multi-center, large-sample RCTs on digital or pharmacological therapies for MAFLD/MASH should be conducted nationwide. (4) A big data platform for dynamic cohort studies of MAFLD should be established to facilitate resource sharing, leveraging the capabilities of artificial intelligence and machine learning to enhance diagnostic and treatment techniques. This initiative aims to address current academic controversies regarding the renaming of NAFLD<sup>170-173</sup> and to develop a Chinese methodology for precise and stratified management strategies for MAFLD based on scientific classification and staging. (5) Given the increasing prevalence of MAFLD in younger populations and chronic HBV-infected individuals, there is a pressing need to strengthen research on the prevention and treatment of FLD in children, adolescents, and patients with CHB infection.<sup>27,174,175</sup>

### Acknowledgments

The expert group for the Guidelines, listed alphabetically by last name, includes: Ji-Hong An (Inner Mongolia Autonomous Region People's Hospital), Hong-Song Chen (Peking University People's Hospital), Yu Chen (Beijing Youan Hospital, Capital Medical University), Xiao-Guang Dou (Shengjing Hospital of China Medical University), Guo-Hong Deng (The First Hospital Affiliated to Army Medical University (Southwest Hospital)), Hui-Guo Ding (Beijing Youan Hospital, Capital Medical University), Yan-Hang Gao (The First Hospital of Jilin University), Yu-Juan Guan (Guangzhou Eighth People's Hospital), Tao Han (Tianjin Union Medical Center, Nankai University), Ying Han (The First Affiliated Hospital of Air Force Medical University (Xijing Hospital)), Peng Hu (The Second Affiliated Hospital of Chongqing Medical University), Yan Huang (Xiangya Hospital, Central South University), Ying-An Jiang (Hubei General Hospital), Jie Li (Peking University

Health Science Center), Jun Li (Jiangsu Province Hospital), Shu-Chen Li (The Second Affiliated Hospital of Harbin Medical University), Rong-Kuan Li (The Second Hospital of Dalian Medical University), Wen-Gang Li (The Fifth Medical Center of Chinese PLA General Hospital), Yu-Fang Li (General Hospital of Ningxia Medical University), Yi-Ling Li (The First Hospital of China Medical University), Shu-Mei Ling (The First Affiliated Hospital of Xi'an Jiao Tong University), Jing-Feng Liu (Fujian Cancer Hospital, Fujian Medical University), Xiao-Qing Liu (Peking Union Medical College Hospital), Lun-Gen Lu (Shanghai General Hospital, Shanghai Jiao Tong University), Xiao-Bo Lu (The First Affiliated Hospital of Xinjiang Medical University), Ming-Qin Lu (The First Affiliated Hospital of Wenzhou Medical University), Xin-Hua Luo (Guizhou Provincial People's Hospital), Xiong Ma (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Yi-Min Mao (Renji Hospital, Shanghai Jiao Tong University School of Medicine), Yu-Qiang Mi (Tianjin Second People's Hospital), Jun-Qi Niu (The First Hospital of Jilin University), Hui-Ying Rao (Peking University People's Hospital), Wan-Hua Ren (Shandong Provincial Hospital), Jia Shang (Henan Provincial People's Hospital), Ming-Hua Su (The First Affiliated Hospital of Guangxi Medical University), Li Wang (Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences), Rong-Qi Wang (The Third Hospital of Hebei Medical University), Zhi-Li Wen (The Second Affiliated Hospital of Nanchang University), Biao Wu (Hainan General Hospital), Chao Wu (The Affiliated Hospital of Nanjing University Medical School (Nanjing Drum Tower Hospital)), Wen Xie (Beijing Ditan Hospital, Capital Medical University), Yao Xie (Beijing Ditan Hospital, Capital Medical University), Shao-Jie Xin (The Fifth Medical Center of Chinese PLA General Hospital), Yong-Ning Xin (Qingdao Municipal Hospital), Hui-Chun Xing (Beijing Ditan Hospital, Capital Medical University), Jing-Hang Xu (Peking University First Hospital), You-Qing Xu (Beijing Tiantan Hospital, Capital Medical University), Bao-Shan Yang (The Second Affiliated Hospital of Harbin Medical University), Chang-Qing Yang (Tongji Hospital, Tongji University), Ji-Ming Yang (Tianjin Second People's Hospital), Li Yang (West China Hospital, Sichuan University), Jin-Hui Yang (The Second Affiliated Hospital of Kunming Medical University), Yong-Feng Yang (The Second Hospital of Nanjing), Hong You (Beijing Friendship Hospital, Capital Medical University), Chao-Hui Yu (The First Affiliated Hospital, Medical School, Zhejiang University), Liao-Yun Zhang (First Hospital of Shanxi Medical University), Da-Zhi Zhang (The Second Affiliated Hospital of Chongqing Medical University), Jing Zhang (Beijing Youan Hospital, Capital Medical University), Ling-Yi Zhang (The Second Hospital of Lanzhou University), Li-Ting Zhang (The First Hospital of Lanzhou University), Xin-Xin Zhang (Ruijin Hospital, Shanghai Jiao Tong University), Jing-Min Zhao (The Fifth Medical Center of Chinese PLA General Hospital), Shou-Song Zhao (The First Affiliated Hospital of Bengbu Medical College), Ming-Hua Zheng (The First Affiliated Hospital of Wenzhou Medical University), Yue-Yong Zhu (The First Affiliated Hospital, Fujian Medical University), Yong-Jian Zhou (Guangzhou First People's Hospital), Hong-Mei Zu (The Fourth People's Hospital of Qinghai Province), Wei-Ze Zuo (First Affiliated Hospital, School of Medicine, Shihezi University), Bi-Hui Zhong (The First Affiliated Hospital, Sun Yat-Sen University).

### Funding

This work was supported by the National Science and Technology Major Project of China (No: 2023ZD0508700).

## Conflict of interest

JGF has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. YMN has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2022. JDJ and LW have been Executive Associate Editors of *Journal of Clinical and Translational Hepatology* since 2013. CS has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2020. JL has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2024. The other authors have no conflict of interests related to this publication.

## Author contributions

Material preparation, data collection and analysis (JGF, YMN, LW), and the first draft of the manuscript (RXY, JGF, XYX). All authors contributed to the study conception and design, commented on previous versions of the manuscript. All authors have read and approved the final version and publication of the manuscript.

## Practice guideline registration

Practice Guideline Registration for Transparency (PRE-PARE2024CN426).

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