بسم الله الرحمن الرحيم

GUIDELINE FOR THE PREVENTION AND TREATMENT OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (VERSION 2024)

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).

- The global prevalence and incidence of NAFLD are increasing alongside the epidemics of obesity and T2DM.

- NAFLD has emerged as a significant public health issue worldwide

Metabolic dysfunction-associated steatohepatitis (MASH) grading and staging system

Grade	Description
Mild (grade 1)	Steatosis (predominantly macrovesicular) involving up to 66% of biopsy; may see occasional ballooned zone 3 hepatocytes; scattered intra-acinar polymorphonuclear cells, intra-acinar lymphocytes; no or mild portal chronic inflammation
Moderate (grade 2)	Steatosis of any degree; ballooning of hepatocytes (predominantly zone 3) obvious; intra-acinar polymorphonuclear cells noted, may be associated with zone 3 pericellular fibrosis; portal and intra-acinar chronic inflammation noted, mild to moderate
Severe (grade 3)	Panacinar steatosis; ballooning and disarray obvious, predominantly in zone 3; intra-acinar inflammation noted as scattered polymorphonuclear cells, ballooned hepatocytes, mild chronic inflammation; portal chronic inflammation mild or moderate
Stage *	**Description**
Fibrosis stage 1 (F1)	Zone 3 perisinusoidal fibrosis; focally or extensively present
Fibrosis stage 2 (F2)	Zone 3 perisinusoidal fibrosis with portal fibrosis
Fibrosis stage 3 (F3)	Zone 3 perisinusoidal fibrosis and portal fibrosis with bridging fibrosis
Fibrosis stage 4 (F4)	Cirrhosis

Grading and staging system for metabolic dysfunction-associated steatohepatitis (MASH), formerly termed nonalcoholic steatohepatitis (NASH).

* Fibrosis stage 0 (F0) is the absence of fibrosis.

- 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**)

- In 2020, an international panel of experts recommended renaming NAFLD to (**MAFLD**).
- the Asian Pacific Association for the Study of the Liver published clinical practice guidelines for the diagnosis and management of MAFLD.

- in 2023, a multi-society Delphi consensus statement led by the **American Association for the Study of Liver Diseases** suggested the name and acronym **(MASLD)** to replace NAFLD.

- **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 **MASLD.**

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.

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
- Dysfunction in adipose tissue, along with IR and low-grade systemic inflammation, leads to increased synthesis of triglycerides 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.

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.

- Overweight and obese populations exhibit similar rates of NAFLD, non-alcoholic fatty liver, NASH, significant fibrosis (≥F2), and advanced fibrosis (≥F3)

- Globally, 19.2% of NAFLD patients have a normal BMI, classified as lean individuals, and 40.8% are non-obese.

- 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.

- 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.

- The prevalence of NAFLD in patients with type 1 diabetes is not higher than in the general population unless combined with obesity and MetS.

- Common risk factors for FLD and fibrosis included
  - male gender,
  - obesity,
  - diabetes mellitus,
  - hypertension,
  - dyslipidemia,
  - MetS,
  - elevated aminotransferase levels
  - and excessive alcohol consumption.

INCREASED RISK OF HEPATIC DECOMPENSATION AND HCC

- The morbidity and mortality of patients 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**.
- four-year follow-up of 1,773 patients with biopsy-proven MAFLD, all-cause mortality increased with fibrosis stage
- Hepatic decompensation increased the all-cause mortality risk in MAFLD patients by 6.8 times
- HCC in noncirrhotic NASH patients is only 0.01% to 0.13%, compared to 0.5% to 2.6% in cirrhotic NASH patients

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.
- The incidence rates of MetS, T2DM, and CKD in NAFLD patients are higher than in the general population.
- 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
- The pooled prevalence of clinical and subclinical coronary artery disease in NAFLD patients was 38.7% and 55.4%, respectively.

INCREASED RISK OF NON-HEPATIC MALIGNANCIES

- NAFLD, along with **its associated metabolic inflammation, abnormal immune surveillance, and** intestinal microbiota imbalance, contributes to carcinogenesis.

- 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.

- is independent of age, gender, smoking, obesity, diabetes, and fibrosis stage.

DIAGNOSIS OF MAFLD ALONE AND MAFLD WITH OTHER LIVER DISEASE

- The diagnosis of MAFLD should meet the following three criteria:
  - (1) Imaging techniques and/or liver biopsy confirming hepatic steatosis; (≥5% macrovesicular steatosis)
  - (2) Presence of one or more components of MetS;
  - (3) Exclusion of other potential etiologies of hepatic steatosis

Table 5. Definitions of metabolic syndrome components

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

Definitions of the metabolic syndrome

Parameters	NCEP ATP3 2005*	IDF 2009	EGIR 1999	WHO 1999	AACE 2003
Required			Insulin resistance or fasting hyperinsulinemia (ie, in top 25% of the laboratory-specific reference range)	Insulin resistance in top 25%[Δ]; fasting glucose ≥6.1 mmol/L (110 mg/dL); 2-hour glucose ≥7.8 mmol/L (140 mg/dL)	High risk of insulin resistance[◇] or BMI ≥25 kg/m^2 or waist ≥102 cm (men) or ≥88 cm (women)
Number of abnormalities	**≥3 of:**	**≥3 of:**	**And ≥2 of:**	**And ≥2 of:**	**And ≥2 of:**
Glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Fasting glucose ≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes	Fasting glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL)		Fasting glucose ≥6.1 mmol/L (110 mg/dL); ≥2-hour glucose 7.8 mmol/L (140 mg/dL)
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol[§]	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol	<1.0 mmol/L (40 mg/dL)	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women)
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides[§]	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides	or ≥2.0 mmol/L (180 mg/dL) or drug treatment for dyslipidemia	or ≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)[¥]	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertension	≥130/85 mmHg or drug treatment for hypertension	≥130/85 mmHg or drug treatment for hypertension	≥140/90 mmHg or drug treatment for hypertension	≥140/90 mmHg	≥130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL: high-density lipoprotein; CVD: cardiovascular disease; BMI: body mass index.

NON-INVASIVE ASSESSMENT OF HEPATIC STEATOSIS

- **Ultrasound i**s the most widely used imaging technique for diagnosing significant hepatic steatosis, including **diffuse and non-homogeneous steatosis.**
- The **controlled attenuation parameter** (CAP)/UAP, based on TE, has **greater sensitivity** in detecting hepatic steatosis compared to routine ultra sound.
- CAP/UAP can also **monitor changes** in liver fat content over time
- Based on the CAP values measured by FibroScan® 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.
- CAP has been shown to be more accurate than ultrasound in diagnosing hepatic steatosis in **CHB patients**

- Factors like obesity, skin-to-liver capsule distance > 25 mm, and the use of XL probes can also lead to overestimation of CAP values

- Quantitative ultrasound fat fraction may offer greater accuracy in diagnosing significant steatosis compared to CAP or UAP.

- **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.
- its high cost and limited availability restrict routine clinical practice.

- 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

NON-INVASIVE ASSESSMENT OF STEATOHEPATITIS AND FIBROSIS

- Serum markers like alanine aminotransferase **(ALT)** and **cytokeratin-18** can **indicate hepatocyte damage** and apoptosis in patients with MAFLD. However, their accuracy is **insufficient for diagnosing MASH**.

- 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

- Other non-invasive fibrosis models, such as the Hepamet fibrosis score, enhanced liver fibrosis, and ADAPT algorithm, are rarely reported

- The **LSM obtained by FibroScan®** 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.

- LSM cut-off values of 8 kPa and 12 kPa are used to advanced fibrosis/advanced chronic liver disease in MAFLD patients, respectively
- LSM cut-off values of 10 kPa and 15 kPa can be used to rule out and rule in **cirrhosis**.

- A **sequential or combined application of FIB-4 and LSM** can improve fibrosis diagnostic accuracy.
- MAFLD patients with FIB-4 ≥ 1.3 and LSM ≥ 8 kPa should undergo further diagnosis and assessment by hepatologists

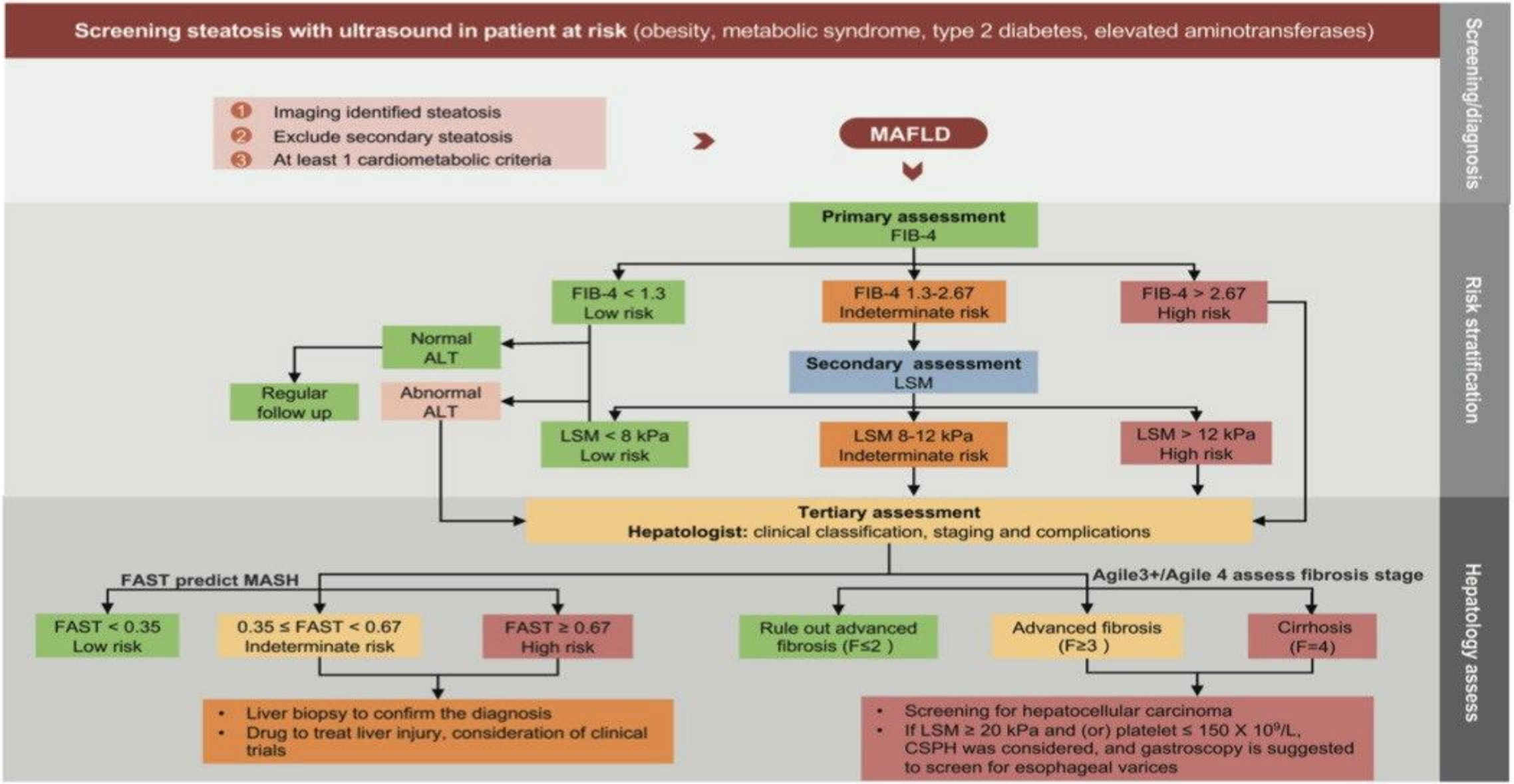


Fig. 2. Screening, diagnosis and assessment of metabolic dysfunction-associated fatty liver disease. ALT, alanine aminotransferase; FIB-4, fibrosis-4; LSM, liver stiffness measurement; FAST, Fibro scan-AST; MASH, metabolic dysfunction-associated steatohepatitis; CSPH, clinically significant portal hypertension.

ASSESSMENT OF LIVER HISTOLOGY

- Indications for liver biopsy in suspected MAFLD patients include: the need for accurate assessment of MASH and fibrosis in clinical trials;

- Liver biopsy specimens require hematoxylin-eosin staining, as well as Sirius red or Masson's trichrome staining.

- 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 elevated serum liver enzymes or advanced fibrosis when two or more liver injury factors coexist;
  - (4) Endoscopic bariatric and metabolic surgery;
  - (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

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.
- MAFLD patients with FIB-4 > 2.67 and LSM by TE > 12 kPa or Agile 3+ ≥ 0.679 should be screened for HCC by serum alpha-fetoprotein and abdominal ultrasound.
- poor ultrasound quality or suspected liver cancer, further evaluation with computed tomography and/or magnetic resonance imaging is recommended.
- suspected intrahepatic cholangiocarcinoma, it is advised to test for serum carcinoembryonic antigen and carbohydrate antigen
- 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 ≥ 20 kPa and/or blood platelet count ≤ 150 × 109/L typically require endoscopic screening for **esophageal varices.**

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

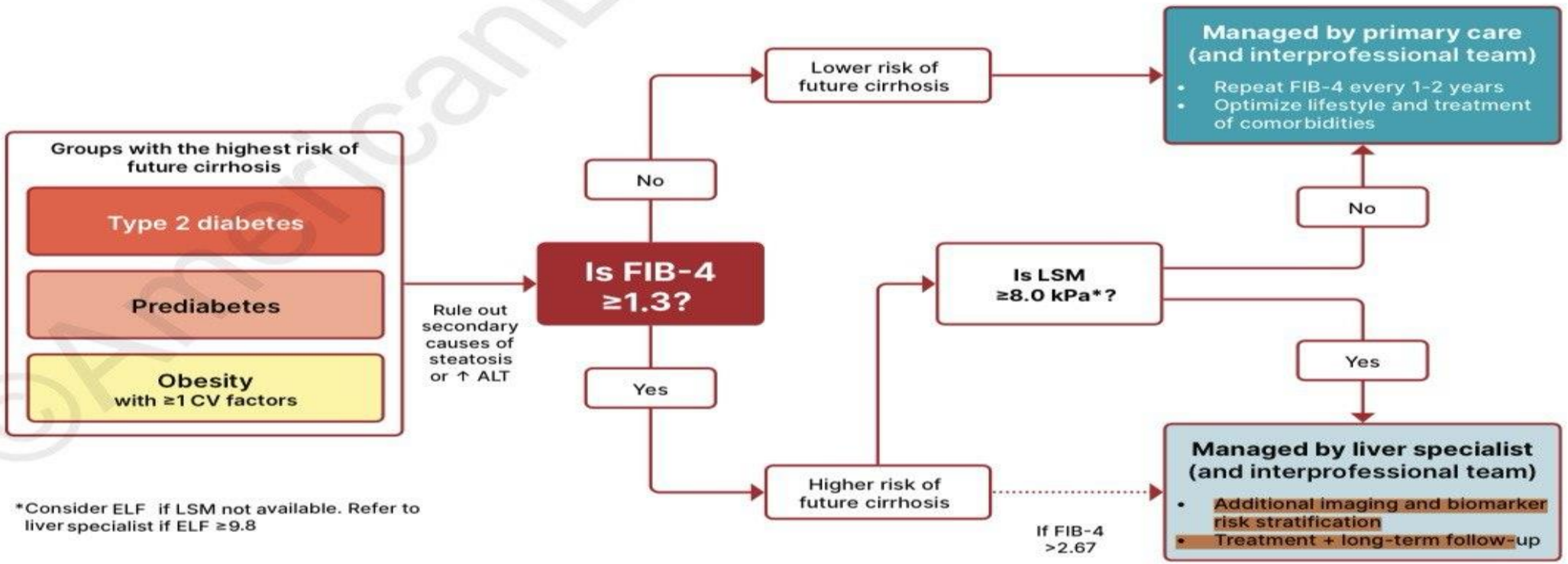


Figure 4.2—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

ASSESSMENT OF EXTRAHEPATIC COMPLICATIONS

- Patients with suspected MAFLD should undergo routine measurements of height, body weight (to calculate BMI), waist circumference, and blood pressure.

- 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.

- 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.

- screening for **atherosclerosis** should be conducted using fundoscopy or carotid artery ultrasound.
- Screening for CVD should be based on the 10-year and lifetime **CVD risk assessment models**
- Screening for **non-hepatic malignancies** should be tailored according to the patient's age, gender, and other risk factors.

TREATMENT

- The treatment of MAFLD requires a multidisciplinary approach, focusing on strategies that aim to
  - reduce bodyweight and waist circumference,
  - improve IR,
  - prevent and manage MetS and T2DM,
  - alleviate MASH,
  - and reverse liver fibrosis

LIFESTYLE MODIFICATION

- adjusting dietary patterns and increasing physical activity are the cornerstone of treating all forms of MAFLD
  - 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.**

- MAFLD patients with a normal BMI should also aim for modest weight loss (3% to 5%) to address metabolic dysfunction and liver disease.
- 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:

- 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,
  - increasing consumption of high-fiber foods such as vegetables, whole grains, and foods rich in unsaturated fatty acids

- 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
- 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.

- 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.

EXERCISE THERAPY:

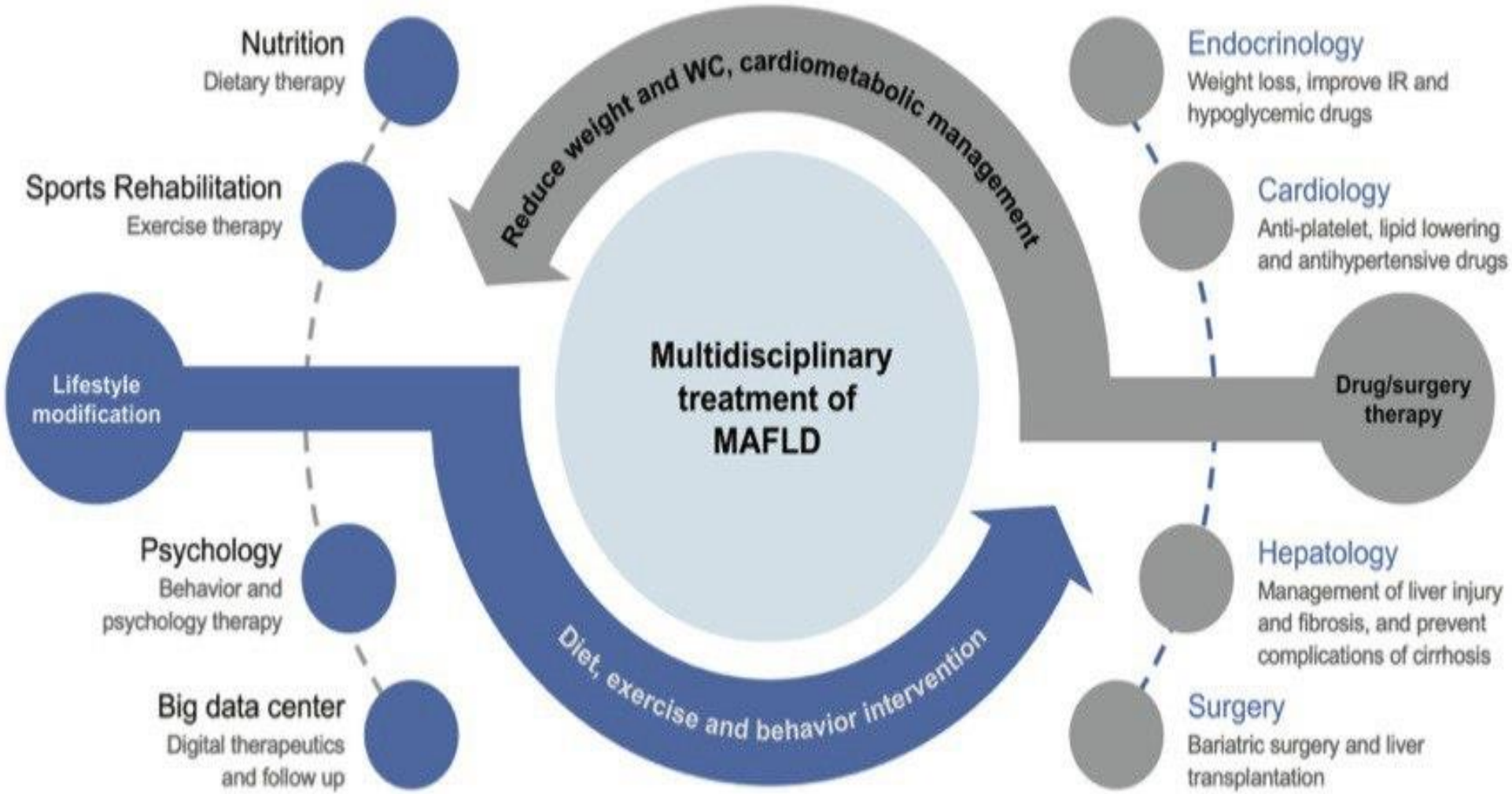
- physical activity, aiming **for moderate-intensity aerobic exercise for at least 150 mins per week** and/or high-intensity interval training for three to five days per week over a period of more than three months

- For instance, brisk walking for 150 mins per week over three months can reduce liver MRI-PDFF by over 30% in MAFLD patients.

- 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.

BEHAVIORAL THERAPY

- Patients with MAFLD should avoid unhealthy behaviors such as irregular eating, soft drink consumption, smoking, alcohol intake, and a sedentary lifestyle
- 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



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

PHARMACOLOGICAL THERAPY

- 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
  - Weight loss drugs:
  - Antidiabetic drugs
  - Lipid-lowering drugs
  - Antihypertensive drugs
  - Therapeutic agents for MASH and fibrosis

WEIGHT LOSS DRUGS:

- Achieving a weight **loss of over 5% within one year** through intensive lifestyle modifications can be challenging for many patients

- patients with MAFLD and a **BMI ≥ 28 kg/m2 can be prescribed weight loss medications** such as orlistat, liraglutide, and beinaglutide.

- For **obese patients with concomitant T2DM,** glucagonlike 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.

ANTIDIABETIC DRUGS

- 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

- Metformin is the first-line treatment for preventing and managing T2DM in overweight or obese patients.
- does not alleviate MASH, it may reduce the risk of HCC in patients with MAFLD.

- **Pioglitazone**, 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.

- it requires constant monitoring for side effects such as weight gain, edema, worsening heart failure, and an increased risk of osteoporosis.

- SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, can help
  - reduce body weight,
  - improve IR,
  - and enhance cardiovascular and renal outcomes.
  - prevent and treat heart failure,
  - lower serum aminotransferase levels,
  - and reduce liver fat content as assessed through imaging
- The primary adverse effects of these medications include genitourinary tract infections, hypovolemia, and osteoporosis.

- Incretin based therapies may be superior to pioglitazone and SGLT- 2 inhibitors for the treatment of MAFLD.

- GLP-1 receptor agonists (e.g., liraglutide and semaglutide) are approved for the treatment of T2DM and obesity,
  - 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..
- semaglutide has not been shown to reverse fibrosis or resolute MASH in patients with compensated cirrhosis

- 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

- newly developed dual agonists demonstrate better therapeutic effects than GLP-1 receptor agonists, warranting further investigation in phase 3 trials.

- no evidence that insulin, acarbose, or dipeptidyl peptidase IV inhibitors have therapeutic effects on MAFLD.

LIPID-LOWERING DRUGS

- should be selected based on CVD risk stratification to maintain serum ldl cholesterol, non-hdl cholesterol, TG, and apo B at target levels

- Statins are the first-line agents for reducing CVD risk and are typically started at low doses; moderate to high doses may be necessary

- statin intolerance or failure to reach lipid goals, adding or switching to ezetimibe or pcsk9 inhibitors
- statins have good hepatic safety profiles and may slow liver disease progression, reduce portal vein pressure, and prolong survival in patients with compensated cirrhosis.

- Recent results indicate that statin use is associated with a lower long-term risk of all-cause mortality, liver-related events, and fibrosis progression

- 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.

- 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).

- 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 ACL

- 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

ANTIHYPERTENSIVE DRUGS

- preferred medications are ACEIs or ARBs.
- clinically significant portal hypertension, non-selective beta-blockers can be used alone or in combination with ACEIs or ARBs
- 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.
- an RCT found that an 81 mg/ day dose of aspirin significantly reduced liver fat content in MAFLD patients.

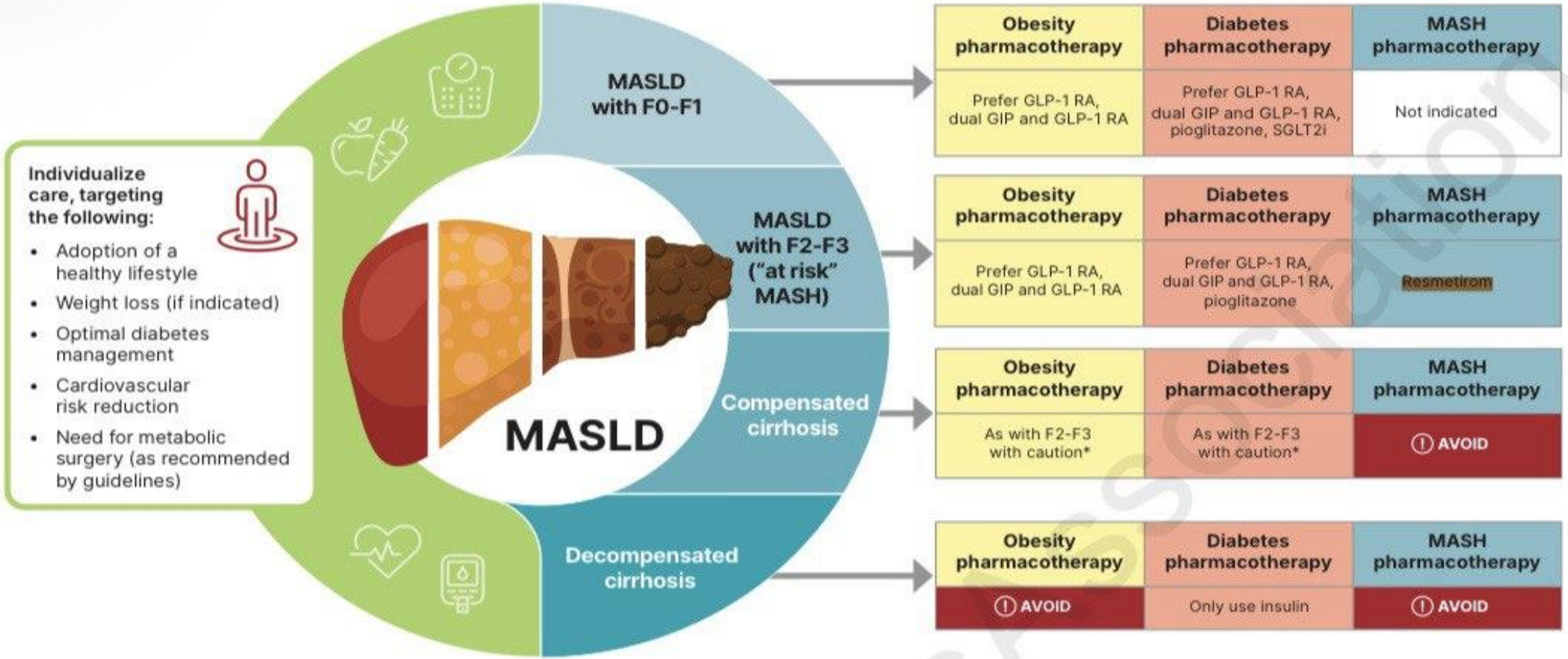
THERAPEUTIC AGENTS FOR MASH AND FIBROSIS

- 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.
  - potential risks of hemorrhagic stroke and prostate cancerlimit its routine long-term use at a high dose.

- **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

- 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 analogs (**Efruxifermin, Pegozafermin**),
  - and the dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist (**tirzepatide)**,

- FDA approved Resmetirom for treating noncirrhotic MASH patients with significant fibrosis.



*Individualized care and close monitoring needed in compensated cirrhosis given limited safety data available.

Figure 4.3—Metabolic dysfunction–associated steatotic liver disease (MASLD) treatment algorithm. F0-F1, no to minimal fibrosis; F2-F3, moderate fibrosis; F4, cirrhosis; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MASH, metabolic dysfunction–associated steatohepatitis; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

- If there is no significant reduction in serum aminotransferase levels after **six months** of treatment, alternative hepatoprotectants should be considered.

SURGICAL THERAPY

- Bariatric surgery
- Liver transplantation

BARIATRIC SURGERY

- 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).
  - Approximately 65% to 90% of patients, with postoperative remission of **MASH and reversion of fibrosis in about 75% and 70%** of cases, respectively.

- overweight or obese who meet the criteria for 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/m2 and accompanied by T2DM

- 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

- The type, safety, and efficacy of bariatric surgery in patients with compensated cirrhosis remain to be clarified.

- 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.

- the risk of complications from bariatric surgery is notably high and severe in patients with decompensated cirrhosis

LIVER TRANSPLANTATION

- MASH-related cirrhosis, ACLF, and HCC are increasingly recognized as indications for liver transplantation worldwide,
- Extrahepatic complications can increase the risk of adverse outcomes following liver transplantation, with CVD being a significant contributor to postoperative mortality,
- 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.

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

- Liver biopsy demonstrating remission of steatohepatitis and reversal of fibrosis are crucial treatment endpoints in clinical trials for fibrotic MASH

- 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.

- Lifestyle interventions have better sustained effects in MAFLD patients with a normal BMI

- 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.

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

- 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

- 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

- 20% decrease in LSM reflects a reduced risk of liver-related events

- Patients with MAFLD, regardless of whether they have concomitant ALD, must reduce alcohol consumption and strive for abstinence whenever possible

- 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

Thank you

For your attention