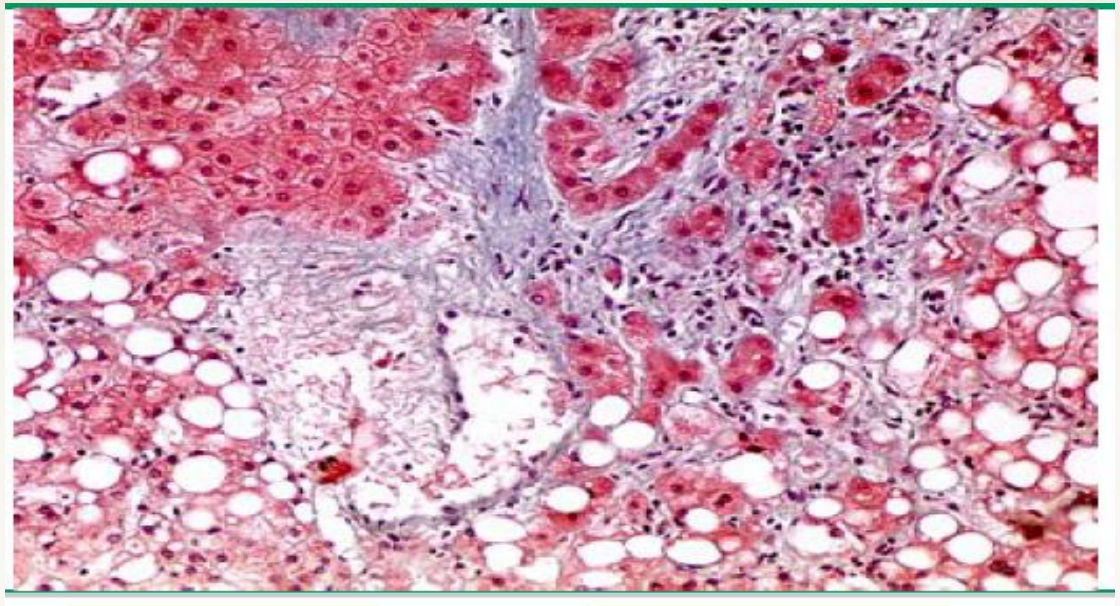

management of metabolic dysfunction-associated steatotic liver disease (MASLD)

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- EASL–EASD–EASO Clinical **Practice Guidelines** on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Journal of Hepatology, September 2024
- **American Diabetes Association Standards** of Care in Diabetes **2026** Metabolic Dysfunction–Associated
- Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the **American Diabetes Association2025**
  - -**Clinical features and diagnosis** of metabolic dysfunction-associated steatotic liver disease (nonalcoholic fatty liver disease) in adults-UpTodate 2025
- **Management** of metabolic dysfunction-associated steatotic liver disease (nonalcoholic fatty liver disease) in adults-UpTodate 2025

- TERMINOLOGY
- Prevalence
- Risk factors
- Screening
- Diagnosis
- Non-pharmacological treatment
- Pharmacological treatment
- Follow-up
- Cirrhosis and investigation

TERMINOLOGY

Metabolic dysfunction-associated steatotic liver disease (MASLD)

- Patients with MASLD alone have fatty liver (>5 percent hepatic steatosis) with at least one risk factor for cardiometabolic dysfunction such as dyslipidemia or obesity ,no other causes of steatotic liver disease, and minimal or no alcohol consumption (ie, <20 g daily for females and <30 g daily for males).

Table 3. Cardiometabolic risk factors in the definition of MASLD.[2]

Metabolic risk factor	Adult criteria
Overweight or Obesity	Body mass index ≥25 kg/m^2 (≥23 kg/m^2 in people of Asian ethnicity) Waist circumference • ≥94 cm in men and ≥80 cm in women (Europeans) • ≥90 cm in men and ≥80 cm in women (South Asians and Chinese) • ≥85 cm in men and ≥90 cm in women (Japanese)
Dysglycaemia or type 2 diabetes	Prediabetes: HbA_{1c} 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dl) *or* Type 2 diabetes: HbA_{1c} ≥48 mmol/mol (≥6.5%) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl) or 2-h plasma glucose during OGTT ≥11.1 mmol/L (≥200 mg/dl) *or* Treatment for type 2 diabetes
Plasma triglycerides	≥1.7 mmol/L (≥150 mg/dl) *or* lipid-lowering treatment
HDL-cholesterol	≤1.0 mmol/L (≤39 mg/dl) in men and ≤1.3 mmol/L (≤50 mg/dl) in women *or* lipid-lowering treatment
Blood pressure	≥130/85 mmHg *or* treatment for hypertension

HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

- **MASLD with metabolic dysfunction-associated steatohepatitis (MASH):**
- histologic evidence of inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without fibrosis.
- **MASH cirrhosis:**
- Patients with MASH cirrhosis have cirrhosis with current or previous histologic evidence of MASH or history of MASLD.

Metabolic dysfunction- and alcohol-associated liver disease (MetALD):

- Patients with liver steatosis, at least one metabolic risk factor, and a history of moderate (but not heavy) alcohol use have **metabolic dysfunction- and alcohol-associated** liver **disease (MetALD**).
- This category recognizes that steatotic liver disease can involve a combination of metabolic dysfunction and alcohol.
- Moderate amounts of alcohol are defined as 20 to 50 g daily (140 to 350 g per week) for females and 30 to 60 g daily (210 to 420 g per week) for males .This range of alcohol intake defines a spectrum between MASLD-predominant and alcohol predominant disease.

Prevalence

- MASLD is seen worldwide with an estimated prevalence of 30 percent (2016:%25)among the general population and with higher prevalence in males compared with females (40 versus 26 percent)

- It has been estimated that approximately 10–30% of persons with isolated steatosis progress to steatohepatitis and advanced liver disease, but the risk is much higher in the presence of T2D (42-65% have steatosis).

Diabets

- **MASLD** is >70% of people with type 2 diabetes.

  Type 1 diabetes:8.8%

- **MASH**:50%

- Between 12 and 20% of people with **type 2 diabetes** have "**at-risk" MASH** (i.e., steatohepatitis with clinically significant fibrosis [≥F2] and at risk for cirrhosis)- **Type 1 diabetes**:5%

- "ADA 2026"

Risk factors

- Obesity
- Type 2 diabetes mellitus
- Dyslipidaemia –Hypertension
- OSA-PCOS
- Menopausal
- Ethnicity
- Smoking
- Alcohol consumption

Obesity

- Overweight or obesity in individuals with compensated cirrhosis at baseline are associated with a higher risk of clinical decompensation, independently of liver function, portal pressure and underlying etiology of liver disease.
- Furthermore, obesity is associated with a significantly increased risk of HCC development and HCC-related mortality. This association was found in persons with cryptogenic cirrhosis and alcoholrelated cirrhosis but not in individuals with liver diseases of other aetiologies.

Type 2 diabetes mellitus

- T2D is also associated with poor outcomes in individuals with biopsy-proven MASH and compensated cirrhosis, including a 4-fold increased risk of death and an approximately 2-fold increased risk of liver-related outcomes, including HCC, over a median follow-up of 5 years.
- Another study reported a 4-fold increased risk of HCC in individuals with T2D and MASH-related cirrhosis followed for 47 months.
- TheEffect of T2D on HCC risk is not unique to MASLD but also extends to other aetiologies.

Dyslipidaemia -Hypertension

- Hypertension per se has been associated with fibrosis progression in a large meta-analysis and in a large retrospective study of 271,906 individuals with MASLD; those with both hypertension and dyslipidaemia had a 1.8-fold higher risk of progression to cirrhosis or HCC compared to individuals with no cardiometabolic risk factor.

- The risk of disease progression and HCC clearly increases in the presence of multiple metabolic risk factors. In a large US cohort, individuals with only one cardiometabolic risk factor (e.g. hypertension, dyslipidaemia, or obesity) had a low risk of progression to cirrhosis or HCC, but each additional metabolic trait led to a stepwise increase in this risk, with T2D having the strongest association.

Obstructive sleep apnoea (OSA) and polycystic ovary syndrome (PCOS)

- Both OSA and PCOS are associated with MASLD, and several studies suggest OSA is also associated with more advanced MASLD/MASH histology, while only one study reported an association between PCOS and **MASH severity or advanced fibrosis.**
- However, the available evidence does not support a strong effect of OSA and PCOS on the risk of liver disease progression or HCC.

Menopausal

- Menopausal status is associated with approximately 2.4-fold higher odds of MASLD.
- Women aged >50 years have increased odds of advanced fibrosis due to MASLD even after adjustment for covariates.
- The risk of severe fibrosis is elevated even in normal-weight post-menopausal women with MASLD compared to normal weight pre-menopausal women with MASLD.
- The association of menopause with severe fibrosis is, in part, mediated by older age and change in body fat composition.

Ethnicity

Ethnicity

- In the US, the prevalence of steatohepatitis with or without T2D is highest in the Hispanic population. It is inherently difficult to dissect the impact of genetic, cultural, socioeconomic and ethnic factors on MASLD progression. However, a meta-analysis of 34 studies reported that the prevalence and severity of MASLD differs among ethnic groups in the US.

Smoking

- Smoking has been associated with an increased risk of HCC independent of aetiology as well as in MASLD specifically.
- In a meta-analysis of 81 studies, the pooled OR for HCC development was 1.55 (95% CI: 1.46 to 1.65) in current smokers and 1.39 (95% CI: 1.26 to 1.52) in former smokers. In addition, the overall adverse health effects further support smoking cessation in individuals with MASLD.

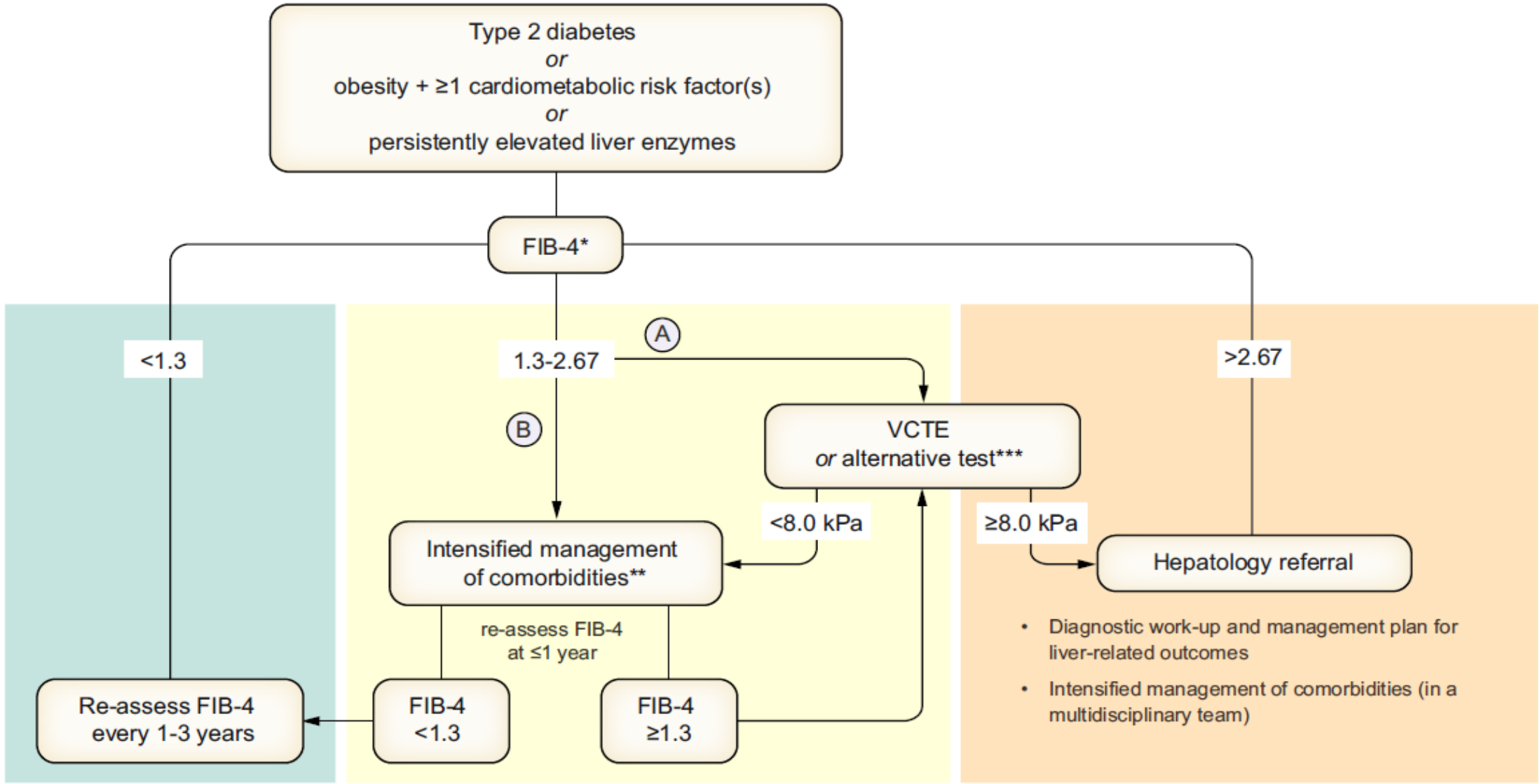
Alcohol consumption

- In young adults, thresholds of healthy alcohol consumption are close to zero.
- In older populations facing a high burden of cardiovascular disease, small amounts of alcohol consumption are associated with improved health outcomes.

- In people with non-cirrhotic MASLD the evidence for low or moderate alcohol consumption is conflicting.
- Earlier cohort and cross-sectional studies on individuals with non-cirrhotic MASLD showed no effect or even protective effects of low moderate alcohol consumption on overall mortality, MASLD and steatohepatitis.

- However, this has been challenged by emerging data from longitudinal studies.
- Hence, an emerging body of evidence now suggests that any level of alcohol consumption, even within recommended limits, is associated with worsening of liver outcomes in MASLD and that moderate levels of alcohol are associated with a doubling of incident liver disease.Recent meta-analyses found no protective effects against cirrhosis at any level of drinking when compared to long-term abstainers.

Screening-Diagnosis



* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)
** *e.g.* lifestyle intervention, treatment of comorbidities (*e.g.* GLP1RA), bariatric procedures
*** *e.g.* MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

- An individual is considered to have elevated liver enzymes when alanine aminotransferase (ALT) is >33 U/L in males and >25 U/L in females. However, individuals with MASLD and normal aminotransferase levels can still have significant steatohepatitis and develop advanced fibrosis or cirrhosis.

- A screening strategy relying on elevated plasma aminotransferases >40 units/L would miss most in- dividuals with MASH in these settings, as at-risk MASH with clinically significant fibrosis (≥F2) is frequently observed with plasma aminotransferases below the commonly used cutoff of 40 units/L.
- ADA2026

- The American College of Gastroenterology considers the upper limit of normal ALT levels to be 29–33 units/L for male individuals and 19–25 units/L for female individuals.
- ADA2026

FIB-4

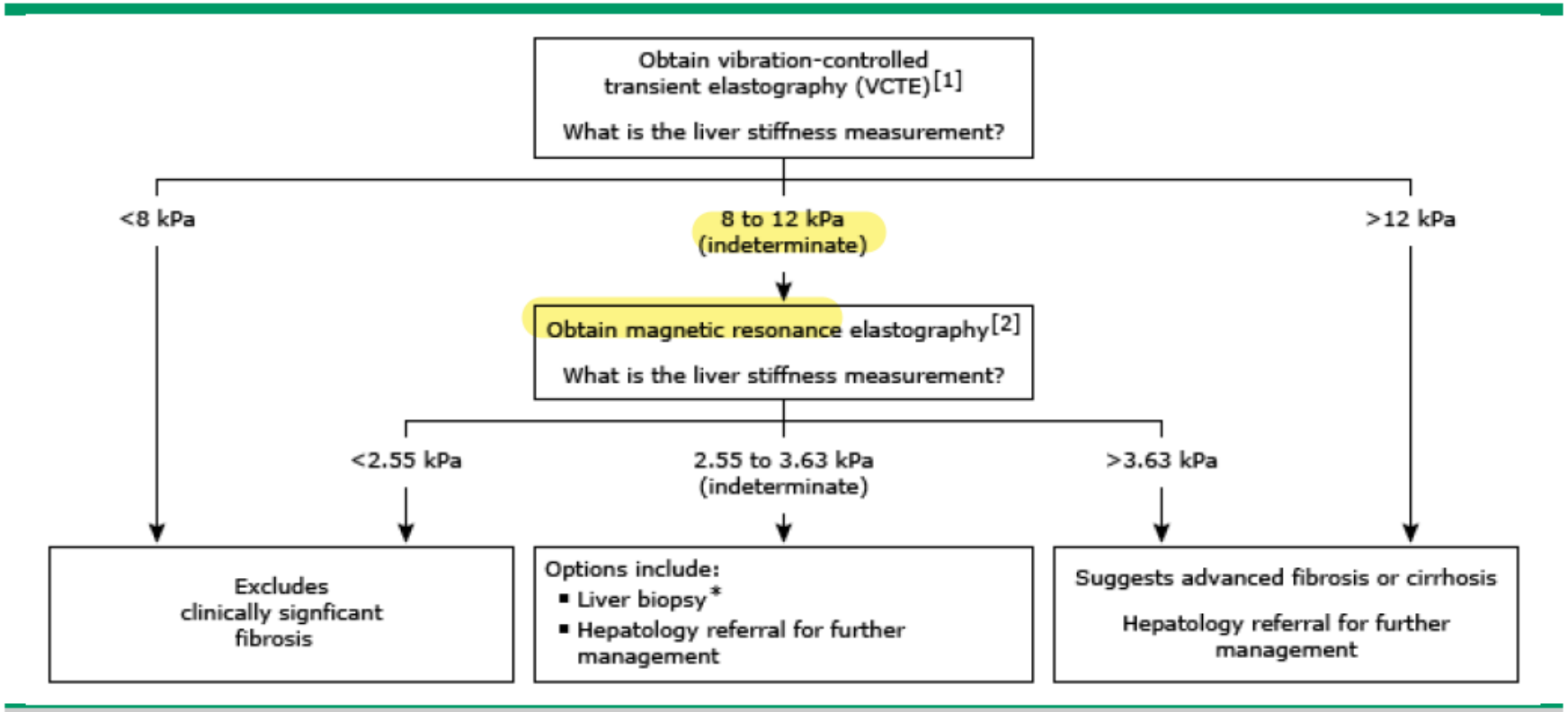
- FIB-4 is the most widely established and available tool. However, its ability to detect fibrosis is limited in the intermediate range (1.3-2.67), in the elderly and in individuals with T2D.
- FIB-4 as a single test may therefore result in a high number of false positives, especially in lower prevalence populations. Both FIB-4 and the NFS have **moderate accuracy** for predicting fibrosis stages >–F3.

- If FIB-4 is below 1.3, these individuals can be assumed to be at low risk of advanced fibrosis and may be re-assessed every 1-3 years.
- However, despite the high negative predictive value, clinicians should recognise that FIB-4 will miss around 10% of individuals with advanced fibrosis, and it has not been formally demonstrated that repeating FIB-4 over time is effective in picking up the remaining individuals.

Vibration-controlled transient elastography (VCTE)

- Special ultrasound devices enable liver transient elastography. With the vibration-controlled transient elastography (VCTE), liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) values are determined which allow for a relatively reliable estimation of the degree of fibrosis and steatosis.
- Unfortunately, adults with class 2 obesity cannot be reliably examined with many of these ultrasound techniques.

An approach to evaluating for fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)



This figure summarizes an approach to evaluating for fibrosis in patients with MASLD. This algorithm is intended for use in conjunction with UpToDate content on the clinical features and diagnosis of MASLD. We use ultrasound-based elastography to evaluate for advanced fibrosis or cirrhosis. If imaging methods are not available, alternatives include serologic tests. Refer to UpToDate content on noninvasive assessment of hepatic fibrosis for details.

Further management of patients with cirrhosis includes screening for and preventing cirrhosis-related complications (eg, variceal bleeding, hepatocellular carcinoma).

♦ روش‌های جایگزین الاستوگرافی در بیمار چاق

۱. استفاده از پروب XL در FibroScan ✅ (اولین انتخاب)

در بیماران چاق، استفاده از **پروب XL** به‌جای پروب استاندارد (M) باعث نفوذ بهتر امواج و **افزایش دقت اندازه‌گیری** می‌شود.

مثال:

بیمار با BMI=38 که با پروب M نتیجه ناموفق دارد، با پروب XL اندازه‌گیری موفق و قابل اعتماد انجام می‌دهد.

۲. الاستوگرافی با MRI (MRE) ⭐⭐ (دقیق‌ترین روش)

Magnetic Resonance Elastography (MRE) دقیق‌ترین روش غیرتهاجمی برای سنجش فیبروز کبد است و تحت تأثیر چاقی قرار نمی‌گیرد.

مزایا:

- دقت بالا حتی در BMIهای بالا
- ارزیابی همزمان کل کبد
- مناسب در موارد اختلاف نتایج

محدودیت: هزینه بالا و دسترسی کمتر

۳. الاستوگرافی سونوگرافیک نقطه‌ای یا برشی (pSWE / 2D-SWE)

این روش‌ها روی دستگاه‌های پیشرفته سونوگرافی انجام می‌شوند و در برخی بیماران چاق موفق‌تر از VCTE هستند.

مثال:

در بیمار چاقی که FibroScan ناموفق بوده، 2D-SWE اطلاعات قابل قبولی از سفتی کبد ارائه می‌دهد.

شایع‌ترین علل مثبت کاذب (به‌صورت خلاصه)

- ALT بالا (هپاتیت حاد)
- انسداد صفراوی
- نارسایی قلبی و احتقان کبد
- انجام تست پس از غذا
- فشار زیاد پروب
- التهاب شدید کبد بدون فیبروز

حین انجام تست

☐ انجام در فضای بین‌دنده‌ای مناسب

☐ حداقل ۱۰ اندازه‌گیری معتبر

☐ IQR/Median < 30% (ترجیحاً <25%)

☐ فشار بیش از حد پروب اعمال نشود

بعد از انجام تست

☐ بررسی همزمان:

- ALT / AST
- ALP / Bilirubin (کلستاز)
- وضعیت قلب (نارسایی قلب راست)

☐ تطبیق عدد LSM با **علت بیماری کبدی**

☐ مقایسه با FibroScanهای قبلی (روند مهم‌تر از عدد منفرد)

✅ چرا باید IQR/Median < 30% باشد؟

وقتی این نسبت **کمتر از ۳۰٪** باشد:

- نوسان اندازه‌گیری‌ها کم است
- عدد گزارش‌شده نماینده واقعی سفتی کبد است
- می‌توان با اطمینان بالینی از آن استفاده کرد

اگر ≥ 30% باشد:

- نتیجه **غیرقابل اعتماد** محسوب می‌شود
- نیاز به تکرار تست یا روش جایگزین وجود دارد

مثال ۱ (قابل اعتماد)

- Median LSM = 10 kPa
- IQR = 2 kPa

$$IQR/Median = 2 \div 10 = 0.2 = 20\%$$

✅ قابل اعتماد

مثال ۲ (غیرقابل اعتماد)

- Median LSM = 8 kPa
- IQR = 3 kPa

$$IQR/Median = 3 \div 8 = 0.375 = 37.5\%$$

Differential diagnosis

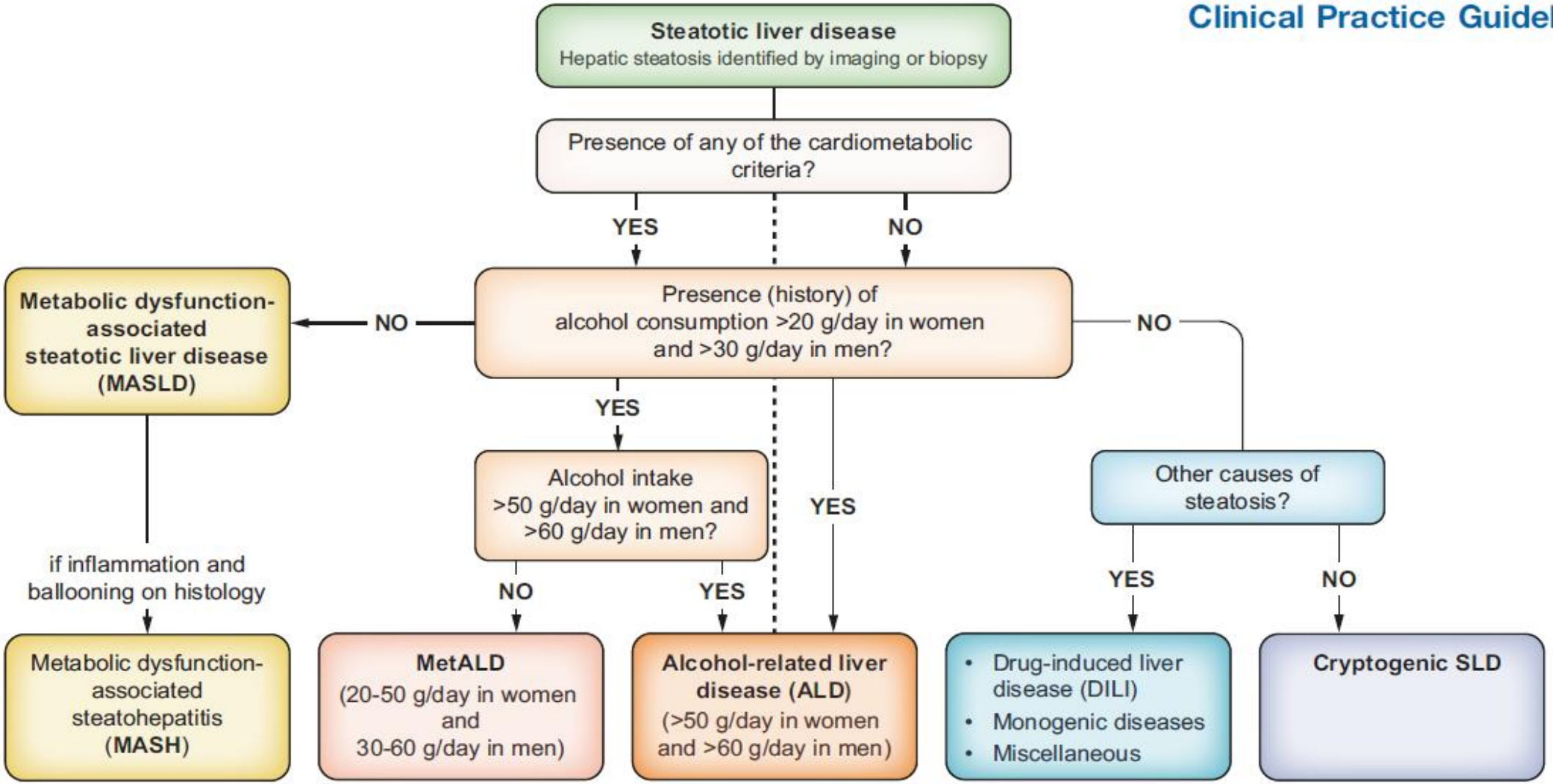


Fig. 1. Flow-chart for SLD and its sub-categories.[2] SLD, diagnosed histologically or by imaging, has many potential aetiologies. MASLD is defined as the presence of hepatic steatosis in conjunction with (at least) one cardiometabolic risk factor and no other discernible cause. The quantity of alcohol intake, the drinking pattern, and the type of alcohol consumed should be assessed in all individuals with SLD using detailed medical history, psychometric instruments and/or validated biomarkers. ALD, alcohol-related liver disease; DILI, drug-induced liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with moderate (increased) alcohol consumption; SLD, steatotic liver disease.

- Hepatitis B surface antigen
- Anti-hepatitis C virus antibody
- Plasma iron, ferritin, and total iron binding capacity
- Antimitochondrial antibody
- Immunoglobulin G (IgG) level, antinuclear antibody, anti smooth muscle antibody (for female patients and/or those with aminotransferases >5 times the upper limit of normal or history of autoimmune disease)
- Ceruloplasmin (for patients <50 years of age or those with neurocognitive symptoms)
- Alpha-1 antitrypsin (AAT) level
- Anti-tissue transglutaminase antibody (tTG-IgA)

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- Finally, there is initial evidence that first-degree relatives of individuals with advanced liver fibrosis due to MASLD are at increased risk of both MASLD (2- to 3-fold higher) and advanced liver fibrosis (12-fold higher), independently of metabolic risk factors.

Recommendations

- Clinicians in specialised centres may consider assessing the genetic risk profile (*e.g. PNPLA3* p.I148M variant and/or polygenic risk scores) to personalise risk stratification, but this concept should be evaluated in larger prospective studies (**LoE 3, open recommendation, consensus**).
- Genetic risk variants can be evaluated in clinical studies for stratification of disease risk progression and sub-phenotyping of MASLD (**LoE 3, open recommendation, strong consensus**).
- Clinicians can consider referring individuals with a strong family history of severe disease in first degree relatives or early presentation with a severe phenotype, especially in the absence of metabolic triggers (and/or *e.g.* in individuals with normal body weight), for the evaluation of coexisting, treatable, genetic causes of liver disease by next-generation sequencing approaches (**LoE 4, open recommendation, consensus**).

- **Initial data suggest that individuals with:**

a) strong family history

b) early disease onset, or

c) lack of accruing factors may benefit from a comprehensive genetic evaluation whole-exome sequencing or targeted panel sequencing) that may identify strong genetic determinants of SLD with potential implications for treatment and family counselling. Using next generation sequencing (NGS), a refined diagnosis (e.g. monogenic SLD) can currently be reached in up to onethird of individuals.

Non-pharmacological treatment

Weight loss

- Encourage calorie deficit that promotes weight loss
- ~5% weight reduction to reduce steatosis
- ~7-10% to reverse steatohepatitis and liver fibrosis

Physical activity

- Discuss goal of performing ≥150 min/week moderate-intensity aerobic activity and resistance activities 2-3 times/week
- Explain that brief sessions (~10 min) can be effective ways to reach goal

Nutrition (healthy eating)

- Emphasize a high-fiber, whole foods eating pattern with personalized goals, that is low in saturated fat and added sugar
- Individuals should abstain from sugar-containing beverages and minimize consumption of ultraprocessed foods

Alcohol

- Assess intake at every visit
- Recommend minimizing alcohol intake in MASLD
- Individuals should abstain if moderate fibrosis is present (≥F2)

DSMES

- Support behavior change to address factors complicating diabetes management
- Address lifestyle modification with medical nutrition therapy

Behavioral health

- Promote stress reduction via positive health behaviors
- Screen for depression and anxiety at least annually and refer to behavioral health professionals when indicated
- Advise adequate sleep and quitting smoking

Figure 3—Lifestyle modification for individuals with prediabetes or diabetes and MASLD.

- In adults with MASLD who are normal weight, are diet and exercise interventions effective in reducing histologically/ non-invasively assessed liver damage/fibrosis and liverrelated outcomes in comparison with no intervention.

Recommendation

- In adults with MASLD, nutraceuticals cannot be recommended since there is insufficient evidence of their effectiveness in reducing histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes in MASLD, nor of their safety (**LoE 2, open recommendation, strong consensus**).

Statement

- In adults with MASLD, coffee consumption has been associated with improvements in liver damage and reduced liver-related clinical outcomes in observational studies (**LoE 4, strong consensus**).

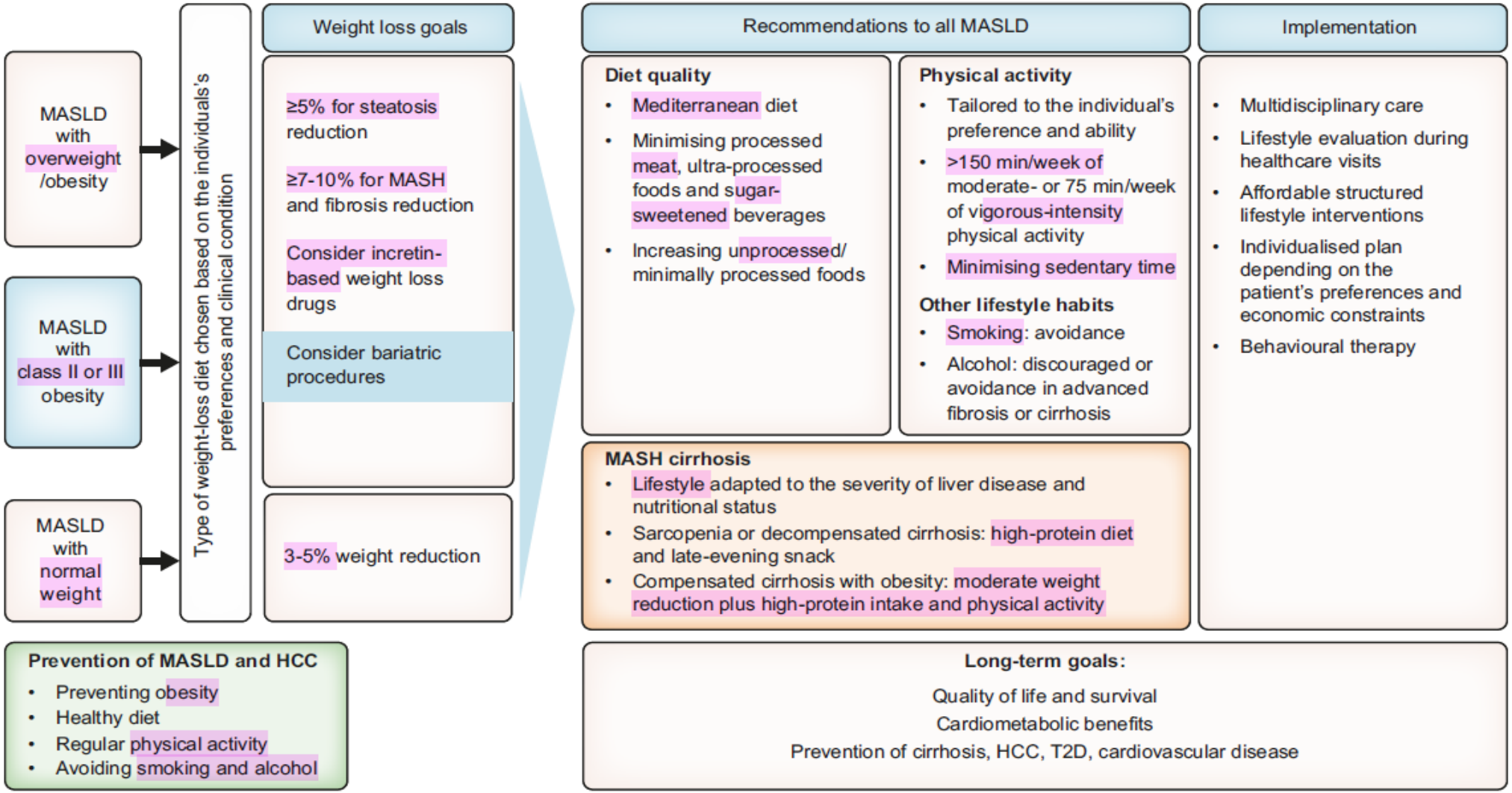


Fig. 3. Lifestyle management algorithm for MASLD. Note: Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals, and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables, fruits (not juice), low-fat dairy, nuts, olive oil, legumes, unprocessed fish and poultry. Overweight/obesity: Overweight: BMI of 25–29.9 kg/m^2 (non-Asian) or 23–24.9 (Asian), Obesity: ≥30 kg/m^2 (non-Asian) ≥25 kg/m^2 (Asian). Class II obesity: BMI ≥35 kg/m^2 (non-Asian) or BMI ≥30 kg/m^2 (Asian). Normal weight: BMI<25 kg/m^2 (non-Asian) or <23 kg/m^2 (Asian). BMI, body-mass index; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

Pharmacological treatment

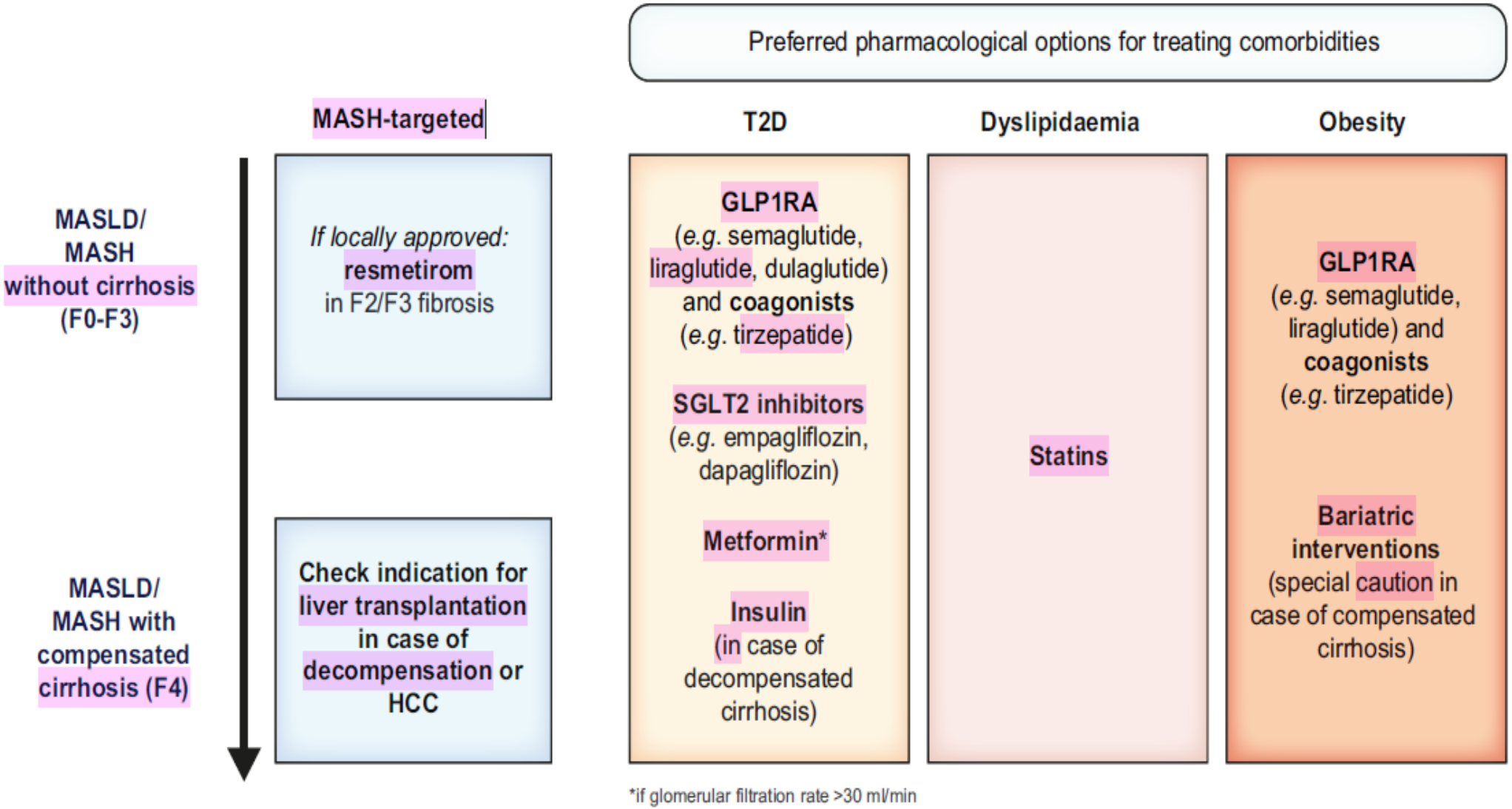


Fig. 4. Treatment recommendations beyond lifestyle modification in MASLD/MASH. The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease. GLP1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Recommendations

- Metformin can be used in adults with compensated cirrhosis and preserved renal function but should not be used in adults with decompensated cirrhosis, especially when there is concomitant renal impairment, because of the risk of lactic acidosis (**LoE 3, strong recommendation, strong consensus**).
- Sulfonylureas should be avoided in adults with hepatic decompensation because of the risk of hypoglycaemia (**LoE 4, weak recommendation, strong consensus**).
- GLP1 receptor agonists can be used in adults with Child-Pugh class A cirrhosis, according to its indication (**LoE 2, weak recommendation, strong consensus**).
- SGLT2 inhibitors can be used in adults with Child-Pugh class A and B cirrhosis (**LoE 4, weak recommendation, consensus**).
- Statins can be used in adults with chronic liver disease, including those with compensated cirrhosis; they should be used in adults according to cardiovascular risk guidelines to reduce cardiovascular events (**LoE 1, strong recommendation, strong consensus**).

تفاوت Child-Pugh و MELD

1. تعریف

Child-Pugh

برای ارزیابی شدت سیروز کبدی و پیش‌آگهی بالینی استفاده می‌شود.

MELD

برای پیش‌بینی مرگ‌ومیر کوتاه‌مدت و اولویت‌بندی بیماران جهت پیوند کبد استفاده می‌شود.

2. معیارها

Child-Pugh (5 parameters)	MELD / MELD-Na (Objective labs)
Ascites	Bilirubin
Hepatic encephalopathy	INR
Bilirubin	Creatinine
Albumin	Sodium (MELD-Na)
INR / PT	—

Child–Pugh Classification Criteria

Parameter	1 point	2 points	3 points
Total bilirubin (mg/dL)	< 2	2–3	> 3
Serum albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR (or Prothrombin time)	< 1.7 (or < 4 sec prolonged)	1.7–2.3 (or 4–6 sec)	> 2.3 (or > 6 sec)
Ascites	None	Mild (controlled)	Moderate–severe (refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

Child–Pugh Classes

Class	Total Score	Severity
Child A	5–6	Well compensated
Child B	7–9	Significant functional compromise
Child C	10–15	Decompensated

Recommendations

- If approved locally and dependent on the label, adults with non-cirrhotic MASH with significant liver fibrosis (stage ≥2) should be considered for treatment with resmetirom as a MASH-targeted therapy, as this treatment demonstrated histological efficacy on steatohepatitis and fibrosis in a large phase III registrational trial with an acceptable safety and tolerability profile (**LoE 2, strong recommendation, consensus**).

- Treatment with resmetirom, if approved locally, may be considered for individuals with MASLD who are non-cirrhotic and with documentation of either: (A) advanced fibrosis; (B) at-risk steatohepatitis with significant fibrosis (by liver biopsy, when available, or by non-invasive panels validated for that purpose); or (C) risk of adverse liver-related outcomes (*e.g.* by elastography- or biomarker-defined thresholds) (**LoE 3, open recommendation, consensus**).

- No MASH-targeted pharmacotherapy can currently be recommended for adults with MASH at the cirrhotic stage (**LoE 5, weak recommendation, strong consensus**).
- Given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis derived from large phase III trials and potential long-term risks, vitamin E cannot be recommended as a MASH-targeted therapy (**LoE 2, weak recommendation, strong consensus**).

Table 5—Liver and cardiorenal effects of glucose-lowering medications

	Effect in MASLD and MASH*				Cardiovascular, renal, and other relevant clinical effects			
Medication	Hepatic steatosis	Steatohepatitis	Fibrosis regression	Reduction of fibrosis progression	ASCVD*	CKD*	HF*	Hypoglycemia¶
Semaglutide**	Beneficial	Beneficial	Beneficial	Potential benefit	Beneficial	Beneficial	Beneficial	Low risk
Tirzepatide***†	Potential benefit	Potential benefit	Potential benefit	Potential benefit	?	?	Beneficial	Low risk
Pioglitazone†	Potential benefit	Potential benefit	Potential benefit	Potential benefit	Beneficial	Neutral	Not recommended in HF stage B, C, or D	Low risk
SGLT2 inhibitors	Potential benefit	?	?	?	Beneficial	Beneficial	Beneficial	Low risk
Metformin¶	Neutral	Neutral	Neutral	Neutral	Potential benefit?	Neutral	Neutral	Low risk
DPP-4 inhibitors¶	Neutral	?	?	?	Neutral	Neutral	Neutral (except saxagliptin, alogliptin?)	Low risk
Insulin¶	Potential benefit	?	?	?	Neutral	Neutral	Neutral	High risk
Sulfonylureas¶	Neutral	?	?	?	Neutral	Neutral	Neutral	High risk

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure. ? indicates unknown. *Includes people with and without type 2 diabetes. ¶Only in people with type 2 diabetes. **Only semaglutide among GLP-1RA has been reported to be of benefit in a phase 2 RCT (154) with improvement in steatohepatitis and more recently in a phase 3 RCT with histological outcomes in MASH, including improvements in steatohepatitis and fibrosis (11). Liraglutide may offer potential benefit, based on results of a phase 2 RCT (157). Other GLP-1RA have not been tested in RCTs with liver histological outcomes. ***Tirzepatide is the only dual GIP/GLP-1RA available and tested with histological outcomes in a phase 2 RCT in MASH (155). †Tirzepatide and pioglitazone are considered of potential benefit based on phase 2 trials.

Liver-directed thyroid hormone receptor agonists

Stepwise Scientific Reasoning

1 Clinical observation

- Hypothyroidism → ↑ LDL, ↑ liver fat
- Hyperthyroidism → ↓ LDL, ↓ liver fat

➡ Thyroid hormones strongly affect liver fat handling.

2 Receptor biology

- **THR-α**: heart, bone → side effects
- **THR-β**: predominantly **liver**

➡ Liver-specific therapeutic target identified.

3 Problem with classic thyroid hormones

- Improve lipids and steatosis
- ❌ Cause tachycardia, arrhythmias, muscle loss

➡ Pathway is correct, drug selectivity was the issue.

4 Pharmacologic innovation

- Development of **THR-β–selective, liver-directed agonists**
- Minimal activation of cardiac THR-α

➡ Metabolic benefit without systemic toxicity.

5 Match with MASLD/MASH pathophysiology

THR-β activation:

- ↑ Fatty acid oxidation
- ↓ De novo lipogenesis
- ↓ Hepatic triglyceride accumulation
- ↓ Inflammation & fibrotic signaling

➡ **Mechanism-based therapy**, not symptomatic treatment.

- In the US, resmetirom is given at a daily dose of 80 mg in individuals with a body weight <100 kg and at 100 mg in those with a body weight >– 100 kg (dose reduction is advised wit concomitant use of moderate CYP2C8 inhibitors such as clopidogrel). At these doses, the most common side effects were diarrhoea (up to 33%), nausea (up to 22%), pruritus (up to 11%) and vomiting (up to 11%).

- Individuals receiving resmetirom should be monitored for gastrointestinal side effects and *thyroid hormone* function.
- Circulating sex hormone-binding globulin (SHBG) levels have been suggested as a surrogate for target engagement.

- Importantly, evidence is currently limited to 52-week histological outcome data. This raises uncertainty as to whether responses will be sustained in the long-term. Similarly, there I currently no evidence to provide confident guidance on when to stop treatment, particularly considering that about 70-80 of participants did not respond to treatment according to histological criteria.

- This includes patients who cannot access (or cannot tolerate) GLP-1-based therapy, as well as those for whom GLP-1-based therapy does not result in sufficient weight loss to normalize transaminases.
- Staging of fibrosis to determine eligibility for treatment with resmetirom (ie, F2 or F3 stage) can be done by liver biopsy or by noninvasive testing.

- Prior to prescribing resmetirom, clinicians should review the patient's prescribed medications, over-the-counter medications, and dietary supplements and use a tool such as the UpToDate drug interactions program to assess specific drug interactions and potential ways to mitigate them. Resmetirom should not be used with OATP 1B1, IB3 inhibitors (eg, cyclosporine) or strong CYP2C8 inhibitors (eg, gemfibrozil).

- Data from clinical trials suggested that resmetirom improved MASH and stage of liver fibrosis. In a trial comparing resmetirom (80 or 100 mg) with placebo in 966 adults with biopsy-confirmed MASH and a liver fibrosis stage of F1B, F2, or F3, resmetirom resulted in higher rates of MASH resolution at 52 weeks (25.9 and 29.9 percent respectively versus 9.7 percent) .

- In addition, resmetirom resulted in higher rates of improving fibrosis by at least one stage (24.2 and 25.9 percent, respectively, versus 14.2 percent). Diarrhea and nausea were reported more frequently in the treatment groups.

GLP-1-based therapies

- We suggest GLP-1-based therapy (tirzepatide, semaglutide, liraglutide) for patients who have MASH with significant fibrosis (stage ≥2) and do not achieve their weight loss goals with lifestyle interventions alone.
- In the United States, MASH with stage 2 or 3 fibrosis is an FDA-approved indication for semaglutide .
- Most patients with MASH also have another FDA-approved indication (eg, diabetes, obesity, or overweight with at least one weight-related comorbidity) for GLP-1-based therapy.

Semaglutide

- Semaglutide improves liver histology in patients with MASH who have stage 2 or 3 fibrosis. In an interim analysis of a phase 3 trial of 800 patients with biopsy-proven MASH (stage 2 or 3 fibrosis), semaglutide 2.4 mg weekly for 72 weeks improved liver fibrosis without worsening of steatohepatitis compared with placebo (in 36.8 versus 22.4 percent of patients; estimated difference 14.4 percent, 95% CI 8-21) .

- More patients in the semaglutide group had resolution of steatohepatitis without worsening of fibrosis (62.9 versus 34.3 percent; estimated difference 28.7; 95% CI 21-26) .

Tirzepatide

- Tirzepatide improves steatohepatitis in patients with MASH who have stage 2 or 3 fibrosis. In a phase 2 trial including 190 patients with biopsy-proven MASH (stage 2 or 3 fibrosis), tirzepatide (5 mg, 10 mg, or 15 mg) weekly for 52 weeks resulted in resolution of MASH without worsening of fibrosis in 44 to 62 percent of patients (depending on the dose), compared with 10 of patients in the placebo group (estimated difference with the 10 mg dose 46 percent, 95% CI 29-62)

Liraglutide

- Liraglutide improves steatohepatitis in patients with MASH. In a phase 2 trial including 52 patients with MASH (of any fibrosis stage) who were assigned to receive liraglutide or placebo for 48 weeks, an end-of-treatment biopsy was performed in 23 patients in the liraglutide arm and in 22 patients in the placebo arm .

- MASH resolved in nine patients (39 percent) who received liraglutide, and in two patients (9 percent) who received placebo (RR 4.3; 95% CI 1.0-17). Patients who received liraglutide were also less likely to have progression of fibrosis (9 versus 36 percent; RR 0.2; 95% CI 0.1-1.0).

Vitamin E

- In the largest RCT to date, vitamin E supplementation (800 IU daily over 2 years) in individuals with non-diabetic MASH resulted in improvements in both steatosis and disease activity, which was corroborated by a reduction in liver enzymes.
- Smaller studies have suggested reduction in liver enzymes but there is currently no clear data on fibrosis improvement and no large phase III trial has been performed.

Ursodeoxycholic acid

- There are three larger, placebo-controlled trials of UDCA in MASH differing in the dose of UDCA used and only two of them report histological endpoints. Despite several limitations and methodological differences, there is a strong indication of biochemical efficacy (ALT reduction) and a good safety profile, but no proof of histological efficacy.

- Synthetic UDCA derivative, 24- norursodeoxycholic acid (norucholic acid), has shown anticholestatic, anti-inflammatory and anti-fibrotic properties in preclinical models and is being tested for MASH with initial results showing improvement in ALT and liver steatosis.

Obeticholic acid

- Obeticholic acid (OCA) is an oral, synthetic analogue of chenodeoxycholic acid designed to have a much stronger, nanomolar, potency as a FXR (farnesoid X receptor) agonist than the native bile acid.
- The drug is approved at a 5 or 10 mg daily dose for second-line therapy in primary biliary cholangitis and was developed for MASH at a higher dose (25 mg daily), based on a phase II placebo-controlled trial showing improvement in fibrosis and liver enzymes after 18 months of treatment..

- Dose-related pruritus and increases in LDL cholesterol are expected class effects of FXR agonists. but additional concerns over the risk benefit ratio (including hepatotoxicity and hepatic events) resulted in a denial of accelerated approval, leading to discontinuation of the clinical outcome phase of the registrational trial and of the development programme in MASH.

Omega-3 polyunsaturated fatty acids

- supplementation with eicosapentaenoic acid (in ethyl ester formulation) did not show any histological efficacy vs. placebo in RCTs. Studies with icosabutate, a structurally engineered omega 3 fatty acid with distinct intracellular distribution and metabolism are ongoing.

Statins

- MASLD induces atherogenic dyslipidaemia and statin therapy is therefore often indicated to prevent cardiovascular events.
- The safety of statins has been well established in individuals with MASLD with no increased risk of hepatotoxicity, yet many individuals with MASLD are undertreated. Case control studies have shown that statin intake is associated with a reduced risk of MASLD, MASH and liver fibrosis, as well as a reduction in the risk of hepatic decompensation, mortality and HCC in individuals with cirrhosis.

- Nonetheless the efficacy of statins, specifically for treating MASH, cannot be established, since there are no large RCTs of statins with histological endpoints. The same holds true for fibrates and ezetimibe. Silymarin (an extract of milk thistle) may improve liver enzymes but the few, small, RCTs available did not document histological improvement.

Sodium-glucose co-transporter-2 inhibitors

- Controlled clinical trials with liver histological endpoints are currently not available.
- Trials in people with T2D (not all with MASLD and some excluding high ALT values) have shown a moderate reduction in liver lipid content with empagliflozin, dapagliflozin and licogliflozin. Reductions in ALT were shown with empagliflozin and licogliflozin.

Peroxisome proliferator-activated receptor agonists

- In several RCTs, pioglitazone, a thiazolidinedione which mainly activates peroxisome proliferator-activated receptor (PPAR)c,has been shown to improve histological features of steatohepatitis, without a clear effect on fibrosis regression even after prolonged (3-year) therapy.

- However, no large, international, phase III trial has been conducted and pioglitazone has been withdrawn from the market in several European countries. The drug has beneficial effects on insulin sensitivity, glycaemic control, serum lipids and prevention of cardiovascular events in individuals with T2D, but the side effect profile (weight gain, pedal oedema, haemodilution, bone loss in post-menopausal women and a debate around the risk ofbladder cancer) has limited its development for MASH.

- A large registrational, phase III trial is ongoing. Saroglitazar, a dual PPARa/c agonist has been shown to improve insulin resistance, liver steatosis and liver enzymes and is approved in India for the treatment of T2D and MASH. Trials with liver histological endpoints are ongoing.

Metformin

- Small and uncontrolled initial trials of metformin have shown an ALT reduction and an insulin-sensitising effect, but were not followed by sufficiently large and well-conducted RCTs.
- Currently, there is no evidence that metformin alone can improve histology in MASH.

- In people with T2D and MASLD-related advanced fibrosis or cirrhosis, metformin may improve transplant-free survival (but not the risk of hepatic decompensation), and reduce the risk of primary liver and extrahepatic cancer. Thus, metformin should not be discontinued in those individuals with cirrhosis (unless discontinuation is required due to hepatic decompensation or renal failure), as this could increase mortality.

Treatment of MASLD: Surgical and endoscopic therapy

Recommendations

- In adults with non-cirrhotic MASLD who have an approved indication, bariatric surgery should be considered, because it can induce long-term beneficial effects on the liver and is associated with remission of type 2 diabetes and improvement of cardiometabolic risk factors (**LoE 3, strong recommendation, strong consensus**).
- In adults with MASLD-related compensated advanced chronic liver disease/compensated cirrhosis who have an approved indication, bariatric surgery can be considered but careful evaluation (indication, type of surgery, presence of clinically significant portal hypertension) by a multidisciplinary team with experience in bariatric surgery in this particular population is required (**LoE 4, weak recommendation, strong consensus**).
- Metabolic/bariatric endoscopic procedures require further validation as MASH-targeted therapy and cannot currently be recommended (**LoE 4, weak recommendation, strong consensus**).

- Roux-en-Y gastric bypass improved or resolved liver fibrosis in 30% of individuals. Interestingly, the percentage of individuals with improved steatosis and hepatic fibrosis was higher in Asian countries.
- However, in a study with control biopsies after surgery, advanced fibrosis (bridging fibrosis or cirrhosis) persisted in 47% of individuals sometimes even 5 years or more post-surgery and despite significant weight loss.

- A meta-analysis that included 33 studies with 1,710 individuals reporting liver-related endpoints (e.g. NITs, liver fibrosis, steatosis) showed a significant improvement in parameters related to liver steatosis and fibrosis with various endoscopic bariatric therapies. However, most included studies were retrospective, with few histology data.

Long-term Monitoring

FIB-4 score <1.3

- we recommend that individuals with an initial FIB-4 score <1.3 be reassessed with repeat FIB-4 measurements in 1–2years.

- A FIB-4 score cutoff of <1.3 should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement.
- Case finding with eventual additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors.

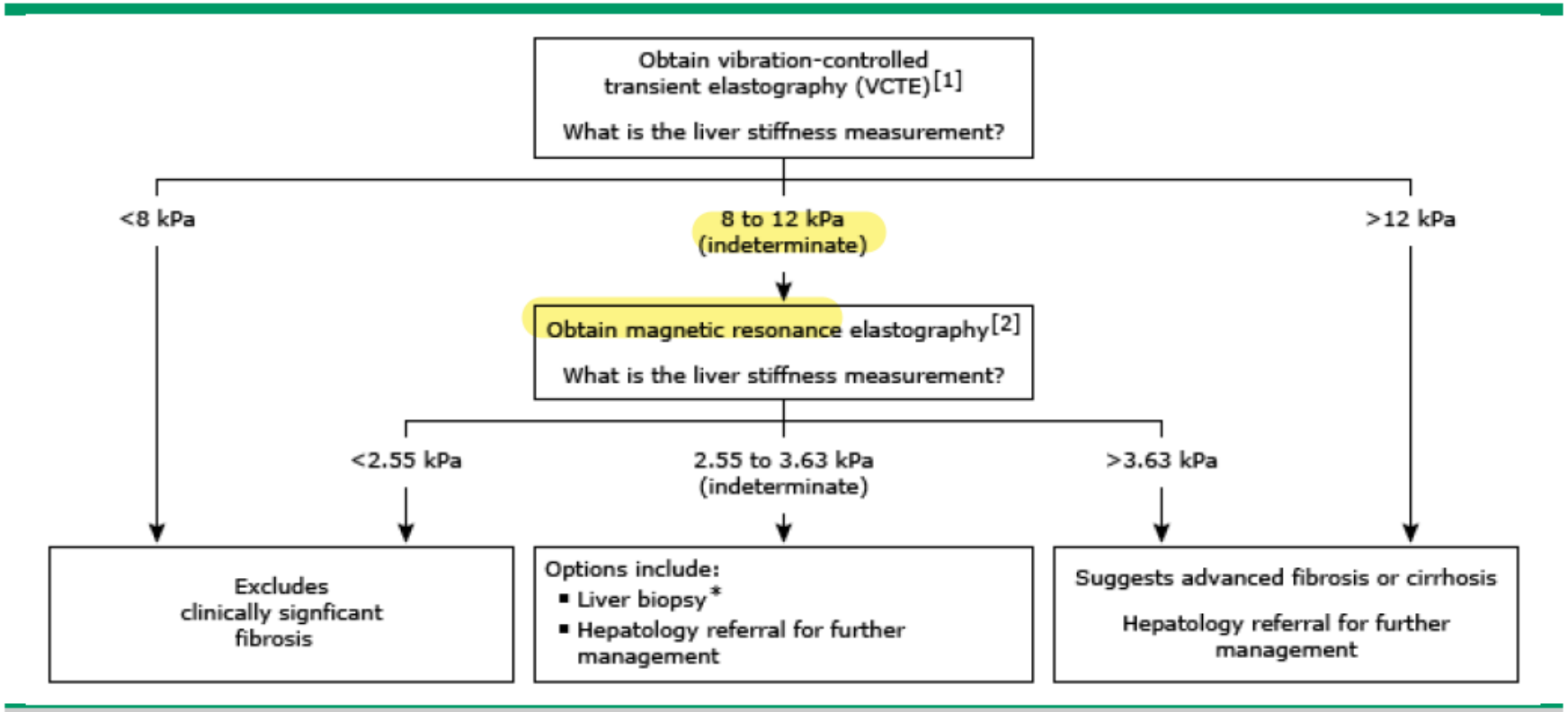
- For these cases transient elastography may also be of benefit as part of risk assessment. The risk of developing MASLD has been independently associated with insulin resistance, weight gain, obesity, and cardiometabolic risk factors.

FIB-4 Score >1.3

- People with a FIB-4 score >1.3 but VCTE-LSM <8.0 kPa can be followed in non-liver specialty clinics with repeat surveillance in 1–2 years.
- Most guidelines recommend LSM by VCTE as the leading disease monitoring tool, as it predicts future outcomes

- People with a FIB-4 score >1.3 and VCTE-LSM >8.0 kPa should undergo more diagnostic testing in gastroenterology or hepatology specialty clinics for confirmation of at-risk MASH or cirrhosis.
- In individuals with cirrhosis, an increase in liver stiffness and a decrease in platelet counts to <150,000 are associated with development of portal hypertension, which is a key driver of clinical decompensation.

An approach to evaluating for fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)



This figure summarizes an approach to evaluating for fibrosis in patients with MASLD. This algorithm is intended for use in conjunction with UpToDate content on the clinical features and diagnosis of MASLD. We use ultrasound-based elastography to evaluate for advanced fibrosis or cirrhosis. If imaging methods are not available, alternatives include serologic tests. Refer to UpToDate content on noninvasive assessment of hepatic fibrosis for details.

Further management of patients with cirrhosis includes screening for and preventing cirrhosis-related complications (eg, variceal bleeding, hepatocellular carcinoma).

- Annual transient elastography along with platelet counts may be considered for this subgroup.
- Screening for HCC and assessment of Model for End-Stage Liver Disease (MELD) score and complication(s) of portal hypertension should be performed every 6 months in individuals with cirrhosis to ensure timely diagnosis of HCC and referral for liver transplant for a rising MELD score, particularly to values of >15.

- MASLD may have an initial FIB-4 score >2.67 .Such individuals can be directly referred to gastroenterologists or hepatologists for evaluation of the presence or absence of cirrhosis and initiation of cirrhosis-related care for HCC surveillance, to prevent decompensation and delay the need for liver transplant, if indicated.

Assessment of Response to Treatment

- FIB-4 is not very sensitive to fibrosis change, and its increase or decrease only occurs after substantial **changes** in fibrosis stage
- Furthermore, short-term improvement (6–12 months) in FIB-4 likely reflects changes in inflammation plasma aminotransferases) rather than fibrosis.

- These data support the use of transient elastography (VCTE-LSM) to evaluate responses to therapeutic intervention. Improvement by >30% represents therapeutic response, whereas an increase by >30% reflects disease progression
- Referral to the gastroenterologist or hepatologist is warranted if there is a suggestion of disease progression.

Portal Hypertention

Recommendations

- Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) ≤15 kPa plus platelet count ≥150 × 10^9/L may be used to rule out clinically significant portal hypertension (CSPH) in adults with MASLD (**LoE 3, weak recommendation, strong consensus**).

- If CSPH is present, non-selective beta-blockers may be started unless contraindicated (**LoE 3, weak recommendation, strong consensus**).

- In adults with compensated advanced chronic liver disease but LSM ≥20 kPa and/or platelet count <150 × 10^9/L, an upper gastrointestinal endoscopy should be performed to screen for varices unless they already fulfil the criteria to initiate non-selective beta-blockers (**LoE 3, strong recommendation, strong consensus**).

Statement

- The threshold of LSM ≥25 kPa to rule in CSPH is only applicable to non-obese (BMI <30 kg/m^2) adults with MASLD; while obesity can confound LSM, current evidence is insufficient to suggest the optimal non-invasive test to rule in CSPH in adults with MASLD and obesity **(LoE 3, strong consensus)**.

Statement

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HCC

Recommendations

- According to current guidelines, hepatocellular carcinoma monitoring programmes should be applied to individuals with MASLD-related cirrhosis (**LoE 3, strong recommendation, strong consensus**).
- Risk stratification can help in optimising strategies for monitoring individuals at higher risk of hepatocellular carcinoma (Table 8) (**LoE 4, weak recommendation, strong consensus**).
- As ultrasound-based surveillance has a low sensitivity for detection of hepatocellular carcinoma at an early-stage, particularly in adults with MASLD-related cirrhosis and obesity, alpha-fetoprotein (AFP) measurement can be combined with ultrasound in individuals at high risk (**LoE 3, open recommendation, consensus**).
- Cross-sectional imaging by MRI may be undertaken in selected adults at high risk with persistent poor visualisation at ultrasound, particularly in individuals with dysplastic or regenerative nodules (**LoE 3, open recommendation, strong consensus**).

Table 8. Factors associated with a higher risk of HCC occurrence in MASLD.

Factor(s)	Ref.
Presence and duration of T2D, obesity or both	57,531
Older age	532,533
Concurrent alcohol intake and/or smoking	532,533
Individuals with FIB-4 >3.25	244
Individuals with LSM >10 kPa and increasing change in LSM over time	185

Statements

- Non-invasive tests have been linked with histologically assessed treatment response, but the most appropriate non-invasive test may depend on the type of intervention and patient-related factors (**LoE 2, strong consensus**).
- Longitudinal changes in non-invasive test results have been correlated with changes in the risk of adverse outcomes on a cohort or population level (**LoE 3, consensus**).
- In the setting of randomised controlled trials and depending on the mode of intervention, changes of non-invasive markers (*e.g.* MRI-PDFF relative reduction by ≥30%, ALT reduction by ≥17 U/L) have been associated with resolution of steatohepatitis (**LoE 2, strong consensus**).
- Liver biopsy is not suited for monitoring disease evolution or response to therapy in routine clinical practice due to its invasiveness and procedure-related limitations (**LoE 5, strong consensus**).

End-stage liver disease

Recommendations

- Adults with obesity and end-stage MASLD listed for liver transplantation should undergo therapeutic interventions aimed at weight reduction without worsening sarcopenia as this will improve peri-operative outcomes (**LoE 3, strong recommendation, strong consensus**).
- Implementation of dietary modification and supervised physical exercise should be the first line management approach with the objective of reducing BMI <40 kg/m^2 and ideally <35 kg/m^2 (**LoE 1, strong recommendation, strong consensus**).
- In adults with end-stage MASLD listed for liver transplantation, pharmacological weight-loss strategies may be considered after careful risk-benefit assessment (*e.g.* presence of sarcopenia, liver function impairment) (**LoE 4, weak recommendation, consensus**).
- In adults with compensated cirrhosis and without clinically significant portal hypertension, sleeve gastrectomy prior to liver transplantation may be considered as an alternative option to dietary or pharmacological weight loss (**LoE 3, open recommendation, strong consensus**).
- In case of decompensated cirrhosis, bariatric surgery is contraindicated and needs to be discussed in the context of considering liver transplantation (**LoE 4, open recommendation, strong consensus**).

Statement

- Weight loss and optimised treatment of comorbidities before transplantation may confer a benefit in terms of cardiovascular morbidity, as well as long-term survival and reduced recurrence of severe MASLD after liver transplantation (**LoE 3, strong consensus**).