

EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) – Summary version[☆]

European Association for the Study of the Liver^{*}

Contents

Definition, prevalence and natural course	2
Prevention.....	3
Screening, case-finding, diagnosis and monitoring.....	4
Treatment of MASLD: General considerations	7
Treatment of MASLD: Non-pharmacological therapy.....	9
Treatment of MASLD: Pharmacological therapy.....	11
Treatment of MASLD: Surgical and endoscopic therapy	13
End-stage liver disease and liver transplantation.....	13
Tables and figures.....	17

Disclaimer

This document provides a summary of the EASL Clinical Practice Guidelines [<https://doi.org/10.1016/j.jhep.2024.04.031>]; for comprehensive information and detailed recommendations, please refer to the full version of the guidelines.

Methodology used for the development of the present CPG

PICO questions were vetted through a simplified Delphi process by an international 46-member panel. Every PICO question that did not reach >75% agreement in the first round of the Delphi process was revised. All suggestions and recommendations reached the threshold of 75% agreement, but some questions, recommendations and statements were adjusted following well-justified comments by the Delphi panel. The process involved multiple rounds of questioning and feedback until a consensus or convergence of opinions was achieved, and the feedback was

incorporated into the final consensus recommendations and statements. The strength of consensus was defined according to the percentage of agreement by the Delphi panel members where $\geq 95\%$ agreement was classified as strong consensus and 75-95% were classified as consensus. Neutral votes were not counted when calculating the consensus. Detailed methodology can be found in the full CPG version.

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These guidelines were developed by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity and jointly published in the Journal of Hepatology and Obesity Facts.

EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024 Jun 5:S0168-8278(24)00329-5. <https://doi.org/10.1016/j.jhep.2025.04.008>

Definition, prevalence and natural course

Is the presence of steatotic liver in the general population an important factor in identifying individuals at risk for liver-related outcomes, independent of the presence of other hepatotoxic factors?

Recommendations

- The incidental finding of steatosis should prompt assessment of the potential aetiology of SLD, alongside tests for the presence of advanced fibrosis, as this could determine the risk of liver-related and/or cardiovascular outcomes and appropriate care (LoE 3, strong recommendation, strong consensus).
- MASLD, ALD and MetALD are the most common causes of SLD, but other causes such as drug-induced liver disease and monogenic SLD should be considered, depending on the context (LoE 3, strong recommendation, strong consensus).
- General population-based screening for SLD is not advised (LoE 3, strong recommendation, strong consensus).

Statement

- While the presence of steatotic liver in the general population is not independently associated with liver-related outcomes, the stage of liver fibrosis and persistently elevated liver enzymes are associated with liver-related outcomes (LoE 3, strong consensus).

Which risk factors and comorbidities have the greatest impact on the natural history of the hepatic disease including hepatocellular carcinoma in MASLD?

Statements

- Type 2 diabetes and obesity (particularly abdominal obesity) are the metabolic diseases with the strongest impact on the natural history of MASLD, including progression to MASLD/MASH-related advanced fibrosis, cirrhosis and hepatocellular carcinoma (LoE 2, strong consensus).
- Males aged >50 years, postmenopausal women, and individuals with multiple cardiometabolic risk factors are at increased risk of progressive fibrosis and the development of cirrhosis and its complications (LoE 2, strong consensus).

Does any alcohol consumption in adults with non-cirrhotic or cirrhotic MASLD have an adverse effect on the natural course of liver disease?

Statements

- Accumulating evidence shows that alcohol consumption and metabolic risk factors have modifying effects on the onset and progression of chronic liver disease which are independent and can be synergistic (LoE 2, strong consensus).
- The presumed beneficial health effects of moderate alcohol consumption are inconsistent across studies and emerging evidence does not support a protective effect of light to moderate amounts of alcohol, particularly in individuals with cardiometabolic risk factors (LoE 3, strong consensus).

Recommendations

- The amount, pattern and history of alcohol intake should be documented in all individuals with SLD (LoE 3, strong recommendation, strong consensus).
- Alcohol intake may be qualitatively and quantitatively assessed by validated instruments and/or specific biomarkers in individuals with SLD (Table 5) (LoE 3, open recommendation, strong consensus).
- Individuals with SLD, particularly those with moderate or high alcohol intake, should be discouraged from consuming alcohol (LoE 3, strong recommendation, consensus).
- All alcohol consumption should be stopped completely and permanently in individuals with advanced fibrosis or cirrhosis (LoE 3, strong recommendation, strong consensus).

Prevention

In the general population or high-risk groups, can nonpharmacological measures be recommended to prevent the development of MASLD and its adverse complications, including hepatocellular carcinoma?

Recommendation

- In the general population, non-pharmacological measures should be recommended to prevent the development of MASLD and its complications, including hepatocellular carcinoma, and preventive measures should be reinforced in high-risk groups (LoE 3, strong recommendation, strong consensus).

Screening, case-finding, diagnosis and monitoring

Should a policy of screening for MASLD at risk of fibrotic disease (or fibrosis progression) in primary care or at the non-hepatology specialist level be implemented in the general population or only in individuals with cardiometabolic risk factors?

Which at-risk individuals should undergo case-finding for MASLD at risk of fibrotic disease (or fibrosis progression) in the primary care (or other specialty) setting to reduce hepatic complications of MASLD?

Recommendations

- Healthcare providers may consider case-finding strategies for MASLD with liver fibrosis in individuals with cardiometabolic risk factors (Table 3), abnormal liver enzymes, and/or radiological signs of hepatic steatosis (LoE 3, weak recommendation, consensus).
- Healthcare providers should look for MASLD with liver fibrosis either in individuals with (A) type 2 diabetes or (B) abdominal obesity and ≥ 1 additional metabolic risk factor(s) (Table 3) or (C) abnormal liver function tests (LoE 3, strong recommendation, consensus).

Statement

- Early diagnosis of fibrosis and subsequent appropriate management can potentially prevent progression to cirrhosis and its complications and may justify screening in these populations at risk (LoE 3, strong consensus).

In the adult population with MASLD, are selected noninvasive scores and imaging modalities more useful than liver enzyme testing for the detection of MASLD with fibrosis? In adults with MASLD or at-risk individuals, are clinical care pathways based on the sequential application of noninvasive scores and imaging cost-effective for the identification and management of individuals with MASLD at risk of fibrotic disease (or of fibrosis progression) compared to referral based on physician's discretion?

Recommendations

- In adults with MASLD, non-invasive scores based on combinations of blood tests or combinations of blood tests with imaging techniques measuring mechanical properties and/or hepatic fat content should be used for the detection of fibrosis since their

diagnostic accuracy is higher than standard liver enzyme testing (alanine [ALT] and aspartate aminotransferase [AST]) (LoE 2, strong recommendation, strong consensus).

- In adults with MASLD, a multi-step approach is recommended (detailed in Fig. 2 and below): First, an established non-patented blood-based score, such as FIB-4, should be used. Thereafter, established imaging techniques, such as liver elastography, are recommended as a second step to further clarify the fibrosis stage if fibrosis is still suspected or in high-risk groups (LoE 2, strong recommendation, strong consensus).
- Tests of specific collagen-related blood constituents (e.g. ELF) may serve as an alternative to imaging to identify advanced liver fibrosis (LoE 2, open recommendation, consensus).
- Clinical care pathways may be adopted based on the sequential application of non-invasive scores and imaging tests in adults with MASLD or at-risk individuals, recognising that most adults with MASLD are seen in non-hepatology settings (LoE 2, weak recommendation, strong consensus).

In adults with MASLD, should non-invasive scores, circulating biomarkers, liver stiffness measurement, and imaging methods replace liver biopsy for the diagnosis of metabolic dysfunction-associated steatohepatitis (MASH) and/or advanced fibrosis?

Recommendation

- Blood biomarker-derived scores and elastography should be used to exclude advanced fibrosis, while elastography is better suited to predict advanced fibrosis (LoE 2, strong recommendation, consensus).

Statements

- None of these non-invasive methods can assess relevant microscopic features of MASLD such as ballooning or lobular inflammation (LoE 2, strong consensus).
- Some blood biomarker-based scores may help to identify individuals with MASH at risk of disease progression (LoE 3, consensus).
- Blood biomarker-derived scores and elastography can help in risk stratification for clinical outcomes, as observational studies have identified thresholds related to liver-related outcomes and mortality (LoE 3, strong consensus).
- In most cases, liver biopsy is not required for clinical management of individuals with MASLD; however, liver biopsy is still required for the definite diagnosis of steatohepatitis and can help to rule out alternative causes of liver disease (LoE 1, strong consensus).

In adults with MASLD, should non-invasive scores, circulating biomarkers, liver stiffness measurement, and imaging techniques be used as a surrogate for liver biopsy to monitor progression of MASH and predict liver-related outcomes?

Recommendations

- In adults with MASLD, sequential assessment with noninvasive tools may assist in ruling out fibrosis progression (LoE 3, weak recommendation, strong consensus).
- In adults with MASLD, non-invasive tools can help predict the risk of overall and liver-related events and mortality (LoE 2, weak recommendation, strong consensus).

In adults with MASLD, does genetic testing (alone or in combination) provide an additional advantage over other non-invasive scores and imaging in predicting risk of liver disease development, severity, progression and liver-related outcomes, or response to specific therapeutic approaches?

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).

Is the assessment of metabolic abnormalities (e.g. insulin sensitivity/resistance) useful for risk stratification or management of adults with MASLD?

In adults with MASLD, should diagnostic procedures be performed for associated comorbidities (e.g. cardiovascular diseases, diabetes, dyslipidaemia or obesity)?

Recommendations

- Clinicians should assess associated comorbidities (e.g. type 2 diabetes, dyslipidaemia, hypertension, kidney disease, sleep apnoea, polycystic ovary syndrome) and cardiovascular risk in adults with MASLD (LoE 2, strong recommendation, strong consensus).
- At initial diagnosis of MASLD and at regular follow-up intervals, laboratory tests and physical examinations for related comorbidities are recommended (Table 7) (LoE 2, strong recommendation, strong consensus).
- Adults with MASLD should be encouraged to participate in extrahepatic cancer screening according to current guidelines, based on their exposure to obesity and type 2 diabetes as risk factors for extrahepatic malignancies (LoE 3, strong recommendation, strong consensus).

- Assessment of insulin resistance (e.g. using the homeostasis model assessment of insulin resistance [HOMA-IR] or estimates derived from the oral glucose tolerance test) may be considered to clarify metabolic dysfunction in adults with (suspected) MASLD and without an established diagnosis of type 2 diabetes (LoE 3, weak recommendation, consensus).

In adults with non-cirrhotic MASLD or MASH, is surveillance indicated for early detection of hepatocellular carcinoma?

Recommendations

- In adults with non-cirrhotic MASLD or MASH in the absence of severe fibrosis (i.e. those with fibrosis stage <F3) assessed by non-invasive markers or liver biopsy, surveillance for early detection of hepatocellular carcinoma is currently not recommended (LoE 3, weak recommendation, consensus).
- In adults with non-cirrhotic MASLD or MASH in the presence of severe fibrosis (F3) assessed by non-invasive markers or liver biopsy, surveillance may be considered based on an individual risk assessment (LoE 4, weak recommendation, strong consensus).

Should hepatocellular carcinoma monitoring programmes be implemented in all adults with MASH-related cirrhosis, or should they be implemented based on risk stratification?

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).

Treatment of MASLD: General considerations

In adults with MASLD, which of the following – reduction of steatosis, resolution of MASH, improvement of fibrosis, stabilisation of fibrosis, prevention of progression to cirrhosis – is the most relevant therapeutic target for improving liver-related outcomes?

Statements

- In adults with MASLD and advanced fibrosis or cirrhosis, regression of fibrosis has been associated with a reduced risk of liver-related outcomes (LoE 2, strong consensus).
- Improvement in disease activity and resolution of steatohepatitis have been associated with regression of fibrosis (LoE 2, strong consensus).
- Reduction of steatosis has been associated with histological improvements (particularly necro-inflammation) in some pharmacological intervention studies (LoE 2, strong consensus).
- Since improved mortality has not been demonstrated for any of these treatment-induced histological changes, further long-term follow-up studies are needed to demonstrate that halting disease progression and/or reduction of steatosis, resolution of steatohepatitis or regression of fibrosis translate into a reduced risk of clinical outcomes (LoE 3, strong consensus).

In adults with MASLD, should non-invasive scores, serum markers, liver stiffness measurements, and imaging be used as a substitute for liver biopsy for monitoring therapeutic responses?

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 $\geq 30\%$, 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).

Recommendations

- At the individual level, non-invasive tests may be repeatedly used to assess fibrosis progression in a tailored fashion but may provide limited information about treatment response (LoE 5, weak recommendation, strong consensus).
- In individual cases and in clinical trials, liver biopsy can be used to monitor disease progression or response to treatment (LoE 1, open recommendation, strong consensus).

In adults with MASLD, can the management of liver disease and extrahepatic comorbidities within multidisciplinary teams involving hepatologists and other specialists improve clinical outcomes?

Recommendation

- Given the multidirectional connections between MASLD and cardiometabolic comorbidities, a multidisciplinary approach is recommended to ensure all components are appropriately targeted to improve both liver-related and extrahepatic outcomes (LoE 3, strong recommendation, strong consensus).

Treatment of MASLD: Non-pharmacological therapy

In adults with MASLD, what is the efficacy of dietary and behavioural therapy-induced weight loss on histologically/ non-invasively assessed liver damage/fibrosis and liver-related outcomes compared with no intervention?

Recommendations

- In adults with MASLD, dietary and behavioural therapy-induced weight loss should be recommended to improve liver injury, as assessed histologically or non-invasively (LoE 1, strong recommendation, strong consensus).
- In adults with MASLD and overweight, dietary and behavioural therapy-induced weight loss should aim at a sustained reduction of $\geq 5\%$ to reduce liver fat, 7-10% to improve liver inflammation, and $\geq 10\%$ to improve fibrosis (LoE 2, strong recommendation, strong consensus).

Statement

- Further follow-up studies are needed to determine the long-term effectiveness of dietary and behavioural therapy-induced weight loss (including its magnitude) on clinical liver-related outcomes and liver-related mortality (LoE 3, strong consensus).

In adults with MASLD, is changing diet quality effective in reducing histologically/non-invasively assessed liver damage/ fibrosis and liver-related outcomes compared with no intervention?

Recommendation

- In adults with MASLD, improving diet quality (similar to the Mediterranean dietary pattern), limiting the consumption of ultra-processed food (rich in sugars and saturated fat) and avoiding sugar-sweetened beverages should be recommended to improve

histologically or non-invasively assessed liver injury (LoE 2, strong recommendation, strong consensus).

Statement

- There is little evidence that improving diet quality beneficially impacts clinical liver-related outcomes (LoE 3, consensus).

In adults with MASLD, are physical activity and exercise effective at reducing histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared with no intervention?

Recommendation

- In adults with MASLD, physical activity and exercise should be recommended to reduce steatosis, tailored to the individual's preference and ability (preferably >150 min/week of moderate or 75 min/week of vigorous-intensity physical activity) (LoE 1, strong recommendation, strong consensus).

Statement

- In comparison to the well-documented cardiometabolic benefits, there is less robust evidence for benefits of physical activity and exercise on histological outcomes, non-invasively assessed liver damage/fibrosis and liver-related clinical outcomes (LoE 5, strong consensus).

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

Recommendation

- In normal-weight adults with MASLD, diet and exercise interventions should be recommended to reduce liver fat (LoE 3, strong recommendation, strong consensus).

Statement

- In normal-weight adults with MASLD, there is currently no evidence regarding the beneficial effect of diet and/or exercise on liver histology, fibrosis and liver-related clinical outcomes (LoE 5, consensus).

In adults with MASLD, are nutraceuticals (food supplements, herbal products, gut microbiota-modifying agents) effective to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared 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).

Treatment of MASLD: Pharmacological therapy

In adults with MASH, is there sufficient evidence to recommend prescription of existing non-glucose-lowering drugs to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

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 noncirrhotic 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).

Statement

- For individuals with MASLD undergoing therapy with resmetirom, data on sustainability of histological benefits, individual prediction of response, liver-related outcomes and long-term safety are not currently available (LoE 5, strong consensus).

In adults with MASH, is there sufficient evidence to recommend prescription of existing glucose-lowering drugs to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes compared to no pharmacological intervention?

Recommendations

- In the absence of a formal demonstration of histological improvement in large, well conducted, phase III trials, glucagon-like peptide 1 receptor agonists (GLP1RA) cannot currently be recommended as MASH-targeted therapies (LoE 5, strong recommendation, strong consensus).
- GLP1RAs are safe to use in MASH (including compensated cirrhosis) and should be used for their respective indications, namely type 2 diabetes and obesity, as their use improves cardiometabolic outcomes (LoE 2, strong recommendation, strong consensus).
- Where available, pioglitazone is safe to use in adults with non-cirrhotic MASH but given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis in large phase III trials, pioglitazone cannot be recommended as a MASH-targeted therapy (LoE 2, weak recommendation, consensus).
- There is insufficient evidence to recommend the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors or metformin as MASH-targeted therapies; however, they are safe to use in MASLD and should be used for their respective indications, namely type 2 diabetes, heart failure and chronic kidney disease (LoE 3, strong recommendation, strong consensus).

Statements

- In case of substantial weight loss induced by GLP1RAs, a hepatic histological benefit could be expected, although this has not been extensively documented so far (LoE 2, strong consensus).
- There is insufficient evidence to support using any other glucose-lowering drug class as MASH-targeted therapies (LoE 5, strong consensus).

In adults with MASH, is there sufficient evidence to recommend prescription of existing weight-loss agents to reduce histologically/non-invasively assessed liver damage/ fibrosis and liver-related outcomes compared to no pharmacological intervention?

Recommendation

- Non-incretin-based weight-loss agents are not recommended as MASH-targeted therapies (LoE 5, strong recommendation, strong consensus).

Treatment of MASLD: Surgical and endoscopic therapy

In adults with MASLD and obesity, are bariatric/metabolic surgery procedures or endoscopic weight-loss interventions effective to reduce histologically/noninvasively assessed liver damage and liver-related outcomes compared with no intervention?

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).

End-stage liver disease and liver transplantation

In adults with MASH-related cirrhosis, should dietary and lifestyle recommendations be adapted to the severity of liver disease, nutritional status, and sarcopenia?

Recommendations

- In adults with MASH cirrhosis, it is recommended that dietary and lifestyle recommendations be adapted to the severity of liver disease, nutritional status and the presence of sarcopenia/sarcopenic obesity (LoE 2, strong recommendation, strong consensus).
- In adults with sarcopenia, sarcopenic obesity or decompensated cirrhosis, it is recommended that a high-protein diet is provided, as well as a late-evening snack (LoE 2, strong recommendation, consensus).
- Moderate weight reduction can be suggested in adults with compensated cirrhosis and obesity, with an emphasis on high protein intake and physical activity to maintain muscle mass and reduce the risk of sarcopenia (LoE 3, weak recommendation, strong consensus).

In adults with MASH-related cirrhosis, how should pharmacologic interventions for diabetes and lipid control or cardiovascular prevention be adapted to the severity of the liver condition?

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).

In adults with MASLD, can non-invasive scores, serum markers, liver stiffness measurements, and/or imaging replace hepatic venous pressure gradient (HVPG) and endoscopy in identifying individuals with clinically significant portal hypertension and varices requiring treatment, respectively?

Recommendations

- Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) ≤ 15 kPa plus platelet count $\geq 150 \times 10^9/L$ 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 $< 150 \times 10^9/L$, 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/m²) 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).

In adults with MASLD who are candidates for liver transplantation, should the evaluation of (cardiometabolic) comorbidities in the pre- and post-transplant phase be different from that of individuals with liver disease of other aetiologies?

Statement

- Adults with MASLD are at increased risk of major cardiovascular events in the pre-, peri- and post-transplant phase (LoE 2, strong consensus).

Recommendations

- Adults with MASLD who are candidates for liver transplantation should be evaluated by a multidisciplinary team for cardiovascular and metabolic comorbidities to mitigate the risk of major cardiovascular events in the pre-, peri- and post-transplant phase (LoE 3, strong recommendation, strong consensus).
- A comprehensive screening for comorbidities in adults with MASLD before liver transplantation (Table 11), including a stepwise and risk-adjusted cardiac work-up algorithm (Fig. 5), may help to optimise management of adults with MASLD before, during and after liver transplantation (LoE 5, weak recommendation, strong consensus).

In potential liver transplant recipients with MASH and severe obesity, do pharmacologic treatments, endoscopic interventions, and bariatric surgery for weight loss improve outcomes before and after transplantation?

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/m² and ideally <35 kg/m² (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).

In adults who received liver transplantation due to MASLD-related end-stage liver disease, can non-pharmacologic or pharmacologic measures reduce the risk of MASLD recurrence and improve long-term outcomes compared with no intervention?

Statements

- In adults transplanted for MASLD-related end-stage liver disease, there is a high risk of recurrence of MASLD after liver transplantation, especially in adults with several metabolic risk factors (LoE 3, strong consensus).
- Adults transplanted for MASLD-related end-stage liver disease are also at risk of cardiovascular events and kidney disease which can negatively impact long-term survival (LoE 2, strong consensus).
- No specific issues related to MASLD are known to alter choice of medication or target values; the risk of recurrence of severe, fibrotic steatohepatitis reinforces the need to obtain optimal control of cardiometabolic risk factors (LoE 5, strong consensus).
- The benefit of controlling weight and obesity-related comorbidities on recurrence of MASLD post-liver transplant and on progression to advanced fibrosis is expected but needs to be demonstrated in dedicated trials (LoE 5, strong consensus).

Recommendations

- In adults transplanted for MASLD-related end-stage liver disease, therapeutic interventions to control obesity and related cardiometabolic complications are recommended (LoE 3, strong recommendation, strong consensus).
- After liver transplantation, standard non-pharmacological dietary and lifestyle interventions should be universally implemented; pharmacological management of hypertension, type 2 diabetes and lipid disorders should be implemented according to general clinical guidelines (LoE 3, strong recommendation, strong consensus).
- GLP1 receptor agonists may be considered to control weight and obesity-related comorbidities, although specific trials in transplant recipients are needed (LoE 5, weak recommendation, strong consensus).

Tables and figures

Table 1. Grades of recommendation.

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, individual preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

Table 2. Level of Evidence based on the Oxford Centre for Evidence-based Medicine (adapted).

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk.
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (<i>i.e.</i> non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain.

Level may be graded down based on study quality, imprecision, indirectness (study does not match questions), because of inconsistency between studies, or because the absolute effect size is very small; level may be graded up if there is a large or very large effect size.

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 <ul style="list-style-type: none"> • ≥ 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	<u>Prediabetes</u> : 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 <u>Type 2 diabetes</u> : HbA _{1c} ≥ 48 mmol/mol ($\geq 6.5\%$) 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	$\geq 130/85$ mmHg or treatment for hypertension

HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

Table 4. SLD due to aetiologies other than MASLD, MetALD or ALD.

Condition	Clinical/lab/histological findings	Diagnostic criteria
Hepatitis C virus-associated steatotic liver (genotype 3)	Low triglycerides, HCV genotype 3	HCV antibody with reflex testing HCV RNA and HCV genotype
Drug-induced liver disease (DILI)	Mostly microvesicular SLD	Investigate for drug intake: <ul style="list-style-type: none"> • Corticosteroids • Tamoxifen • Amiodarone • Irinotecan • Methotrexate • Lomitapide • Valproate • 5-Fluorouracil Liver biopsy for confirmation
Hypobetalipoproteinaemia	Low triglycerides and cholesterol, fat malabsorption, vitamin A deficiency	ApoB level, genetic testing (<i>APOB</i> , <i>MTP</i> , <i>PCSK-9</i> , targeted panel sequencing)
Lipodystrophy	Accumulation of fat in the visceral area and in the muscle (generally inherited or induced by HAART therapy)	CT scan or MRI, targeted panel sequencing for congenital lipodystrophies, MRI
LAL deficiency (Wolman disease, cholesteryl ester storage disease-CESD)	Elevated LDL-C and triglycerides, low HDL-C, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis	Enzyme assay, genetic testing (LIPA)
Pregnancy associated	HELLP syndrome Acute onset	Elevated liver enzymes and low platelets, haemolysis, SLD at abdominal ultrasound
Wilson disease	Younger age, neuropsychiatric symptoms, low ceruloplasmin	24-h urine copper excretion; quantitative copper on liver biopsy, genetic testing (<i>ATP7B</i>)
Nutrient deficiency/malnutrition	Parenteral nutrition, bypass surgeries, bariatric surgery, anorexia	Nutrient levels
Celiac disease	Diarrhoea, iron deficiency, vitamins deficiency	Tissue transglutaminase IgA, duodenal biopsy
Endocrine diseases	Hypothyroidism, PCOS, growth hormone (GH) deficiency, panhypopituitarism (primary or secondary)	TSH, fT4, fT3, endocrine testing
Other inherited metabolic conditions	Early age and severe onset, absence of triggering factors, systemic involvement, positive history of advanced disease in first degree relatives	Targeted panel sequencing, whole exome sequencing (WES)

ALD, alcohol-related liver disease; ApoB, apolipoprotein B; fT3, free triiodothyronine; fT4, free thyroxine; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; HELLP, haemolysis, elevated liver enzymes and low platelets; LAL, lysosomal acid lipase; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome; SLD, steatotic liver disease; TSH, thyroid-stimulating hormone.

Table 5. Tools to quantify alcohol consumption and identify alcohol use disorders.⁵²⁷

Psychometric instruments	Biomarkers
<ul style="list-style-type: none"> Medical history (including current and prior alcohol intake and drinking pattern) Quantity frequency questionnaires and diaries (Timeline Followback) Apps (e.g. Drinkaware) AUDIT (Alcohol Use Disorders Inventory Test) questionnaire – 10 questions AUDIT-C (shortened version, 3 questions) SIAC (Systematic Inventory of Alcohol consumption, 3 questions) 	Indirect alcohol markers: <ul style="list-style-type: none"> GGT, AST, AST>ALT, MCV, % CDT Direct alcohol markers: <ul style="list-style-type: none"> Alcohol (EtOH) in breath and/or serum Ethyl glucuronide (in urine or hair) Phosphatidylethanol Less established: ethyl sulfate, fatty acid ethyl esters

AST/ALT, aspartate/alanine aminotransferase; CDT, carbohydrate-deficient transferrin; GGT, gamma-glutamyltransferase; MCV, mean corpuscular volume.

Table 6. Targets of different non-invasive techniques (selection) and suggested thresholds for ruling out/in certain features of MASLD.

Non-invasive test	Biological processes reflected	Rule-out cut-off	Rule-in cut-off	Prediction of liver-related outcomes
Primary target: Hepatic steatosis				
US scan – standard	Lipid content	N/A	N/A	+
VCTE: CAP (Controlled attenuation parameter) ¹⁶⁶	Lipid content		S1: 248 dB/m S2: 268 dB/m S3: 280 dB/m	?
MRI – MRI-PDFF ¹⁶³	Lipid content		S1: 5% S2: 11-18% S3: 16-23%	+
Primary target: Hepatic fibrosis				
AST/ALT ratio ^{152,184}	Stress to hepatocytes	F3: 0.8	F3: 1.0	+
FIB-4 ^{140,158,184}	Stress to hepatocytes, hypersplenism	F2: 0.66-0.89 F3: 1.3	F2: 2.67 F3: 2.67	++
APRI ^{158,184}	Stress to hepatocytes, hypersplenism	F3: 0.5	F3: 1.5	++
NFS ^{138,184}	Stress to hepatocytes, hypersplenism, metabolic burden	F3: -1.455	F3: 0.676	++
ELF ^{147,259}	Collagen metabolism	F3: 7.7	F3: 9.8	+++
ADAPT ¹⁴⁹	Collagen metabolism, hypersplenism, metabolic burden	F3: 4.46	F3: 7.15	?
VCTE: LSM (liver stiffness) ^{156,184,259}	Fibrosis, extracellular volume fraction	F3: 8 kPa	F3: 12 kPa	+++
US – 2D-SWE ¹⁵⁵	Fibrosis, extracellular volume fraction	F3: 8 kPa	F3: 10.5 kPa	+++
MRI – MRE ^{170,358}	Fibrosis, extracellular volume fraction		F2: 3.14 kPa F3: 3.53 kPa F4: 4.45 kPa	+++
MEFIB ^{169,170}	Stress to hepatocytes, fibrosis, hypersplenism	F2: MRE <3.3 kPa and FIB-4 <1.6	F2: MRE ≥3.3 kPa and FIB-4 ≥1.6	+++
Primary target: “At-risk MASH”				
FAST ^{168,184}	Stress to hepatocytes, fibrosis, lipid content	0.35	0.67	++
MAST ¹⁶⁷	Stress to hepatocytes, fibrosis, lipid content	0.165	0.242	++
Corrected T1 ¹⁶⁰	Extracellular volume fraction, (fibrosis)	825 ms	875 ms	++
NIS2+ ³⁵²	Stress to hepatocytes, fibrosis, extracellular matrix remodelling	0.46	0.68	?

ADAPT, age, presence of diabetes, PRO-C3, and platelet count; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; F1-F4, fibrosis stage (F2: moderate fibrosis, F3: severe fibrosis, F4: cirrhosis); FAST, FibroScan-AST; MAST, MRI-AST; MEFIB, MRE combined with FIB-4, MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; PDFF, proton density fat fraction; S1-S3, stage of steatosis (S1: mild (<10% hepatocytes), S2: moderate (10% –30% hepatocytes), S3: severe (>30% hepatocytes) steatosis); SWE, shear-wave elastography; VCTE, vibration-controlled transient elastography; US, ultrasound.

The predictive value of the test/procedure for liver-related outcomes (e.g. cirrhosis complications, HCC, liver-related death) is qualitatively depicted (+low, ++ moderate, +++ high, ? unknown).

Merged cells represent non-invasive techniques with single cut-offs.

Table 7. Diagnostic procedures to identify relevant comorbidities of MASLD.

Comorbidity	Assessment/parameter	Ref.
Obesity	Body mass index Waist circumference Waist to height ratio <i>Further investigations*:</i> Body composition analysis (if available) TSH and free thyroxine (if suspicion of hypothyroidism)	528,529
Type 2 diabetes or insulin resistance	Fasting plasma glucose HbA _{1c} Oral glucose tolerance test, 2-h post-load glucose Fasting plasma insulin and/or C-peptide HOMA-IR <i>Further investigations*:</i> Insulin resistance indices from oral glucose tolerance test or mixed meal tests	220,221
Dyslipidaemia	Fasting plasma triglycerides Fasting plasma total, LDL and HDL cholesterol Once in a lifetime: measurement of lipoprotein (a) <i>Further investigations*:</i> Non-esterified fatty acids Apolipoprotein B	530
Kidney disease	Creatinine in plasma and urine Albumin in serum and urine Estimated glomerular filtration rate (eGFR)	
Cardiovascular disease	Fasting plasma uric acid Serum high-sensitivity C-reactive protein (hsCRP) Serum ferritin Systolic and diastolic blood pressure <i>Further investigations*:</i> 24-h ambulatory blood pressure monitoring Echocardiography for heart failure Serum NT-ProBNP Transferrin saturation	25,26
Atherosclerosis	Complete blood count; Platelets Elevated lipoprotein (a) is an independent causal risk factor for atherosclerotic cardiovascular disease <i>Further investigations*:</i> Fibrinogen Homocysteine Von Willebrand factor antigen Carotid artery intima media thickness EchoDoppler plaque instability Coronary artery calcification	25,26
Obstructive sleep apnoea	Neck circumference Epworth score <i>Further investigations*:</i> Sleep studies Overnight pulse oximetry Polisomnography CPAP trial	64
PCOS	Sex hormones: LH, FSH, testosterone, SHBG Ovarian ultrasound	66

CPAP, continuous positive airway pressure; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity CRP; LDL, low-density lipoprotein; LH, luteinising hormone; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin; TSH, thyroid-stimulating hormone.

*According to clinical evaluation and a priori probability.

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

Table 9. Proposed tools for HCC risk stratification in MASLD-related cirrhosis.

NITs	Formula/model variables/data	Study cohorts	Performance	Ref.
HCC risk score	Age + sex + platelet count + albumin + AST/ $\sqrt{\text{ALT}}$ available at: www.hccrisk.com	7,068 individuals with MASLD-related cirrhosis (407 incident HCC) Mean FU: 3.7 years	Derivation cohort, C-index = 0.749 Validation cohort, C-index = 0.718	534
aMAP	$(0.06 \times \text{age (years)} + 0.89 \times \text{sex (M = 1; F = 0)} + 0.48 \times [(\log_{10} \text{ bilirubin } (\mu\text{mol/L}) \times 0.66 + \text{albumin (g/L)} \times -0.085) - 0.01 \times \text{platelets } (\times 10^3/\text{mm}^3) + 7.4]/14.77 \times 100$	Overall individuals, n = 17,374 NVH validation cohort, n = 720 Total: 1,389 individuals with MASLD Median FU: 4.61 years F3-F4, n = 243 (17.5%)	NHV cohort: Overall, C-index = 0.85 Cirrhosis, C-index = 0.61 Overall, C-index = 0.887 F3-F4, C-index = 0.754	535 536
GALAD	$-10.08 + 0.09 \times \text{age (years)} + 1.67 \times \text{gender (M = 1, F = 0)} + 2.34 \times \log_{10} \text{AFP (ng/ml)} + 0.04 \times \text{AFP-L3 } (\%) + 1.33 \times \log_{10} \text{DCP (ng/ml)}$	389 individuals with MASH (28 incident HCC) Median FU: 167 months Cirrhosis, n = 77 (19.6%)	Higher GALAD score in individuals who developed HCC vs. individuals HCC-free as early as 1.5 years before HCC diagnosis	537
HEDS study	Risk factor associated to HCC development in individuals with cirrhosis: Male gender (OR = 2.47; 95% CI 1.54–4.07; $p < 0.001$) Years with cirrhosis (OR = 1.06; 95% CI 1.02–1.1; $p = 0.004$) Family h/o of liver cancer (OR = 2.69; 95% CI 1.11–5.86; $p = 0.02$) Age (OR = 1.17; 95% CI 1.03–1.33; $p = 0.02$) Obesity (OR = 1.7; 95% CI, 1.08–2.73; $p = 0.02$) AST (OR = 1.54; 95% CI 0.97–2.42; $p = 0.06$) AFP (OR = 1.32; 95% CI 0.97–1.77; $p = 0.07$) Albumin (OR = 0.7; 95% CI 0.46–1.07; $p = 0.10$)	Total: 1,325 individuals with cirrhosis (95 incident HCC) Median FU: 2.2 years MASLD, n = 327 (24.9%); 19 incident HCC	Performance of the multivariate set of risk factors: C-index = 0.73	538
THRI	Age + etiology + gender + platelets Age: <45 years = 0 points; 45–60 years, 50 points; >60 years, 100 points Etiology: autoimmune/HCV SVR, 0 points; other, 36 points; MASLD, 54 points; HCV/HBV, 97 points Gender: Female = 0 points; Male = 80 points Platelets: >200 = 0 points; 140–200 = 20 points; 80–130 = 70 points; <80 = 89 points Total: 0–366 points	Derivation cohort: 2,079 individuals with cirrhosis MASLD, n = 111 (5.3%) Total: 2,491 individuals with cirrhosis MASLD, n = 1,182 (48%)	10-year HCC incidence: low-risk (<120) = 3%; medium-risk ^{120–240} = 10% high-risk (>240) = 32% C-index = 0.69	539 540
LiverRisk score	Linear regression model using age (years), blood glucose, cholesterol, AST, ALT, GGT and platelets Available at: https://www.liverriskscore.com	Derivation cohort: 14,726 participants without known liver disease from the general population undergoing transient elastography for assessment of liver fibrosis. Two external validation cohorts: 4,370 and 3,999 individuals	8-year risk of HCC in the high-risk group = 4.4% 8-year risk of HCC development in the two lower risk groups $\leq 0.1\%$	143

AFP, alpha-fetoprotein; DCP, Des- γ -carboxy prothrombin; FU, follow-up; NHV, non-viral hepatitis; NIT, non-invasive test; OR, odds ratio.

Table 10. Summary of protein, energy, and dietary pattern recommendations for adults with cirrhosis as indicated by medical associations' Practice Guidance/Guidelines. In addition, individuals with cirrhosis must abstain from alcohol.

Society/Association	EASL 2019 ⁴⁴⁰		ESPEN 2019 ⁴⁴⁷ and joint ESPEN/UEG guideline 2023 ⁴⁵⁰		AASLD 2021 ⁴⁴⁶	
	Mixed BMIs	Obese (BMI >30 kg/m ²)	Mixed BMIs	Obese (BMI >30 kg/m ²)	Non-obese	Obese (non-hospitalised, clinically stable)
Daily energy	35 kcal/kg actual BW (in nonobese individuals)	>5-10% WR, moderately hypo-caloric diet (-500-800 kcal/d)	30-35 kcal/kg only for DC. Regular energy requirements in CC	WR. No need for increased energy intake	≥35 kcal/kg body weight/day	25-35 kcal/kg/day for individuals with BMI 30-40 kg/m ² , and 20-25 kcal/kg/day for individuals with BMI ≥40 kg/m ² . WR if medically required, under the supervision of a multidisciplinary team. Caution applied to prescribing weight loss in decompensated cirrhosis.
Daily protein	1.2-1.5 g/kg actual BW	>1.5 g/kg IBW	1.2 g/kg (for non-malnourished individuals with CC) to 1.5 g/kg (for malnourished and/or sarcopenic cirrhosis)	Individuals with overweight or obesity and compensated cirrhosis: 1.2 g/kg ABW/d. Individuals with overweight or obesity and compensated cirrhosis undergoing weight-loss programs: 1.2-1.5 g/kg ABW/d. Individuals with overweight or obesity and compensated cirrhosis and malnutrition or sarcopenia: 1.5 g/kg ABW/d.	1.2-1.5 g/kg IBW. For individuals with cirrhosis who are critically ill, a target of 1.2-2.0 g/kg IBW	Intake of target protein (1.2-1.5 g/kg/day) and physical activity are required to reduce the loss of muscle contractile function and muscle mass that can occur with weight loss.
Meal patterns	Split food intake into 3 main meals and 3 snacks		Three to five meals a day and a late evening snack		Maximum interval of 3-4 hours between nutritional intake while awake. To minimise nocturnal fasting time, an early breakfast and/or late-evening snack recommended	
Dietary protein source in case of HE	Individuals may tolerate animal protein (meat) less well than vegetable protein (beans, peas, etc.) and dairy proteins		In individuals who are protein "intolerant", vegetable proteins should be used		A diverse range of protein sources, including vegetable and dairy products, should be encouraged.	

ABW, adjusted body weight; BMI, body mass index; CC, compensated cirrhosis; DC, decompensated cirrhosis; HE, hepatic encephalopathy; IBW, ideal body weight; WR, weight reduction.
 ABW = reference body weight (in which BMI = 25) + 0.33(actual body weight - reference body weight).

[†]In a case of fluid retention, body weight should be corrected by evaluating the individual's dry weight.

Table 11. Screening and management for comorbidities in individuals with MASLD before liver transplantation. Modified from.^{488,526}

Condition	Recommendation
Type 2 diabetes	<ul style="list-style-type: none"> Screen for impaired fasting glucose (IFG) or glucose tolerance (IGT) and/or T2D (OGTT, HbA1c) Achieve good glycaemic control before LT Preferentially use weight-lowering (e.g. SGLT2 inhibitors, GLP1RA) or weight-neutral (e.g. metformin) glucose-lowering medication, considering risk of other diabetes complications, if liver and/or renal function allow this
Nutrition	<ul style="list-style-type: none"> Assess nutritional status before LT Assess alcohol consumption Healthy diet, physical exercise and lifestyle modification (including weight reduction in individuals with obesity) represent pillars in pre-LT management
Cardiovascular	<ul style="list-style-type: none"> Pre-LT cardiovascular risk stratification is mandatory Risk-adapted algorithm of cardiac work-up should be followed (see Fig. 5) LT candidates with cardiovascular risk should be managed with goal-directed medical management (e.g. statins, anti-platelet agents, beta blockers, RAAS blockers), based on the stage of cirrhosis and renal function
Kidney	<ul style="list-style-type: none"> Kidney function should be adequately monitored before LT Comedications need to be adjusted (or replaced) dependent on kidney function
Malignancies	<ul style="list-style-type: none"> Screening for pre-LT malignancies should follow the same protocols applied to individuals with non-MASLD related cirrhosis (including gastrointestinal and genital cancers)

GLP1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; OGTT, oral glucose tolerance test; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter-2.

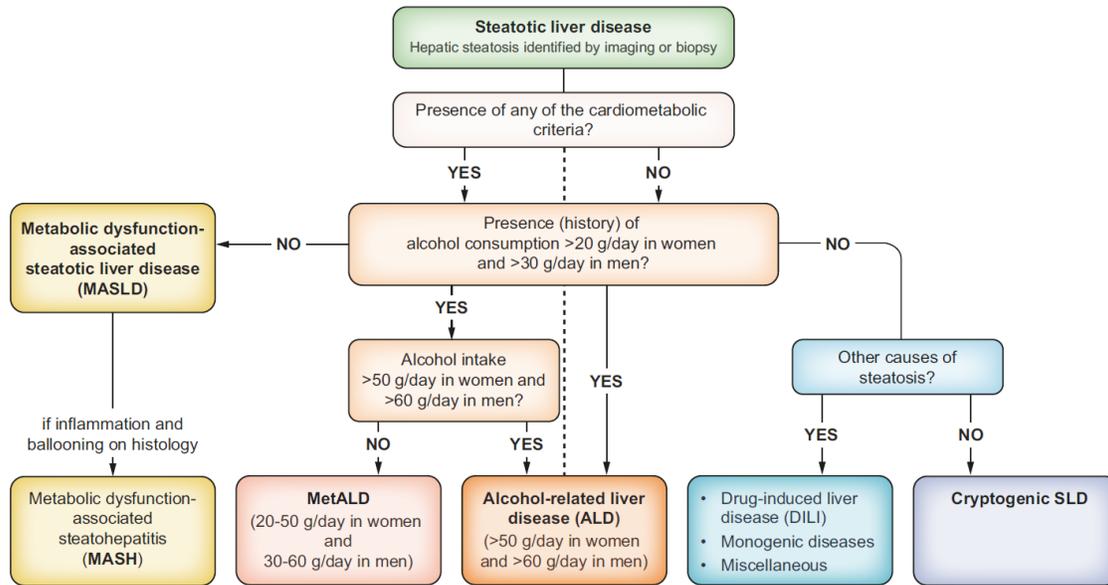
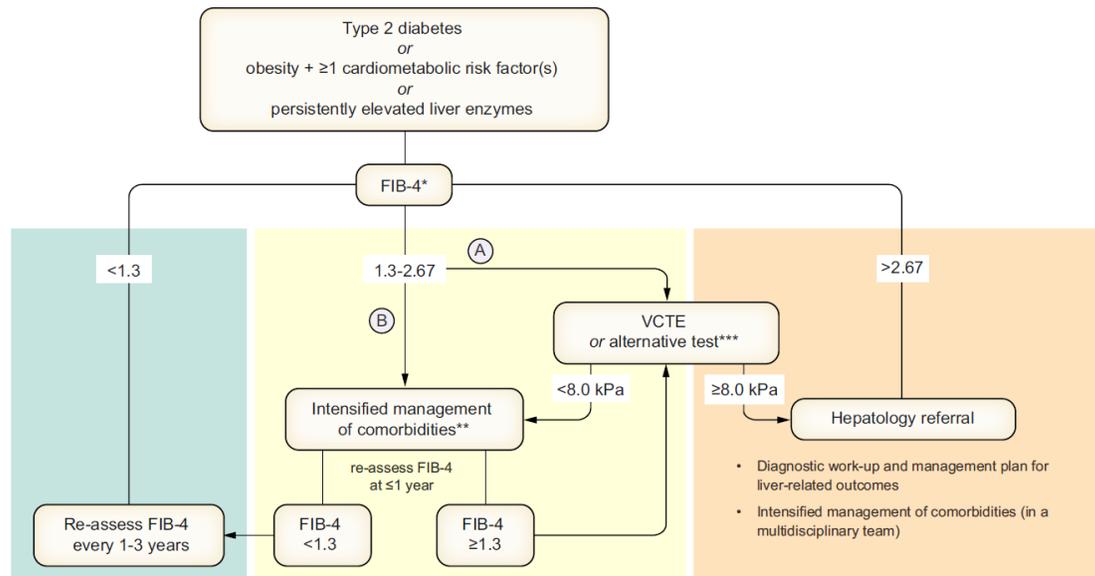


Fig. 1. Flow-chart for SLD and its sub-categories.² SLD, diagnosed histologically or by imaging, has many potential aetiologies. MASLD is defined as the presence of hepatic steatosis in conjunction with (at least) one cardiometabolic risk factor and no other discernible cause. The quantity of alcohol 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.



* 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

Fig. 2. Proposed strategy for non-invasive assessment of the risk for advanced fibrosis and liver-related outcomes in individuals with metabolic risk factors or signs of SLD. Individuals with (A) T2D or (B) abdominal obesity and ≥1 additional cardiometabolic risk factor(s) or (C) persistently elevated liver enzymes should undergo a multi-step diagnostic process, as indicated in the figure, to identify individuals with MASLD and advanced fibrosis. The algorithm can also be applied in case of incident finding of steatosis. This strategy is intended to identify individuals at risk of developing liver-related outcomes. ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; GLP1RA, glucagon-like peptide-1 receptor agonist; MRE, magnetic resonance elastography; SLD, steatotic liver disease; SWE, shear wave elastography; VCTE, vibration-controlled transient elastography.

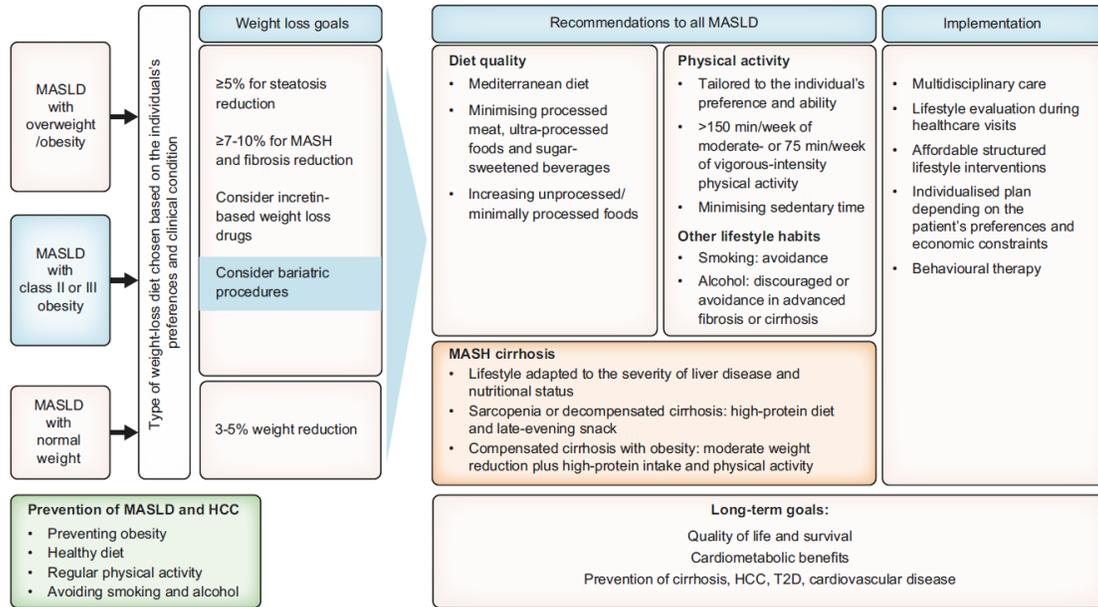


Fig. 3. Lifestyle management algorithm for MASLD. Note: Behavioural therapy includes: self-monitoring, clinicians providing affected individuals with self-efficacy and motivation, setting realistic negotiable goals, and overcoming barriers. Examples of unprocessed/minimally processed foods: vegetables, fruits (not juice), low-fat dairy, nuts, olive oil, legumes, unprocessed fish and poultry. Overweight/obesity: Overweight: BMI of 25–29.9 kg/m² (non-Asian) or 23–24.9 (Asian), Obesity: ≥30 kg/m² (non-Asian) ≥25 kg/m² (Asian). Class II obesity: BMI ≥35 kg/m² (non-Asian) or BMI ≥30 kg/m² (Asian). Normal weight: BMI <25 kg/m² (non-Asian) or <23 kg/m² (Asian). BMI, body-mass index; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

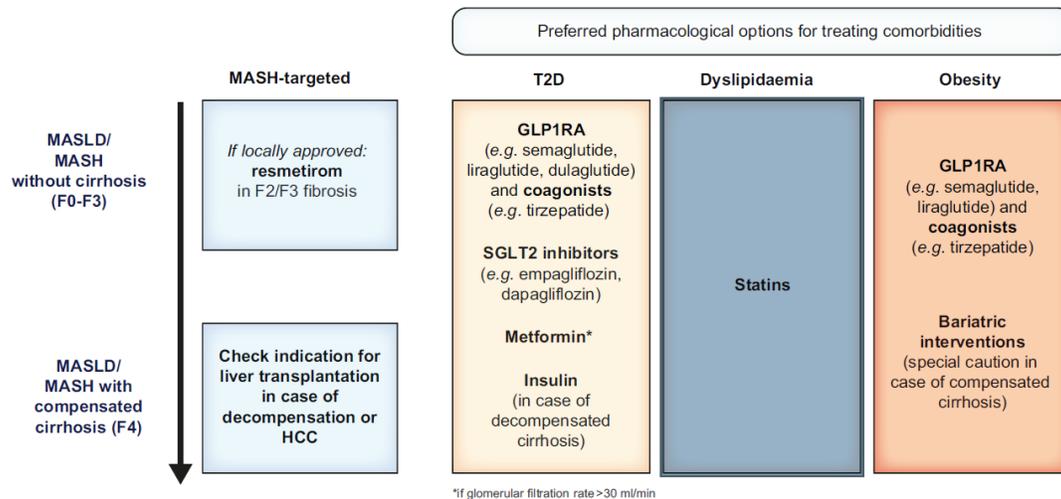


Fig. 4. Treatment recommendations beyond lifestyle modification in MASLD/MASH. The recommended choice of pharmacological treatment options in individuals with MASLD/MASH is dependent on comorbidities and stage of disease. GLP1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma;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

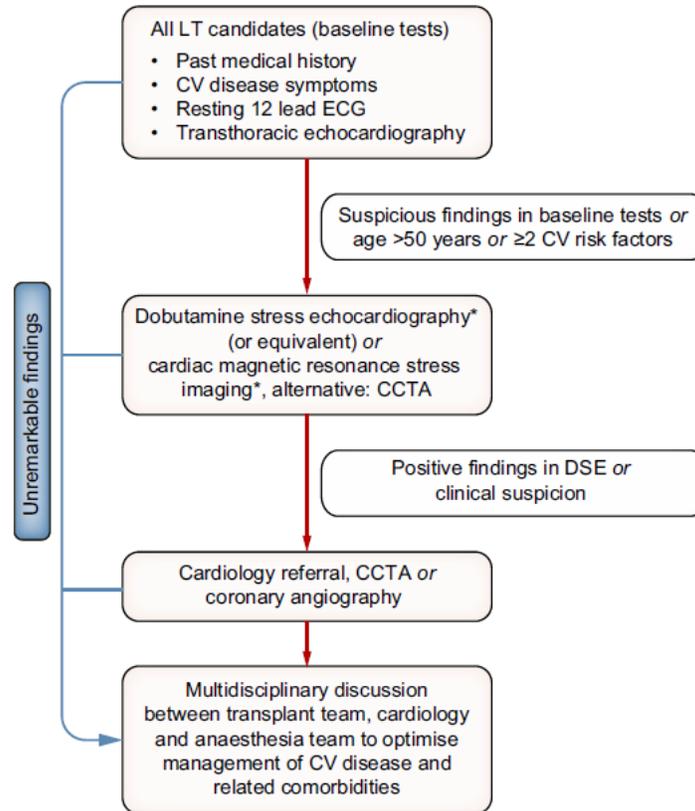


Fig. 5. Cardiovascular work-up algorithm in the evaluation of individuals with MASLD before liver transplantation. Adults with MASLD who are candidates for liver transplantation should be evaluated by a multidisciplinary team using a stepwise and risk-adjusted cardiac work-up algorithm to mitigate the risk of major cardiovascular events in the pre-, peri- and post-transplant phase (modified from^{488,526}). CCTA, coronary computed tomography angiography; CV, cardiovascular; DSE, dobutamine stress echocardiography; ECG, electrocardiogram; LT, liver transplantation; TTE, transthoracic echocardiography. *Indicates suboptimal sensitivity in high-risk populations.

Box 1. Key research agenda in MASLD (selected topics).**General management, natural history, prevention and screening**

- To develop widely implementable, efficient and cost-effective point of care diagnostics for case-finding; to define referral pathways for individuals with cardiometabolic risk factors in different national healthcare contexts.
- To understand individual susceptibility and determinants of fibrosis progression, course of cirrhosis and HCC occurrence in individuals with MASLD.
- To better describe the natural history of the MetALD segment of the SLD population and to develop reliable and quantitative biomarkers of alcohol consumption; to examine the relationship between metabolic dysfunction and amount of alcohol consumed on the progression of liver injury.
- To develop and implement national policies increasing awareness of SLD and prevention of MASLD in individuals of all ages including children and adolescents.

Use of non-invasive tests (NITs) in MASLD

- To qualify the most performant biomarkers for different contexts of use (diagnostic, monitoring, prognostic and treatment response) in individuals with MASLD.
- To determine, in the context of pharmacological therapy, if improvement in histological surrogates translates into clinical benefit; if changes in NITs mirror histological changes; and if future trials can use NITs as surrogates of treatment response.
- To determine personalised, risk-based HCC surveillance strategies in both cirrhotic and non-cirrhotic MASLD and MetALD individuals.
- To understand how AI-assisted diagnostics, including digital pathology, can improve risk stratification, determine treatment response and facilitate the conduct of therapeutic trials.
- To evaluate the application of Baveno VII criteria of clinically significant portal hypertension and the role of spleen stiffness measurement in individuals with MASLD.

Treatment for MASLD and comorbidities

- To improve on personalised lifestyle and dietary approaches for weight reduction, maintenance of weight loss and the identification of individuals most likely to benefit from non-pharmacological interventions alone.
- To identify early predictors of non-response to pharmacological intervention and to define clear stopping rules for MASH-targeted pharmacotherapy in non-responders.
- To evaluate the impact of controlling metabolic comorbidities on the hepatic disease course in MASLD.
- To determine weight loss-independent mechanisms of MASLD improvement for incretin-based, weight loss-based or glucose-lowering treatments.
- To determine whether improvement in steatotic liver injury will have a beneficial effect on metabolic dysfunction and control of comorbidities in MASLD.
- To prospectively assess the potential additive or synergistic effects of combining drugs intended to treat MASH and/or cardiometabolic comorbidities.
- To develop effective pharmacological treatments for individuals with MASH-related cirrhosis.

MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with moderate alcohol consumption; NIT, non-invasive test; SLD, steatotic liver disease.