Metabolic dysfunction-associated steatotic liver disease management in Saudi Arabia: A modified Delphi-based adaptation of international standards

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Abstract

The reclassification of nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) marks a significant shift in understanding liver disease, particularly in Saudi Arabia, where metabolic disorders are highly prevalent. This study aimed to develop expert consensus recommendations for early detection, specialist referral, and management of MASLD/metabolic dysfunction-associated steatohepatitis (MASH) in Saudi Arabia. A modified Delphi process was used to establish consensus among an expert panel of 15 multidisciplinary specialists, including hepatologists, endocrinologists, gastroenterologists, and primary care physicians. The panel addressed six key areas: terminology and epidemiology, screening, risk categories, hepatocellular carcinoma surveillance, first-line treatment, and advanced therapeutic options. A literature review spanning January 2011 to May 2024

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Submitted: 04-Jun-2025 **Revised:** 26-Jun-2025 **Accepted:** 04-Aug-2025 **Published:** 01-Sep-2025

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/SJGA
	DOI: 10.4103/sjg.sjg_199_25

How to cite this article: Abaalkhail F, Sanai FM, AlSwat K, Alzanbagi A, Aljedai A, Alshehri A, *et al.* Metabolic dysfunction-associated steatotic liver disease management in Saudi Arabia: A modified Delphi-based adaptation of international standards. Saudi J Gastroenterol 0;0:0.

informed evidence-based recommendations, assessed using the Grading of Recommendations, Assessment, Development, and Evaluation criteria. The consensus established screening criteria for high-risk groups, emphasizing noninvasive tests (NITs) such as Fibrosis-4 (FIB-4), enhanced liver fibrosis (ELF) score, and magnetic resonance elastography (MRE). Risk stratification thresholds were defined: FIB-4 ≥2.67, liver stiffness measurement (LSM) >12 kPa, and MRE >5.0 kPa indicate advanced fibrosis requiring specialist referral. Treatment recommendations emphasized a multidisciplinary approach, incorporating lifestyle modifications, pharmacotherapy (including glucagon-like peptide-1 receptor agonists [GLP-1 RA], sodium-glucose cotransporter-2 [SGLT2] inhibitors, and pioglitazone), and surgical interventions when appropriate. Bariatric surgery was recommended for eligible patients with noncirrhotic MASLD. This consensus provides evidence-based guidance for MASLD/MASH management in Saudi Arabia, highlighting early detection through NITs, risk-stratified care pathways, and multidisciplinary treatment strategies essential for improving patient outcomes in the region.

Keywords: Disease management, MASH, MASLD, noninvasive tests, risk stratification, screening, Saudi Arabia

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a significant public health challenge globally. Within the spectrum of NAFLD, nonalcoholic steatohepatitis (NASH), which represents a more advanced stage, results in hepatic cirrhosis and elevates the likelihood of hepatocellular carcinoma (HCC) development. The increasing worldwide prevalence of chronic liver disease is significantly driven by NAFLD/NASH.[1,2] The global incidence of NASH increased from 88,180 in 1990 to 172,330 in 2019, while the prevalence increased from 561,370,000 in 1990 to 1,235,700,000 in 2019, predominantly impacting young adults aged 15 to 49 years.[1] In Saudi Arabia, the prevalence of NAFLD in children and adults increased from 28.02% in 2012 to 33.11% in 2019; these rising numbers are consequential of the rising rates of obesity, diabetes, and metabolic syndrome in the country.[2]

The nomenclature for NAFLD and NASH has recently evolved to accurately indicate the underlying disease pathophysiology. In 2023, based on expert consensus and mounting evidence of metabolic dysfunction as the primary driver, these conditions were renamed to metabolic (dysfunction)-associated steatotic liver disease (MASLD) and metabolic (dysfunction)-associated steatohepatitis (MASH), respectively.[3-5] As in other developed countries, the increasing prevalence of metabolic syndrome in Saudi Arabia results in a substantial pool of individuals at risk for MASLD/MASH, indicating the importance of screening high-risk groups for MASLD/MASH.[6] Despite the growing burden of MASLD/MASH in the region, there is limited awareness about the disease among healthcare professionals (HCPs), including primary care physicians (PCPs) and specialists.[7] To address these issues, a modified Delphi consensus was conducted involving a panel of experts with varied clinical backgrounds to develop expert consensus recommendations on early detection, specialist referral, and management of MASLD/MASH in Saudi Arabia. We aimed to provide evidence-based data to assist physicians, affected and at-risk individuals, HCPs, and health policymakers in Saudi Arabia and Middle Eastern countries to make informed decisions with the aim to reduce the burden of MASLD/MASH on the healthcare system. These recommendations are intended to guide clinical practice across diverse clinical settings in the region.

METHODOLOGY

Consensus development process

A steering committee (SC) was set up in early September 2023 with members from the Saudi Society for the Study of Liver Diseases and Transplantation (SASLT), Saudi Society of Clinical Pharmacy (SSCP), Saudi Scientific Diabetes Society (SSDS), Saudi Society of Family and Community Medicine (SSFCM), and Saudi Gastroenterology Association (SGA), to discuss the challenges associated with the diagnosis of MASLD/MASH in Saudi Arabia and develop consensus recommendations on diagnostic and treatment management of MASLD/MASH. The multidisciplinary, multisociety panel consisted of 15 experts/key opinion leaders (3 SC members and a working group of 12 members, including hepatologists [n = 8], endocrinologists [n = 3], gastroenterologist [n = 1], PCPs [n = 2], and clinical pharmacologist [n = 1]) from Saudi Arabia. The members of the panel were selected based on their research involvement in MASLD/MASH, diabetes, metabolic disorders, and clinical expertise, in addition to being seconded by their professional societies. On December 30, 2023, an expert panel meeting was conducted. The panel established objectives and key issues,

formulated the guidelines' key questions, and structured them using the PICO framework: *P* (patient, problem, or population), I (intervention), C (comparison, control, or comparator), and O (outcome). These PICO questions were refined through a simplified Delphi process. Six areas deemed fundamental for including in the Delphi consensus meeting on diagnosis, treatment, and management were identified by relevant panel experts, namely, (1) terminology and epidemiology, (2) screening, (3) risk categories, (4) hepatocellular carcinoma (HCC), surveillance, (5) first-line treatment recommendations for MASLD/MASH, and (6) pharmacotherapy/bariatric surgery/liver transplantation (LT). Thirty-two clinically relevant gap statements segregated into the above six categories were drafted. These statements, accompanied by supporting evidence, were sent to all panel members.

A detailed literature review was carried out to identify the gaps in the current diagnosis, treatment, and management of MASLD/MASH globally and in Saudi Arabia. Data from PubMed and Google Scholar were used to identify relevant articles between January 2011 and May 2024 using keywords such as NASH, NAFLD, MASLD, diagnostics, treatment, intervention, and management [Supplementary Table 1]. To ensure comprehensive coverage of all relevant evidence and literature, we included both the former terminology (NAFLD/NASH) and the updated nomenclature (MASLD/MASH) in our search strategy. Furthermore, studies not published in English or falling outside the January 2011 to May 2024 timeframe or did not focus on the diagnosis, treatment, or management of MASLD/MASH (including NAFLD/NASH) were excluded from the review. The articles were evaluated based on the consensus guidelines' objective to tackle the burden of MASLD/MASH. The evidence was graded based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria [Supplementary Table 2 for GRADE criteria].[8-10]

Consensus voting and data collection

All 15 panel members participated in the voting process in the first round. A modified Delphi process involving anonymous voting through an electronic system via a survey link (Microsoft Forms) was conducted. For consensus agreement, a 3-point Likert-scale response category, "agree," "neutral," or "disagree" for each statement, was used. In case of a "disagree" or "neutral" response, the specific reason was duly collected. The consensus level was predefined as ≥75% of agreement/disagreement. Voting for all statements was mandatory. PICO questions failing to achieve >75% agreement in the first round of the modified Delphi process was revised, and resent to the panelists for a second round of Delphi. The panel conducted clinical discussions centered on creating recommendations based on published literature on the diagnosis and management of MASLD/MASH. In cases where there were insufficient data, recommendations were developed based on the opinions of the experts [Supplementary Table 1]. An overview of the entire process is presented in Figure 1. This study is not registered on any online platform.

RESULTS

Consensus recommendations

Nomenclature change and burden of MASLD/MASH in Saudi Arabia

Adopting the updated terminology of MASLD/MASH over NAFLD/NASH enables physicians to better articulate the metabolic basis of the disease and avoid the use of potentially stigmatizing language in patient care. It also promotes consistent clinical communication and accurate disease documentation among HCPs in Saudi Arabia. While the term "non-alcoholic" is commonly used in NASH and

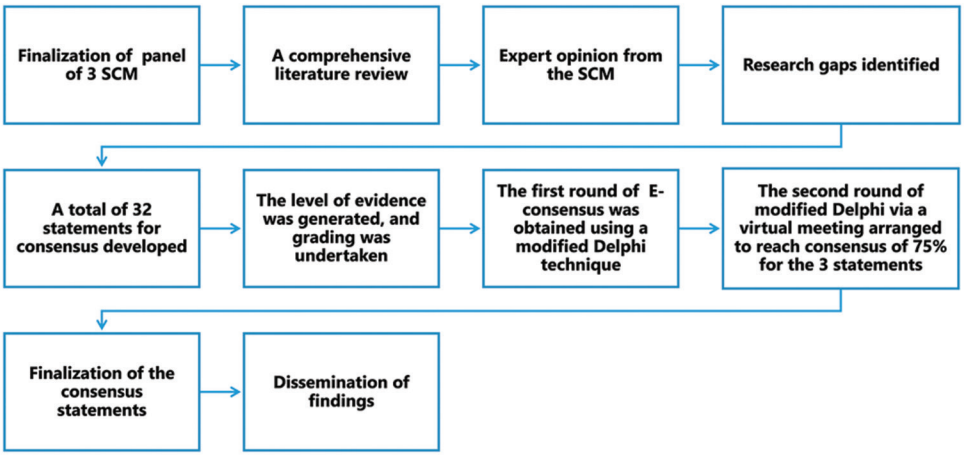

Figure 1: Overview of the consensus process

NAFLD, it has been acknowledged worldwide that it does not accurately reflect the current understanding of disease drivers. In 2023, international liver disease organizations and patient associations recommended the change in nomenclature of NAFLD to MASLD, aiming for a more positive, nonstigmatizing, health-seeking term. The umbrella term steatotic liver disease (SLD) encompasses diagnostic subgroups, including drug-related conditions and MASLD/MASH. The paradigm shift in nomenclature from NAFLD/NASH to MASLD/MASH represents a crucial evolution in our understanding and approach to metabolic liver disease. This change was developed from the multistakeholder consensus by major international societies, including the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), in collaboration with Asociación Latinoamericana para el Estudio del Hígado (ALEH) and participation from societies such as Asian Pacific Association for the Study of the Liver (APASL) and others. It addresses several critical issues in patient care and disease conceptualization.[11] The term "fatty liver disease" carries negative connotations and fails to acknowledge the complex metabolic underpinnings of the condition, potentially hampering patient engagement and healthcare-seeking behavior.[11] Furthermore, existing data on fatty liver disease related to metabolic dysfunction likely underrepresent the issue due to underdiagnosis and reliance on exclusionary diagnostic criteria. Diagnostic challenges may lead to misclassification and under-reporting of metabolic dysfunction-related fatty liver disease due to the region's relatively high viral hepatitis prevalence. This highlights the necessity for definitive diagnostic criteria.[12] Thus, the overarching term of SLD and the more specific term MASLD were proposed to provide an affirmative nonstigmatizing description of the condition instead of a diagnosis of exclusion. The patients who were previously under NAFLD and NASH can be covered by the categories of MASLD and MASH. Metabolic and alcohol-associated risk factors that coexist are accordingly put under the category of MetALD.[3] Studies have shown that a large majority of patients diagnosed with NAFLD would also meet the criteria for MASLD due to the shared characteristics of hepatic steatosis and metabolic risk factors like obesity, diabetes, and hypertension. Two studies (European/Caucasian and Asian) assessed MASLD criteria in biopsy-proven NAFLD cohorts. Of 1783 patients, 99.9% met ≥1 metabolic risk factor: increased BMI (97.5%), insulin resistance (84.7%), hypertension (82.6%), dyslipidemia (80.9%), and hypertriglyceridemia (74.5%), while 55.4% met all five criteria. A Swedish study (using biopsy/imaging) reported 99.6% of 3377 patients assessed met ≥1 metabolic risk factor.[13-15]

The new terminology addresses the stigmatization associated with the "non-alcoholic" prefix while better reflecting the underlying metabolic pathophysiology of the disease.[16,17] This change aligns with the current understanding of risk factors and facilitates more precise diagnostic criteria through the incorporation of specific cardiometabolic parameters, potentially enabling improved patient stratification and targeted therapeutic approaches.[17,18] The standardized nomenclature also promotes consistency in research and supports regulatory frameworks for drug development.[16,19] Importantly, the new MASLD terminology better reflects pediatric liver disease by focusing on metabolic risk factors rather than using potentially confusing alcohol-related terminology when communicating with parents.[19] Song *et al.* performed a population screening study that reaffirmed that the discrepancy between MASLD and NAFLD is negligible, suggesting that previous NAFLD research applies to the MASLD framework.[14] However, this transition presents notable challenges, including the substantial effort required to update existing clinical protocols, research databases, and educational materials.[16] Healthcare providers and patients may initially struggle with the new terminology, potentially leading to communication barriers.[18] Furthermore, the long-term clinical implications of these new classifications remain to be fully elucidated, which could impact treatment strategies and disease management protocols.[17]

There are 141.51 million cases of MASLD in the MENA region, with 24.96 million cases of MASLD with type 2 diabetes mellitus (T2DM).[20] As per the Global Burden of Disease (GBD) 2019, MASLD prevalence in Saudi Arabia from 2012 to 2019 increased with an annual percent change (APC) of +2.43%. While males maintained higher prevalence, females showed a more rapid increase (APC +2.77% vs +2.19% in males). Concurrent rises were observed in cardiovascular disease (3.79% to 4.47%) and T2DM (5.16% to 6.96%). MASLD-related mortality demonstrated the highest rate of increase with an APC of +1.15%. Importantly, the prevalence of MASLD rose among children and adults from 28.02% (n = 8.34 million) to 33.11% (n = 11.83 million),[2] and to 68.7% among patients with T2DM.[20] Elevated body mass index (BMI), low high-density lipoprotein (HDL) cholesterol levels, and inadequate dietary management are critical contributors that heighten MASLD risk in patients with T2DM, especially within Saudi Arabia.[21,22] A modeling analysis study by Alswat *et al.* predicted a significant increase in MASLD cases by 2030, with Saudi Arabia reaching 12.5 million cases. The burden of advanced liver disease, including cirrhosis and hepatocellular carcinoma, is expected to at least double by 2030.[23] Moreover, another study by Alswat *et al.* observed a high prevalence of metabolic comorbidities, including hyperlipidemia, T2DM, hypertension, and elevated ALT

levels in this population.[24] In a study conducted in Abha city, southwestern Saudi Arabia, the overall prevalence of MASLD among patients with T2DM was 72.8% (n, 178/245) with 68% of patients (n, 121) having grade 1 MASLD.[21] The MASLD risk was significantly higher among patients with T2DM who were overweight (adjusted odds ratio [aOR]: 6.112, 95% confidence interval [CI]: 1.529–4.432) or had obesity (aOR: 10.455, 95% CI: 2.645–41.326).[22] The prevalences of both T2DM (16.4% pooled prevalence)[25] and obesity (35.1%–34.8% in men and 30.1%–35.6% in women) are reportedly on the rise in Saudi Arabia.[26] Untreated MASH is known to develop into progressive fibrosis, cirrhosis, and HCC.[27,28] Obesity is a prevalent risk factor for MASLD[24] and increases the risk of cancer, particularly HCC.[28] Moreover, the severity of obesity is inked to a heightened risk of both advanced liver fibrosis and HCC in MASLD.[28] Advanced age (>50 years), coupled with insulin resistance, and multiple cardiometabolic risk factors increase the chances of developing MASH, severe fibrosis or cirrhosis, and both overall and liver-related mortality.[27] The prevalence of MASLD/MASH is projected to drastically increase over the next 13 years in Saudi Arabia, UAE, and Kuwait, with a doubling of fibrosis cases, tripling of cirrhosis and liver cancer, and a fourfold increase in liver failure/transplant patients. The economic burden of MASLD/MASH is substantial, with discounted lifetime costs of standard care totaling over $40 billion in Saudi Arabia, $1.6 billion in the UAE, and $6.4 billion in Kuwait, comprising 5.8–7.7% of national healthcare spending in 2019. MASLD/MASH requires higher prioritization in Middle Eastern public health policy to address this escalating regional burden.[29] Based on these considerations, nomenclature-based recommendations are presented in Table 1.

Table 1: Recommendations for change of nomenclature from NAFLD/NASH to MASLD/MASH to address the growing burden of MASLD/MASH in Saudi Arabia

Statement	Level of Evidence	Consensus
A change in nomenclature from NAFLD/NASH to MASLD/MASH is recommended in regular clinical practice in Saudi Arabia	High	100%
There has been a steady rise in the prevalence of MASLD in Middle Eastern countries, including Saudi Arabia, over the past decade.	High	100%
T2DM and obesity are the major risk factors for MASLD/MASH, including progression to advanced fibrosis and the development of HCC in patients with MASLD.	High	100%

HCC, Hepatocellular carcinoma; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; NAFLD, Non-alcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; T2DM, Type 2 diabetes mellitus

Screening criteria for MASLD/MASH in Saudi Arabia

Currently, no guidelines advocate for universal MASLD screening globally, though early detection in at-risk individuals is increasingly emphasized.[30] Although serum aminotransferases and conventional liver ultrasound are commonly used in clinical practice, these traditional screening methods demonstrate significant limitations in accurately detecting and staging MASLD.[31,32] Current noninvasive markers lack sufficient diagnostic precision to definitively identify MASH, requiring a liver biopsy for confirmation. However, these markers remain valuable tools for initial MASLD assessment and risk stratification. NITs have emerged as valuable tools for assessing liver fibrosis in MASLD, particularly in ruling out advanced fibrosis.[33] Newsome *et al.* introduced and validated the FAST score, integrating LSM and controlled attenuation parameters, through FibroScan® and combining it with AST levels. This score employs dual cutoffs for exclusion and diagnosis of fibrotic MASH, achieving an area under the receiver operating characteristic (AUROC) value of 0.85 (95% CI: 0.83–0.87).[34] The Fibrotic NASH Index detects fibrotic MASH in MASLD patients through AST, HDL, and glycated hemoglobin levels. However, the most widely validated and frequently utilized serum biomarkers for advanced fibrosis are FIB-4 and NAFLD Fibrosis Score (NFS). Their capacity to identify advanced fibrosis is strong, with an AUROC ranging from 0.7 to 0.8.[33] FIB-4 achieved a relatively high negative predictive value (NPV) of 81.7% to exclude advanced fibrosis in patients with MASLD but a suboptimal positive predictive value (PPV) of 58.6%.[35] It calculates a score based on the patient's age, AST, ALT, and platelet count and can identify those with advanced fibrosis with a high degree of accuracy.[33,36] Numerous studies have validated the accuracy of FIB-4 in detecting advanced fibrosis and cirrhosis.[37-39] Incorporating FIB-4 into hepatocellular injury would streamline the identification of patients with significant fibrosis, who may require further evaluation and treatment.[40] The simplicity of the calculation allows healthcare providers to efficiently screen patients and identify those who may benefit from additional testing, such as LSM (FibroScan) or liver biopsy.[36] NFS, with an AUROC for advanced fibrosis identification exceeding 0.8, demonstrated a high NPV of ≥88% for exclusion and PPV of ≥82% for identification using cutoff values of −1.455 and 0.68, respectively. This scoring system could obviate the necessity for liver biopsy in 75% of cases while preserving a prediction accuracy of 90%.[35]

Furthermore, the aspartate aminotransferase (AST) to platelet ratio index (APRI) with an AUROC of 0.75 identifies advanced fibrosis with NPV and PPV

of 76.2% and 61.4%, respectively.[35] In addition, the FibroScan-AST (FAST) score achieved a PPV of 83% and an NPV of 85%.[34] Patients categorized in the intermediate or high-risk group for liver disease progression are recommended to undergo additional NITs to evaluate the presence and extent of advanced liver fibrosis. Alternatively, LSM has been shown to accurately identify advanced fibrosis (F3) and cirrhosis (F4) in patients with chronic liver disease.[38] LSM alterations can predict clinical outcomes in MASLD patients. Therefore, regular evaluation of LSM values is crucial for tracking fibrotic burden changes.[41-43] ELF test, which measures the serum levels of hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of metalloproteinase 1, has been validated as a reliable marker of fibrosis stage. It shows good predictive performance for liver disease-related risk factors.[44] It demonstrated a sensitivity of 90% for predicting fibrosis and an NPV of 92% for ruling out significant fibrosis, with an AUROC of 0.80.[35] Magnetic resonance elastography (MRE) performed on existing magnetic resonance imaging machines employs a phase contrast approach to evaluate liver stiffness by analyzing the propagation of mechanical waves. It has become the most accurate NIT for evaluating liver fibrosis, exhibiting significant accuracy and consistency.[35]

A multistep approach is recommended in adult patients with MASLD, wherein first FIB-4 should be used by practitioners due to its simplicity, low cost, and widespread availability. Imaging methods like liver elastography can be used as a secondary step to provide further clarification on the fibrosis stage, particularly in cases where fibrosis remains uncertain or in patients with high-risk factors. This sequential testing strategy enables healthcare providers to avoid unnecessary testing in low-risk individuals while ensuring comprehensive evaluation for high-risk patients, especially those with diabetes, obesity, or metabolic syndrome [Figure 2][36,45,46] The NITs are recommended to further stratify intermediate- and high-risk patients and guide appropriate management decisions.

For patients with LSM values <8 kPa, current guidelines recommend repeating surveillance testing every 2–3 years. This approach is based on the understanding that these patients have a low likelihood of progression to cirrhosis or HCC in the short term.[47,48] Patients with LSM values between 8 kPa and 12 kPa fall into an intermediate-risk group, so a liver biopsy or MRE should be performed to accurately assess the degree of fibrosis and guide treatment decisions. MRE, in particular, has shown excellent performance in evaluating liver stiffness and can offer a less invasive, highly accurate alternative to biopsy.[47,49]

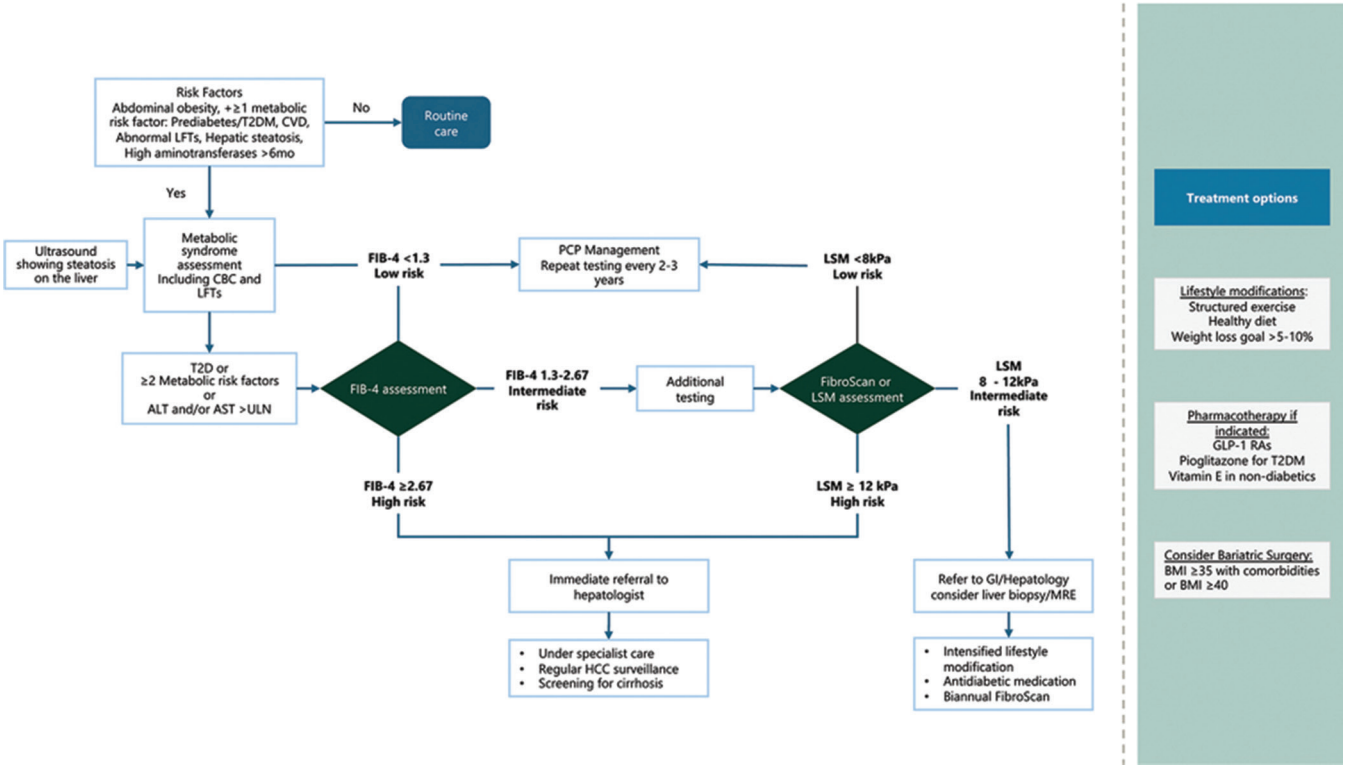

Figure 2: Algorithm for clinical assessment – a multistep approach. Note: The algorithm starts with the current method and initially focuses on high-risk individuals, allowing for future expansion as healthcare resources become available. This targeted approach prevents overburdening the healthcare system while still addressing the most urgent needs

For patients with LSM >12 kPa, which indicates a high likelihood of advanced fibrosis or cirrhosis (F3–F4), immediate referral to a hepatologist is recommended for further management.[47,50] The rationale for these recommendations stems from evidence demonstrating that patients with advanced fibrosis are at high risk of developing serious liver-related complications, and timely referral allows for appropriate interventions to improve long-term outcomes.

Abdominal obesity, particularly visceral adiposity, serves as a critical driver of insulin resistance and metabolic dysfunction, significantly increasing the risk of MASLD development. Studies have demonstrated that individuals with abdominal obesity combined with metabolic risk factors show a 2- to 3-fold higher risk of developing advanced liver disease compared to those without these risk factors.[1,51] The presence of MASLD/MASH correlates strongly with liver fat accumulation and progression to steatohepatitis.[52] Persistent elevation of aminotransferases (>6 months), with alanine aminotransferase (ALT) levels of more than 19 and 30 IU/L in women and men, respectively, increases the risk of MASLD/MASH. Moreover, abnormal ALT can increase the risk of MASLD by 2.7 times.[53] Cardiovascular disease risk factors significantly overlap with MASLD risk and are the most common mortality factor independent of other metabolic comorbidities.[54] Furthermore, in individuals with obesity, T2DM significantly elevates the incidence of moderate and advanced fibrosis risk by 1.8- and 2.5-folds, respectively.[55] Therefore, systematic screening for fibrosis is recommended every 2–3 years[56] for all high-risk groups using noninvasive tests (NITs) such as Fibrosis-4 (FIB-4), enhanced liver fibrosis (ELF) score, or liver stiffness measurement (LSM) by transient elastography (Fibroscan®).

Bariatric surgery facilitates sustained weight reduction of approximately 30% and the remission of T2DM, thereby lowering cardiovascular and cancer mortality, which are predominant mortality factors in MASLD/MASH.[57] The evaluation of MASLD in bariatric surgery candidates is crucial as these conditions can significantly impact surgical outcomes and long-term liver health. Bariatric and metabolic surgeries are associated with an improvement in obesity-related comorbidities; however, outcomes for patients with MASLD vary with the severity of liver disease.[58] NITs such as aspartate aminotransferase (AST)/ALT ratio and risk scores such as FIB-4 are effective for screening patients with elevated liver fibrosis risk. Evaluating advanced fibrosis in MASLD is crucial for practical and prognostic reasons, especially before bariatric surgery. It prevents complications related to cirrhosis, particularly in those with decompensated liver cirrhosis.[50,58] Individuals requiring bariatric surgery must be assessed for MASLD-related fibrosis, with liver biopsy considered if preoperative evaluation reveals uncertain or high fibrosis risk.[50]

The presence of diabetes is a critical risk factor in MASLD that requires serious attention. Type 2 diabetes mellitus (T2DM) accelerates fibrosis progression, which is a predictor of long-term outcomes in MASLD, including liver-related issues and overall mortality. Additionally, it facilitates the onset of HCC. Furthermore, diabetes has been identified as the primary independent metabolic risk factor for HCC, highlighting its significant influence on MASLD progression.[59] A cross-sectional study on patients (n = 659) with type 1 diabetes (T1D) noted that patients with HbA1c above 7.6% (60 mmol/mol) showed significantly higher MASLD indices (HSI 38 ± 6 vs. 36 ± 5, $p < 0.001$; FLI 26 ± 26 vs. 19 ± 19, $p < 0.001$), and higher proportions of MASLD identified by HSI (57 vs. 44%, $p < 0.001$). The study concluded that maintaining optimal blood glucose levels plays a critical role in MASLD development among adults with T1D, regardless of excess body weight or obesity.[60] Also, MASLD is linked to a 2.2-fold higher risk of developing diabetes, regardless of age, sex, body fat distribution, or other metabolic risk factors.[61] Patients with T1D, who have additional cardiometabolic risk factors such as obesity, metabolic syndrome features, elevated aminotransferases (>30 U/L), or hepatic steatosis, should be screened for MASLD with clinically significant fibrosis (stages F2–F4) using the FIB-4 score.[50] Despite the high prevalence of MASLD which involves hepatocellular injury, mean levels of AST and ALT are often within normal limits, indicating that normal liver enzymes do not exclude fatty liver, necessitating the use of FIB-4 in such cases.[62] Therefore, routine screening for MASLD with clinically significant fibrosis using FIB-4 is an evidence-based recommendation to guide clinical management in T1D patients with metabolic risk factors. However, a retrospective study in patients with diabetes (n = 1115) noted that despite low-risk scores on FIB-4 testing, the patients had fourfold likelihood of having significant or advanced liver fibrosis, which may be a limitation of FIB-4 test.[63]

Table 2 provides the key recommendations, after careful consideration of all evidence, for screening patients with MASLD/MASH.

Risk factors and stratification for MASLD/MASH

The use of NITs such as LSM by TE or MRE allows for the initial assessment of liver stiffness, but values in this intermediate range require more detailed evaluation to distinguish between significant fibrosis and milder forms of liver damage.[49] Timely referral to specialized care is crucial

Table 2: Consensus recommendations for screening patients for MASLD/MASH

Statement	Level of Evidence	Consensus
Individuals with abdominal obesity and ≥1 additional metabolic risk factors, such as prediabetes, T2DM, cardiovascular disease, abnormal liver function tests, hepatic steatosis, and high plasma aminotransferase levels (over 6 months) should be considered as a "high-risk" group. Screening for MASLD/MASH and advanced fibrosis is recommended for this "high-risk" group.	High	100%
Individuals undergoing bariatric surgery should be evaluated for the presence and severity of MASLD/MASH. If NITs fail to achieve adequate presurgical stratification of liver fibrosis, a liver biopsy may be recommended. (This statement did not reach majority consensus in round 1 and was modified in round 2 with the consensus of all experts present.)	Moderate	60% in Round 1 and 100% Round 2
Serum aminotransferases or liver ultrasound tests to assess liver diseases are not sensitive enough to assess MASLD and the related disease severity; hence, they are not recommended as a screening method for MASLD.	Moderate	80%
Multiple NITs such as FIB-4 score, APRI, FAST, and NFS have been evaluated with variable performance. These NITs are recommended to confirm that there is no advanced fibrosis in the MASLD population.	Moderate	100%
In adults with MASLD, a multistep approach for assessment is recommended. FIB-4 test should be the first line of assessment for practitioners due to its simplicity, low cost, and easy availability.	Moderate	93.3%
FIB-4 is recommended as the most validated calculation, and its incorporation in HSI will be beneficial in identifying patients with advanced fibrosis.	Moderate	100%
Clinicians should prefer the use of LSM to stage the risk of fibrosis in patients with MASLD as it is best validated to identify the advanced disease and predict liver-related outcomes preferentially in patients at risk of advanced liver fibrosis.	Moderate	100%
Patients with T1D along with cardiometabolic risk factors (such as obesity), features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis (on imaging) are recommended to be screened for MASLD with clinically significant fibrosis (stages F2–F4) using FIB-4 score.	Moderate	100%
Patients with LSM values <8 kPa (low-risk group) should undergo repeat surveillance testing in 2–3 years, while those with LSM ≥8 to 12 kPa (intermediate-risk group) should have a liver biopsy or MRE for monitoring with a re-evaluation of risk in 2–3 years, and those with LSM >12 kPa (high-risk group) should be immediately referred to hepatologists.	Moderate	100%

APRI, Aspartate aminotransferase to platelet ratio index; FAST, FibroScan-aspartate aminotransferase; F2, Moderate liver scarring; F4, Live cirrhosis; FIB-4, Fibrosis-4; HSI, Higher MASLD indices; LSM, Liver stiffness measurement; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; MRE, Magnetic resonance elastography; NFS, Non-alcoholic fatty liver disease Fibrosis Score; NITs, Noninvasive tests; T1D, Type 1 diabetes T2DM, Type 2 diabetes mellitus

to assess the risk of complications such as cirrhosis and HCC and to determine if further therapeutic interventions are needed.[47,50]

For patients in low-risk categories (FIB-4 <1.3, ELF <7.7, LSM <8.0 kPa), the current consensus is that routine 6–12 monthly follow-up and monitoring in a primary care setting by their PCPs is appropriate, as the risk of progression to cirrhosis or liver-related morbidity is minimal. Regular follow-up can focus on managing comorbid conditions such as metabolic syndrome or diabetes.[47,50,64] Thus, PCPs can effectively oversee care in these patients, ensuring that any changes in their liver health are detected early through periodic NITs.

The thresholds of FIB-4 score ≥2.67, LSM >12 kPa, ELF >1.5, or MRE >5.0 kPa are indicative of significant fibrosis or advanced liver damage and suggest that the patient may be at an increased risk for liver-related complications. A FIB-4 score above 2.67 strongly correlates with cirrhosis and high liver-related morbidity.[65] Similarly, LSM >12 kPa is a marker for advanced fibrosis (F3) or cirrhosis (F4) and is predictive of an increased risk of complications such as variceal bleeding or HCC.[47] The ELF test score >10.35 suggests advanced liver fibrosis and increased risk for liver decompensation.[65] Also, MRE ≥3.3 kPa and FIB-4 score ≥1.6 ruled in significant (F2) or higher fibrosis with a PPV of 97.1% in a cross-sectional study of a prospective cohort of 238 patients with MRE and biopsy-proven MASLD.[47,66] Given these findings, patients with any of these high-risk markers should be immediately referred to a hepatologist for further evaluation and management, including possible liver biopsy, surveillance for HCC, and consideration of therapies aimed at halting disease progression. Early referral to specialized care is critical in this high-risk group to prevent progression to liver failure and improve long-term survival.

Liver biopsy is an invasive procedure associated with potential complications, including pain, bleeding, and potentially life-threatening procedures, with sampling variations that could lead to errors in fibrosis staging.[22] For cirrhosis, a 15–25 mm long biopsy is considered sufficient specimen for accurate evaluation.[67] However, a liver biopsy may be necessary to confirm the diagnosis of steatohepatitis, particularly in patients with ambiguous results from NITs, as the biopsy can directly assess histological features of inflammation and hepatocyte ballooning.[68] Furthermore, in cases where there is suspicion of other concurrent liver diseases (such as viral hepatitis or autoimmune liver disease), a biopsy can help distinguish MASLD from other pathologies that might require different therapeutic

management.[49,50] Evidence-based recommendations are provided in Table 3.

Hepatocellular carcinoma surveillance in patients with MASLD/MASH

The risk of HCC increases significantly in individuals with advanced fibrosis or cirrhosis due to the underlying chronic inflammation and hepatocyte damage seen in severe MASLD.[69] An analysis by the US Liver Transplant Registry revealed that the proportion of MASLD patients awaiting liver transplantation rose from 6.4% in 2002 to 23% in 2016. MASH was recognized as the most rapidly increasing etiology of HCC, resulting in an 8.5-fold escalation throughout the study duration.[70] The annual incidence of HCC in patients with cirrhosis due to MASLD is estimated to exceed 1.5%. Consequently, regular screening for HCC is recommended for this population. Patients with a FIB-4 score >2.67, LSM >16.1 kPa, and MRE >5.0 kPa are considered to be at high risk for severe liver fibrosis and HCC. These thresholds indicate the presence of advanced fibrosis (F3) or cirrhosis (F4), both of which significantly increase the risk for liver-related complications, including the development of HCC.[28,31] Therefore, patients with these high-risk markers should undergo HCC surveillance to detect complications at an early, treatable stage.

Nevertheless, surveillance of HCC is challenging with varying guidelines. The AASLD recommends HCC surveillance only in MASLD for patients with cirrhosis,[71] the EASL guidelines recommend additional individual risk assessment in patients with F3 fibrosis,[45] and the American Gastroenterological Association[54] recommends surveillance for advanced fibrosis when at least two noninvasive tests yield consistent results. The challenge posed by the late diagnosis of HCC necessitates early identification during its clinical progression to improve the chances for curative or ablative treatments.

Hence, the recommendation of HCC surveillance should be considered for patients with advanced fibrosis (F3) or cirrhosis (F4) as part of a comprehensive management plan. If NITs indicate F3 fibrosis or higher, patients should undergo HCC screening every 6 months.[72] The decision to initiate HCC surveillance should be individualized based on a comprehensive assessment of the patient's risk factors, including age, comorbidities (such as diabetes or obesity), and family history of liver cancer.[50,73] Therefore, while routine screening is not advised for noncirrhotic MASH with mild to moderate fibrosis, those with severe fibrosis (F3) should be carefully monitored for the potential development of HCC [Table 4].

Table 3: Consensus recommendations for risk factors for MASLD/MASH in Saudi Arabia

Statement	Level of Evidence	Consensus
Patients in low-risk categories (FIB-4 <1.3, ELF <7.7, LSM <8.0kPa) are recommended to be managed by their PCPs regularly during follow-up in the primary healthcare setting.	High	93.3%
Patients with an LSM score of 8 kPa–12 kPa are considered to be in 'intermediate risk' group. It is recommended that 'intermediate risk' group should be referred to gastroenterologists/hepatologists where liver biopsy, sequential LSM, or MRE can be performed to confirm the risk status or disease stage.	Low	100%
Patients with FIB-4 score ≥2.67, LSM >12 kPa, ELF >1.5, or MRE >5.0 kPa are considered to be at high-risk and should be referred to hepatologists without delay.	Moderate	93.3%
We recommend that liver biopsy should generally be avoided in the management of patients with MASLD, except in specific circumstances where it is advised, namely: a) To confirm the diagnosis of steatohepatitis, b) When a discrepancy exists between NITs and clinical findings indicating advanced fibrosis, c) When there is a possibility of other concurrent liver diseases.	High	93.3%

ELF, Enhanced liver fibrosis; FIB-4, Fibrosis-4; LSM, Liver stiffness measurement; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; MRE, Magnetic resonance elastography; NITs, Noninvasive tests; PCPs, Primary care physicians

First-line treatment recommendations for MASLD/MASH

A multidisciplinary treatment approach is recommended for the management of MASLD due to the complex interplay between liver pathology and various cardiometabolic comorbidities. It is closely linked to conditions such as obesity, T2DM, hypertension, and dyslipidemia, all of which contribute to both liver and cardiovascular diseases.[74] Interestingly, a cross-sectional study in patients with T2DM found that higher carbohydrate intake was

Table 4: Consensus recommendations for HCC surveillance for MASLD/MASH

Statement	Level of Evidence	Consensus
Regular severe fibrosis/HCC surveillance is recommended for patients with FIB-4 score >2.67, LSM >12 kPa, and MRE >5.0 kPa.	Low	100%
While noncirrhotic MASH may be associated with HCC, routine screening is not recommended for patients without severe MASLD-related fibrosis (<F3); however, HCC surveillance should be considered in adults with severe fibrosis (F3 stage) determined by noninvasive markers or liver biopsy following an individual risk assessment.	Moderate	93.3%

F3, Advanced fibrosis; FIB-4, Fibrosis-4; HCC, Hepatocellular carcinoma; LSM, Liver stiffness measurement; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; MRE, Magnetic resonance elastography

associated with liver steatosis in those aged ≤50 years.[75] Effective management includes not only pharmacologic treatments aimed at controlling diabetes and lipids but also lifestyle interventions such as weight loss, exercise, and dietary modifications, all of which can benefit both liver function and cardiovascular health.[27,47] Collaborative care ensures that all aspects of a patient's health are addressed, leading to improved outcomes in both liver-related and extrahepatic conditions.

Weight loss is one of the most effective interventions for improving liver function and mitigating the risks associated with MASLD. Weight loss greater than 10% is generally associated with the best outcomes for MASH and a reduction in cardiovascular risks.[76] Normal-weight adults may exhibit insulin resistance, ectopic fat deposition, and other metabolic disturbances that contribute to MASLD.[77] Diet and physical activity can significantly impact liver fat content even in the absence of significant weight loss.[27,77] Therefore, while weight loss may not be the primary goal in normal-weight adults with MASLD, dietary and exercise interventions remain crucial for improving liver health and preventing disease progression.

Structured and individualized exercise programs are crucial for achieving and maintaining weight loss, they also improve insulin sensitivity, decrease liver fat, and reduce the incidence of cardiovascular disease, a frequent comorbidity of MASLD.[27] In addition to exercise, dietary modifications are essential, with recommendations focusing on reducing saturated fats, refined sugars, and starches, which contribute to both liver fat accumulation and insulin resistance.[78] Overall, a holistic approach involving weight loss, physical activity, dietary changes, and control of metabolic syndrome-related conditions is critical to improve both liver health and extrahepatic outcomes in patients with MASLD [Table 5].

Table 5: Consensus recommendations for first-line treatment of MASLD/MASH

Statement	Level of Evidence	Consensus
A multidisciplinary treatment approach (including PCPs, endocrinologists, hepatologists/gastroenterologists, and cardiologists) is recommended owing to the multidirectional connections between MASLD and cardiometabolic comorbidities to improve both liver-related and extrahepatic outcomes.	High	100%
Patients with excess body fat and MASLD should be recommended for lifestyle modifications, including participating in structured and customized exercise programs, adopting better eating habits and a healthy diet (with less saturated fat and starch), aiming for weight loss (at least 5%, or ideally more than 10%), and controlling MetS-associated cardiometabolic issues.	High	100%
In normal-weight adults with MASLD, diet and exercise interventions are recommended to reduce liver fat.	Moderate	93.3%

MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; PCPs, Primary care physicians

Pharmacotherapy/bariatric surgery/liver transplantation recommendations for MASLD/MASH

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose linked transporter-2 inhibitors (SGLT-2Is), and pioglitazone (peroxisome proliferator-activated receptor gamma agonist) are effective in treating hyperglycemia, lowering cardiovascular risk, and providing hepatic benefits in MASLD.[79] Treatment with pioglitazone improves liver injury rates in patients with T2DM. However, combined therapy with pioglitazone and exenatide results in a more significant decrease in ALT levels (GLP-1RA).[80] GLP-1 RAs not only improve metabolic parameters but also have direct beneficial effects on the liver, including reductions in liver stiffness.[28,80] GLP-1 RAs, pioglitazone, and SGLT-2Is may be considered for patients with T2DM and MASLD, primarily due to their cardiometabolic benefits, including improved glycemic control, weight reduction, and positive effects on cardiovascular health.[80] However, long-term trials assessing the efficacy of GLP-1RAs in liver fibrosis are currently lacking. Immediate improvements in lipotoxicity and collagen production may necessitate prolonged observation and treatment for fibrosis regression.[80,81]

Given the dual benefit of improving both liver and metabolic health, these therapies are recommended for patients with T2DM and advanced fibrosis due to MASH. By targeting both insulin resistance and liver fat, pioglitazone and GLP-1 RAs help to prevent disease progression, reduce the risk of cardiovascular events, and improve overall clinical outcomes.

Importantly, a phase 3 trial of the GLP-1 RA, semaglutide administered at a dose of 2.4 mg once weekly, demonstrated that when combined with lifestyle intervention, it is an effective treatment for obesity. The combination resulted in a mean weight loss of 14.9% from baseline—significantly higher than placebo and existing antiobesity medications. The drug's effectiveness is highlighted by 86% of participants achieving clinically meaningful weight loss (≥5%), with about 50% reaching ≥15% weight loss and one-third achieving ≥20% weight loss, comparable to the outcomes associated with bariatric surgery. Beyond weight loss, significant improvements in cardiometabolic risk factors and metabolic benefits were noted.[82] Furthermore, a retrospective study involving 420 patients with diabetes on semaglutide showed clinically

significant improvement in transaminases and MASH scores (NFS, FIB-4, APRI).[83] Current medications for chronic weight management (orlistat, phentermine-topiramate, naltrexone-bupropion, and liraglutide 3.0 mg) yield 4%–7% more weight loss than placebo,[84] whereas semaglutide is associated with approximately double the weight loss.[84,85] A recent phase 3 trial of semaglutide (dose-escalated from 0.25 mg to 2.4 mg over 16 weeks) demonstrated superior efficacy compared to placebo in improving steatohepatitis and fibrosis outcomes (62.9% of patients achieved steatohepatitis resolution without fibrosis progression versus 34.3% with placebo, while 36.8% demonstrated liver fibrosis reduction), with concurrent improvements in glucometabolic parameters and hepatic biomarkers. The trial evidence establishes semaglutide's therapeutic potential for managing MASLD/MASH with fibrosis and reinforces its clinical utility through superior histologic improvements, positioning it as a promising therapy for patients with metabolically associated steatohepatitis and fibrosis. However, the specific safety and efficacy profile of semaglutide in post-liver transplant recipients remains to be established. The existing data do not provide direct insights into the post-transplant setting, necessitating dedicated studies to evaluate semaglutide's role in this specialized population before clinical implementation can be recommended.[86,87]

The phase 2 trial of tirzepatide (a dual GLP-1RA and gastric inhibitory polypeptide [GIP] receptor agonist) demonstrated notable efficacy in addressing MASH with moderate to severe fibrosis among participants with biopsy-confirmed MASH and stage F2 or F3 fibrosis. The treatment included weekly subcutaneous administration of 5-mg, 10-mg, or 15-mg doses. The highest dose (15 mg) achieved MASH resolution without worsening fibrosis in 62% of participants compared to 10% in the placebo group. Additionally, all three doses showed improvement in fibrosis staging in approximately 51%–55% of participants versus 30% in the placebo group.[88] Both semaglutide and tirzepatide are approved for diabetes treatment in Saudi Arabia, USA, Europe, and UAE. The SURPASS-3 substudy demonstrated that tirzepatide was significantly more effective than insulin degludec in reducing liver fat content in patients with T2DM. The pooled analysis of tirzepatide 10 mg and 15 mg showed an absolute reduction in liver fat content of -8.09% compared to -3.38% with insulin degludec, indicating a significant treatment difference of -4.71%. Patients on tirzepatide showed more than 30% liver fat reduction compared to those on insulin degludec. These findings suggest that tirzepatide, as a dual GIP and GLP-1 RA, offers substantial metabolic benefits beyond glycemic control, particularly in addressing fatty liver disease in T2DM.[89]

In a similar vein, oral resmetirom, a thyroid hormone receptor beta (THRβ) agonist, a nuclear hormone receptor predominantly expressed in the liver, and a key metabolic pathway regulator,[90] has been evaluated in a phase 3 trial on adult patients with biopsy-confirmed MASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). The study demonstrated that resmetirom (80–100 mg daily) was effective in treating MASH with liver fibrosis. Both doses (80 mg and 100 mg) showed significant superiority over placebo in achieving MASH resolution (25.9% and 29.9% vs. 9.7%) and fibrosis improvement (24.2% and 25.9% vs. 14.2%). These findings suggest that resmetirom could represent a promising therapeutic option for MASH with liver fibrosis, addressing a significant unmet medical need.[91] However, while the abovementioned drugs show promise, further research and real-world evidence are needed to fully establish their safety and efficacy in the management of MASLD/MASH, particularly in the long term.

While medications used for T2DM have shown promise in MASLD treatment, other antidiabetic medications have also been investigated for their potential benefits in MASLD-related outcomes. Metformin use was associated with a reduction in HCC incidence in patients with T2DM (odds ratio [OR]: 0.50; 95% CI: 0.34–073). Sulfonylurea (OR: 1.62; 95% CI: 1.16–2.24) and insulin (OR: 2.61; 95% CI: 1.46–4.65) were associated with increased HCC incidence.[28] Medications including metformin, sulfonylurea, insulin, SGLT-2Is, and dipeptidyl peptidase-4 inhibitors have not shown significant enhancements in liver histology endpoints in patients with MASLD.[28] Hence, these medications are not advised as there is insufficient evidence of their positive benefits in patients with MASLD/MASH.

Total vitamin E intake, including dietary and supplementary forms, has a protective association with MASLD (OR: 0.9592; 95% CI: 0.9340–0.9851; $P = 0.0039$) and showed a beneficial effect in preventing MASLD, especially in those without hyperlipidemia.[92] Vitamin E is recommended as an option for the treatment of MASLD in individuals without diabetes, based on evidence demonstrating an improvement in steatohepatitis in this population. However, vitamin E is not currently recommended for individuals with T2DM or advanced fibrosis due to insufficient evidence.[64] Vitamin E can potentially be utilized for managing MASH, weighing the risks and benefits carefully.[54]

In Saudi Arabia, approved agents for MASLD/MASH are limited to medications officially approved for related metabolic conditions such as T2DM and obesity, including GLP-1 receptor agonists (e.g., semaglutide), pioglitazone, and SGLT-2 inhibitors, which may be used off-label for hepatic

benefits. Emerging agents, such as resmetirom (a THR-β agonist), are under clinical investigation and not yet approved for MASLD/MASH management in Saudi Arabia.[23,86]

In adults with noncirrhotic MASLD without contraindications, bariatric surgery is recommended as it has the potential to induce a positive impact on the liver for an extended period and is linked to the remission of T2DM and improvement of cardiometabolic risk factors.[27] It has also been linked to MASH resolution and improvement of fibrosis in up to 85% and 33% of patients, respectively.[28] Patients with class II and class III obesity who qualify for bariatric surgery typically have MASLD or MASH along with a BMI of >40 kg/m^2 or ≥35 kg/m^2 and obesity-related comorbidities.[27,57] For adults with MASLD-related compensated advanced chronic liver disease or compensated cirrhosis with an approved indication, a multidisciplinary team with experience in bariatric surgery is recommended to carefully evaluate the indication, and the type of surgery, to optimize management of related comorbidities.[27,50]

Furthermore, endoscopic bariatric and metabolic therapies (EBMTs) are advancing rapidly and are generally seen as less invasive than bariatric surgery.[93] These protocols align with the standards set by the American Society of Gastrointestinal Endoscopy taskforce: a total body weight loss of over 5%, an excess body weight loss of over 25%, and a risk of adverse events of less than 5%. The EBMT procedures can be primarily grouped into restrictive, malabsorptive/metabolic, and aspiration techniques based on their intended outcomes.[93] These techniques though have only a transient effect on weight, with most patients regaining weight making it an inefficient option for long term.[94] However, a recent meta-analysis involving 863 patients indicates potential histologic improvement from these procedures.[95] The current evidence base for EBMT in MASLD remains limited, particularly regarding specific liver-related outcomes. Most available studies rely on surrogate markers such as liver biochemistry and noninvasive fibrosis scores, rather than robust endpoints such as histological improvement or disease progression. This dependence on indirect measurements, coupled with inadequate sample sizes in existing research, creates significant uncertainty about the actual effectiveness of these interventions for MASLD. The lack of well-designed studies with liver-specific primary endpoints makes it challenging to develop evidence-based recommendations for individual patient care.[96] Adverse events related to the device (such as nausea, vomiting, abdominal pain, with serious adverse events occurring in up to 19% of cases) are a significant concern.[96,97]

MASLD is becoming the most common reason for liver transplants (LTs) globally, including end-stage liver disease and HCC. It commonly represents a systemic metabolic syndrome, necessitating a multidisciplinary approach for appropriate presurgical assessment in patients. This is crucial to attain a post-transplant result similar to that of other LT indications. Patients with MASLD/MASH are also more susceptible to cardiovascular events, diabetes, high cholesterol, obesity, kidney-related disorders, and recurring MASH after a transplant. Patients with MASH have a higher risk of dying from heart and brain-related issues compared to those without MASH, especially in the first year following a liver transplant. It has been found that implementing a post-transplant multidisciplinary approach involving hepatologists, endocrinologists, and advanced practice nurses reduces cardiovascular events from 14% to 6%. This approach focuses on preventing and detecting risk factors early.[27,98,99] Evidence-based recommendations are provided in Table 6.

DISCUSSION

The reclassification of NAFLD to MASLD[3] marks a significant step in redefining the approach to liver disease, particularly in regions such as Saudi Arabia, where the prevalence of metabolic disorders is high. This shift not only offers a more accurate reflection of the disease's metabolic origins but also removes the stigma associated with terms such as "fatty liver," which may hinder patient engagement and healthcare-seeking behavior. In Saudi Arabia, the high prevalences of conditions such as obesity, T2DM, and metabolic syndrome contribute substantially to the burden of MASLD, with studies showing alarming rates of the disease, particularly among those with obesity or diabetes.[2,6,20,22,25,26,55] The link between obesity and MASLD highlights the importance of early screening and lifestyle interventions to prevent progression to more severe liver outcomes, including fibrosis and HCC.[6,26,100] The newly introduced diagnostic criteria, as well as the redefined terminology, should encourage better detection, improved patient management, and more effective public health initiatives tailored to the unique challenges faced in the Saudi Arabian context.

Although universal screening guidelines are still lacking, targeted screening for at-risk individuals, particularly those with obesity, metabolic syndrome, and elevated aminotransferases, is gaining importance. The correlation between abdominal obesity, insulin resistance, and MASLD progression highlights the need for comprehensive screening in high-risk populations. NITs such as FIB-4 and LSM are crucial tools for identifying advanced

Table 6: Consensus recommendations for pharmacotherapy/bariatric surgery/liver transplantation for MASLD/MASH

Statement	Level of Evidence	Consensus
Pioglitazone (usually 15 mg–30 mg daily for 6–12 months) has shown benefits in patients with T2DM and obesity. Hence, pioglitazone is recommended for patients with T2DM with biopsy-proven MASH and advanced fibrosis.	High	80%
GLP-1 RAs, pioglitazone, or SGLT2 inhibitors may be considered for patients with T2DM and MASLD to provide cardiometabolic benefits; however, due to limited evidence supporting their effectiveness in treating steatohepatitis specifically, their recommendation for this purpose is restricted.	Moderate	73.3%
For patients with MASLD/MASH and a BMI >27 kg/m^2, T2DM, cardiovascular disease, or other obesity-related conditions, GLP-1 RAs (semaglutide 2.4 mg/week or liraglutide 3 mg/day) are recommended alongside lifestyle interventions, while dual GIP receptor and GLP-1 RAs (such as tirzepatide) for obesity and oral resmetirom (80–100 mg daily) for MASH with liver fibrosis may be considered; however, further research and real-world evidence are needed before fully recommending these drugs in clinical practice.	Moderate	73.3%
Insufficient evidence of effectiveness restricts the use of metformin, acarbose, dipeptidyl peptidase IV inhibitors, ursodeoxycholic acid, and insulin, and these drugs are not recommended for treating MASH (with no impact on hepatocyte necrosis or inflammation).	High	93.3%
Vitamin E (800 mg orally once daily for 12 weeks) can be considered for the treatment of patients with MASH without T2DM for steatosis reversal, improvement in the degree of fibrosis, and ALT reduction. However, insufficient evidence of its effectiveness in improving MASH with T2DM and advanced fibrosis restricts its recommendation in such patients.	High	93.3%
It is recommended for clinicians to consider bariatric surgery as an option to treat MASLD and improve cardiometabolic health in patients having a BMI of ≥35 kg/m^2 with comorbidities (≥35–39.99 kg/m^2 in Saudi Arabian populations) and ≥40 kg/m^2 even without comorbidities in Saudi Arabian populations. However, for patients with well-compensated cirrhosis, a multidisciplinary team review is essential before proceeding with surgery. In cases of decompensated cirrhosis, bariatric surgery is contraindicated unless it is performed concurrently with liver transplantation.	High	86.7%
Clinicians should be careful when considering bariatric surgery for patients with MASH and compensated cirrhosis. Bariatric surgeries are recommended to be personalized and performed at specialized centers involving a multidisciplinary team.	High	93.3%
Endoscopic bariatric surgery and metabolic therapies, as well as orally ingested devices, are not currently recommended for MASLD patients due to insufficient clinical evidence.	High	93.3%
Adults with MASLD are at increased risk of major cardiovascular events in the pre-, peri-, and post-transplant phases. Hence, a multidisciplinary management or integrated comprehensive care approach to MASH and MASH-associated comorbidities is recommended to reduce morbidity and mortality in patients with MASH before and after liver transplantation.	High	100%

ALT, Alanine Transaminase; BMI, Body mass index; GLP -1 RAs, Glucagon-like peptide-1 receptor agonists; GIP, Gastric inhibitory polypeptide; MASH, Metabolic dysfunction-associated steatohepatitis; MASLD, Metabolic dysfunction-associated steatotic liver disease; SGLT2, Sodium-glucose cotransporter-2; T2DM, Type 2 diabetes mellitus

liver fibrosis and cirrhosis, guiding clinical management decisions without the need for invasive liver biopsies. Bariatric surgery has proven beneficial for managing obesity-related comorbidities, including MASLD, by improving liver outcomes and reducing cardiovascular mortality.[24,34,35,38,49,101,102] However, the presence of severe liver disease can impact surgical success, necessitating careful presurgical evaluation. Furthermore, in patients with diabetes and metabolic risk factors, routine use of FIB-4 is recommended for identifying those at higher risk of significant fibrosis. By integrating NITs into clinical practice, healthcare providers can better stratify risk, allow early intervention, and improve patient outcomes.

Integrating NITs such as LSM via TE and MRE has significantly enhanced the ability to assess liver fibrosis in MASLD patients. However, intermediate LSM values (8–12 kPa) necessitate further evaluation to accurately differentiate between significant fibrosis and milder liver damage. In such cases, liver biopsy may be warranted for definitive diagnosis, particularly when clinical decision-making is challenging. For patients with low-risk markers, such as FIB-4 <1.3 and LSM <8.0 kPa, routine follow-up by PCPs is generally sufficient, with a focus on managing comorbidities such as metabolic syndrome. However, for those with high-risk markers (e.g., FIB-4 ≥2.67 or LSM >12 kPa), referral to specialized care is essential. While liver biopsy remains the gold standard for diagnosing steatohepatitis and distinguishing it from other liver diseases, the decision to perform a biopsy should be carefully considered due to its invasive nature.[31,33,35,36,65,101] Timely, specialized care for high-risk patients, guided by accurate NITs, can significantly improve long-term outcomes and reduce mortality.

The management of MASLD requires a holistic, multidisciplinary approach due to its complex link with

metabolic comorbidities.[100] Treatment strategies must address both liver pathology and associated cardiovascular risks. Lifestyle modifications, including weight loss, exercise, and dietary adjustments, are key to improving liver function and overall metabolic health.[103] Weight loss, particularly over 10%, has shown substantial benefits in reducing both liver fat and cardiovascular risks, even in non-obese individuals.[104] Exercise and dietary changes, such as reducing saturated fats and refined sugars, further help manage liver fat content and insulin resistance.[105]

Pharmacologic interventions such as GLP-1RAs, pioglitazone, and SGLT-2Is also play a crucial role in managing MASLD, especially in patients with T2DM. These agents improve glycemic control, promote weight loss, and reduce cardiovascular risks. The CORDIAL study demonstrated that GLP1RA use was associated with slowed fibrosis progression in patients with T2DM.[106] However, long-term data on their efficacy in liver fibrosis are still needed.[84,85,107] In more severe cases, bariatric surgery and endoscopic metabolic therapies offer promising solutions for patients with advanced obesity and MASLD. These procedures can significantly impact liver function and metabolic health. Additionally, for patients undergoing liver transplants, a comprehensive post-transplant care team is essential to reduce complications and improve outcomes, as patients with MASLD are at higher risk for cardiovascular and metabolic issues after transplant.

Strengths and limitations

This comprehensive consensus addresses the critical need for MASLD/MASH management guidance in Saudi Arabia, given the region's high prevalence of metabolic diseases. The rigorous methodology and evidence-based implementable recommendations appropriately emphasize the necessary multidisciplinary management approach.

However, important limitations include potential selection bias in expert panel composition and literature selection, inherent diagnostic accuracy limitations from relying on noninvasive tests versus histological assessment, and absence of long-term outcome data for newer agents, particularly GLP-1 receptor agonists, limiting definitive efficacy recommendations for fibrosis regression. Additionally, safety and efficacy data for emerging agents in post-liver transplantation patients remain notably absent.

Implementation challenges may arise in resource-limited settings where access to advanced noninvasive testing modalities such as FibroScan and magnetic resonance elastography remains limited in primary care.

CONCLUSION

Addressing both the liver pathology and the associated cardiometabolic comorbidities is crucial for improving patient outcomes. Weight loss, exercise, and dietary changes are foundational strategies that not only benefit liver function but also reduce cardiovascular risks. Pharmacologic therapies, such as GLP-1RAs, pioglitazone, and SGLT-2Is, offer promising results in managing MASLD, particularly in patients with T2DM. However, further research is needed to fully understand their long-term impact on liver fibrosis. In advanced cases, bariatric surgery and emerging endoscopic metabolic therapies present valuable options for patients with severe obesity and metabolic dysfunction. Ultimately, a coordinated, team-based approach is essential, particularly in complex cases or in the post-liver transplant phase, to ensure effective management and improve liver and overall metabolic health.

These recommendations provide a practical framework for clinicians to implement comprehensive MASLD care, emphasizing risk stratification through noninvasive testing, lifestyle interventions, and appropriate pharmacological therapy, which when integrated into routine clinical practice should enhance early detection, improve patient outcomes, and optimize the management of both hepatic and metabolic manifestations of this increasingly prevalent disease.

Acknowledgement

We thank Dr. Shruti Shah, Dr. Anuradha Chatterjee and Ms. Sistla Pavana Goury of Turacoz Healthcare Solutions (www.turacoz.com) for providing medical writing support.

Financial support and sponsorship

The funding support for manuscript writing was provided by Novo Nordisk.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Consensus search string and statements with the level of evidence and recommendations

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
Terminology						
1. In 2023, international liver disease organizations and patient associations changed the nomenclature of NAFLD, aiming for a more positive, non-stigmatizing, health-seeking term. The umbrella term SLD encompasses diagnostic subgroups, including drug-related conditions and metabolic dysfunction-associated steatotic liver disease MASLD/MASH. We recommend using MASLD/MASH instead of NAFLD/NASH in regular clinical practice in Saudi Arabia.	A multisociety Delphi consensus statement on new fatty liver disease nomenclature (Rinella *et al*., 2023a)	Consensus statement	1a	High	100%	
Epidemiology						
2. There has been a steady rise in the prevalence of MASLD in Middle Eastern countries, including Saudi Arabia, over the last decade.	Non-Alcoholic Fatty Liver Disease among Type-2 Diabetes Mellitus Patients in Abha City, South Western Saudi Arabia (Alsabaani *et al*., 2018)	Cross-sectional study	2b	High	100%	
	Prevalence of metabolic dysfunction-associated steatotic liver disease in the Middle East and North Africa (Younossi *et al*., 2024)	SLR-Meta analysis	1a			
3.T2DM and obesity are the significant risk factors for MASLD/MASH. They are strongly associated with the progression to MASLD/MASH-related advanced fibrosis and HCC.	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a	High	100%	
	Clinical and Metabolic Characteristics of Non-Alcoholic Fatty Liver Disease Patients in Saudi Arabia: Data from the Systematic Observatory Liver Disease (SOLID) Registry (Alswat *et al*., 2021)	Observational Study	2b			
	Transient elastography for the prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes: Evidence from the CORDIAL cohort study (Alfadda *et al*., 2022)	Longitudinal Cohort Study	2b			
	AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review (Loomba *et al*., 2020)	Expert Review	5			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
Screening						
4. Individuals with abdominal obesity and ≥1 additional metabolic risk factors, such as prediabetes, T2DM, cardiovascular disease, abnormal liver function tests, hepatic steatosis, and high plasma aminotransferase levels (over 6 months) should be considered as a "high-risk" group. Screening for MASLD/MASH and advanced fibrosis is recommended for this "high-risk" group.	High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels (Portillo-Sanchez *et al*., 2015)	Cross-sectional study	2b	High	100%	
	Systematic review of existing guidelines for NAFLD assessment (Monelli *et al*., 2021)	SLR	1a			
	The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments (Targher *et al*., 2021)	Review	5			
	Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)(Tacke *et al*., 2024)	CPG of (EASL) EASD, and (EASO)EASL	1a			
5. Individuals undergoing bariatric surgery should be evaluated for the presence and severity of MASLD/MASH. A liver biopsy may be recommended if pre-surgical stratification suggests an indeterminate or high risk of liver fibrosis.	Prevalence of Non-alcoholic Fatty Liver Disease and Steatohepatitis Risk Factors in Patients Undergoing Bariatric Surgery (Morita *et al*., 2015)	Prospective study	2b	High	60%	Modified Statement: 100%
	Evaluation of Liver Function Tests and Risk Score Assessment to Screen Patients for Significant Liver Disease Prior to Bariatric and Metabolic Surgery (Antipass *et al*., 2020)	Retrospective Study	2b			
	The Prevalence of NAFLD and Fibrosis in Bariatric Surgery Patients and the Reliability of Noninvasive Diagnostic Methods (Soresi *et al*., 2020)	Retrospective Study	2b			
	American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD) (Cusi *et al*., 2022)	CPG of AASLD	1a			
Screening methods–Noninvasive tests						
6. Serum aminotransferases or liver ultrasound tests to assess liver diseases are not sensitive enough to assess MASLD and the related disease severity, hence not recommended as a screening method for MASLD.	Non-invasive testing and risk-stratification in patients with MASLD (Zoncapè *et al*., 2024)	Review	5	Moderate	80%	
	High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels (Portillo-Sanchez *et al*., 2015)	Cross-sectional study	2b			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
7. Multiple NITs such as FIB-4 score, APRI, FAST, and NFS score have been evaluated with variable performance. These NITs are recommended to confirm that there is no advanced fibrosis in the MASLD population.	AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review (Wattacheril *et al*., 2023)	Expert Review	5	Moderate	100%	
	Performance of non-invasive fibrosis scores in non-alcoholic fatty liver disease with and without morbid obesity (Drolz *et al*., 2021)	Retrospective Study	2b			
	Utility of FibroScan-based scoring systems to narrow the risk group of nonalcoholic fatty liver disease with comorbidities (Miura *et al*., 2022)	Cross-sectional Study	2b			
	FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study (Newsome *et al*., 2020)	Prospective Study	2b			
8. In adults with MASLD, a multi-step approach for assessing fibrosis is recommended. The FIB-4 test should be the first line of assessment for practitioners due to its simplicity, low cost, and easy availability.	Low Accuracy of FIB-4 and NAFLD Fibrosis Scores for Screening for Liver Fibrosis in the Population (Graupera *et al*., 2022)	Cross-sectional Study	2b	Moderate	93.33%	
	Non-invasive tests for liver fibrosis in NAFLD: Creating pathways between primary healthcare and liver clinics (Castera, 2020)	Review	5			
9. FIB-4 is recommended as it is the most validated calculation, and its incorporation in HSI will be beneficial in identifying patients with advanced fibrosis.	AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review (Wattacheril *et al*., 2023)	Expert review	5	Moderate	100%	
	EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis and update (Berzigotti *et al*., 2021)	EASL CPG	1a			
10. Patients in the intermediate or high-risk group are recommended to undergo additional evaluation for advanced fibrosis prediction using various NITs like LSM, ELF test, and MRE.	FIB-4 Improves LSM-Based Prediction of Complications in Overweight or Obese Patients With Compensated Advanced Chronic Liver Disease (Mendoza *et al*., 2022)	Retrospective Cohort Study	2b	Moderate	100%	
	Low Accuracy of FIB-4 and NAFLD Fibrosis Scores for Screening for Liver Fibrosis in the Population (Graupera *et al*., 2022)	Cross-sectional Study	2b			
	Analytical performance of the Enhanced Liver Fibrosis (ELF) Test on the Atellica IM Analyzer (Palladino *et al*., 2023)	Analytical Validation Study	4			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
	Magnetic Resonance-Based Assessments Better Capture Pathophysiologic Profiles and Progression in Nonalcoholic Fatty Liver Disease (Choi *et al*., 2021)	Cross-sectional Study	2b			
11. Clinicians should prefer the use of LSM to stage the risk of fibrosis in patients with MASLD, as it is best validated to identify the advanced disease and predict liver-related outcomes preferentially in patients at risk of advanced liver fibrosis.	New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD (Boursier *et al*., 2019)	Prospective Study	2b	Moderate	100%	
	Monitoring Occurrence of Liver-Related Events and Survival by Transient Elastography in Patients With Nonalcoholic Fatty Liver Disease and Compensated Advanced Chronic Liver Disease (Petta *et al*., 2021)	Retrospective Study	2b			
	Repeated liver stiffness measurement compared with paired liver biopsy in patients with non-alcoholic fatty liver disease (Kamarajah *et al*., 2018)	Longitudinal Study	2b			
Screening of patients with different comorbidities and fibrosis stages and linkage to care						
12. Patients with T1D along with cardiometabolic risk factors (such as obesity), features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis (on imaging) are recommended to be screened for MASLD with clinically significant fibrosis (stages F2–F4) using FIB-4 score.	The Utility of Noninvasive Scores in Assessing the Prevalence of Nonalcoholic Fatty Liver Disease and Advanced Fibrosis in Type 2 Diabetic Patients (Singh *et al*., 2018)	Retrospective Study	2b	Moderate	100%	
	Shear Wave Elastography Reveals a High Prevalence of NAFLD-related Fibrosis even in Type 1 Diabetes (Meyer *et al*., 2022)	Observational Study	2b			
	American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD) (Cusi *et al*., 2022)	AACE CPG	1a			
13. We recommend that patients with MASLD with LSM values <8 kPa (low-risk group) should undergo repeat surveillance testing in 2–3 years, whereas those with LSM ≥8 kPa (intermediate-risk group) should have a liver biopsy or MRE for monitoring with a re-evaluation of risk in 2–3 years, and those with LSM >12 kPa (high-risk group) should be immediately referred to hepatologists.	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5	Moderate	86.67%	
	Embedding assessment of liver fibrosis into routine diabetic review in primary care (Mansour *et al*., 2021)	Real-world Cohort Study	2b			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
Risk categories						
14. Patients in low-risk categories (FIB-4 <1.3, ELF <7.7, LSM <8.0 kPa) are recommended to be managed by their PCPs regularly during follow-up in the primary healthcare setting.	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5	High	93.33%	
	Combination of Fibrosis-4, liver-stiffness measurement, and Fibroscan-AST score to predict liver-related outcomes in nonalcoholic fatty liver disease (Wong *et al*., 2023)	Retrospective Cohort Study	2b			
	AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease (Rinella *et al*., 2023b)	Practice Guideline	1a			
	Identification of high-risk subjects in nonalcoholic fatty liver disease (Stern and Castera, 2023)	Review	5			
	Guideline-based management of metabolic dysfunction-associated steatotic liver disease in the primary care setting (Allen *et al*., 2024)	Review	5			
15. Patients with an LSM score of 8 kPa– 12 kPa are considered to be in "intermediate risk" group. It is recommended that the "intermediate risk" group should be referred to gastroenterologists/ hepatologists where liver biopsy, sequential LSM, or MRE can be performed to confirm the risk status or disease stage.	Clinical Application of Transient Elastography in the Diagnosis of Liver Fibrosis: an Expert Panel Review and Opinion (Expert Panel on Liver Stiffness, 2014)	Expert Panel Review	5	Low	100%	
	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5			
16. Patients with FIB-4 score ≥2.67, LSM >12 kPa, ELF >1.5, or MRE >5.0 kPa are considered to be at high risk and should be immediately referred to hepatologists.	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5	Moderate	93.33%	
	FIB-4 Improves LSM-Based Prediction of Complications in Overweight or Obese Patients With Compensated Advanced Chronic Liver Disease (Mendoza *et al*., 2022)	Retrospective Cohort Study	2b			
	Guideline-based management of metabolic dysfunction-associated steatotic liver disease in the primary care setting (Allen *et al*., 2024)	Review	5			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
17. We recommend that liver biopsy should generally be avoided in the management of patients with MASLD, except in specific circumstances where it is advised, namely:	The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases (Chalasani *et al*., 2018)	Practice Guidance	1a	High	100%	
a) To confirm the diagnosis of steatohepatitis b) When a discrepancy exists between NITs and clinical findings indicating advanced fibrosis	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5			
c) When there is a possibility of other concurrent liver diseases.	Transient elastography for the prevalence of non-alcoholic fatty liver disease in patients with type 2 diabetes: Evidence from the CORDIAL cohort study (Alfadda *et al*., 2022)	Longitudinal Cohort Study	2b			
Hepatocellular carcinoma surveillance						
18. Regular severe fibrosis/HCC surveillance is recommended for patients with FIB-4 score >2.67, LSM >16.1 kPa, and MRE >5.0 kPa.	AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review (Loomba *et al*., 2020)	Expert Review	5	Low	100%	
	Hepatic Outcomes of Nonalcoholic Fatty Liver Disease Including Cirrhosis and Hepatocellular Carcinoma (Alqahtani *et al*., 2023)	Review	5			
19. While noncirrhotic MASH may be associated with HCC, routine screening is not recommended for patients without severe MASLD-related fibrosis (<F3); however, HCC surveillance should be considered in adults with severe fibrosis (F3 stage) determined by noninvasive markers or liver biopsy following an individual risk assessment.	Surveillance of Hepatocellular Carcinoma in Nonalcoholic Fatty Liver Disease (Sumida *et al*., 2020)	Review	5	Moderate	93.33%	
	Surveillance for Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease: Universal or Selective? (Plaz Torres *et al*., 2020)	Review	5			
	Saudi Association for the Study of Liver diseases and Transplantation practice guidelines on the diagnosis and management of hepatocellular carcinoma (Alqahtani *et al*., 2020)	Practice Guidelines SASLT	1a			
First-line treatment recommendations for MASLD/MASH						
20. A multidisciplinary treatment approach (including PCPs, endocrinologists, hepatologists/gastroenterologists, and cardiologists) is recommended owing to the multidirectional connections between MASLD and cardiometabolic comorbidities to improve both liver-related and extrahepatic outcomes.	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a	High	100%	
	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
21. Patients with excess body fat and MASLD should be recommended for lifestyle modifications including participating in structured and customized exercise programs, adopting better eating habits and a healthy diet (with less saturated fat and starch), aiming for weight loss (at least 5%, or ideally more than 10%), and controlling MetS-associated cardiometabolic issues.	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a	High	93.33%	
	Positive Effects of Exercise Intervention without Weight Loss and Dietary Changes in NAFLD-Related Clinical Parameters: A Systematic Review and Meta-Analysis (Babu *et al*., 2021)	SLR	1a			
	Evidence-based clinical advice for nutrition and dietary weight loss strategies for the management of NAFLD and NASH (Hydes *et al*., 2020)	Review	5			
22. In normal-weight adults with MASLD, diet and exercise interventions are recommended to reduce liver fat	Weight change and resolution of fatty liver in normal weight individuals with nonalcoholic fatty liver disease (Sinn *et al*., 2021)	Longitudinal Study	2b	Moderate	93.33%	
Pharmacotherapy recommendations for MASLD/MASH						
23. Pioglitazone (usually 15 mg–30 mg daily for 6–12 months) has shown benefits in patients with T2DM and obesity. Hence, pioglitazone is recommended for patients with T2DM with biopsy-proven MASH and advanced fibrosis.	Response to pioglitazone in non-alcoholic fatty liver disease patients with vs. without type 2 diabetes: A meta-analysis of randomized controlled trials (Wang *et al*., 2023)	Metanalysis of RCTs	1a	High	80%	
	AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review (Loomba *et al*., 2020)	Expert Review	5			
	AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease (Rinella *et al*., 2023b)	CPG	1a			
24. GLP-1 RAs, pioglitazone, or SGLT-2 inhibitors may be considered for patients with T2DM and MASLD to provide cardiometabolic benefits; however, due to limited evidence supporting their effectiveness in treating steatohepatitis specifically, their recommendation for this purpose is restricted.	New anti-diabetic agents for the treatment of non-alcoholic fatty liver disease: a systematic review and network meta-analysis of randomized controlled trials (Kongmalai *et al*., 2023)	SLR and Metanalysis of RCTs	1a	High	73.33%	Experts decided to remain with 73.3% consensus and go ahead with the statement finalization
	AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease (Rinella *et al*., 2023b)	CPG	1a			
	Consensus statement from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Fundación Clínica Médica Sur, A.C. (Iorga *et al*., 2020)	Review	5			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
25. For patients with MASLD/MASH and a BMI >27 kg/m^2, T2DM, cardiovascular disease, or other obesity-related conditions, GLP-1 RAs (semaglutide 2.4 mg/week or liraglutide 3 mg/day) are recommended alongside lifestyle interventions, while dual GIP receptor and GLP-1 RAs (such as tirzepatide) for obesity and oral resmetirom (80–100 mg daily) for MASH with liver fibrosis may be considered; however, further research and real-world evidence are needed before fully recommending these drugs in clinical practice.	Evidence-based clinical advice for nutrition and dietary weight loss strategies for the management of NAFLD and NASH (Hydes *et al*., 2020)	Review	5	Moderate	73.33%	The final statement achieved 73.3% consensus among the expert panel and was subsequently ratified for inclusion in the recommendations
	Next Generation Antiobesity Medications: Setmelanotide, Semaglutide, Tirzepatide and Bimagrumab: What do They Mean for Clinical Practice? (Ryan, 2021)	Review	5			
	Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis (Loomba *et al*., 2024)	RCT	1a			
	A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis (Harrison *et al*., 2024)	RCT	1a			
26. Insufficient evidence of effectiveness, restrict the use of metformin, acarbose, dipeptidyl peptidase IV inhibitors, UDCA, and insulin. These drugs are not recommended for treating steatohepatitis (with no impact on hepatocyte necrosis or inflammation).	AGA Clinical Practice Update on Screening and Surveillance for Hepatocellular Carcinoma in Patients With Nonalcoholic Fatty Liver Disease: Expert Review (Loomba *et al*., 2020)	Expert Review	5	High	93.33%	
	Twelve week liraglutide or sitagliptin does not affect hepatic fat in type 2 diabetes: a randomised placebo-controlled trial (Smits *et al*., 2016)	RCT	1b			
	Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. (Musso *et al*., 2012)	SLR and Metanalysis of RCTs	1a			
27. Vitamin E (800 mg orally once daily for 12 weeks) can be considered for the treatment of patients with MASH without T2DM for steatosis reversal, improvement in the degree of fibrosis, and ALT reduction. However, insufficient evidence of its effectiveness in improving MASH with T2DM and advanced fibrosis restricts its recommendation in such patients.	Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease (Kanwal *et al*., 2021)	Review	5	High	93.33%	
	Response to pioglitazone in non-alcoholic fatty liver disease patients with vs. without type 2 diabetes: A meta-analysis of randomized controlled trials (Wang *et al*., 2023)	Metanalysis of RCTs	1a			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
Option of bariatric surgery						
28. It is recommended for clinicians to consider bariatric surgery as an option to treat MASLD and improve cardiometabolic health in patients having a BMI of ≥35 kg/m^2 with comorbidities (≥35–39.99 kg/m^2 in Saudi Arabia populations) and ≥40 kg/m^2 even without comorbidities in Saudi Arabia populations. However, for patients with well-compensated cirrhosis, a multidisciplinary team review is essential before proceeding with surgery. In cases of decompensated cirrhosis, bariatric surgery is contraindicated unless it is performed concurrently with liver transplantation.	American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD) (Cusi *et al*., 2022)	AACE Guidelines	1a	High	86.67%	
	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a			
	Bariatric surgery for non-alcoholic fatty liver disease: Indications and post-operative management (Geerts and Lefere, 2023)	Review	5			
29. Clinicians should be careful when considering bariatric surgery for patients with MASH and compensated cirrhosis. Bariatric surgeries are recommended to be personalized and performed at specialized centers involving a multidisciplinary team.	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a	High	93.33%	
	American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD) (Cusi *et al*., 2022)	AACE Guidelines	1a			

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Supplementary Table 1: Contd...

Statements	Evidence	Study type	Level of Evidence	Grade of Evidence	Round 1 Voting Consensus (%)	Round 2 Voting Consensus (%)
30. Endoscopic bariatric surgery and metabolic therapies, as well as orally ingested devices, are not currently recommended for patients with MASLD due to insufficient clinical evidence.	Endoscopic Bariatric and Metabolic Therapies and Their Effects on Metabolic Syndrome and Non-alcoholic Fatty Liver Disease - A Systematic Review and Meta-Analysis (Lee *et al*., 2022)	SLR and Metanalysis	1a	High	93.33%	
	Bariatric endoscopic-surgical therapies for NAFLD. Should they be considered viable options among current treatments? (Juárez-Hernández *et al*., 2022)	Review	5			
	American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD) (Cusi *et al*., 2022)	AACE Guidelines	1a			
Liver transplantation in MASLD/MASH						
31. Adults with MASLD are at increased risk of major cardiovascular events in the pre-, peri- and post-transplant phases. Hence, a multidisciplinary management or integrated comprehensive care approach to MASH and MASH-associated comorbidities is recommended to reduce morbidity and mortality in patients with MASH before and after liver transplantation.	EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) (Tacke *et al*., 2024)	CPG of (EASL), EASD, and (EASO)EASL	1a	Moderate	100%	
	Liver transplantation for non-alcoholic fatty liver disease: indications and post-transplant management (Battistella *et al*., 2023)	Review	5			
32. In transplant recipients with MASH or recurrent/high risk of *de novo* MASLD, it is recommended to prevent weight gain, with lifestyle modification being the first line of therapy. Modification of immunosuppressive regimen to optimize management of comorbid metabolic complications and use of therapeutic interventions to control cardiometabolic complications are also recommended.	Factors Impacting Survival in Those Transplanted for NASH Cirrhosis: Data From the NailNASH Consortium (Rinella *et al*., 2023c)	Retrospective Cohort Study (Observational)	2b	Moderate	100%	
	Liver transplantation for non-alcoholic fatty liver disease: indications and post-transplant management (Battistella *et al*., 2023)	Review	5			
	Management of Recurrent and De Novo NAFLD/NASH After Liver Transplantation (Germani *et al*., 2019)	Review	5			
	EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) (Liver *et al*., 2024)	CPG	1a			

ALT: Alanine transaminase; APRI: AST to platelet ratio index; BMI: Body mass index; ELF: Enhanced Liver Fibrosis (Test); FAST: FibroScan-AST (Score); FIB-4: Fibrosis-4 (Index); GIP: Glucose-dependent insulinotropic polypeptide; GLP-1 RAs: Glucagon-like peptide-1 receptor agonists; HCC: Hepatocellular carcinoma; HIS: Hepatic Steatosis Index; IV: Intravenous; LSM: Liver Stiffness Measurement; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; MetS: Metabolic syndrome; MRE: Magnetic resonance elastography; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; NFS: NAFLD Fibrosis Score; NITs: Non-invasive tests; PCPs: Primary care physicians; SGLT-2: Sodium-glucose co-transporter-2; SLD: Steatotic liver disease; T1D: Type 1 diabetes; T2DM: Type 2 diabetes mellitus; UDCA: Ursodeoxycholic acid

Supplementary Table 2: Oxford Grading System

1A.

Level of Evidence	Therapy/prevention, etiology/harm	Prognosis
1a	Systematic review (with homogeneity) of randomized controlled trials (RCTs)	Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual RCT (with narrow confidence of interval [CI])	Individual inception cohort study with >80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or none case series
2a	Systematic review (with homogeneity) of cohort studies	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs.
2b	Individual cohort study (including low-quality RCTs; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" research and ecological studies	"Outcomes" research
3a	Systematic review (with homogeneity) of case–control studies	
3b	Individual case–control study	
4	Case series (and poor-quality cohort and case–control studies)	Case series (and poor-quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

1B

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	Very low	Any estimate of the effect is very uncertain. Expert opinion • No direct research evidence • One or more studies with very severe limitations