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Management of metabolic dysfunction–associated steatotic liver disease (MASLD)—An expert consensus statement from Indian diabetologists' perspective

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Abstract

In India, the increasing prevalence of diabetes and obesity poses a significant threat towards a surge in the incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD). Concomitant with the evolving guidelines, there is a need to direct and spread awareness among practicing diabetologists to identify and screen high-risk individuals for MASLD for timely management. Its asymptomatic nature and the evolving guidelines on diagnosis have hindered the precise estimates of MASLD in the high-risk group of individuals in a clinical setting. Therefore, an expert panel of diabetologists from India convened to review, discuss and document the approach towards screening, diagnosis and management of MASLD. Serum biomarkers, simple non-invasive tools and imaging techniques could direct the risk stratification of the patients. Early lifestyle interventions including weight loss and exercise are beneficial. The pharmacological landscape of drugs directed to insulin resistance, lipid metabolism, oxidative stress, inflammation, apoptosis and fibrogenesis pathways for the management of MASLD is expanding. In summary, the consensus statements are expected to serve as a useful guide in the screening and management of MASLD in the region and to direct a well-planned study design that could enhance the scientific value of these statements.

KEYWORDS
diabetologist, India, metabolic dysfunction-associated steatotic liver disease, prognosis scoring, risk stratification, screening, serum biomarkers, transient elastography, type 2 diabetes mellitus

1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a new unified nomenclature based on several factors, including a greater understanding of pathophysiology, the psychosocial impact of the earlier nomenclature and the emergence of newer therapeutic options. A re-evaluation of the existing guidelines is needed, taking into consideration all the abovementioned aspects. The term 'fatty liver' was introduced as early as 1836 by Thomas Addison.[1] Subsequent liver biopsy studies conducted between 1980 and 1990 revealed non-alcoholic fatty infiltration in the liver. This research led to the introduction of the term non-alcoholic steatohepatitis (NASH) in 1980 by Ludwig and colleagues.[2] In 1987, Schaffner and Thaler further refined the terminology and coined the term non-alcoholic fatty liver disease (NAFLD) to describe milder cases of steatosis.[3]

Recent pathophysiology studies have linked obesity, dietary composition, ethnicity and genetic factors to the risk of NAFLD.[4,5] In 2020, an international consensus panel proposed the term 'Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)'.[6] This terminology encompassed liver disorders regardless of an individual's alcohol consumption pattern and amount.[6] Later on in 2023, taking cognizance of the stigmatization associated with the term 'fatty', the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) introduced the term 'Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)'.[7] Figure 1 illustrates the progression of nomenclature over the years, leading to the new nomenclature, MASLD. The concept of MASLD has evolved, reflecting on 'the hepatic manifestation of the metabolic syndrome'.[7] The diagnosis of MASLD first requires exclusion of liver disorders stemming from secondary causes with evidence of hepatic steatosis (>5%) along with the presence of at least one of five cardiometabolic criteria: overweight/obesity, prediabetes/diabetes mellitus (DM), high triglycerides, low high-density lipoprotein (HDL) or hypertension.[7] While the term NAFLD limited the focus primarily to gastroenterologists,[8] MASLD broadens the scope for involvement of other healthcare practitioners (HCPs), encouraging collaborative

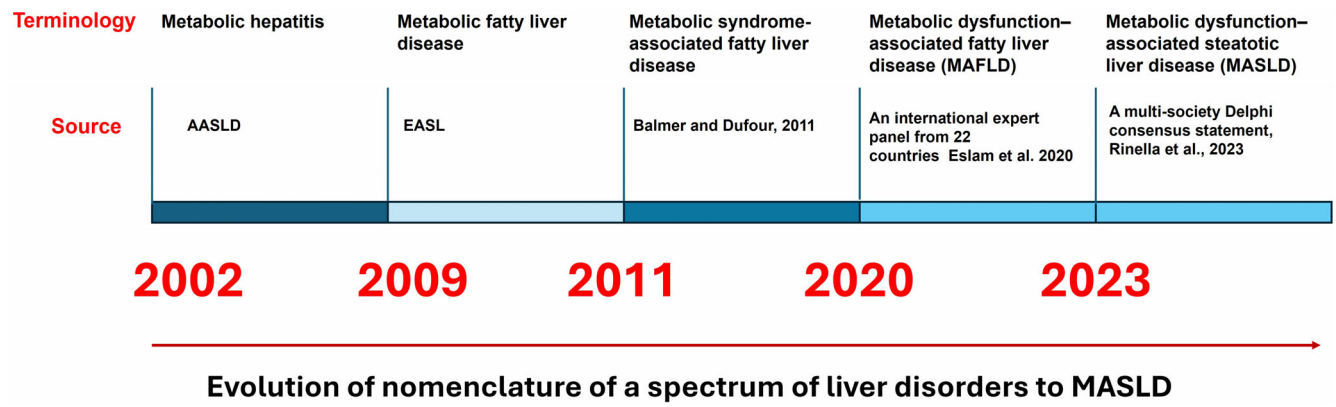


FIGURE 1 Timelines and the evolution of nomenclature from non-alcoholic fatty liver disease (NAFLD) and management of metabolic dysfunction–associated steatotic liver disease (MASLD). AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver.

TABLE 1 Prevalence estimates of metabolic dysfunction–associated steatotic liver disease (MASLD) across the globe.

	Population type	Prevalence	Reference
North America	General population	35.3%–47.8%	Teng et al., 2023[17]
Latin America	General population	24%	Rojas et al., 2022[18]
	Obese/Diabetes population	68%	Rojas et al., 2022[18]
Europe	General population	24%	Lazarus et al., 2021[19]
	Diabetes population	56.0%	Cholongitas et al., 2021[20]
Asia-pacific region	General population	29.8%	Younossi et al., 2023[21]
	Diabetes population	52.7%	Younossi et al., 2024[22]
Middle East and North Africa	General population	42.6%	Younossi et al., 2023[21]
	Diabetes population	68.7%	Younossi et al., 2023[21]
Sub-Saharan Africa	General population	13.5%	Spearman et al., 2021[23]
South-East Asia	General population	29.3%	Younossi et al., 2023[21]
	Diabetes population	45.2%–56.5%	Prasetya et al., 2013[24] Kalra, 2013[25]

efforts to enhance patient awareness, screening and detection.[9] Given that DM significantly heightens the risk of developing MASLD, diabetologists play a crucial role in the prevention, early diagnosis and management.[10] Research has shown a bi-directional relationship between type 2 diabetes mellitus (T2DM) and MASLD, with insulin resistance as a crucial factor in the pathophysiology of both disorders.[11] An association of visceral fat and physical inactivity with glucose intolerance and insulin resistance has been shown in several epidemiological studies from India.[12–14] Oxidative stress has also been shown to be independently associated with NAFLD in India.[15] The growing prevalence of diabetes and prediabetes in India also calls for a population-wide screening and investigation of MASLD.[16]

2 | PURPOSE OF THIS CONSENSUS

The increasing trend in the prevalence of obesity, diabetes and the associated risk of MASLD emphasizes the need to identify and screen the high-risk group of individuals to initiate timely management. Concomitant to the evolving definitions and the lack of guidelines for uniformity in the diagnostic criteria, the prevalence data of MASLD lack accuracy. Epidemiological studies from different countries, including India, report varying estimates influenced by diverse clinical symptoms, stages of disease manifestation and differences in the diagnostic modalities (Tables 1 and 2).

In essence, the underreporting of prevalence might have underestimated the realistic burden of MASLD, especially in the high-risk group of individuals in India. Therefore, a panel of diabetologists and endocrinologists from India convened to review the risk factors of MASLD and strategies to prevent and manage the condition in individuals at risk. The idea was to obtain consensus statements intended to serve as useful guidance for healthcare professionals in India from a diabetologists' perspective, specifically in the screening, management and clinical research of MASLD. In this paper, the terms NAFLD and MASLD have been used interchangeably in the context of discussion to reflect the time when specific guidelines or criteria were defined.

TABLE 2 Indian prevalence estimates of non-alcoholic fatty liver disease (NAFLD).

Reference	Study	Population	Prevalence
Mukherjee et al., 2024[26]	Single centre cross-sectional study	Newly diagnosed diabetes population of North Bihar, India	73.6%
Shalimar et al., 2022[27]	Meta-analysis	• Adult population • Children • Non-obese children • Obese children	• 38.6% (95% CI: 32–45.5) • 35.4% (95% CI 18.2–54.7) • 12.4 (95% CI 4.4–23.5) • 63.4 (95% CI 59.4–67.3)
Prabhakar et al., 2024[28]	Cross-sectional study	Population from randomly selected regions across Delhi	56.4%
Niriella et al., 2023[29]		• General population (heterogeneous) • Individuals with metabolic diseases • Non-obese population • Rural communities • Urban communities	• 26.9% • 54.1% • 11.7% • 22.6% • 32.9%
Kalra et al., 2022[30]	Retrospective observational study	Individuals with diabetes	44.5%
Chalmers et al., 2019[31]	Cohort	Population of Trivandrum district of Kerala, India	49.8%
Kalra et al., 2013[25]	Cohort	Individuals with T2DM	56.5%
Das et al., 2010[32]	Prospective epidemiological study	Adult population from rural part of west Bengal	8.7%
Mohan et al., 2009[33]	Epidemiology Study	Population from rural or urban communities of Chenani, India	32%

Abbreviation: T2DM, type 2 diabetes mellitus.

3 | METHODOLOGY

3.1 | Panel generation and statement development

The consensus panel was formed through a systematic and inclusive process, engaging diabetologists from various regions across India (Flowchart S1). The panel comprised 30 leading diabetologists and subject-matter experts.

3.2 | Execution of the consensus guidance development

The consensus method[7,34,35] followed a sequential process comprising the following steps: (1) topic selection (prevalence, associated risks, diagnosis and management), (2) expert group composition, (3) literature review, (4) formulation of statements and (5) peer review within the panel. The entire process was executed in three phases.

The first phase, held on 15 May 2024, involved a virtual meeting to define the topics, divide the panellists into groups and allocate topics for review. During the second phase, the panellists convened over a virtual meeting on 2 August 2024, where each group presented a detailed literature review and proposed statements relevant to the Indian clinical setting. Extensive discussions were held on the inferences and practicality of translating these findings to the Indian clinical scenario, and the meeting was recorded. Although formal voting was not conducted before and after the discussions, each consensus statement was finalized with the approval of all members present.

The agreed statements and evidence were then moved to the third phase, which involved an independent manuscript writing team. This team synthesized the presented literature evidence and statements into a manuscript draft. The draft was reviewed by all 30 panel members, who had volunteered to be co-authors, and approved in its entirety. There were three rounds of iterations, and the final draft was circulated to obtain consensus from the committee members.

4 | PREVALENCE OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

Statement 1. Differences in diagnostic modalities and clinical presentations have contributed to variations in epidemiological estimates. Given the evolution of clear diagnostic criteria, the epidemiological estimates of MASLD need to be revisited.

Statement 2. Concomitant with the increasing trend in obesity and diabetes, MASLD has emerged as a public health concern in the Indian population.

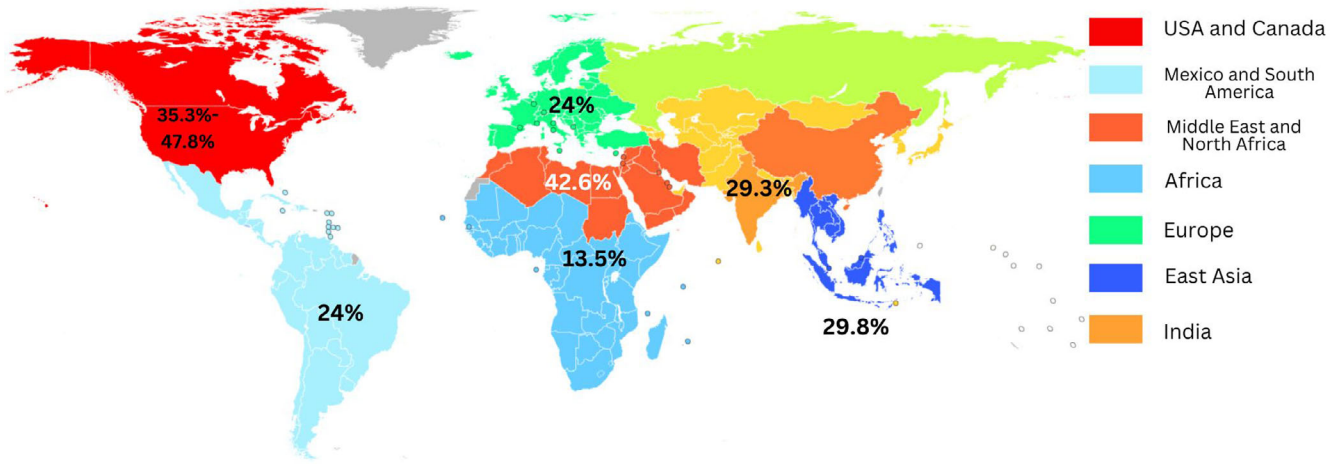


FIGURE 2 Global prevalence estimates of metabolic dysfunction–associated steatotic liver disease (MASLD). The percentages provided indicate the prevalence of MASLD in the corresponding regions.

Globally, the burden of MASLD has witnessed a significant rise, parallel with an increasing prevalence of obesity, insulin resistance, diabetes, dyslipidaemia and hypertension.[36,37] NAFLD prevalence is reported to range from 13% to 48% in the general population (Table 1; Figure 2), 45%–70% in individuals with T2DM (Table 1), and 27%–57% in clinic-based cohorts.[28,29,38,39] The association of MASLD with Type 1 diabetes mellitus (T1DM) has also been studied well globally and in India.[40] Admittedly, although the number of research publications has steadily increased over the last two decades, only a limited number of epidemiological studies on MASLD in India are available (Table 2).[41] Obviously, there is a need for more epidemiological data on MASLD in India. This calls for large-scale research collaboration among clinicians and researchers to develop well-defined guidelines for all aspects of MASLD. Among the Indian population, excessive and regular intake of carbohydrate-rich diet and the rise in physical inactivity have contributed to the rising threat of metabolic disorders and MASLD.[42,43] Recognizing the burden and the need for early diagnosis and management, in 2021, the Government of India has taken a conscientious initiative to include MASLD into its National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS).[27,44] Several directional efforts are being undertaken in the form of several studies and consensus statements towards guideline development for early diagnosis and prevention of MASLD burden in the country.[45,46]

4.1 | Remarks

In India, lack of infrastructure, non-availability of ultrasonography or FibroScan at many centres, lack of trained healthcare professionals, asymptomatic nature of the disease, variabilities in risk factors and lack of national screening programmes can contribute to the underestimation of the prevalence and burden of MASLD. A concerted effort is needed to create an elevated nationwide awareness backed by a population-wide screening programme. There is also a fresh need to extensively document the prevalence of MASLD through large epidemiological studies nationwide.

5 | PATHOGENESIS OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

The central theme in the pathogenesis of MASLD leading to the development of hepatic steatosis is the dysregulation of fatty acid metabolism in the liver, which disrupts the harmony of energy generation and lipid storage mechanisms (Figure 3). In the early 2000s, the pathogenesis of NAFLD was explained by the 'two-hit hypothesis' that attributes the development of fatty liver to (a) excessive hepatic lipid deposition and (b) subsequent activation of inflammatory cascades, oxidative stress and fibrogenesis in hepatocytes.[47] However, recent research paved the way for understanding more complex molecular and metabolic changes associated with a broader range of risk factors of NAFLD, leading to a 'multi-hit theory'.[47] This theory identifies insulin resistance, dietary influences, hyperglycaemia, dyslipidaemia, genetic predispositions and epigenetic modifications as lead factors.[47] MASLD is an outcome of ectopic fat accumulation in the liver due to adipocyte insulin resistance, thereby diverting free fatty acids from adipocytes to the liver. In contrast, metabolic dysfunction-associated steatohepatitis (MASH) is a result of toxic effects of accumulated lipids in the liver, referred to as hepatic lipotoxicity.

Genetically susceptible individuals with unfavourable environmental factors (inappropriate diet, lack of physical activity and air pollution) are at high risk for MASLD.[48,49] With respect to air pollution, recent studies from India have shown a strong association between $PM_{2.5}$ (particulate matter) levels and incident of type 2 diabetes,[50] lipid abnormalities[51] and hypertension.[52] These are key metabolic abnormalities in MASLD. Further studies are needed in India on the association of air pollution directly with MASLD. Biochemically, prolonged cumulative

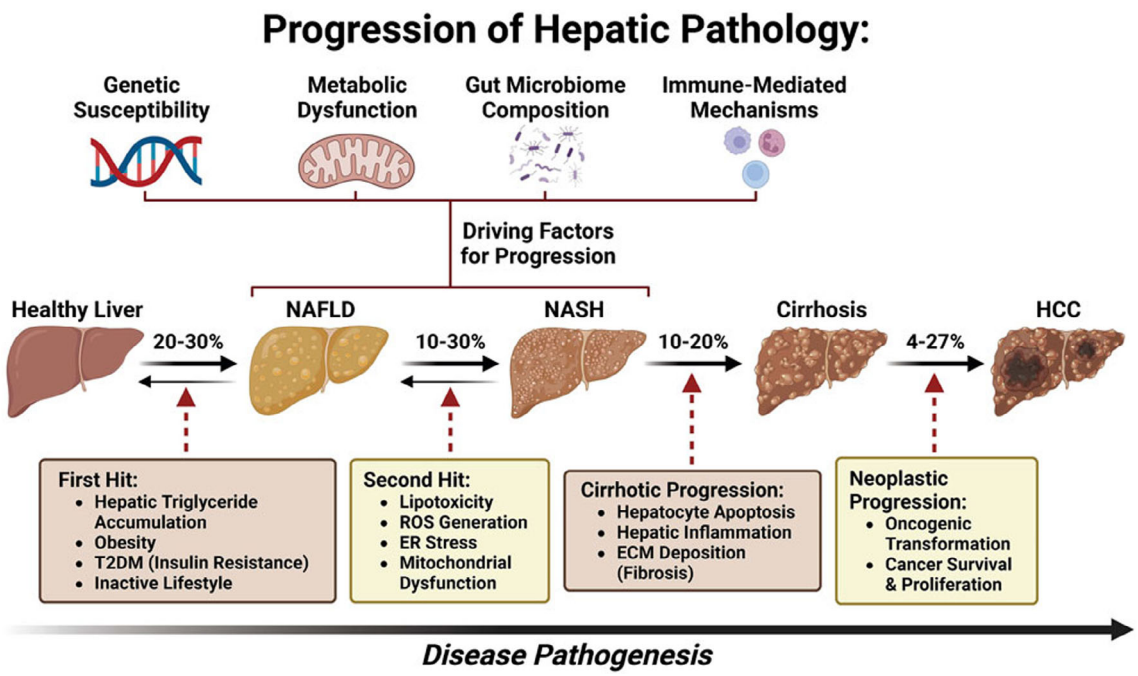


FIGURE 3 Pathophysiology of metabolic dysfunction–associated steatotic liver disease (MASLD). ECM, extracellular matrix; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus. Source: Reproduced from Wang Y, Fleishman JS, Li T, Li Y, Ren Z, Chen J, Ding M. Pharmacological therapy of metabolic dysfunction–associated steatotic liver disease-driven hepatocellular carcinoma. *Front Pharmacol*. 2024;14:1336216. doi: 10.3389/fphar.2023.1336216.

intake of excessive diet (>10% of energy requirement) can disrupt metabolic homeostasis[53] resulting in insulin resistance. Disinhibition of lipolysis occurs when there is insulin resistance in the adipose tissues, thereby increasing the circulation of free fatty acids in the blood and their delivery to the liver.[54] This augments hepatic de novo lipogenesis (DNL) due to the enhanced activity of two key enzymes—acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS)—that govern the rate-limiting steps of the DNL pathway. This lipotoxic environment in hepatocytes leads to endoplasmic reticulum stress and mitochondrial dysfunction associated with releasing reactive oxygen species.[55] Lipotoxicity can trigger immune cell infiltration in the liver, which can lead to DNA damage at a cellular level.[56] Insulin resistance also contributes to inflammation by promoting the secretion of pro-inflammatory cytokines in hepatocytes. Chronic inflammation can progress from NAFLD to NASH and fibrosis.[56]

There are several suggestions towards the pathophysiology of NAFLD in T1DM.[40]

1. Insulin resistance (IR).
2. Poor lipolysis leads to enhanced synthesis and attenuated clearance of triglycerides in the liver.
3. Blood glucose induces carbohydrate response element-binding protein (ChREBP) and sterol regulatory element-binding protein 1c (SREBP-1c), which can enhance lipogenesis.
4. Glucose transporter 2 (GLUT2) expression is upregulated, which increases glucose transportation and accumulation in hepatocytes.[40]

Research has also identified an association between suboptimal thyroid function, IR and metabolic syndrome with the pathophysiology of MASLD.[57] Thyromimetics activate nuclear thyroid hormone receptor-β (THR-β) mediated signalling in the liver to increase the expression of lipases, bile acid synthesis, lipophagy and mitophagy, leading to hepatic fat clearance.[57]

6 | SCREENING AND IDENTIFICATION OF PATIENTS

Statement 3. MASLD is not only present in obese individuals but also among healthy-weight individuals.

Statement 4. Individuals with at least 5% steatosis, with elevated liver enzyme profile, with a family history of a first-degree relative with liver cirrhosis, and overweight to obese individuals with, or without metabolic dysregulation, individuals with Type 2 diabetes or prediabetes may be followed up for evaluating the disease progression of MASLD.

Statement 5. Individuals with a history of polycystic ovarian syndrome, obstructive sleep apnoea, chronic kidney disease, history of cholecystectomy or HIV infection may be considered for screening of MASLD.

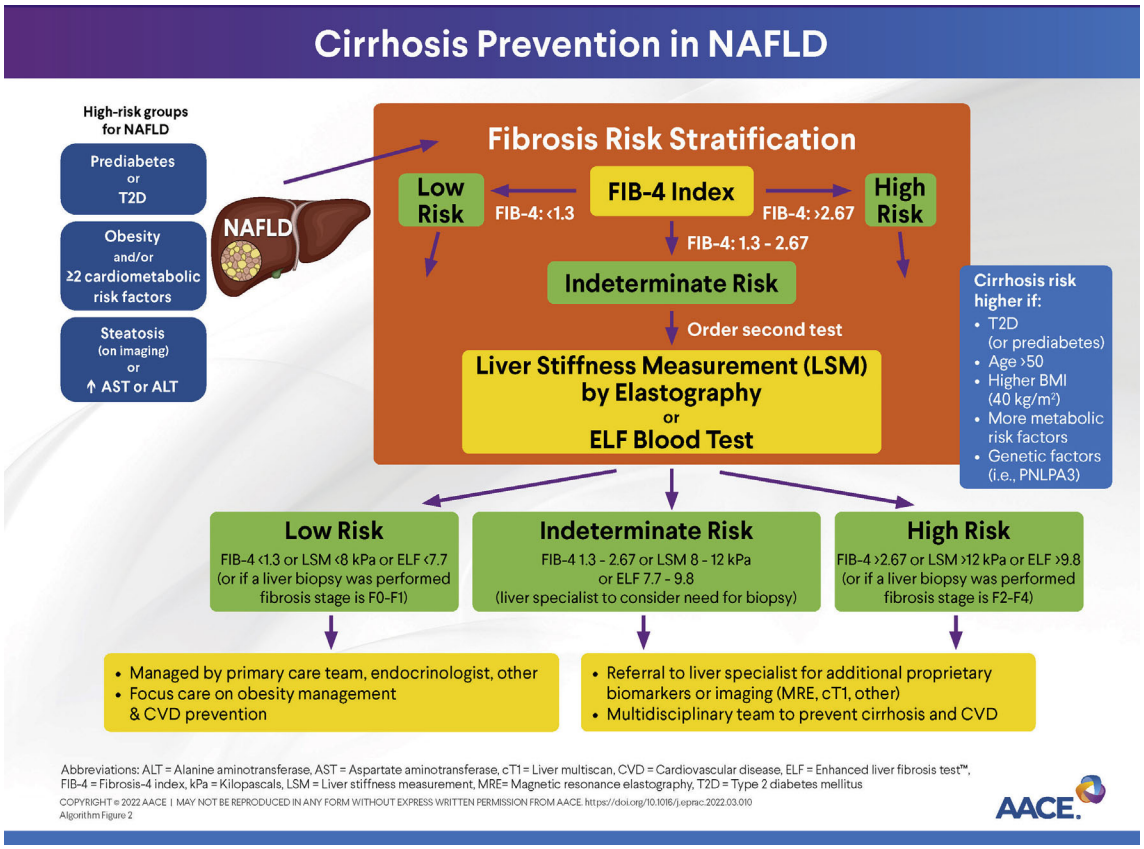


FIGURE 4 Risk stratification and diagnosis algorithm of metabolic dysfunction–associated steatotic liver disease (MASLD). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; cT1, liver multi-scan; CVD, cardiovascular disease; ELF, enhanced liver fibrosis test™; FIB-4, fibrosis-4 index; kPa, kilopascals; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; PNPLA3, patatin-like phospholipase domain-containing 3; T2D, type 2 diabetes. Source: Reprinted with permission from Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Non-alcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. 2022;28(5):528–562. Doi: 10.1016/j.eprac.2022.03.010.

6.1 | Who is at risk of developing metabolic dysfunction–associated steatotic liver disease?

In its preliminary stages, MASLD often presents without apparent symptoms. Many individuals do not undergo screening or seek medical attention unless symptoms such as abdominal discomfort, fatigue or abnormal liver function tests prompt further investigation. Contrary to earlier belief, MASLD is not only observed in obese or overweight individuals but also among those with a healthier weight (Figure 4).[58–61]

6.2 | Whom to screen for metabolic dysfunction–associated steatotic liver disease?[62–67]

Table 3 provides the factors and criteria to be considered while screening for MASLD.

6.3 | How to diagnose metabolic dysfunction–associated steatotic liver disease? (Figure 5)

Statement 6. Owing to their inherent limitations, the assessment of liver steatosis and fibrosis should rely on multiple modalities, including imaging and testing for serological markers. Fibrosis-index-4 [derived from age, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and platelet] is a useful prognostic tool for screening and risk stratification.

Statement 7. In Indian clinical practice, vibration-controlled transient elastography (VCTE) remains the best-validated imaging modality for the diagnosis and staging of disease progression of MASLD. Acoustic radiation force impulse (ARFI) imaging is an emerging tool for the diagnosis of MASLD.

TABLE 3 Factors to be considered while screening for disease progression of metabolic dysfunction–associated steatotic liver disease (MASLD).

Criteria
Anyone with liver steatosis on imaging
Unexplained elevation in liver enzymes (plasma aminotransferase levels [>30 U/L])
First-degree relative of a patient with MASLD/cirrhosis
Anyone with one or more of the following risk factors • Overweight or obese individuals (Asian Indian Body Mass Index criteria: BMI >23 kg/m^2). • Waist circumference ≥90 cm in men and ≥80 cm in women. • Prediabetes or type 2 diabetes (T2DM) or treatment for diabetes. • Plasma triglycerides ≥1.7 mmol/L (≥150 mg/dL) or on lipid lowering treatment. • HDL-cholesterol ≤1.0 mmol/L (≤40 mg/dL) in men and ≤1.3 mmol/L (≤50 mg/dL) in women or on lipid lowering treatment. • BP ≥130/85 mmHg or on treatment for hypertension.
Also, screen individuals with • Polycystic ovarian syndrome • Obstructive sleep apnoea • Chronic kidney disease • History of cholecystectomy • HIV infection

Abbreviations: BMI, body mass index; BP, blood pressure; HIV, human immunodeficiency virus; HDL, high-density lipoprotein; MASLD, metabolic dysfunction–associated steatotic liver disease.

Statement 8. A liver biopsy may be considered in individuals undergoing bariatric surgery, in those suspected of having a high risk for MASLD progression.

The diagnosis of MASLD is considered a diagnosis of exclusion. This means that it is crucial to rule out other liver disorders by testing for plasma iron, ferritin, total iron-binding capacity, ceruloplasmin, alpha-1 antitrypsin level, the absence of hepatitis B, hepatitis C, anti-mitochondrial antibodies, IgG levels, anti-nuclear antibody, autoimmune hepatitis and anti-tissue transglutaminase antibody.[68] The individual can be evaluated for steatosis or fibrosis after screening based on clinical suspicion and the patient's history. Standard biochemical tests can guide this assessment to measure changes in serum liver enzyme levels, supplemented with imaging techniques. The role of ultrasonography, especially in detecting hyperechoic liver, is high, with 85% sensitivity and 95% specificity, although it has a low sensitivity among those with significant obesity.[69] To assess hepatic fibrosis (including steatohepatitis and cirrhosis), non-invasive scores, vibration-controlled transient elastography (VCTE), imaging technology, serum biomarkers (direct and indirect) and liver biopsy are employed.[62] Table 4 provides a list of markers of fibrogenesis and fibrinolysis. Indirect markers detect alterations in hepatic function that do not directly reflect the changes in the extracellular matrix metabolism. Direct markers indicate extracellular matrix turnover and fibrosis.[70] Serologic testing and ultrasound-based transient elastography (TE) are used for increased sensitivity and specificity.[62,69,71]

Prognostic scoring systems such as fibrosis 4 (FIB-4) score, NAFLD Fibrosis Score (NFS) and AST to Platelet Ratio Index (APRI) remain valuable tools for predicting liver-related outcomes and mortality (Table 5). The FIB-4 score, which includes age, AST, ALT and platelet count, provides a reliable estimate of liver fibrosis and progression risk.[72] Similarly, the NFS and APRI scores help assess the severity of liver disease and predict adverse outcomes. These scoring systems are crucial for stratifying patients and guiding clinical decision-making, complementing other diagnostic and prognostic methods.[73]

6.4 | Imaging modalities for diagnosis of metabolic dysfunction–associated steatotic liver disease

Elastography estimates liver stiffness by monitoring the extent of propagation of mechanical waves through tissues. It can be ultrasound-based [TE, acoustic radiation force impulse (ARFI) imaging, strain elastography] or magnetic resonance-based MRI [magnetic resonance elastography (MRE)]. Transient elastography (TE) is commonly used to measure the speed of shear waves.

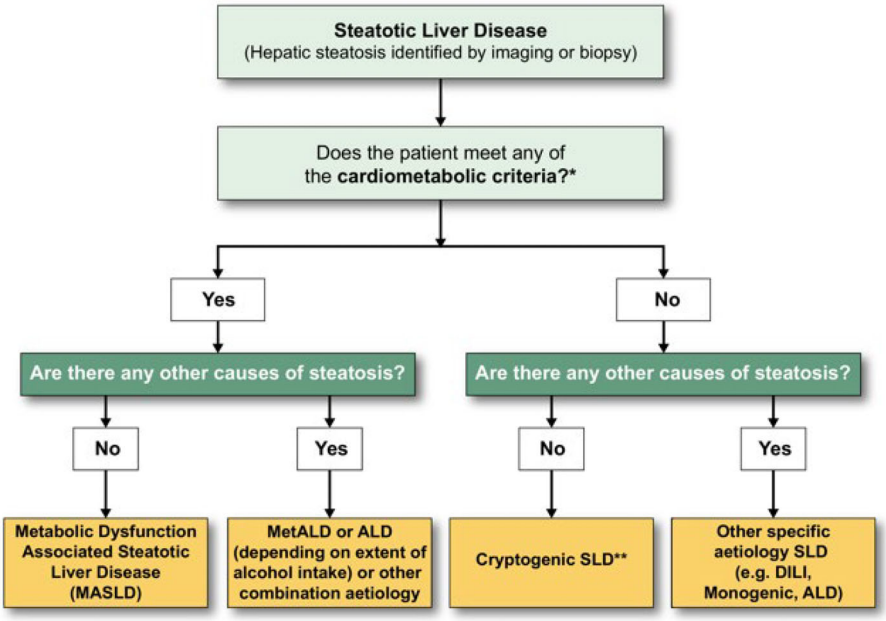
6.5 | Transient elastography

Vibration-controlled transient elastography (VCTE) is a 1-D technique performed using a FibroScan that uses a mechanical external push for shear wave imaging to estimate liver stiffness.[74] The results are presented as liver stiffness measurement (LSM) in kPa and controlled attenuation parameter (CAP) in dB/m. The system offers flexibility to toggle between three probes (M, S, XL) that operate at different ultrasound frequencies for different measurements or use in children.[74] In a cohort study of 16 603 patients, the performance of VCTE-based scores was better than most non-invasive scores and was similar to histologic findings of fibrosis staging.[75] With repeated evaluations, scores remained generally consistent, and individuals who demonstrated improvement exhibited a markedly lower risk of liver-related events.[75]

6.6 | Acoustic radiation force impulse imaging

Acoustic radiation force impulse (ARFI) imaging is a non-invasive ultrasound technique used to assess liver stiffness.[76] It can help distinguish between various stages of liver disease, aiding in early detection and management of MASLD. It measures tissue elasticity by generating mechanical shear waves, providing quantitative data on fibrosis. There are two types of ARFI: point shear wave elastography and 2-D shear wave elastography.[76] ARFI elastography demonstrated a sensitivity of 82% and specificity of 85% in detecting liver fibrosis, correlating well with histopathological findings.[77] Figure 5 showcases the algorithms for the diagnosis of MASLD.

(A)



(B)	Cardiometabolic criteria (at least 1 out of the following 5 criteria) for Asian Indian adults
1	BMI >23 Kg/m^2 or waist circumference ≥90 cm (M) ≥80 cm (F)
2	Fasting serum glucose ≥ 100 mg/dL or 2-hour post-load glucose levels ≥140 mg/dL, HbA1c ≥5.7% Type 2 diabetes or treatment for type 2 diabetes
3	Blood pressure ≥130/85 mmHg or on specific antihypertensive drug treatment
4	Plasma triglycerides ≥150 mg/dL or on lipid lowering treatment
5	Plasma HDL-cholesterol ≤40 mg/dL (M) and ≤50 mg/dL (F) or lipid lowering treatment

FIGURE 5 (A) Screening criteria for metabolic dysfunction–associated steatotic liver disease (MASLD).[7] (B) Cardiometabolic criteria for Asian Indian adults. ALD, alcohol-related liver disease; BMI, body mass index; BP, blood pressure; DILI, drug-induced liver injury; F, female; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; M, male; MetALD, metabolic dysfunction and alcohol-related liver disease; SLD, steatotic liver disease; WC, waist circumference. Source: (a) Reprinted with permission from Rinella ME, Lazarus JV, Ratziu V, et al. NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology*. 2023;78(6):1966–1986. Doi: 10.1097/HEP.0000000000000520. Epub 2023 Jun 24.

7 | MANAGEMENT OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

7.1 | Early interventions—lifestyle modifications

Statement 9. Weight loss is associated with reversal of steatosis and regression of steatohepatitis.

The first and most important steps in the management of MASLD are intensive lifestyle modification. Indeed, weight loss management through lifestyle modifications is the cornerstone of treatment in MASLD patients. Quantitatively, a weight loss of ≥5%, 7%–10% and ≥10%, is associated with a reduction in steatosis, an improvement in steatohepatitis and an improvement in fibrosis, respectively.[78]

7.2 | Diet and exercise

Diet and exercise reduce liver fat in normal-weight individuals with MASLD. Dietary changes such as adopting a low-calorie, low-fat, low-glycaemic index diet and increased physical activity have been shown to reverse early histologic damage associated with MASLD.[79] The

TABLE 4 Markers of fibrogenesis and fibrinolysis.[59]

Matrix deposition	Matrix degradation
Procollagen I peptide	MMP-2
Procollagen III peptide	TIMP-1, -2
Type I collagen	Cytokines
Type IV collagen	TGF-beta
YKL-40 (chondrex)	TGF-alpha
Laminin	PDGF
Hyaluronic acid	

Abbreviations: MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase.

typical Indian diet predominantly consists of cereals and whole grains (50%–70%), while often falling short of the recommended intake of proteins, fruits and vegetables.[43,80] According to the EAT-LANCET Commission report, the diet across different Indian states and income groups is largely unhealthy.[43] In the Indian population, the Indian Council of Medical Research-National Institute of Nutrition (ICMR-NIN) recommends minimizing the consumption of ultra-processed foods and foods high in fat, sugar and salt to reduce the risk of non-communicable diseases.[80] The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study, one of the largest epidemiological assessments of metabolic non-communicable diseases (NCDs) in India, revealed that approximately 101 million people are living with diabetes and 136 million with prediabetes.[81] Additionally, the study found a high prevalence of abdominal obesity (351 million individuals) and hypertension (315 million individuals).[81] Dietary analysis from the study indicated an excessively high carbohydrate intake, comprising 60%–70% of total energy, while consumption of protein and dietary fibre was low.[82] The study estimated that substituting 10%–15% of refined carbohydrates—particularly those with a high glycaemic index—with protein sources (preferably plant-based) and incorporating healthy fats such as monounsaturated and polyunsaturated fats may significantly contribute to lowering the burden of metabolic NCDs in India, particularly type 2 diabetes.[82,83]

Mediterranean diets, characterized by a high intake of olive oil (rich in monounsaturated fatty acids) and fish (rich in omega-3 polyunsaturated fatty acids) and vegetarian diets that are rich in dietary fibre, polyphenols, folate and carotenoids, offer hepatic benefits in MASLD and provide cardiovascular protection as well.[84] Conversely, diets high in red and processed meats (which are rich in saturated fats), as well as sugars (particularly fructose) have been linked to the development of MASLD.[84]

According to a recent World Health Organization (WHO) report, the extent of insufficient physical activity has almost doubled among the Indian population from 22% in 2000 to 49% in 2022.[43] This further contributes to the disease burden of the country. Regular physical activity improves body composition, enhances insulin sensitivity in the liver and adipose tissues and may exert benefits independent of weight loss. Combining aerobic exercise and resistance training reduces steatosis and improves cardiometabolic outcomes.[85] Exercise has been shown to increase butyrate production, which supports colonic epithelial cell health, enhances mucosal immunity and reduces pathogens. It also boosts primary bile acid secretion, promotes cholesterol turnover, fosters the growth of beneficial bacteria and affects gut transit time and substrate delivery to the microbiota. Evidence for the positive effects of nutraceuticals in the management of MASLD is lacking, although some studies suggest that an intake of ≥3 cups of coffee per day may be beneficial.[86]

8 | PHARMACOLOGICAL INTERVENTIONS

Statement 10. The pharmacological landscape for managing metabolic-associated steatotic liver disease (MASLD) is evolving. Currently, Resmetirom is approved for the treatment of MASH by US-FDA. In India, Saroglitazar is approved by the Drug Controller General of India (DCGI) for the treatment of MASLD and non-cirrhotic MASH. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as Semaglutide and others are considered as promising agents in the management of MASLD.

The drugs that have been used in the management of MASLD with no substantial supportive evidence for continued use include vitamin E, ursodeoxycholic acid, omega-3 polyunsaturated fatty acids, silymarin and orlistat.[87] A farnesoid X receptor (FXR) agonist, obeticholic acid, has some evidence to modulate bile acid synthesis and to improve insulin sensitivity, thus reducing hepatic steatosis.[88]

Several off-label medications such as metformin, GLP-1 RA, sodium-glucose cotransporter 2 (SGLT2) inhibitors, vitamin E, pioglitazone and ezetimibe have also been in use with levels that suggest some benefits. None of the existing anti-hyperglycaemic agents have proven direct hepatic benefits in MASLD. However, GLP-1 RA, pioglitazone, SGLT2i and metformin are preferred for treating hyperglycaemia in patients with T2DM and MASLD as they might have additional hepatic benefits. Insulin therapy is recommended in patients with decompensated cirrhosis.[62]

Promising agents that provide direct hepatic benefits include resmetirom (Table 6). Resmetirom has demonstrated improvement in hepatic fibrosis[88] and is approved by the Food and Drug Administration (FDA) for the treatment of NASH with fibrosis. Unlike other treatments, resmetirom does not target insulin resistance. As a partial agonist of THR-β, resmetirom promotes lipophagy and hepatic fatty acid β-oxidation, thereby reducing liver fat.[89,90] However, resmetirom is currently unavailable in India and poses a substantial economic burden.

In India, Saroglitazar (4 mg/day), a peroxisome proliferator-activated receptor (PPAR)-α/γ agonist, is approved for treating MASLD and MASH.[91,92] Its safety and efficacy were evaluated in a 52-week, double-blind, placebo-controlled, phase 3 clinical trial

TABLE 5 Scoring systems in metabolic dysfunction–associated steatotic liver disease.

Score	Application	Formula	Criteria
Fib-4 Index	Fibrosis scoring system and assessment of risk	$FIB-4=\frac{(Age(years)\ x\ AST(U/L))}{PLT\ (10^9/L)\ x\ \sqrt{ALT(U/L)}}$	• <1.3: low risk • 1.3–2.67: indeterminate risk • >2.67: high risk
APRI	Fibrosis scoring system	$APRI=\frac{(AST\ level/ULN)}{PLT\ (10^9/L)\ x\ 100}$	Ratio of AST/platelet count[a] • <0.5-low risk • 0.5–1.5: indeterminate risk • >1.5: high risk
NFS	Advanced fibrosis scoring system	*NAFLD fibrosis score* $=\frac{1.675+0.037*age+0.094*BMI\left(\frac{kg}{m^2}\right)+1.13*IFG}{Diabetes+0.99\left(\frac{AST}{ALT}\right)-0.013*PLT\ \left(\frac{10^9}{L}\right)-0.66*albumin\left(\frac{g}{l}\right)}$ Age in years; Diabetes: Yes = 1; No = 2	Advanced fibrosis • < −1.455: low risk • −1.455–0.675: intermediate risk • >0.675: high risk

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; IFG, impaired fasting glucose; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score.
[a]There are variations of this cut-off in the literature.

TABLE 6 The regulatory status of drugs considered in the management of metabolic dysfunction–associated steatotic liver disease in India.

Drug class	Drug name	Approval status in India
Antidiabetic agents	Metformin, pioglitazone, SGLT2i	Approved for T2DM
GLP1-RA	Semaglutide, tirzepatide	Approved for T2DM and obesity
THR-β agonist	Resmetirom	US-FDA approved for MASH
(PPAR)-α/γ agonist	Saroglitazar	Approved for MASLD and non-cirrhotic MASH in India by DCGI

Abbreviations: (PPAR)-α/γ, peroxisome proliferator-activated α/γ receptors; DCGI, drug controller general of India; GLP1-RA, glucagon-like peptide-1 receptor agonists; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium-glucose cotransporter 2 (SGLT-2) inhibitors; T2DM, type 2 diabetes mellitus; THR-β, thyroid hormone receptor beta; US-FDA, U.S. Food and Drug Administration.

involving 102 adults with biopsy-confirmed NASH (fibrosis stages 1–3) and a NAFLD Activity Score (NAS) of ≥4. The trial showed that 52.3% of patients on Saroglitazar achieved a ≥2 decrease in NAS, across at least two components, without worsening fibrosis, compared to 23.5% on placebo ($p = 0.0427$).[93] Currently, Saroglitazar is only available in India, and more long-term data, especially on renal and cardiovascular safety, are needed.

Injectable semaglutide has shown some evidence to prevent the progression and regression of fibrosis.[94] About 37.0% of people treated with semaglutide 2.4 mg improved liver fibrosis with no worsening of steatohepatitis compared to 22.5% on placebo.[94] Additionally, cost considerations will be a major factor in the MASLD treatment in the Indian setting. However, the pharmacoeconomic data of the therapies for MASLD management is lacking in India. This lends scope for future studies to compare and evaluate cost considerations including cost effectiveness of various agents.

Since cardiovascular disease is the leading cause of morbidity and mortality in MASLD, statins should be recommended in all MASLD patients to prevent cardiovascular complications. Statins can be used safely in those with MASLD and might impart some hepatic benefits.[95] A non-pharmacological approach, bariatric surgery, may be considered in adults with non-cirrhotic MASLD.[96] However, a bariatric surgery review is not within this article's scope.

Statement 11. In the Indian context, the frequency of follow-ups with a FibroScan and FIB-4 score to assess disease progression and response to treatment is not well-defined.

Statement 11.1. All the therapeutic options must be evaluated in the Indian context.

Statement 11.2. Only when individuals do not respond to lifestyle interventions might pharmacological options be considered. However, on a need basis, pharmacological options may be considered for individualization of treatment.

9 | EMERGING CONCEPTS IN THE MANAGEMENT OF METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

Statement 12. Patients with long-term endocrinopathies must be screened for MASLD. Treatment of these endocrinopathies is essential to reduce the incidence and progression of MASLD.

Statement 13. Association of various endocrinopathies, infections such as HIV and risk factors such as smoking

TABLE 7 Emerging scores and tools in the diagnosis and risk stratification of metabolic dysfunction–associated steatotic liver disease.

Tool/Score	Purpose (early detection/ risk stratification)	Formula/ Criteria
Lipid accumulation product[105]	Early detection of MASLD	Men – *Waist circumference* $(cm) - 65 \times$ *triglyceride concentration* $(mmol/L)$ Women – *Waist circumference* $(cm) - 58 \times$ *triglyceride concentration* $(mmol/L)$
Hepatic Steatosis Index (HSI)[106,107]	Early detection of hepatic steatosis	$HSI = 8 * \frac{ALT}{AST} + BMI + 2\,(if\ diabetic) + 2\,(if\ female)$ HSI score <30 – rule out steatosis HSI score >36 ruling in steatosis
NAFLD ridge score[108,109]	Early detection of MASLD	$NRS = (-0.214 \times HDL) + (0.053 \times TG) + (0.144 \times HbA1c) + (0.032 \times WBC) + (0.132 \times Hypertension(yes = 1; no = 0))$ <0.24 – ruling out MASLD >0.44 – strong likelihood of MASLD

Abbreviations: HSI, hepatic steatosis index; LAP, lipid accumulation product; NRS, NAFLD ridge score.

TABLE 8 Emerging concepts in biomarkers of metabolic dysfunction–associated steatotic liver disease.

	Indication	Cut-offs
Cytokeratin-18 fragments[110]	Reflection of severity of MASLD and magnitude of hepatocyte apoptosis	>130.5 IU/L – suggestive of NASH
Procollagen-C3[111]	Reflection of the severity of MASLD	15.5 ng/mL– suggestive of advanced fibrosis

Abbreviation: MASLD, metabolic dysfunction–associated steatotic liver disease.

with the development and progression of MASLD require more evidence.

Statement 14. The emerging concept in diagnosing MASLD focuses on early diagnosis of the disease at a population level using the simplest possible tools.

Several non-diabetic endocrinopathies, including growth hormone deficiency and hypopituitarism, facilitate hepatic fat accumulation, steatosis and fibrosis.[97] Thyroid hormones play a crucial role in regulating hepatic lipogenesis and fatty acid oxidation processes and have garnered considerable research interest for their potential application in preventing and treating MASLD.[98] Studies from different parts of India have shown an independent association between MASLD and hypothyroidism.[99–103] Human immunodeficiency virus (HIV) infection could impede adipogenesis and adipokine synthesis, thereby promoting the development of metabolic syndrome.[104] A combination of risk factors such as smoking, tobacco consumption and diabetes is associated with a higher prevalence of fibrosis.

Tables 7 and 8 summarize the list of emerging screening tools and biomarkers along with their criteria for stratification/diagnosis.[105–111]

Artificial intelligence (AI)-driven tools could offer non-invasive and precise liver fibrosis measurements, facilitating personalized therapies for MASLD management. Integrating AI-driven digital pathology with spatially resolved omics data and clinical outcomes could lead to the development of new histopathology-based metrics, potentially refining classifications for MASLD stratification and prognostication.

Machine learning models have introduced a new dimension to MASLD prognostication. For example, the XGBoost model achieved an impressive area under the curve (AUC) of 0.95 (sensitivity-0.82), (specificity-0.91) in identifying individuals at high risk for MASLD, surpassing traditional biomarkers like FIB-4 and APRI, with AUCs around 0.50. The XGBoost model and random forest models combined with sequential forward selection and clinical data demonstrated accuracy of 0.90 and 0.81, respectively.[112]

Molecular biomarkers such as circulating cell-free DNA, their specific methylation patterns[113] and microRNAs (miRNAs), including miRNA-122 and miRNA-34a, could potentially identify the extent of liver damage and disease severity. miRNA-122, for example, a study has demonstrated an AUC of 0.82 in distinguishing MASLD from healthy controls, while miRNA-34a achieved an AUC of 0.78 in differentiating NASH from NAFLD.[114]

Statement 15. An emerging concept in the classification and prognostication of MASLD is using a non-invasive, multi-omics approach to accurately classify, stage and prognosticate patients with MASLD.

Genetic research of phenotypically well-defined large cohorts has identified several key variants [patatin-like phospholipase domain-containing 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), glucokinase regulator (GCKR) and membrane-bound O-acyltransferase 7 (MBOAT7)] associated with the risk of MASLD and disease progression.[36] The PNPLA3 I148M variant increases liver fat accumulation and progression to fibrosis.[115] Variants at these loci have been shown to influence lipid handling in hepatocytes, impacting processes such as substrate delivery for DNL, lipid droplet formation, mitochondrial lipid utilization, fatty acid compartmentalization, catabolism and the assembly and secretion of very low density lipoprotein (VLDL).[116] A comprehensive approach of genetic studies complementing the non-invasive imaging modalities could better help with risk stratification and personalized management strategies.

Given the increased risk of sarcopenia in advanced liver disease, it is crucial for patients to be regularly screened. Sarcopenic obesity, defined as the coexistence of sarcopenia and obesity, has been observed in 3.2% of community-dwelling individuals in Northern India.[117] The South Asian Working Action Group on Sarcopenia (SWAG-SARCO) 2021 consensus has highlighted several research gaps concerning sarcopenic obesity in South Asia.[118]

Lipidomic and metabolomic interrogations in MASLD patients reveal parallel, distinct changes in metabolomic profiles at various stages, especially at the fibrosis stage, F2–F3. The liver's oxidative stress-buffering potential via ether lipids appears to be one of the key changes in the progression to late-stage NASH.[119]

Recent advances in gut microbiome analysis have revealed distinct microbial signatures of the gut-liver axis associated with MASLD and NASH. The integration of microbiome analysis into MASLD research represents a promising area for personalized medicine and therapeutic intervention.[120]

> **Statement 16.** Drugs directed to insulin resistance, lipid metabolism, oxidative stress, inflammation, apoptosis and fibrogenesis are in various stages of clinical trials for potential use in the management of MASLD.

Acetyl-CoA carboxylase (ACC) inhibitors such as Firsocostat target the enzyme crucial for DNL, thereby reducing hepatic fat accumulation.[121] Similarly, stearoyl-CoA desaturase-1 (SCD1) inhibitors aim to modulate lipid metabolism by preventing the formation of monounsaturated fatty acids from saturated ones, reducing lipo-toxicity in the liver.[122] The inhibitors of the apical sodium-dependent bile acid transporter are being explored for their potential to modulate bile acid reabsorption and lipid metabolism, offering a novel approach to reducing liver fat content.[123]

Lipotoxicity and oxidative stress pathways are other potential targets owing to their roles in driving liver injury in MASLD. Peroxisome proliferator-activated receptor (PPAR) agonists, including dual and pan-PPAR agonists, are under investigation for their ability to enhance fatty acid oxidation and reduce lipotoxicity.[124] Agonists of fibroblast growth factors 19 and 21 (FGF19 and FGF21) are being explored for their hepatoprotective effects, which include reducing lipotoxicity and oxidative stress, as well as improving lipid metabolism and insulin sensitivity.[125]

Inflammation and immune activation are critical in MASLD progression, particularly in transitioning from simple steatosis to steatohepatitis. Inhibitors targeting amine oxidase copper-containing 3 (AOC3) aim to reduce leukocyte recruitment and inflammation.[126] Dual antagonists of C-C chemokine receptors 2 and 5, such as cenicriviroc, block the recruitment of monocytes and macrophages to the liver, pivotal in inflammation and fibrosis. Toll-like receptor 4 (TLR4) inhibitors are also being evaluated for their potential to modulate inflammatory responses and prevent liver injury.[127]

Another target is the prevention of apoptosis, or programmed cell death, which directly contributes to liver injury and fibrosis. Pan-caspase inhibitors such as emricasan, apoptosis signal-regulating kinase 1 (ASK1) inhibitors and ferroptosis inhibitors are designed to prevent hepatocyte apoptosis, thereby reducing liver damage and subsequent fibrosis.[128–130]

Finally, fibrogenesis, the excessive formation of scar tissue in the liver, is a critical target in preventing the progression of MASLD to cirrhosis. Cyclophilin inhibitors, such as rencofilstat, aim to inhibit the activity of hepatic stellate cells, which are central to the fibrotic process, thereby reducing the deposition of extracellular matrix proteins and preventing fibrosis progression.[131]

Researchers are exploring exosome-based therapies for drug delivery, targeted interventions and modulation of inflammatory processes in the treatment of MASLD.[132,133]

10 | CONCLUSIONS

The burden of MASLD has increased exponentially with the rising prevalence of obesity, T2DM and metabolic syndrome in India. Large-scale population-wide studies and guidelines are required to define diagnostic criteria and decision-making algorithms for managing MASLD in the Indian population. With several therapeutic agents under evaluation, there is a need to validate biomarkers and predict patient responses to the treatment. Considering the socio-economic diversity and out-of-pocket medical expenses, economically feasible treatment-effective alternatives must be evaluated for safety and efficacy in the population. Simple validation tools with imaging modalities guided by machine learning algorithms could be valuable in risk stratification. They could be close to accurately predicting the extent of the progression of the disease. Genetic studies and research collaborations for gathering real-life experiences could foster advancements towards individualized therapy. These advances will enable updated guidelines specific to MASLD patient profiles among the Indian population. This consensus statement is meant to stimulate further research in the field of MASLD in India.

AUTHOR CONTRIBUTIONS

Viswanathan Mohan, Anil Bhansali and Shashank Joshi contributed to the supervision, concept, design and revision of the article. All the other authors contributed to the design and revision of the article. All authors gave final approval to submit the article for publication.

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CONFLICT OF INTEREST STATEMENT

OL has consulting relationships with Zydus Healthcare and Zydus Hospital, Ahmedabad; SS has attended advisory board of Novo Nordisk, Torrent, USV, Eris and Astra Zeneca and has been speaker at conferences organized by above and Zydus, Alembic and NATCO Pharmaceuticals; VM has acted as consultant and speaker, received research or educational grants from Novo Nordisk, Abbott, Sanofi, Servier, Boehringer Ingelheim, Eli Lilly, Lifescan, Roche, MSD, Novartis, Bayer, USV, Dr. Reddy's, Sun Pharma, INTAS, Lupin, Glenmark, Zydus, IPCA, Torrent, Cipla, Biocon, Primus, Franco Indian, Wockhartd, Emcure, Mankind, Medtronics, Fourrts, Apex, GSK and Alembic; AZ, AB, AM1, AM2, AB, AD, BS1, BS2, DS, KS, ND, NK, PT, PK, RN, RS1, RS2, SK, SD, SA, SP, SG, SJ, SA, SG2, SG3 and VP have none to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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