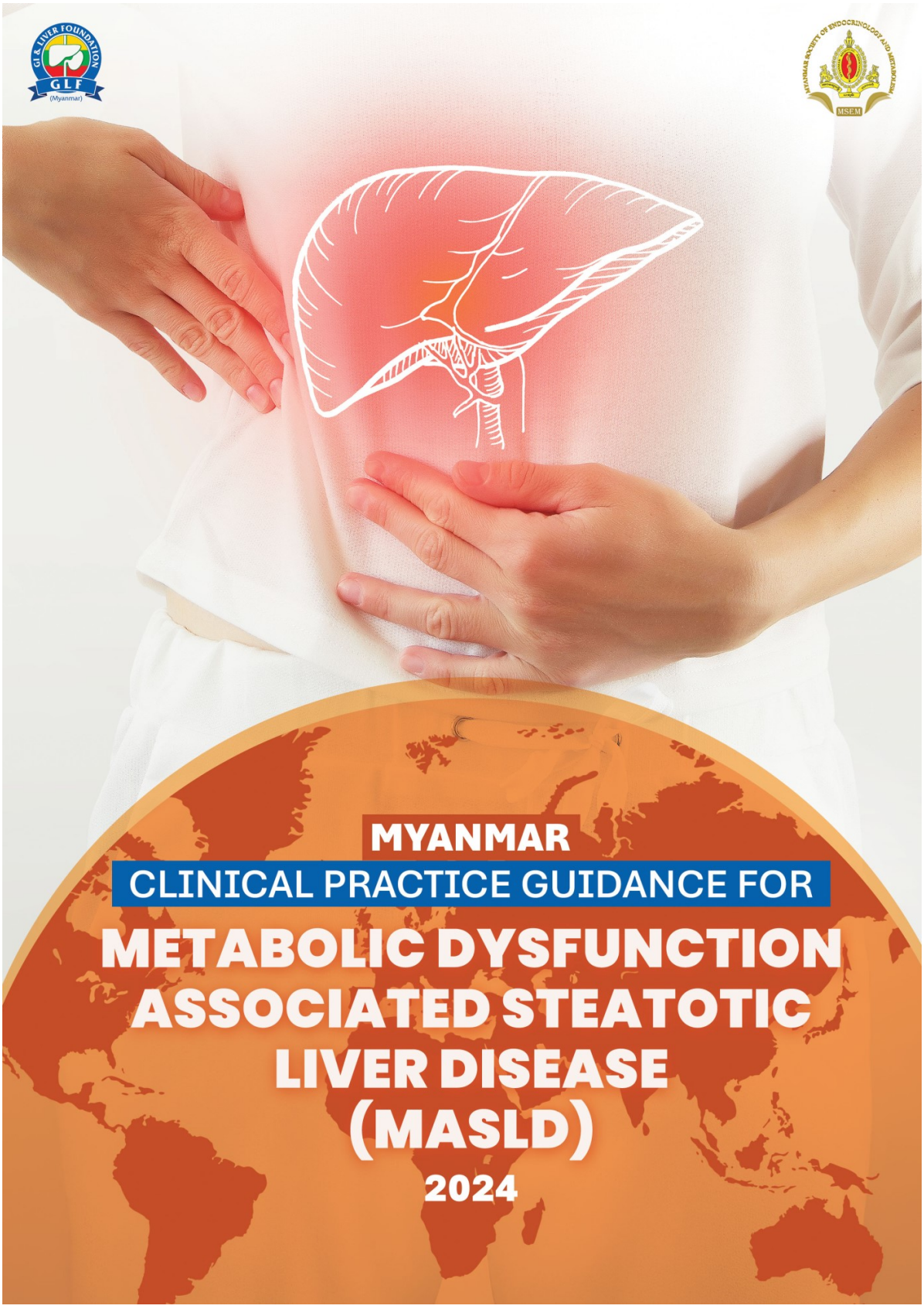
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(Myanmar)
MYANMAR SOCIETY OF ENDOCRINOLOGY AND METABOLISM
MSEM
MYANMAR
CLINICAL PRACTICE GUIDANCE FOR
METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)
2024

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Risk Factors, Diagnosis and Management of MASLD: 2024 Myanmar Clinical Practice Guidance Recommendations by GI and Liver Foundation (Myanmar) & Myanmar Society of Endocrinology and Metabolism (MSEM)

Preamble

GI and Liver Foundation (Myanmar) has produced clinical practice guidelines on Hepatitis B, Hepatitis C and Cirrhosis of the Liver to assist all the practicing doctors in the treatment of Liver Diseases.

However, AASLD has recently adopted a policy to differentiate between guidelines and guidance. AASLD published guidelines on some topics and guidance on some other diseases.

And therefore, it's time for GLF (Myanmar) to review the policy whether it should be clinical practice guidelines or guidance in future publications. For that purpose, GLF (Myanmar) decided to follow the AASLD policy.

According to the AASLD, practice guidelines use clinically relevant questions, which are then answered by systematic reviews of the literature and followed by data-supported recommendations. The guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system ("GRADE"). (AASLD Family of Websites:**AASLD.org**)

AASLD also publishes guidance on aspects of some topics. Practice guidances are based on a comprehensive review and analysis of relevant published data and put forward guidance statements to help clinicians understand and implement the most recent evidence. (AASLD Family of Websites:**AASLD.org**)

By AASLD policy mentioned above what GLF (Myanmar) has published are not practice guidelines but practice guidance. Therefore, future GLF (Myanmar) clinical practice publications will be labelled as "GLF (Myanmar) Clinical Practice Guidance".

Professor Khin Maung Win
MBBS, M.Med.Sc (Int. Med), FRCP (London), FRCP (Glasgow), FRCP (Edin), FAASLD
Chairman, Yangon GI and Liver Centre (YGLC)
Founder and Senior Patron, GI and Liver Foundation (Myanmar)

Foreword

I am honored as well as privileged to write a foreword for the "Myanmar Clinical Practice Guidance on the Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)" which is the collaborative effort between the Myanmar GI & Liver Foundation [GLF (Myanmar)] and Myanmar Society of Endocrine and Metabolism [MSEM]. MASLD is a growing public health concern globally nowadays, which does not spare Myanmar as a developing country with a low-income economy. As sedentary lifestyles and dietary changes proliferate, the prevalence of MASLD is expected to rise significantly. However, there are many barriers to early diagnosis and effective management of MASLD in Myanmar: namely, the asymptomatic nature of the disease in the early stage, limited diagnostic facilities in the country, under-resourced healthcare infrastructure, and insufficient public and provider awareness about MASLD.

This guidance will serve as a crucial resource in addressing a growing health concern within the country. This guidance aims to provide healthcare professionals with essential insights and strategies for early diagnosis and management, ultimately enhancing patient outcomes. By fostering awareness and advocating for policy development this document seeks to improve public health response to MASLD in Myanmar, aligning with global health initiatives and addressing local needs effectively.

I extend my deepest appreciation to all those involved in bringing this guidance to fruition. I truly believe this resource will contribute significantly to the advancement of the management of MASLD in our nation.

Professor Tint Swe Latt
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October 23, 2024

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ABBREVIATIONS

11βHSD1	Inhibition of 11β-hydroxysteroid Dehydrogenase 1
AACE	American Association of Clinical Endocrinologists
AASLD	American Association for the Study of Liver Diseases
ACEIs	Angiotensin-converting Enzyme Inhibitors
AH	Arterial Hypertension
ALD	Alcohol-related Liver Disease
ALEH	Latin American Association for the Study of the Liver
ALT	Alanine Transaminase
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST to Platelet Ratio Index
ARBs	Angiotensin Receptor Blockers
BB	Beta Blocker
BMI	Body Mass Index
BP	Blood Pressure
CAP	Controlled Attenuation Parameter
CCB	Calcium Chanel Blocker
CHB	Chronic Hepatitis B
CIH	Chronic Intermittent Hypoxia
CKD	Chronic Kidney Disease
CMRFs	Cardiometabolic Risk Factors
CT scan	*Computed Tomography* scan
CVD	Cardiovascular Disease
CV risk	Cardiovascular Risk
DASH	Dietary Approaches to Stop Hypertension
DIFLD	Drug Induced Fatty Liver Disease
DM	Diabetes Mellitus
DNL	De Novo Lipogenesis

EASL	European Association for the Study of the Liver
ELF	Enhanced Liver Fibrosis
ER	Endoplasmic Reticulum
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 Index
GC	Glucocorticoid
GH	Growth hormone
GLF	GI and Liver Foundation
GLP-1RA	GLP1 Receptor Agonists
HCC	Hepatocellular Carcinoma
HDL	High-density Lipoprotein
HIFs	Hypoxia-inducible Factors
HPA	Hypothalamic-Pituitary-Adrenal
HRT	Hormonal Replacement Therapy
HTN	Hypertension
IGF-1	Insulin-like Growth Factor 1
IGFBPs	Insulin-like Growth Factor Binding Proteins
LDL	Low-density Lipoprotein
LSM	Liver Stiffness Measurement
LV	Left Ventricular
MAFLD	Metabolic Dysfunction Associated Fatty Liver Disease
MASH	Metabolic Dysfunction Associated Steatohepatitis
MASLD	Metabolic Dysfunction Associated Steatotic Liver Disease
MetALD	Metabolic Dysfunction and Alcohol-associated Steatotic Liver Disease
MMDA	Myanmar Diabetes Association
MRE	Magnetic Resonance Elastograph
NAFL	Nonalcoholic Fatty Liver

NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NCDs	Non Communicable Diseases
NFS	NAFLD Fibrosis Score
NICE	National Institute for Health and Care Excellence
NIT	Non Invasive Test
OSA	Obstructive Sleep Apnoea
PAP	Positive Airway Pressure
PCOS	Polycystic Ovarian Syndrome
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PDFF	MRI–proton Density Fat Fraction
PNPLA-3	Patatin-like Phospholipase Domain-containing 3
RAAS	Renin-Angiotensin-Aldosterone System
RCTs	Randomised Controlled Trials
ROS	Reactive Oxygen Species
SGLT2	Sodium-glucose co-transporter-2
SLD	Steatotic Liver Disease
SNS	Sympathetic Nervous System
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride
TH	Thyroid Hormone
TPN	Total Parenteral Nutrition
TSH	Thyroid Stimulating Hormone
VCTE	Vibration-Controlled Transient Elastography
WAT	White Adipose Tissue
YGLC	Yangon GI & Liver Centre

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Introduction

Unified global approaches to nomenclature and disease definition are critical for increasing disease awareness, driving policy change, identifying those at risk, facilitating diagnosis and access to care. Language can create or exacerbate stigma, marginalise segments of the affected population and, ultimately, contribute to health inequalities. It has been known for many years that being overweight or obese is associated with hepatic steatosis, hepatocyte injury and liver inflammation and fibrosis. This was formally recognized by the term “Nonalcoholic Steatohepatitis” in 1980 by Jurgen Ludwig. [1]

Subsequently, the term nonalcoholic fatty liver disease (NAFLD) was used to describe the histological spectrum of steatosis (fat accumulation in the liver without inflammation or liver damage) to steatohepatitis (inflammation of the liver associated with steatosis), which includes its subtypes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The histological classification was further expanded upon by various scoring systems categorising steatosis, disease activity and fibrosis. [2-4]

In 2007, the Asian-Pacific Working Party for NAFLD introduced an operational definition for NAFLD. This definition allowed diagnosis based on ultrasonography findings on the condition that significant alcohol consumption, medications causing hepatic steatosis, and other chronic liver diseases were ruled out.

In 2010, the European Association for the Study of the Liver (EASL) issued a position statement recognizing that although NAFLD historically had been diagnosed by excluding other chronic liver diseases, its close association with metabolic syndrome and its frequent overlap with other liver conditions strongly supported a need for updated terminology.

Although the term NAFLD continued to be widely used in major international guidelines, there were indications of an impending shift. For instance, the 2016 EASL guidelines introduced the term “primary NAFLD” to refer specifically to “NAFLD associated with metabolic risk factors”. Similarly, the Asian-Pacific Working Party introduced a “positive” definition for NAFLD in its 2017 guidelines.

While the nomenclature is widely used, it has always been appreciated that the term “nonalcoholic" did not accurately capture what the aetiology of the disease was, and notably, the term ‘fatty’ has been considered to be stigmatising by some. Furthermore, there are individuals

with risk factors for NAFLD, such as type 2 diabetes, who consume more alcohol than the relatively strict thresholds used to define the nonalcoholic nature of the disease that are not adequately recognised by existing nomenclature, are excluded from trials and consideration for treatments. [5]

Indeed, there is a recognition now that there are overlapping biological processes which may contribute to both NAFLD and alcohol-related liver disease (ALD). All of these factors have led to growing dissatisfaction with the current nomenclature. This was summarised in a paper by Eslam *et al* in 2020 and led to the proposal to use the term "metabolic dysfunction associated fatty liver disease" (MAFLD), which includes patients with a fatty liver regardless of the amount and pattern of alcohol intake under this terminology. [6,7] While MAFLD was accepted by some, concerns were raised about the mixing of aetiologies, continued use of the term 'fatty' considered stigmatising by many, restricting the population to those with 2 metabolic risk factors and allowance of more liberal alcohol use. [8-10] The introduction of the term "metabolic dysfunction-associated fatty liver disease (MAFLD)" received endorsement from the Asian Pacific Association for the Study of the Liver (APASL), multiple national societies' and various stakeholders globally.

In June 2023, a global Delphi consensus process, jointly led by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), in partnership with the Latin American Association for the Study of the Liver (ALEH), additional societies, academic experts including hepatologists, gastroenterologists, paediatricians, endocrinologists, hepatopathologists and public health and obesity experts along with colleagues from industry, regulatory agencies and patient advocacy organisations proposed a revised nomenclature that includes updated definitions for the conditions previously categorized under the term NAFLD. [11] Under the umbrella term of steatotic liver disease (SLD), metabolic dysfunction-associated steatotic liver disease (MASLD) replaces the traditional term "NAFLD" and metabolic-dysfunction associated steatohepatitis (MASH) instead of nonalcoholic steatohepatitis (NASH).

This updated terminology highlights the disease's association with metabolic dysfunction, aiming to reduce stigma linked to terms like "nonalcoholic" and "fatty". The terms MAFLD and MASLD share more similarities than differences and have succeeded in providing a more suitable name for the condition.

1. MAFLD vs MASLD

Although the term nonalcoholic fatty liver disease (NAFLD) continued to be widely used in major international guidelines, it has always been appreciated that the term “nonalcoholic" did not accurately capture what the aetiology of the disease was, and notably, the term ‘fatty’ has been considered to be stigmatising by some. Furthermore, there are individuals with risk factors for NAFLD, such as type 2 diabetes, who consume more alcohol than the relatively strict thresholds used to define the nonalcoholic nature of the disease that are not adequately recognised by existing nomenclature, are excluded from trials and consideration for treatments.

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This updated terminology highlights the disease's association with metabolic dysfunction, aiming to reduce stigma linked to terms like "nonalcoholic" and "fatty". [21]

The overarching term of steatotic liver disease (SLD) includes MASLD (defined by specific criteria detailed below). It introduces a new overlap category for individuals with cardiometabolic risk factors (CMRFs) and varying levels of alcohol consumption, termed metabolic dysfunction and alcohol-associated steatotic liver disease (MetALD). It also acknowledges other causes of hepatic steatosis, such as alcohol-associated liver disease (ALD) with or without metabolic risk factors, drug-induced liver injury, monogenic diseases, and other etiologies. [15]

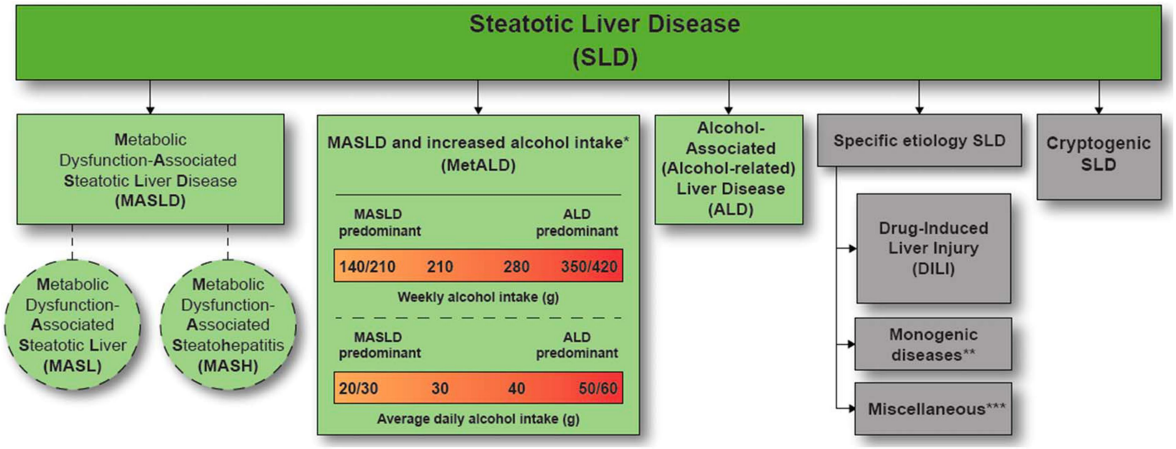


Figure 1. Schema of SLD and subcategories.

MASLD is defined as the presence of hepatic steatosis accompanied by any cardiometabolic risk factors (CMRFs), provided that there are no other causes of hepatic steatosis. If additional drivers of steatosis are identified, this is consistent with a combination etiology. In the case of alcohol, this is termed MetALD or ALD, depending on the extent of alcohol intake. The definition of MASLD excludes patients with consumption of >20 g/30 g of alcohol per day in females and males, respectively. [15]

Table 1. Adult Criteria to define MASLD [22]

At least 1 out of 5:
• BMI ≥ 23 kg/m3 **OR** WC > 90 cm (M) 80 cm (F)
• Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose level ≥ 7.8 mmol/L [≥ 140 mg/dL] **OR** HbA1C ≥ 5.7% OR type 2 diabetes **OR** treatment for type 2 diabetes
• Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
• Plasma triglyceride ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
• Plasma HDL-cholesterol ≤ 1.1 mmol/L [40 mg/dL] (M) ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

2. Epidemiology and Natural History of MASLD

2.1 Epidemiology of MASLD

The prevalence of MASLD worldwide in the general population has increased from 25% in 2016[15] to over 30% at present, with a steadily increasing incidence reflecting a growing public health concern. [16-18] According to the meta-analysis data, the prevalence of MASLD in Asia is estimated to be 29%, [19] and it was found to be highest in Southeast Asia, at 42%. [20] The prevalence was higher in patients with risk factors for MASLD, including Type 2 Diabetes Mellitus (T2DM), overweight or obesity, and metabolic syndrome. However, MASLD and MASH can be observed in lean or non-obese patients, accounting for 22% of all MASLD patients. [19]

It has been estimated that approximately 10–30% of individuals with isolated steatosis may progress to steatohepatitis and advanced liver disease. [21] Moreover, the recent meta-analysis revealed that the risk of progression is significantly higher in the presence of type 2 diabetes, with 42-65% of individuals. [11,22]

According to data from the National Survey of Diabetes Mellitus and Risk Factors for Non Communicable Diseases (NCDs) in Myanmar, diabetes was present in 10.8% of the population, with a higher prevalence of 11.5% in men compared to 9.2% in women. The survey also revealed that 19.7% of individuals had prediabetes, with 16.5% of men and 23% of women affected. The study identified increasing age, urban residency, a large waist circumference, and elevated triglyceride levels as significant risk factors for both diabetes and prediabetes. [23]

Although a large-scale study on MASLD has not yet been conducted locally, the rising trend of T2DM, obesity, and obesity-related conditions suggests that MASLD is also becoming more prevalent. A retrospective descriptive analysis of the registry data of 817 patients from Yangon GI & Liver Centre (YGLC) showed that 56% had steatosis of varying grades, and 37% had severe steatosis. 11% of patients had clinically significant fibrosis F2-F4 by FibroScan®. 14% of patients had Type 2 Diabetes mellitus (Submitted).

Myanmar has also one of the highest prevalence of viral hepatitis B and C. Concurrent MASLD and viral hepatitis are not uncommon; MASLD is observed in 30% to 34% of patients with chronic hepatitis B (CHB). [24] Patients with chronic hepatitis B (CHB) who also have

MASLD and metabolic comorbidities face a higher risk of developing advanced liver diseases like fibrosis, cirrhosis, and HCC, as well as increased liver-related mortality, with this risk being more significant in those with low viral loads. [25,26] Therefore, these patients must receive aggressive management of their metabolic comorbidities.

2.2 Natural History of MASLD

The transition from MASLD to MASH is quite dynamic (Figure 2). Individuals with MASLD might develop fibrosis and progressive liver disease as time progresses, with a greater risk observed in those with steatohepatitis compared to those with simple steatosis which requiring 14 years per stage of fibrosis, whereas in MASH, each stage progresses over 7 years. [27] Importantly, approximately 20% of individuals with MASH may be classified as ‘‘rapid progressors,’’ in whom each stage progresses in less than 7 years. Predictors of rapid progression may include higher serum ALT, presence of diabetes, family history of cirrhosis in first-degree relatives, and possibly genetic susceptibility. [28]

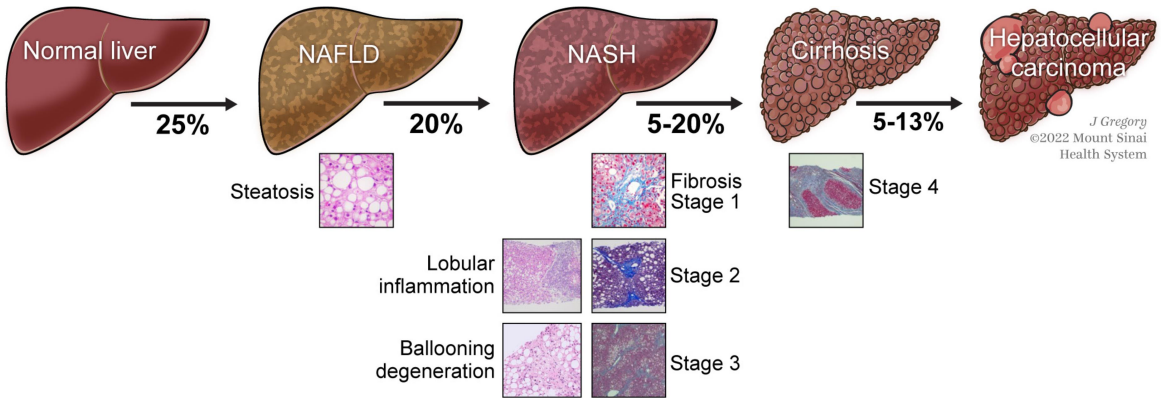


Figure 2. Schematic of the progression of MASLD to cirrhosis and HCC.

It is estimated that only 20% of individuals with MASLD have MASH, and 20% of these individuals may progress to cirrhosis over 3–4 decades. [28] People with MASH-related cirrhosis carry an ~1.5%–2% per year risk of developing incident HCC. [29] Although HCC has been reported in non-cirrhotic individuals with MASLD at a higher rate than for other chronic liver disease etiologies, the incidence rate of HCC is still too low to recommend routine HCC screening unless there is advanced fibrosis or cirrhosis.

It has been well-established that cardiovascular disease (CVD) is the leading cause of mortality among patients with MASLD, followed by cancer and then liver disease. However,

when cirrhosis has developed, liver disease becomes the dominant risk of mortality. [30,31] Furthermore, MASLD was associated with an increased risk of all-cause mortality. [32]

The risk of liver-related complications and mortality increases significantly with higher fibrosis stage. [33] Patients with cirrhosis due to MASLD have an annual risk of developing hepatocellular carcinoma (HCC) between 1% and 4%, whereas non-cirrhotic MASLD patients have a much lower annual risk of less than 0.1%. [34]

MASH-related HCC is increasing, and over the last decade it has been the etiology with the greatest increase in HCC incidence requiring liver transplantation. MASH-related HCC is now the second leading indication for liver transplantation in the United States and is likely to become the leading indication within a decade. [35]

MASLD is associated not only with liver-related complications and cardiovascular disease (CVD) but also with a higher risk of extrahepatic malignancies, including gastrointestinal, breast, and thyroid cancers, [36] and an increased risk of developing non-fatal cardiovascular disease, heart failure, [37] T2DM and diabetes-related peripheral polyneuropathy, obstructive sleep apnoea and chronic kidney disease. [38,39]

Recommendation (MASLD and Natural History)

1. GI and Liver Foundation (GLF) Myanmar and Myanmar Diabetes Association (MMDA) endorses the term Steatotic Liver Disease (SLD) as an overarching term, with its subcategories, including Metabolic dysfunction-associated steatotic liver disease (MASLD), for their clarity and enhanced clinical applicability.
2. MASLD is defined by the presence of hepatic steatosis combined with cardiometabolic risk factors (CMFRs) if there is no other cause of hepatic steatosis.
3. The presence of MASLD is tightly linked to type 2 diabetes (T2D), obesity, and other cardiometabolic risk factors.
4. The risk of progression to advanced liver disease is significantly higher in the presence of type 2 diabetes mellitus (T2DM).
5. MASLD is associated with not only cirrhosis of liver or hepatocellular carcinoma (HCC) but also an increased risk of T2DM and diabetes-related peripheral polyneuropathy, obstructive sleep apnoea (OSA), chronic kidney disease, fatal and nonfatal cardiovascular events, extrahepatic malignancies, including gastrointestinal, breast, and thyroid cancer.
6. Concurrent MASLD and viral hepatitis recommended to have thorough management of cardiometabolic comorbidities.

3. Molecular and Cellular Pathogenesis

A ‘two-hit’ theory was posited for several years to explain MASH pathogenesis. This theory suggests that in the setting of steatosis alone (i.e., MASLD), a second ‘hit’ from other factors (for example, oxidant stress) was required for the development of MASH; however, this view is now outdated. There are many molecular pathways that contribute to the development of MASH, and it is not even certain whether MASH is always preceded by MASLD. Moreover, pathogenic drivers are not likely to be identical among all patients. Thus, both the mechanisms leading to disease and their clinical manifestations are highly heterogeneous.

Over nutrition with a poor-quality diet rich in glucose, high-fructose corn syrup and saturated fats leads to increased intrahepatic triglycerides characteristic of metabolic dysfunction-associated steatotic liver disease (MASLD) through several pathways. Hyperinsulinaemia in response to excess glucose intake in conjunction with muscle insulin resistance resulting from increased deposition of intramuscular fat leads to hepatic de novo lipogenesis. In parallel, white adipose tissue (WAT) dysfunction resulting from excess dietary fats leads to an excess of triglyceride uptake from chylomicron remnants and fatty acid delivery to the liver. Lipotoxic injury from the excess triglyceride content in the hepatocytes triggers an aberrant wound repair response culminating in fibrosis (Figure 3).

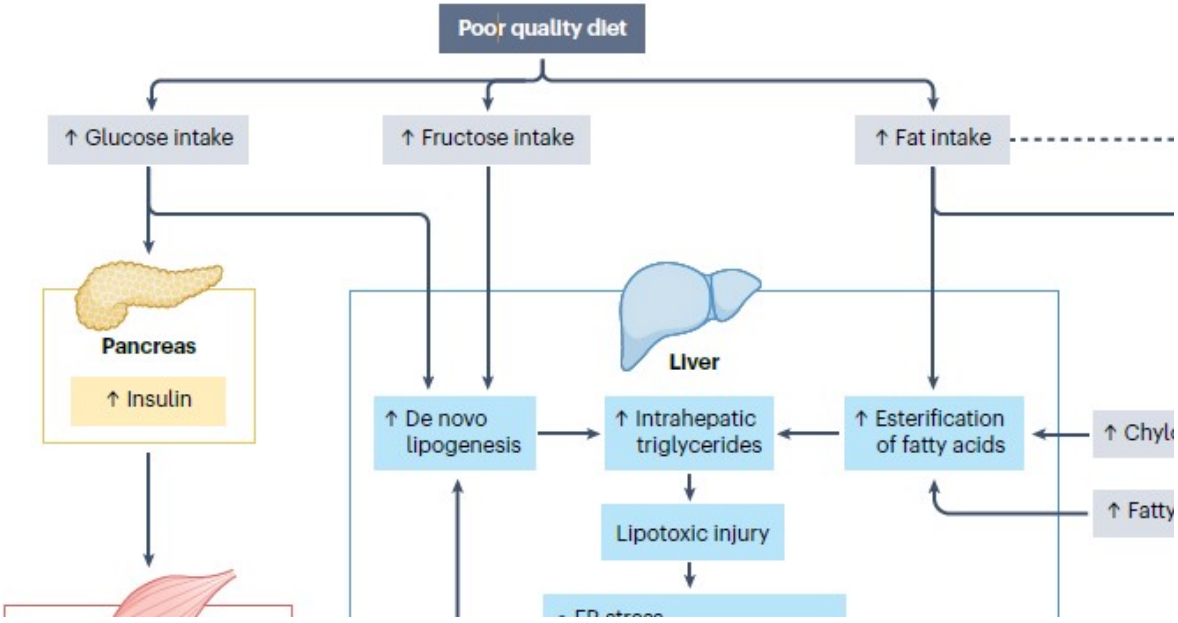


Figure 3. Pathogenesis of MASLD

In defining pathogenic drivers of MASLD and MASH, a basic concept is that the liver's capacity to handle the primary metabolic energy substrates, carbohydrates and fatty acids, is overwhelmed, leading to accumulation of toxic lipid species. These metabolites induce hepatocellular stress, injury and death, leading to fibrogenesis and genomic instability that predispose to cirrhosis and hepatocellular carcinoma. Thus, simplification the sources and fates of fatty acids in hepatocytes is essential for understanding the metabolic underpinnings of MASH. When fatty acids are either supplied in excess or their disposal is impaired, they may serve as substrates for the generation of lipotoxic species that provoke endoplasmic reticulum (ER) stress and hepatocellular injury. Elucidating the pathways leading to lipotoxicity, ER stress and cell injury has led to rational therapeutic targeting.

The presence and severity of MASLD and MASH are substantially determined by factors that govern the supply and disposition of fatty acids, diacylglycerols, ceramides, cholesterol, phospholipids, and other intrahepatic lipids. Energy oversupply and limited adipose tissue expansion contribute to insulin resistance and metabolic disease. [40] When energy intake exceeds metabolic needs and disposal capacity, carbohydrates, in the form of dietary sugars (eg, fructose, sucrose, and glucose), drive the formation and accumulation of intrahepatic fat from de novo lipogenesis (DNL). [41,42] There is substantial interindividual heterogeneity in the role of DNL among patients with MASLD. [43,44] In addition, the type of fat consumed plays a role in the development of MASH, with a higher risk associated with saturated versus unsaturated fat consumption (Figure 4). [45-46]

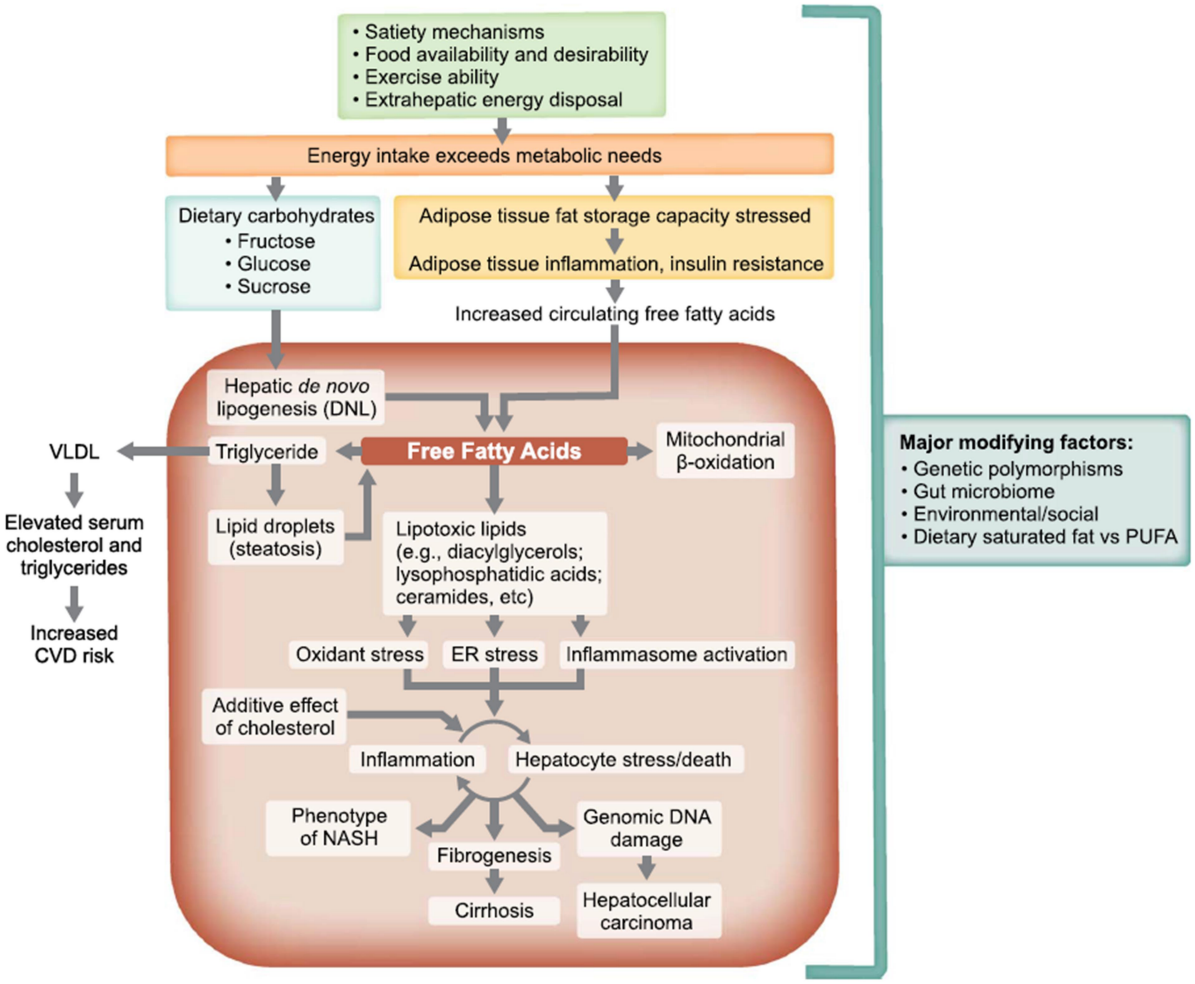


Figure 4. Pathogenic drivers of MASLD as therapeutic targets.

Insulin resistance is nearly universal in patients with MASLD and is present in the liver, adipose tissue, and muscle. Adipose tissue insulin resistance is characterized by increased release of free fatty acids from adipocytes (lipolysis) in the fasting state and worsens with the progression of MASLD to MASH. [40,48,50]

Important factors that govern energy disposal include the frequency and intensity of exercise, the activation of brown adipose tissue to an energy-consuming thermogenic phenotype, and counter-regulatory mechanisms that diminish energy disposal in response to reductions in calorie intake. [40,51] The ability and desire to engage in regular exercise can be strongly influenced by personal, community, corporate, societal, and legislative decisions, all of which thus have roles in the development of MASH.

The heterogeneity of factors contributing to the pathophysiology of MASH among patients has impeded the development of diagnostic tests and therapeutics. [52] Although in some

patients, the development and progression of MASH are driven by substrate overload and insulin resistance, in other patients, disease progression is heavily influenced by genetic factors impacting hepatocyte lipid handling. [44]

Genetic polymorphisms have been associated with more advanced liver disease and the development of HCC in MASH. The I148M polymorphism of PNPLA3 impairs lipolysis of triglyceride in lipid droplets, [53] and polymorphisms in other proteins that play a role in hepatocyte fat metabolism have also been linked to the prevalence and severity of MASLD, including transmembrane 6 superfamily member 2 (*TM6SF2*), which may play a role in cholesterol metabolism, [54] and *MBOAT7*, which influences phospholipid metabolism. [56] Recently, loss-of-function variants in *HSD17B13*, a gene that encodes an enzyme that also localizes to lipid droplets in hepatocytes, have been linked to protection against MASH, progressive fibrosis, and HCC. [57] Rare loss-of-function mutations in *CIDEB*, a protein needed for activation of DNL, [58] have also been shown to be protective. [59]

A host of additional factors, the review of which is beyond the scope of this guidance, contribute to heterogeneity in disease activity and progression. [50,60-65] Additional factors such as hepatocyte uric acid production, exposure to products derived from the gut microbiome, and perhaps low hepatic magnesium levels, may also contribute to the MASH phenotype. [66-71] Transcriptomic profiling of large cohorts of patients is further contributing to our understanding of this disease heterogeneity and its progression. [72,73] The response of the liver to lipotoxic injury includes activation and recruitment of resident macrophages, which further contributes to hepatocellular injury and stellate cell activation as part of a complex interplay among hepatic cell types. [62,74,75] Although markers of oxidative stress have been a consistent finding in MASH, its role in the pathogenesis of MASH in humans remains uncertain. [75]

Key Points (Molecular and Cellular Pathogenesis)

1. Fundamental elements of MASH pathogenesis include an imbalance between nutrient delivery to the liver and their utilization and disposal coupled with adipose tissue dysfunction. Interindividual differences in genetic, dietary, behavioral, and environmental factors influence disease course.
2. Systemic inflammation, particularly stemming from dysfunctional adipose tissue, contributes to disease progression.
3. Insulin resistance contributes to the development of MASLD and promotes disease progression.

4. Risk Factors and Comorbid Conditions associated with MASLD and respective treatments

4.1 Risk Factors for MASLD

4.1.1 Metabolic risk factors

The risk factors for MASLD are the same ones that are associated with metabolic syndrome. [76] The prevalence of MASLD was 4-fold higher in individuals with metabolic syndrome than those without it. [77] The presence of multiple traits of metabolic syndrome was associated with a higher likelihood of more severe liver disease. [78]

(a) Central Obesity: In Myanmar, 22.4% of adults between the ages of 25 and 64 are overweight, and 5.5% are obese, according to data from the 2014 WHO nationwide STEPS survey. [79] It has been discovered that 91% of individuals with obesity have MASLD. [80] Losing weight is the sole established way to improve and resolve MASLD, while gaining weight raises the chance of incident MASLD. [81]

(b) Insulin resistance or type *2* diabetes mellitus: Insulin resistance facilitates adipose tissue lipolysis, which releases free fatty acids and deposits in the liver, resulting in steatohepatitis. According to a number of population-based research, people with type 2 diabetes have a higher prevalence of MASLD, which can range from 30% to 70%. [82]

(c) Hypertension: A meta-analysis involving patients with pathologically established MASLD discovered a correlation between hypertension and the advancement of liver fibrosis. [83]

(d) Hyperlipidaemia: Research has indicated that MASLD is substantially linked to low levels of high-density lipoprotein (HDL) cholesterol and a higher prevalence of hypertriglyceridemia; non-HDL cholesterol was linked to higher levels of fatty liver. [84] It has been demonstrated that statins slow the advancement of hepatic fibrosis, lower the risk of hepatic decompensation, and lower the overall mortality risk in patients with chronic liver disease. [85]

4.1.2 Other potential risk factors for MASLD

(a) Ethnicity: Black people have a lower risk, whereas Asian and Hispanic people have higher risk. [86]

(b) Genetic predisposition: MASLD is more common and severe when certain genetic variations are present. According to a meta-analysis study, PNPLA-3, or patatin-like

phospholipase domain-containing 3, not only caused a 73% increase in liver fat formation but also more aggressive illness. [87]

(c) Sex and age: Men are typically more likely than women to have MASLD. [88] Because risk factors like metabolic syndrome, type 2 diabetes, and hypertension are more common with increasing age, there is an increased chance of developing MASLD. [89] Furthermore, an investigation revealed that growing older is a risk factor for severe liver fibrosis in MASLD. [89]

(d) Nutritional: Total parenteral nutrition (TPN) and refeeding syndrome, rapid weight loss, and jejunoileal bypass surgery can result in SLD. [90] Sugars encourage de novo lipogenesis and stimulate an inflammatory response that results in apoptosis of hepatocyte. [91] Patients with MASLD can effectively reduce their hepatic fat level by taking omega-3 fatty acids, according to a meta-analysis of ten randomised controlled studies. [92] A Mediterranean diet lowers insulin resistance and MASLD, according to one study involving 584 patients. [93]

(e) Physical activity: The chance of developing MASLD rises with inactivity. [94] In teenagers with MASLD, regular aerobic exercise for 6–12 weeks was helpful in lowering the accumulation of visceral fat and hepatic steatosis. [95] Nonetheless, some research revealed that brief exercise had no impact on the amount of fat stored in the liver. [96]

(f) Sleep: Some researchers have demonstrated the link between sleep deviation and poor sleep quality with obesity, which is one factor in the pathophysiology of MASLD. [97]

(g) Obstructive sleep apnoea syndrome

(h) Endocrine diseases: hypopituitarism, hypothyroidism and polycystic ovary syndrome

(i) Other disorders of the liver: Wilson's disease and hepatitis C.

Recommendations (Risk Factors)

7. The following metabolic risk factors are linked to MASLD. If any of these risk factors are present, MASLD should be investigated. On the other hand, it is important to look for these risk factors in patients with MASLD.
   - Central Obesity
   - Insulin resistance or type 2 diabetes mellitus
   - Hypertension
   - Hyperlipidemia

8. The following are other potential risk factors for MASLD. For patients who have these potential risk factors, there should be a high index of suspicion for MASLD.
   - Ethnicity: Black people have a lower risk, whereas Asian and Hispanic people have higher risk
   - MASLD running in the family
   - Men are more likely to have higher risk than woman
   - Increasing age
   - Nutritional: fast weight loss, jejunoileal bypass surgery, and total parenteral nutrition (TPN) and refeeding syndrome
   - Physical inactivity
   - Poor sleep quality and sleep deprivation
   - Obstructive sleep apnea syndrome
   - Endocrine conditions, such as hypothyroidism and polycystic ovarian syndrome
   - Other disorders of the liver, like Wilson's disease and hepatitis C

4.2 Comorbid conditions associated with SLD and respective treatments

4.2.1 Obesity in patients with MASLD

Obesity (particularly, increased truncal subcutaneous fat and visceral fat) and type 2 diabetes are the metabolic diseases with the strongest impact on the natural history of MASLD, including progression to MASLD/MASH-related advanced fibrosis, cirrhosis and hepatocellular carcinoma. [62]

In the management of obesity, lifestyle change which primarily consists of nutritional therapy and physical activity is the first-line therapy followed by medications. Weight reduction either with or without increased physical activity, leads to improvements in biomarkers, including liver enzymes, steatosis, MASH, and fibrosis found in clinical trials. [98]

4.2.1.1 Weight loss goals

In adults with MASLD and overweight, dietary and behavioral therapy-induced weight loss should aim at a sustained reduction of at least ≥ 5% to reduce liver fat, 7-10% to improve inflammation and ≥ 10% to improve fibrosis. [99-101]

4.2.1.2 Weight loss management in MASLD

Weight loss management should be multidisciplinary care approach with affordable structured lifestyle intervention, individualized plan depending on patient's preference and economic constraint. [101]

Dietary macronutrient content and distribution is important in MASLD, weight loss achieved through caloric deficit, irrespective of the specific dietary approach [102] is effective in reducing hepatic steatosis [103] and necroinflammation, although results are more variable for fibrosis. [104] Hypocaloric low-carbohydrate diets and low-fat diets appear to be similarly effective in reducing liver lipid content and related biomarkers. [47]

Calorie-restricted DASH (Dietary Approaches to Stop Hypertension) diet, diets rich in fruit, vegetables, whole grains and low-fat dairy and low in saturated fat and refined grains, also results in beneficial weight loss and reduced ALT levels in persons with obesity and MASLD. [105] Modification of macronutrient composition (reduction of saturated fat, starch, and added sugars, ultra-processed food, sugar-sweetened beverages) and enriched with high fiber and

unsaturated fats (e.g., Mediterranean diet) should be encouraged due to their additional cardiovascular benefits. [106]

Physical activity and exercise are strongly recommended to reduce steatosis, tailored to the individual's preference and ability (preferably >150 min/week of moderate or 75 min/week of vigorous-intensity physical activity) because 3-month aerobic exercise regimen (three 90-minute sessions/week) reduced liver steatosis and liver stiffness, independent of weight loss [107]. There was no specific weight loss benefit associated with different types of exercise training programs (either aerobic, resistance, or lifestyle) [108], but evidence indicates higher intensity activity or exercise has better effects on weight loss if combine with caloric restriction.

Table 2. Preferred pharmacological options for treating comorbidities (Obesity and Type 2 Diabetes)

<table>
<tr><th colspan="2">MASLD/ MASH without cirrhosis</th></tr>
<tr><th>Obesity</th><th>Type 2 Diabetes</th></tr>
<tr><td rowspan="2">• GLP-1RA
(e.g. Semaglutide, Liraglutide) and coagonists (e.g. Tirzepatide)
• Bariatric interventions
(Special caution in case of compensated Cirrhosis)</td><td>• GLP-1RA
(e.g. Semaglutide, Liraglutide,) and coagonists (e.g. Tirzepatide)
• Pioglitazone
• SGLT2 inhibitors
(e.g. empagliflozin, dapagliflozin)</td></tr>
<tr><td>• Insulin (in case of decompensated cirrhosis)</td></tr>
</table>

(a) Weight loss medications

Medications for obesity have been approved by the FDA for chronic weight management for individuals with a BMI of ≥ 30 kg/m^2 or those with a BMI of 27 to 29.9 kg/m^2 and one or more obesity associated comorbid conditions (e.g., type 2 diabetes, hypertension, and/or dyslipidemia). [109] Medications for the management of obesity have not undergone rigorous testing in RCTs using liver histology (ie, paired liver biopsies) as the primary outcome in persons with MASLD. [110]

For chronic weight management in individuals with a BMI of ≥ 27 kg/m^2 and MASLD or MASH, clinicians should consider with preference to GLP1 receptor agonists (GLP-1RA)

Semaglutide, Liraglutide [111] or Tirzepatide [112] with the best evidence as adjunctive therapy to lifestyle modification to promote cardiometabolic health and treat or prevent T2D, CVD, and other end-stage manifestations of obesity.

Table 3. Anti-obesity medications

Medications	Weight loss	Effect on MASLD
Oral lipase Inhibitor (Orlistat 120 mg capsules three times a day)	5% weight loss	Reduced the aminotransferase levels but failed to improve liver histology [113] Orlistat does not have drug specific effects in steatohepatitis, improvement in liver histology is proportional to the magnitude of weight loss.
Combination of Orlistat 120 mg and Resveratrol 100 mg three times a day	>5% weight loss	Assessment of liver health using Controlled Attenuation Parameter (CAP) scores indicated a significant reduction in hepatic steatosis [114]
Liraglutide 0.6–3 mg SC daily	6.4% weight loss	Normalize plasma aminotransferase levels and reduce liver fat content on imaging in individuals with MASLD [115]
Semaglutide, 0.25–2.4 mg SC weekly	15.8% weight loss	Demonstrated resolution of steatohepatitis but no fibrosis improvement
Tirzepatide 5 - 15 mg SC weekly	20.9% weight loss	Shown to significantly reduce both liver and visceral fat in those with T2D, in association with major weight loss (comparable to bariatric surgery) [112] and promising results on steatohepatitis resolution from a phase II study in MASH

FDA approved oral antidiabetic medication, oral semaglutide 7 mg and 14 mg tablet once a day given as monotherapy reduces body weight compared to placebo at 26 weeks in patients with early T2D managed with diet and exercise –0.9 kg [7 mg] to –2.3 kg [14 mg] and this reduction was sustained to 52 weeks. [116] Weight loss was greater with oral semaglutide 14 mg than the active comparators liraglutide 1.8 mg, empagliflozin 25 mg, and sitagliptin 100 mg [117] although it has not been approved as anti-obesity medication yet.

(b) Bariatric surgery

Bariatric/metabolic should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery as bariatric surgery can resolve MASH [118,119], and it can induce long-term beneficial effects on the liver and is associated with remission of Type 2 diabetes and improvement of cardiometabolic risk factors. [120]

Indications for bariatric surgery are BMI ≥40 kg/m^2, or BMI ≥35–40 kg/m^2 in the presence of associated comorbidities, or BMI ≥30–35 kg/m^2 if people have T2D and/or hypertension with poor control despite optimal medical therapy. [101] Bariatric/metabolic procedure should be considered in persons with MASLD and a BMI of ≥ 35 kg/m^2 (≥ 32.5 kg/m^2 in Asian populations. [99] In case of decompensated cirrhosis, bariatric surgery is contraindicated because it can increase 10-fold higher risk of death than those with compensated cirrhosis. [121]

Recommendations (Obesity)
9. In adults with MASLD and overweight, weight loss should aim at a sustained reduction of at least ≥ 5% to reduce liver fat, 7-10% to improve inflammation and ≥ 10% to improve fibrosis.
10. Caloric restricted, reduction of saturated fat and starch, limiting the consumption of ultra-processed food (rich in sugars and saturated fat) and avoiding sugar-sweetened beverages should be recommended.
11. In adults with MASLD, physical activity should be encouraged in all individuals with obesity, tailored to the individual's preference and ability (preferably >150 min/week of moderate or at least 75 min/week of vigorous-intensity physical activity).
12. FDA approved medications for obesity should be consider in chronic weight management for individuals with a BMI of ≥ 30 kg/m^2 or those with a BMI of 27 to 29.9 kg/m^2 and one or more obesity associated comorbid conditions.
13. Injectable GLP1 receptor agonists such as Semaglutide, Liraglutide or Tirzepatide are preferred as anti-obesity medications as adjunctive therapy to lifestyle modification for individuals with obesity and MASLD or MASH.
14. Bariatric/metabolic procedure should be considered in persons with MASLD and a BMI of ≥ 35 kg/m^2 (≥ 32.5 kg/m^2 in Asian populations) but not recommend in those with decompensated cirrhosis patients.

4.2.2 Management of Type 2 Diabetes in MASLD

The treatment recommendations for persons with Type 2 Diabetes and MASLD are centered on the dual purpose of treating hyperglycemia and/or obesity and steatohepatitis, especially if clinically significant fibrosis is present, to prevent development of cirrhosis [3]. In adults with MASH, is there insufficient evidence to recommend prescription of existing glucose-lowering drugs as a MASH-targeted therapy to reduce histologically/non-invasively assessed liver damage/fibrosis and liver-related outcomes. [101] However, optimizing glycemic control using preferred agents that have benefit on steatohepatitis, pioglitazone and GLP-1 RA in persons with obesity, prediabetes, or T2D with MASLD. [99]

4.2.2.1 Individual HbA1c target

HbA1c < 7% for persons without concurrent serious illness and at low hypoglycemic risk. In advanced cirrhosis (eg. Child class B or C with clinical evidence of comorbidities varices, portal hypertension, ascites etc.), caution with risk of hypoglycemia and avoid oral agents. [99]

4.2.2.2 Glucose lowering medications

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) (Semaglutide, Liraglutide) are safe to use in MASH (including compensated cirrhosis) demonstrated resolution of steatohepatitis but no fibrosis improvement [110] and should be used for their respective indications, such as type 2 diabetes and obesity, as their use improves cardiometabolic outcomes. The newer dual (GLP1-GIP RA) agonists, Tirzepatide has been approved for the treatment of T2D, also approved for obesity shows absolute reduction in liver fat content. [109]

Pioglitazone activates peroxisome proliferator-activated receptor (PPAR)ϒ, has been shown to improve histological features of steatohepatitis, [122] without a clear effect on fibrosis regression even after prolonged (up to 3-years) therapy [123] is safe to use in adults with non-cirrhotic MASH.

Sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors) (empagliflozin, dapagliflozin and canagliflozin) are approved for T2DM, chronic kidney disease and heart failure because of their beneficial effect on cardiovascular and renal outcomes. [124] They induce renal glucosuria, weight loss, blood pressure reduction, and protection from major cardiovascular

outcomes, including heart failure. The weight loss is due to renal energy loss and reduction in fat mass, with reductions in both visceral and abdominal subcutaneous adipose tissue. [125] Trials in people with T2DM (not all with MASLD and some excluding high ALT values) have shown a moderate reduction in liver lipid content, with empagliflozin, [126] dapagliflozin. Reductions in ALT were shown with empagliflozin. Although Empagliflozin, Dapagliflozin cannot be recommended as MASH-targeted therapies, they are safe to use in MASLD and should be used for their respective indications such as type 2 diabetes, heart failure and chronic kidney disease. [127]

Other glucose lowering medications, metformin, acarbose, dipeptidyl peptidase IV inhibitors [128], and insulin [129] are not recommended for the treatment of steatohepatitis but they can be continued as needed for the treatment of hyperglycemia in persons with T2D and MASLD. In advanced cirrhosis, there is limited data of oral diabetes medications and GLP-1RA, avoid metformin. Insulin is preferred medication for those with advanced cirrhosis. [129]

Table 4. Available medications with demonstrable histological benefit in patients with biopsy-confirmed MASH.

Medication	Liver related and non-liver related effects	Adverse effects
PO Pioglitazone 30–45 mg daily [130]	Improves steatosis, activity and MASH resolution, Improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss
SGLT2 inhibitors [126,127]	Reduction in steatosis by imaging. Improves CV and renal outcomes; benefit in heart failure, modest weight loss	Risk of genitourinary yeast infection, volume depletion, bone loss
Liraglutide 1.8 mg SC daily [111]	Improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease	Gastrointestinal, gallstones (related to weight loss), pancreatitis
Semaglutide, 0.25–2 mg SQ weekly [110]	Improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention	
Tirzepatide 5 - 15 mg SC weekly [112]	Improvement in insulin sensitivity, significant weight loss	

None of the medications are approved for treatment of MASH but can be used in carefully selected individuals with MASLD and comorbid conditions such as diabetes and obesity.

Recommendation (Type 2 Diabetes)
15. Optimize glycemic control (HbA1c < 7%) by using preferred agents that effect steatohepatitis whenever possible. 16. GLP-1RAs (Semaglutide, Liraglutide) are safe to use in MASH (including compensated cirrhosis) and should be used for type 2 diabetes and obesity as they improve cardiometabolic outcomes. 17. The newer dual (GLP1-GIP RA) agonists, Tirzepatide has been approved for the treatment of T2D and obesity shows absolute reduction in liver fat content. 18. Pioglitazone is safe to use in adults with non-cirrhotic MASH but given the lack of robust demonstration of histological efficacy on steatohepatitis and liver fibrosis. 19. Sodium-glucose cotransporter-2 (SGLT2) inhibitors or metformin are safe to use in MASLD and should be used for their respective indications, type 2 diabetes, heart failure and chronic kidney disease.

4.2.3 MASLD and Hypertension

MASLD and arterial hypertension (AH) are common noncommunicable diseases in the global population. [131]

4.2.3.1 MASLD as Independent Risk Factor for Arterial Hypertension Development

Much evidence demonstrated the correlation between the presence and severity of MASLD and the incidence of arterial hypertension (AH). MASLD is significantly associated with a ~1.7-fold increased risk of developing incident hypertension. [132]

(a) Pathophysiology

MASLD is a potential driver of hypertension in the general population. [133] The possible pathophysiological mechanisms are

1. Liver steatosis is strongly associated with insulin resistance and hyperinsulinemia. Insulin resistance is associated with low-grade systemic inflammation and endothelial dysfunction leading to vasoconstriction. [134]
2. In addition, the action of insulin on sodium handling is frequently preserved in insulin resistance and contributes to sodium retention and arterial hypertension. [134]
3. Oxidative stress, hyperactivity of the sympathetic nervous system and the angiotensin aldosterone systems are common abnormalities in MASLD as well as in hypertension. [39]

(b) Significance of MASLD in Hypertension

Not only the presence of MASLD but also an increased content of liver fat (detected by MRI) correlated with a higher risk of hypertension (HR 2.16, $p = 0.025$). [135]

Interestingly, with resolution of fatty liver at follow-up, risk of incident hypertension is comparable to that in the group of patients with a healthy liver (aOR = 1.21) (95% CI 0.90, 1.63; $p = 0.21$). [136] These findings suggest that improving liver steatosis may reduce the risk of developing AH over time. [137]

4.2.3.2 Arterial Hypertension as Independent Risk Factor for MASLD Development

Increasing evidence show that AH is a predictor of the development and progression of MASLD. In the patients with AH, the risk of hepatic steatosis is nearly 1.5- 2 fold higher. [138,139,140]

(a) Pathophysiology

Insulin Resistance - Uncontrolled AH leads to a decrease in peripheral circulation, contributing to peripheral insulin resistance and hyperinsulinaemia which is a common basic pathophysiologic mechanism of MASLD. [131]

Visceral Obesity and alteration in adipokine - like increased leptin and reduced adiponectin are common finding in AH as well as MASLD. [141]

Oxidative Stress and Biologically Active Substances – uncontrolled AH can cause endothelial dysfunction, oxidative stress. An increase in free radical activity is the major process leading to the release of proinflammatory profibrogenic cytokines and hepatokines, leading to hepatic steatosis and fibrosis. [142]

RAAS and SNS activation – common finding in AH and have influence on insulin resistance, visceral obesity, endothelial damage and finally development of MASLD.

(b) Significance of Hypertension in MASLD

Timely control of AH with the achievement of target values (BP < 140/90 mmHg) reduce both the likelihood of developing MASLD by over 40% and the likelihood of liver fibrosis progression. [140]

4.2.3.3 Treatment of Hypertension in patients with MASLD

Treatment of hypertension to achieve the target BP will help in preventing the development of MASLD as well as progression of liver fibrosis in patient with MASLD. Generally, all antihypertensive agents can be used in patients with MASLD, some have beneficial effect not only on hypertension but also on MASLD.

An increase in intrahepatic vascular resistance has been observed in MASLD, leading to tissue hypoxia and triggering disease progression. Therefore, vasoconstriction antagonist might be used for the treatment of MASLD. In general, based on animal experiments, antihypertensive

drugs like ACEi and ARBs (losartan, termisartan, valsartan) have shown efficacy in treatment of MASLD; however, their similar effects in MASLD patients require clinical verifications. [143]

Amlodipine besylate and amlodipine aspartate exert multifactorial improvements in MASLD and hypertension by modulating gut microbiota. [144] Therefore, these agents may serve as promising therapeutic agents for treating hypertension in patients with MASLD.

Table 5. Hypertension Management in MASLD

	Fibrosis risk stratification		
	Low risk FIB-4: <1.3 LSM < 8kPa ELF <7.7	**Intermediate risk** FIB-4:1.3 – 2.67 LSM 8 – 12 kPa ELF 7.7 – 9.8	**High risk** [a] FIB-4: >2.67 LSM >12 kPa ELF >9.8
General goal	Optimize BP control and improve cardiovascular health using preferred agents, whenever possible. Assess every 3 months and intensify therapy until goal achieved.		
Goal (individualize) [b,c,d]	Systolic <130 mmHg/ Diastolic <80 mmHg	Systolic <130 mmHg/ Diastolic <80 mmHg	Systolic <130 mmHg/ Diastolic <80 mmHg; individualize if decompensated cirrhosis
Dietary recommendations	In addition to general dietary recommendations, reduce sodium and increase high potassium foods (e.g., DASH diet)		
Pharmacotherapy for hypertension [e]	First-line therapy: ACEIs and ARBs.	First-line therapy: ACEIs and ARBs.	Same but avoid ACEI or ARB if decompensated cirrhosis
Intensification of therapy	Second agent: CCB, BB [f] or thiazide diuretic (as additional agents as needed)		Same but individualize if decompensated cirrhosis. Use diuretics with caution (risk of excessive diuresis).
Additional options	Additional BP medication choices: alpha blockers, central agents, vasodilators, aldosterone antagonist.		Same but individualize if decompensated cirrhosis.

a. Advanced cirrhosis defined as persons with cirrhosis based on biopsy and Child class B or C and clinical evidence of comorbidities (varices, portal hypertension, ascites, etc.)

b. AACE recommends that BP control be individualized, but that a target of <130/80 mmHg is appropriate for most persons.

c. Less-stringent goal may be considered for frail persons with complicated comorbidities or those who have adverse medication effects.

d. A more intensive goal (<120/80 mmHg) should be considered for some persons if this target can be reached safely without adverse effects from medication

e. If initial BP >150/100 mmHg, start with dual therapy (ACEIs or ARBs + CCB, BB or thiazide diuretics)

f. Prefer weight neutral BB: carvedilol, nebivolol

Recommendation (Hypertension)

20. BP goal of <130/80 mmHg is recommended for most of the patients with MASLD but individualized BP for those with decompensated cirrhosis.
21. ACEIs and ARBs are recommended as first line antihypertensive therapy in patients with MASLD except in decompensated cirrhosis.
22. CCB, BB and thiazide diuretics are recommended as second agent if BP goal cannot be reached by first line therapy. Caution should be made with the use of diuretic in patient with decompensated cirrhosis.
23. If the BP goal cannot be reached by those agents, additional BP medication like alpha blocker, central agents, vasodilators, aldosterone antagonist, should be considered.

4.2.4 MASLD and Dyslipidemia

MASLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, central obesity, and hypertension). [145] Patients with MASLD have two-fold increased risk of lipid abnormalities and more atherogenic lipid subfractions like sdLDL compared to those without MASLD. [146,147] On the other hand, individuals with NASH resolution have improved plasma HDL and TG levels and favorable impact on lipoprotein subfractions like increase mean peak LDL diameter (1.007 vs. 0.996, P=0.004), and higher frequency of LDL phenotype A (58% vs. 33%, P=0.003). [148,149]

4.2.4.1 Management of Atherogenic Dyslipidemia in MASLD [150]

Lipid risk levels are similar in the presence of MASLD or MASH.

Table 6. Management of Atherogenic Dyslipidemia in MASLD

General goal	Early intensive management of dyslipidemia needed to reduce cardiovascular risk. Intensify therapy until the lipid goal is reached.		
Dietary recommendations	Increased fiber intake (>25g/d), prioritize vegetables, fruits, whole grains, nuts. Reduce saturated fat & added sugar (e.g., Mediterranean diet)		
Lipid risk levels	**High CV Risk** ≥2 risk factors and 10-year risk 10-20 % Diabetes or CKD ≥3 With no other risk factors	**Very high CV risk** Established CVD or 10-year risk > 20% Diabetes with >1 risk factor, CKD ≥3, HeFH	**Extreme CV risk** Progressive CVD CVD + Diabetes or CKD ≥3 or HeFH FHx premature CVD (<55 yrs male, <65 yrs female)
LDL-C goal (mg/dL)	<100	<70	<55
Non-HDL-C goal (mg/dL)	<130	<100	<80
Triglyceride goal (mg/dL)	<150	<150	<150
Apo-B goal (mg/dL)	<90	<80	<70
First line pharmacotherapy: Statins	Use a moderate-to-high intensity statin[2], unless contraindicated. Statins are safe in MASLD or NASH but do not use in decompensated cirrhosis (Child C)		
If LDL-C not at goal: intensify statin therapy	Use higher doe or higher potency statins		
If LDL-C not at goal (or statin intolerant): add 2nd agent, then add 3rd agent	Ezetimibe, PCSK9 inhibitor, Bempedoic acid, colesevelam, inclisirin		
If Triglycerides > 500 mg/dL	Fibrates, Rx grade omega 3 FA, icosapent ethyl (if diabetes, optimize glycemic control and consider pioglitazone)		
If TG 135 – 499 mg/dL on max statin dose	Emphasize diet (as above)	Add icosapent ethyl	Add icosapent ethyl

1. Major Risk Factors: Age >40, DM, HTN, FHx of early CVD, low HDL-C, elevated LDL, smoking, CKD 3,4
2. High Intensity Statin Therapy: rosuvastatin 20, 40 mg/d, atorvastatin 40, 80 mg/d
3. Other lipid modifying agents should be used in combination with maximally tolerated statins if goals not reached: ezetimibe, PCSK9 inhibitor, bempedoic acid, cholesevelam, or inclisirin.
4. Assess adequacy and tolerance of therapy with focused laboratory evaluations and patient follow up.
5. Niacin may lower triglyceride but does not reduce CVD and worsen insulin resistance. It may promote hyperglycemia in a population at high risk of diabetes.
6. Icosapent ethyl 4g/d is recommended as an adjunct to maximally tolerated statin therapy to reduce the risk of cardiovascular disease in high risk persons.

Recommendation (Dyslipidemia)

24. Diagnosis of dyslipidemia is made by lipid profile (total cholesterol, LDL, non-HDL, HDL, and triglycerides)
25. ApoB analysis (if available) should be done in people with high TG, DM, obesity, metabolic syndrome, or very low LDL-cholesterol levels.
26. Individual Risk Stratification can be made by an estimation of the 10-year CVD risk using the SCORE2 for people < 70 years of age and the SCORE2-OP (older people) for individuals ≥ 70 years of age.
27. Determine the Treatment Targets for Serum Lipids based on individual risks.
28. Treatment includes non-pharmacological and pharmacological management.
29. Non-pharmacological management consists of life-style management including diet, alcohol, smoking cessation, and exercise.
30. Pharmacological management –
    (a) statins are first line therapy and safe in patients with MASLD including advanced liver disease. Statins are also considered safe in compensated cirrhosis and may have beneficial effects on future development of decompensation and HCC.
    (b) if statin monotherapy does not achieve therapeutic goals, combination with other lipid lowering agents, such as ezetimibe, PCSK-9 inhibitors, inclisiran, bempedoic acid, fibrates, omega 3 fatty acids, or icosapent ethyl, should be considered.
    (c) In patients with MASLD and severely elevated triglycerides levels (eg, >500 mg/dL), fibrates, or a combination of fibrates with prescription grade omega-3 fatty acids or icosapent ethyl, should be used to reduce the risk of pancreatitis. If there is associated diabetes, optimize glycemic control and consider pioglitazone.
    (d) If TG 135 – 499 mg/dL on maximally tolerated statin dose, icosapent ethyl should be added to patients with very high and extremely high CV risk.

4.2.5 MASLD and Cardiovascular Disease

4.2.5.1 MASLD and Vascular Disease

Adverse cardiovascular events observed in MASLD consist of increased carotid intima-media thickness, atherosclerosis, and vasculitis. [151] These vascular impairments can lead to hypertension, stroke, coronary artery disease, ischemic heart disease, heart attack, and sudden cardiac death. Patients with MASLD are at higher risk of mortality from atherosclerotic cardiovascular disease due to elevated VLDL production, IR, hypertension, and inflammation. [152] MASLD has been suggested to be involved with initiating and progressing coronary artery disease. Coronary artery calcification scores, a marker of coronary atherosclerosis, are significantly increased in patients with MASLD. All of these studies demonstrate that MASLD shares a significant relationship with vascular alterations contributing to an increased risk of cardiovascular disease. Preventive strategies for vascular-related complications should be engaged in MASLD patients to lessen atherosclerotic associated cardiovascular disease and death. [153-155]

4.2.5.2 MASLD and Heart Disease

The relationship between MASLD and the occurrence of cardiac remodeling and dysfunction has been well documented. [156] Numerous human studies have described the altered myocardial structure and early left ventricular (LV) systolic and diastolic dysfunction in MASLD children and adults. [157,158] Patients with MASLD were also reported to have higher LV mass, increased or decreased wall thickness, altered global longitudinal strain, LV systolic and diastolic dysfunction assessed by reduced ejection fraction, lower early diastolic relaxation (e′) velocity, and increased LV filling pressure (E⁄e) which can lead to heart failure over time. There are various underlying mechanisms by which MASLD can be a driver of pathological cardiovascular remodeling. These mechanisms include IR, inflammation, mitochondrial dysfunction, oxidative stress, and activation of the SNS and RAAS. [159] Furthermore, hypertension can significantly contribute to cardiac and vascular remodeling in MASLD patients.

Multiple studies have shown that patients with MASLD are at a higher risk of having heart failure (HF) than those without MASLD. There is an association between the condition of MASLD and increased risk of new-onset heart failure even without common CVD risk factors.

[160] Previous studies have linked HF with both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) in MASLD patients. [161-164]

Cardiac arrhythmias (Atrial fibrillation and Ventricular arrhythmia) are associated with an increased risk of blood clots leading to stroke, heart failure, and sudden cardiac death. Association between MASLD and cardiac arrhythmia has been documented. [165-167] In summary, cardiac arrhythmias are associated with MASLD and significantly contribute to cardiac events and death among patients.

4.2.5.3 CVD in a Subpopulation of MASLD: Lean MASLD

Patients with non-obese MASLD are also at increased risk of atrial fibrillation, atherosclerotic CVD, cardiac remodeling, and diastolic dysfunction contributing to an increased risk of death. [168-172] Visceral obesity can drive the development of CVD through increased release of inflammatory adipokines, increases in apolipoproteins and LDL, and promotion of insulin resistance. [173]

4.2.5.4 Therapies Used in Treating CVD in MASLD Patients

There are no specific treatments approved for MASLD, and patients are typically treated for accompanying diseases (obesity, type 2 diabetes mellitus, oxidative stress, and hypertension) which can have beneficial effects on cardiovascular disease. [174]

Recommendation (Cardiovascular Disease)
31. HMG-CoA reductase inhibitors (statins) are recommended for MASLD/MASH patients with hypercholesterolemia. However, the effect of ezetimibe is not constant.
32. In MASLD/MASH patients with type 2 diabetes, SGLT2 inhibitor improves liver enzymes and histological findings, and its administration is, therefore, suggested.
33. In MASLD with type 2 diabetes, GLP-1 analogue has been found to improve liver function and liver histological findings.
34. ARB or ACEI is recommended for MASLD patients with hypertension.
35. Vitamin E improves hepatic biological and histological parameters in patients with MASH, and is recommended. However, its safety over the long term in patients with CVD, congestive heart failure, or bladder cancer has not yet been fully assessed.

4.2.6 Associated Endocrine Disorders

MASLD often occurs associated with endocrinopathies. Evidence suggests that endocrine dysfunction may play an important role in MASLD development, progression, and severity. It appears likely that there is a link between several endocrine disorders and MASLD other than the typically known type 2 diabetes mellitus and metabolic syndrome although there is controversial and insufficient evidence in this area of knowledge.

4.2.6.1 Hypothalamic and Pituitary Dysfunction

(a) Adult Growth Hormone Deficiency

Growth hormone (GH) deficiency is generally associated with several metabolic changes, including increased visceral adipose tissue, decreased lean body mass, dyslipidemia, and hypertension. [175,176] Insulin resistance and glucose intolerance are probably due to specific changes in fat distribution which lead to metabolic syndrome (MS) in patients with untreated GH deficiency. [177] Several cross-sectional studies reported an increased prevalence of liver dysfunction and MASLD in patients with hypopituitarism, particularly those with GH deficiency. [178]

The restoration of GH levels in adults with GH deficiency reduces body fat, increases lean mass, and ameliorates the lipid profile. [179,180] A few small studies have shown that GH replacement improves hepatic injury, as observed by a rapid decrease in serum liver transaminases and gamma-glutamyl transferase levels, steatosis, lobular inflammation, hepatocyte ballooning and the severity of fibrosis. [181,182]

(b) Acromegaly

Increased levels of GH are associated with increased lipolysis and favorable body composition, with increased lean body mass and decreased visceral and subcutaneous adipose tissue. [183] However, acromegaly also promotes insulin resistance with consequent hyperglycemia, hyperinsulinemia, hypertriglyceridemia and an increased risk of overt diabetes. [184]

While some studies including patients with active acromegaly found that intrahepatic lipid is relatively low in comparison to healthy subjects, [185] others showed that hepatic steatosis

is a common comorbidity in acromegaly, hypothesizing that lipotoxicity and insulin resistance may outweigh the direct hepatic effects of GH. [186]

Acromegaly treatment with surgery or medical therapy improves metabolic risk by increasing insulin sensitivity. [185] However, GH, IGF-1, insulin-like growth factor binding proteins (IGFBPs) and medical treatment have a complex relationship with insulin sensitivity and hepatic steatosis.

(c) Hyperprolactinemia

Pathological increases in prolactin levels have been frequently associated with metabolic disturbances, namely, weight gain, obesity, hyperinsulinemia and reduced insulin sensitivity, all considered important players in the pathogenesis of MASLD. [187]

In human studies, lower prolactin levels were found in patients with more severe hepatic steatosis, suggesting a possible involvement of prolactin in the progression of MASLD. [188] Although prolactin is thought to reduce liver fat content, it is plausible that chronic hyperprolactinemia is involved in the development of MASLD.

Normalization of prolactin levels with dopamine agonists correlated with weight loss. Furthermore, treatment with dopamine agonists improves insulin sensitivity, glycemic control, and lipid profile, reducing triglycerides and total and LDL cholesterol. [189]

(d) Thyroid Dysfunction

Thyroid dysfunction, explicitly, hypothyroidism, has been proposed as a possible contributory mechanism for the pathophysiology of MASLD. [190] A large metanalysis that included a total of 15 studies and 44,140 individuals suggested that hypothyroidism is significantly associated with the presence and severity of MASLD. [191] It is biologically plausible that the thyroid axis plays an important role in MASLD development, as thyroid hormones (TH) are crucial in the regulation of numerous metabolic processes, such as cholesterol and lipid metabolism and intra-hepatic concentration, circulating lipoprotein levels, body weight and insulin resistance. [192–193] TH regulate the expression of several hepatic lipogenic genes and recent studies have shown that several genes whose expression are altered in MASLD are also regulated by thyroid hormone (TH). [196,197]

In a meta-analysis, it was found that TSH levels may be positively correlated with MASLD, independent of TH levels, and that thyroid stimulating hormone (TSH) levels increase with the progression of MASLD. [194] Regarding treatment of MASLD and hypothyroidism, some improvements have been made by levothyroxine replacement therapy in addition to lifestyle changes. [195]

4.2.6.2 Reproductive System Dysfunction

(a) Hypogonadism

MASLD seems to be ubiquitous comorbidity in patients with hypogonadism. [198] The association between hypogonadism and MASLD seems to be bidirectional and causality is difficult to establish. There is a positive association between lower levels of testosterone and the prevalence of MASLD. [199,200]

Hypogonadism is associated with important cardiovascular risk factors, such as general and visceral obesity, impaired insulin sensitivity, hypertension and dyslipidemia [190] which are crucial contributors to the development of MASLD.

Hormonal replacement therapy (HRT) with testosterone seems to ameliorate these changes and may be considered a protective strategy to be taken into account. Clinical studies show that long-term testosterone replacement improves MS components and ameliorates liver enzymes changes in men with hypogonadism. [201]

(b) Menopause

Menopause is a physiological condition of estrogen deficiency with an important impact on women's health. The risk of development and progression of MASLD increases with the duration of estrogen deficiency. Accordingly, women with premature menopause are at increased risk of severe liver fibrosis. [202] Thus, both menopausal status and menopause onset age should be taken into account when determining fibrosis risk among women with MASLD. An epidemiological study evidenced a higher prevalence of MASLD in postmenopausal female patients when compared with men. [203]

The fat redistribution associated with menopause increases the risk of insulin resistance, dyslipidemia, hypertension and diabetes and consequently, may increase the risk of MASLD. [204] Among post-menopausal women, HRT is associated with a reduced risk of MASLD and

fibrosis progression. The administration of HRT among post-menopausal women appears to be protective against MASLD development but whether it affects fibrosis progression is still unclear. [202]

(c) Polycystic Ovarian Syndrome (PCOS)

Recent guidelines define PCOS as a clinical and/or biochemical hyperandrogenism, chronic oligo-anovulation and polycystic ovarian morphology. [205] A high percentage of women with PCOS present with obesity and metabolic syndrome. Evidence suggests that the prevalence of MASLD is increased in women with PCOS, regardless of weight and metabolic syndrome. The prevalence of MASLD in women with PCOS is 35 to 70%, compared with 20 to 30% in age- and body mass index (BMI)-matched control women. [206] PCOS is a prevalent condition among patients with biopsy-confirmed MASLD (approximately 50–70%) and the risk of MASLD development in POCS patients is two-fold higher compared with control women. [207] Women with POCS are also more likely to have more severe histological features, such as MASH, advanced fibrosis and cirrhosis. [208] Hyperandrogenism may be considered a central contributor to MASLD development as evidenced by women with POCS and higher androgen levels have greater intra-hepatic fat content compared with women with POCS and lower androgen levels. [209]

Preliminary results show that liraglutide and other glucagon-like peptide-1 receptor agonists can decrease the intra-hepatic fat content and visceral adipose tissue among obese women with PCOS. Additionally, the prevalence of MASLD was reduced by two thirds in obese women with PCOS treated with liraglutide. [210]

4.2.6.3 Adrenal Gland Disorders

(a) Hyperaldosteronism

Hyperaldosteronism results in the development of insulin resistance in patients with previously normal insulin metabolism (10-year follow-up). [211] Activation of the RAAS leads to altered insulin/IGF-1 signaling pathways in several tissues, namely, the liver. [212] Local hepatic increased insulin resistance may lead to inadequate lipid accumulation and eventually, to MASLD. [213]

(b) Cushing's syndrome

The effects of glucocorticoid (GC) on lipid metabolism, fat accumulation, and MASLD development are complex. Hepatic dysfunction may impair GC metabolism and alter the adrenal axis. A small study with 50 patients reported MASLD in 20% of patients with Cushing's syndrome, results similar to a retrospective study with a prevalence between 26 and 33%. [214,215]

Interestingly, one study by Ahmed et al. has defined two seemingly protective phases of altered hepatic cortisol metabolism in progressive MASLD. [216] In steatosis, increased cortisol clearance leads to lower local levels of this hormone, consequently preserving the hepatic metabolic phenotype and limiting lipid accumulation. On the other hand, increased cortisol regeneration and therefore, higher local cortisol levels are present in MASH, possibly to limit hepatic inflammation. This distinction is particularly pertinent when looking at inhibition of 11β-hydroxysteroid dehydrogenase (111βHSD1) as a potential therapeutic target. Inhibition of 11βHSD1 might be favorable in steatosis since it would further reduce local levels of cortisol. However, 11βHSD1 inhibition in NASH could be detrimental, as it would worsen the inflammatory response. Therefore, the histological stage of MASLD may dictate whether 11βHSD1 inhibition is beneficial. [217]

Recommendation (Associated Endocrine Disorders)
36. Since higher rates of MASLD have been reported in patients with associated endocrine diseases such as hypothyroidism, hypogonadism, growth hormone deficiency, polycystic ovary syndrome, acromegaly and Cushing's syndrome, screening of MASLD is considered in those patients.
37. In patients with MASLD, screening of associated endocrine disorders is recommended for those patients who have suspicious symptoms of endocrine disorder.
38. Treatment of endocrine disorders result in improvement of hepatic steatosis and/ or fibrosis in most cases.

4.2.7 MASLD and Obstructive Sleep Apnoea (OSA)

OSA is characterized by recurrent upper airway collapse during sleep, resulting in sleep fragmentation and recurrent oxyhemoglobin desaturation, termed chronic intermittent hypoxia (CIH).[223] Sleep fragmentation and CIH, as hallmarks of OSA, contribute multiple molecular mechanisms that are subsequently responsible for the development of MASLD.

Sleep fragmentation of OSA causes increased activity of the sympathetic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and oxidative stress reaction, which subsequently led to decreased insulin-mediated glucose uptake and secretion of insulin. It can also increase levels of ROS, inflammation, and pancreatic β cell apoptosis, consequently resulting in insulin resistance and reduced glucose tolerance, thereby leading to MASLD. [220]

Chronic intermittent hypoxia (CIH) contributes to the progression of MASLD through the following mechanisms:

1. Hypoxia-inducible factors (HIFs) exacerbate MASLD by promoting insulin resistance, hepatic inflammation, mitochondrial dysfunction, and oxidative stress. [222]
2. Endoplasmic reticulum stress enhances oxidative stress, further impacting MASLD. [221]
3. Activation of ROS-induced TLR4/MAPK/NF-kB pathways increase hepatic inflammation, leading to steatosis. [219]
4. Induction of dyslipidemia and impairment in gut barrier function exacerbates MASLD. [218]

Patients with OSA, particularly those who are obese, should undergo routine screening for MASLD using biochemical indicators, liver ultrasound, CT, or fibroscan. This screening aims to determine the potential association between OSA and MASLD, assess the extent of fatty liver, enhance the hypoxic state, delay the progression of MASLD, and improve liver function. [221]

There is currently a lack of efficacious pharmaceutical interventions for addressing the co-occurrence of OSA and MASLD. Correcting hypoxemia in individuals with OSA has the potential to ameliorate the severity of MASLD. However, non-pharmacotherapies such as positive airway pressure (PAP), exercise, oral appliance therapy, surgery (metabolic bariatric surgery, uvulopalatopharyngoplasty, etc.,) and hypoglossal nerve stimulation might be possible

approaches for correcting OSA hypoxemia to improve MASLD. Among these therapeutic approaches, PAP may be beneficial to MASLD with OSA independent of metabolic risk factors. [223]

Recommendation (Obstructive Sleep Apnoea)
39. Bidirectional screening programs should be adopted for patients with OSA and patients with MASLD. 40. Positive airway pressure therapy may be beneficial to MASLD with OSA by ameliorating OSA-induced hypoxia.

4.2.8 MASLD and Chronic Kidney Disease

Metabolic dysfunction associated steatosis liver disease (MASLD) and chronic kidney disease (CKD) are two global public health problems that affect almost 30 % and up to ~10–15 %, respectively, of the general adult population in many parts of the world. [224-225]

4.2.8.1 Risk of CKD in MASLD

In 2022, a comprehensive meta-analysis of 13 longitudinal studies (published until August 2020), including a total of about 1.2 million middle-aged individuals (28.1 % of whom had MASLD), showed that MASLD was significantly associated with a nearly 1.5-fold increased risk of incident CKD, and this CKD risk was further increased with more advanced liver disease, especially with the severity of hepatic fibrosis. [39]

In 2022-2023 studies, MASLD on ultrasonography was associated with an increased risk of incident CKD even after adjusting for age, sex, obesity, hypertension, dyslipidemia, serum liver enzymes and baseline eGFR. [226-232] MASLD had a ~2-fold increased risk of developing ESRD than those without MASLD (232). Liver fibrosis progression (non-invasively assessed by MASLD fibrosis score) was also associated with a significantly higher risk of incident CKD. [233]

4.2.8.2 Impact of combination of MASLD and CKD

The coexistence of MASLD and CKD, but not MASLD or CKD alone, was a significant risk factor for ischemic heart disease. [234] It remained significant after adjustment for age, sex, smoking, family history of ischemic heart disease, and presence of obesity, diabetes, hypertension, or dyslipidemia. MASLD was also significantly associated with higher risks of adverse clinical outcomes and all-cause mortality in patients with CKD. [235]

(a) Putative mechanisms linking MASLD to CKD

The precise pathophysiological mechanisms linking these two diseases are not fully understood and likely involve the liver and many extra-hepatic organs. CKD is a multisystem disease that shares a plethora of cardiometabolic risk factors with MASLD, making it challenging to dissect causative relationships between the two conditions.

(b) Metabolic syndrome and liver-mediated mechanisms

Many of the cardiometabolic features of MASLD are shared risk factors with both CVD and CKD and can contribute to the progression of both liver disease and CKD by creating a systemic milieu of metabolic and vascular dysfunction and low-grade inflammation. [236]

(c) Adipose tissue, lipid droplets and PPAR-γ dysfunction connecting MASLD and CKD

Obesity-associated adipose tissue dysfunction may also contribute to the development of systemic low grade inflammation, strongly associated with CKD and MASLD. [237,238] Dysfunction in PPAR-γ signaling with obesity is an important factor, leading to detrimental changes in lipid handling, inflammation and fibrosis that may potentially 'drive' the development and progression of both MASLD and CKD. [239]

(d) Intestinal dysfunction and dysbiosis affecting MASLD and CKD

Intestinal dysbiosis is a hallmark characteristic of both MASLD and CKD. [240,241] Alterations in intestinal bacterial populations in MASLD and CKD typically cause a loss of bacterial richness and diversity and a depletion of beneficial bacteria such as Lactobacillus and Bifidobacterium. Conversely, Enterobacteria and Enterococci are enriched in patients with MASLD and CKD. [242]

(e) Genetic predisposition to both MASLD and CKD

Several MASLD-associated polymorphisms, such as those in PNPLA3, TM6SF2, HSD17B13, MBOAT7 or GCKR, have also been shown to increase the risk of incident CKD. [243]

4.2.8.3 Pharmacotherapies beneficially affecting both MASLD and Chronic Kidney Disease

When considering potential drug treatments that may benefit MASLD and CKD, it is important to consider drug actions that are of benefit, both to attenuate fat, inflammation and fibrosis in the liver and factors that have been shown to improve CKD (or risk factors for CKD).

(a) Sodium-glucose cotransporter-2 inhibitors

A recent post-hoc analysis of two large double-blind randomized controlled trials (the CANVAS trials) showed that in patients with T2DM, treatment with canagliflozin vs. placebo resulted in significant improvements in some non-invasive fibrosis biomarkers. [244] SGLT2

inhibitors may also decrease uric acid-induced renal damage by lowering serum uric acid concentrations [245] and also benefit albuminuria by reducing low-grade inflammation [246], fibrogenic response, apoptosis, and glucose-induced oxidative stress. [247] Thus, in people living with T2DM who have MASLD, there is a strong case for the use of SGLT2 inhibitors for patients with CKD or at high risk of CKD.

(b) Peroxisome proliferator-activated receptor-gamma agonists

Pioglitazone is a selective agonist regulating the PPAR-γ nuclear receptor activity. [248] The European and American guidelines for the treatment of MASLD recommended the use of the peroxisome proliferator-activated receptor-gamma agonist (PPAR-γ) pioglitazone in adults with biopsy-confirmed MASH, regardless of the presence or absence of T2DM. [249,76] PPAR-γ is also abundantly expressed in the kidney in the medullary collecting duct, paraurethral and bladder epithelial cells, as well as podocytes, mesangial cells, and vascular endothelial cells. [239] The PPAR-γ function in the kidney ranges from energy metabolism and cell proliferation to inflammatory suppression. [239] Pioglitazone should be considered when not contraindicated in patients with MASLD, not least because of benefits in the kidney in patients at risk of CKD. But in some cases, safety concerns (moderate weight gain, peripheral edema, and moderately increased risk of distal bone fractures in postmenopausal women) may limit the long-term use of pioglitazone in clinical practice.

(c) Incretin receptor agonists

The two major classes of incretin receptor agonists showing considerable promise in treating the early stages of MASLD are glucagon-like peptide-1 (GLP-1) receptor agonists (especially subcutaneous semaglutide) and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonists (tirzepatide). [250] These drugs are very effective in facilitating weight loss, and have been recently evaluated their effectiveness in treating MASLD. [251] GIP and GLP-1 also have anti-inflammatory and anti-reactive oxygen species effects. They may benefit the vasculature by inhibiting macrophage infiltration and increasing nitric oxide production. [252] These agonists may confer cardiovascular protection that benefits the kidney in people with MASLD.

(d) Renin-angiotensin-system inhibitors

Although ACE inhibitors and angiotensin II receptor blockers are clinically effective in a range of adverse cardiovascular, renal and diabetes-related outcomes, it is difficult to prove antifibrotic effects on liver fibrosis in adult patients with MASLD. [253]

(e) Finerenone

It is a new nonsteroidal, selective mineralocorticoid receptor antagonist. Although treatment with finerenone has been shown to result in lower risks of CKD progression and adverse cardiovascular outcomes in people with T2DM with CKD [254], its effect on liver disease in MASLD is uncertain. [255]

Recommendation (Chronic Kidney Disease)
41. People living with MASLD fibrosis, should be screened renal function at the start of diagnosis and monitored regularly.
42. In treatment of patient with MASLD who have CVD or CKD or are at high risk of these adverse outcomes, SGLT2 inhibitors, PPAR-γ agonists such as pioglitazone, and incretin receptor agonists, angiotensin II receptor blockers or renin- angiotensin-system inhibitors, should be considered.

4.2.9 MASLD and Extrahepatic Malignancy

Recent evidence shown that the patients with MASLD are increased risk for overall mortality and liver-related mortality. [256] MASLD is associated with the gastrointestinal tract malignancies including colorectal, gastric/oesophageal, and pancreatic. Additionally, MASLD was associated with other malignancies such as breast, uterine, prostate, renal and haematologic malignancies. [257] People with MASLD had a nearly 2-fold increase in the overall risk of incident cancers when compared to an age- and sex-matched general population in large longitudinal cohort study. [265]

4.2.9.1 Pathological Links Between MASLD, Colorectal Adenomas and Cancer

There is no exact pathological links between MASLD, colorectal adenomas and cancer. Obesity is a common risk factor for the development of MASLD and colorectal cancer (CRC)

independent of geographic locations, race and ethnicity. [258] Insulin resistance is the key association between the obesity and development of colorectal malignancies. [259] In addition to the insulin resistant, low-grade chronic inflammation is the key role in cancer initiation and growth via the stimulation of insulin like growth factor-1 axis. [257]

4.2.9.2 MASLD and Colorectal Neoplasms

Several studies showed that the association between the MASLD and colorectal adenomatous polyps/colorectal malignancies. MASLD was associated with an increased risk of developing colorectal adenomatous polyps [260] MASLD was significantly associated with colorectal malignancies in males but not in females [261] and especially in patients with obesity. [262] The risk of developing colorectal neoplasms increased with worsening fatty liver severity. [263] Some studies showed the different results with no significant association between the MASLD and colorectal cancers. [264]

4.2.9.3 MASLD and Other Extrahepatic Malignancies

MASLD was strongly associated with the development of oesophageal cancer. But some studies showed the contrary result. [261] MASLD was a significant risk factor for developing gastric cancer especially in patient with obesity [262,263], uterine cancer [265], and pancreatic cancer. [266] MASLD was also a significant risk factor for recurrence and progression of breast cancer [267, 268] and prostate cancer. [269]

Recommendation (Extrahepatic Malignancy)
43. MASLD is a risk factor for developing extrahepatic malignancies including gastrointestinal cancers (colorectal cancer, oesophageal cancer, pancreatic cancer and gastric cancer) and other hormone sensitive cancers (breast cancer, uterine cancer and prostate cancer).

5. Initial Evaluation of a Patient with MASLD

Patients with MASLD are most commonly referred with incidentally noted hepatic steatosis on imaging or elevated liver chemistries. It is important to note that normal values provided by most laboratories are higher than what should be considered normal in MASLD, in which a true normal alanine aminotransferase (ALT) ranges from 29 to 33 U/L in men and from 19 to 25 U/L in women.[1] Initial evaluation of such patients should include screening for metabolic comorbidities, assessment of alcohol intake, and exclusion of other causes of liver disease as well as physical examination to identify signs of insulin resistance and advanced liver disease (Table 7).

Table 7: Initial evaluation of a patient with MASLD

History	- Weight history - Medical comorbidities - Recent and current medications - Family history of T2DM, MASLD, or cirrhosis - Screening for OSA - Alcohol use, including amount, pattern of use and duration
Physical examination	- Body fat distribution - Features of insulin resistance - Features of advanced liver disease
Laboratory tests	- Complete blood picture - Liver function tests, liver enzymes - Fasting plasma glucose - Glycated hemoglobin (HbA1c) - Fasting lipid profile - Creatinine - Urine microalbumin or protein to creatinine ratio in DM patients - HBsAg, HCV Ab screening - Consider as appropriate other causes of steatosis/steatohepatitis
Imaging tests	- USG (abdomen) - Fibroscan

When the clinical profile is atypical (eg, not associated with metabolic comorbidities) or accompanied by additional signs or symptoms suggesting additional/alternate etiologies, less common causes of steatosis or steatohepatitis should be excluded (e.g.,

Hypobetalipoproteinemia, LAL deficiency, Nutrient deficiency (eg, carnitine, choline), Wilson disease, Celiac disease). Rare causes of steatosis or fibrosing steatohepatitis can present in isolation or explain an exaggerated MASH phenotype and should be considered in specific clinical contexts. Several drugs can also lead to hepatic steatosis or steatohepatitis or exacerbate disease in those with underlying MASLD and should be identified during initial evaluation (Table 10). Although gene-based risk stratification is currently not recommended in clinical practice, familial aggregation of insulin resistance supports gene-environment interactions in the risk for MASLD, MASH, and advanced fibrosis.

5.1 Initial Evaluation in Primary Care or Hepatologist Care

In most patients, MASLD is asymptomatic or associated with vague symptoms, often leaving patients undiagnosed. The prevalence of advanced disease is lower in primary care practices than in hepatology practices, and thus, the approach to evaluation is context dependent (Figure 5)**.**

Patients with steatosis noted on imaging or for whom there is a clinical suspicion of MASLD, such as those with metabolic risk factors or unexplained elevation in liver chemistries, should undergo further evaluation. In settings with a low prevalence of advanced fibrosis, such as in the primary care setting, the emphasis is on excluding advanced fibrosis using a test with a high negative predictive value. When the fibrosis-4 index (FIB-4) is <1.3, patients can be followed in the primary care setting and reassessed periodically.

Patients without prediabetes/type 2 diabetes mellitus (T2DM) and 1–2 metabolic risk factors can be reassessed every 2–3 years. Patients with prediabetes/T2DM or 2 or more metabolic risk factors are at higher risk for disease progression, and more frequent FIB-4 monitoring (eg, every 1–2 y) should be considered.

In patients older than age 65, a FIB-4 cutoff of >2.0 should be used. FIB-4 has low accuracy in those under age 35; thus, secondary assessment should be considered in those <35 with increased metabolic risk or elevated liver chemistries. FIB-4 should not be used in acutely ill patients. In patients with FIB4 ≥1.3, a secondary assessment should be done [preferentially vibration-controlled elastography (VCTE) or Enhanced Liver Fibrosis (ELF) initially] or the patient referred for further risk stratification (if being seen in a non-gastroenterology/ hepatology setting). Direct referral to gastroenterology/hepatology should be considered in those with

aminotransferases persistently (>6 months) above normal to exclude other causes of liver disease or when FIB4 > 2.67 due to the increased risk of clinically significant fibrosis.

In higher prevalence settings, such as gastroenterology/hepatology clinics, additional risk assessment with magnetic resonance elastography (MRE) may be appropriate when noninvasive tests (NITs) are indeterminate or there is clinical suspicion of more advanced disease. Identification of cirrhosis should prompt screening for HCC and esophageal varices. In addition, MRE or corrected T1 (cT1) may help identify patients with "at-risk" MASH (MASH with MASLD activity score ≥4 and fibrosis stage ≥2) who may benefit from a therapeutic intervention as they become available.

If cirrhosis is suspected based on NITs, clinical data, or imaging findings, then cirrhosis-based management may be initiated without a liver biopsy. Liver biopsy should be considered when NITs suggest significant fibrosis (≥F2), especially if additional evaluation suggests the presence of "at-risk" MASH (eg, using FAST, MEFIB, MAST, or cT1), NIT assessment is indeterminate, aminotransferases are persistently elevated (>6 months), or additional/alternate diagnoses are suspected. Note that in patients with confirmed or suspected advanced fibrosis, an ELF ≥11.3 is a predictor of future liver-related events and is approved for this purpose; use of other ELF cutoffs in secondary risk assessment is based on expert option.

Patients at all stages of disease should be counseled on lifestyle modifications, and those with ≥F2 fibrosis targeted for pharmacological interventions as they become available. Specific threshold values of NITs are approximations supported by current evidence and are meant to guide clinical management through primary care to gastroenterology/hepatology practices rather than be interpreted in isolation.

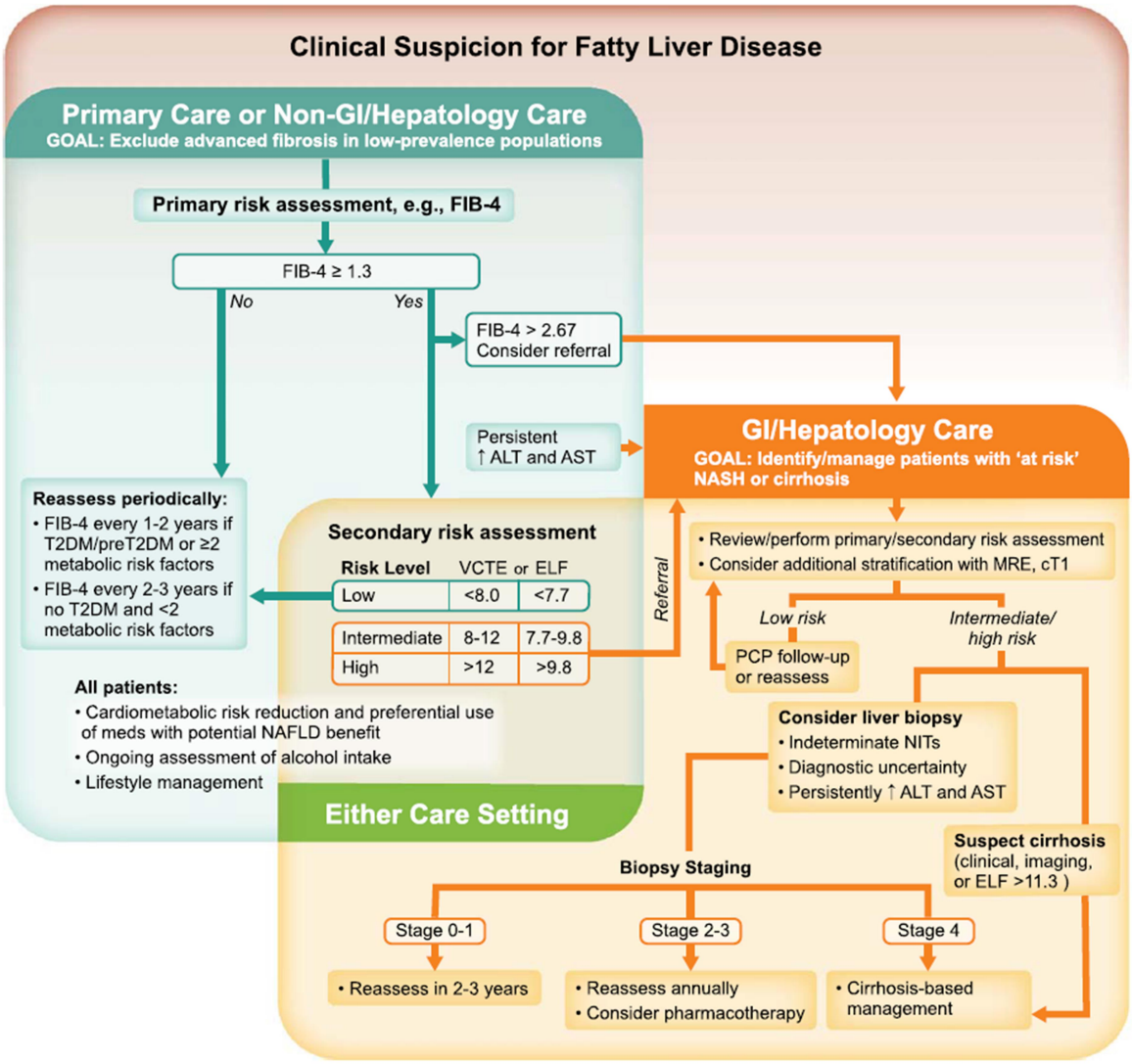


Figure 5. Algorithm for the evaluation of patients at risk for or with established MASLD across practice settings.

5.2 Investigation for Presence of Clinically Significant Fibrosis

Targeted screening of populations at increased risk for advanced liver disease is advised to identify and manage those with clinically significant fibrosis (stage ≥2). Screening in high-risk populations, such as those with T2DM, obesity with metabolic complications, a family history of cirrhosis, or significant alcohol use, may identify those with asymptomatic but clinically

significant fibrosis. [24] Early identification of such at-risk patients allows for interventions that prevent future hepatic complications. [25]

Careful assessment of family history is important because first-degree relatives of probands with MASH cirrhosis have a 12-fold higher risk of advanced fibrosis. [26] The risk of MASLD and advanced fibrosis may be increased, even among non-related household members, likely because of related similar environmental risk factors, lifestyle patterns, and gut microbiota. [27]

Recommendation (Initial Evaluation)
44. General population-based screening for MASLD is not advised. 45. All patients with hepatic steatosis or clinically suspected MASLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4. 46. High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis. 47. Patients with MASH cirrhosis are at the highest risk for liver-related outcomes and require routine surveillance for HCC, esophageal varices, and monitoring for decompensation. 48. Patients with suspected advanced MASH or discordant NITs should be referred to a specialist for evaluation, management, and/or further diagnostic evaluation. 49. Aminotransferase levels are frequently normal in patients with advanced liver disease due to MASH and should not be used in isolation to exclude the presence of MASH with clinically significant fibrosis. 50. First-degree relatives of patients with MASH cirrhosis should be counseled regarding their increased individual risk and offered screening for advanced hepatic fibrosis.

5.3 MASLD with Alcohol Consumption

Alcohol use can be an important contributor to fatty liver disease progression and should be quantified in all patients. [270] Alcohol intake can be broadly classified as mild [up to 20 g (women) and 30 g (men) per day], moderate [21–39 g (women) and 31–59 g (men) per day] or heavy [≥40 g (women) and ≥ 60 g (men) per day] [271]

MetALD, describes those with MASLD who consume greater amounts of alcohol 20-50 g/day for females and 30-60 g/day for males, respectively (one unit of alcohol equal to 10 g of alcohol in general). Any level of alcohol consumption, including social drinking, was associated with an increased risk of HCC development. [272]

Moderate alcohol use increases the probability of advanced fibrosis, particularly in patients with obesity or T2DM, indicating potential synergistic effects of insulin resistance and alcohol on liver disease progression. [270] Heavy alcohol consumption accelerates liver injury and fibrosis progression and should be avoided in patients with MASLD/ MASH. [270] In addition, daily alcohol may increase the risk for HCC and extrahepatic malignancies. Obesity and alcohol use synergistically increase the risk of liver injury, cirrhosis, HCC, and death from liver disease. [271] The impact of alcohol use (type, pattern, frequency, duration, and quantity) on the natural history of MASLD/MASH requires further investigation.

Recommendation (Alcohol Consumption)
51. In patients with MASLD, alcohol can be a cofactor for liver disease progression, and intake should be assessed on a regular basis. 52. Patients with clinically significant hepatic fibrosis (≥ F2) should abstain from alcohol use completely. 53. There is no safety level of alcohol drinking & total abstinence is recommended in patients with MASLD.

5.4 Drugs that cause MASLD

Drugs represent an alternative cause of fatty liver disease and the term that corresponds to this injury is drug induced fatty liver disease (DIFLD). It is a specific form of DILI, characterized by intracellular lipid accumulation in hepatocytes with steatotic changes as the

predominant histopathological pattern. [273] DIFLD is often accompanied by inflammation and oxidative stress, which leads to the development of drug induced steatohepatitis (DISH). [274] Chronic liver injury leads to hepatocyte death, followed by the activation of stellate cells which finally results in liver tissue fibrosis. [275]

This conversion to MASH appears to involve genetic and environmental factors. [276] MASLD and obesity may enhance the risk of hepatotoxicity of various drugs. [277] The possible mechanisms by which certain drugs are able to accelerate progression of MASLD include induction of oxidative stress, diminished mitochondrial fatty acid oxidation, increased de novo lipogenesis, and damaged egress of VLDL from liver cells. [278]

DIFLD is a product of direct impact of drugs on the liver, mostly associated with the extended intake of medications. In addition, there are numerous drugs which can cause progression of steatohepatitis. Several drugs can also lead to hepatic steatosis or steatohepatitis or exacerbate disease in those with underlying MASLD and should be identified. It is important to emphasize that drug withdrawal or dose adjustment are so far the best therapeutic recommendation when it comes to DIFLD cases.

Table 8: Drugs that cause MASLD

Macrovesicular liver steatosis [279-281]	**Microvesicular liver steatosis** [282,283]	**Steatohepatitis** [283,284]
- Glucocorticoids - Amiodarone - Methotrexate - Estrogens - Tamoxifen - Nonsteroidal - Anti-inflammatory drugs - Paracetamol - 5-fluorouracil - Metoprolol	- Valproic acid - Tetracycline - Ibuprofen - Zidovudine - Glucocorticoids	- Valproic acid - Tamoxifen - Amiodarone - Propranolol

Recommendation (Drugs that cause MASLD)
54. Several drugs can also lead to hepatic steatosis or steatohepatitis or exacerbate disease in those with underlying MASLD and should be identified.
55. Common recommendation is the withdrawal of the potential offending agent.

5.5 MASLD in lean individuals

Although MASLD is commonly associated with obesity, it can also occur in non-overweight (BMI <25 kg/m2 in Western or <23 kg/m2 in Asian individuals) patients. [285] The prevalence of MASLD in lean individuals varies from 4.1% in United States [286] to as high as 19% in Asia. [287] Alcohol use and alterations in the gut microbiome may also contribute to MASLD in lean individuals. [288] Genetic factors likely play a significant role in MASLD in lean individuals, but the overall genetic contribution to MASLD requires further study. [40]

Lean individuals with MASLD are more commonly of Hispanic or Asian origin, which is likely in a higher prevalence of the PNPLA3 I148M polymorphism. [287] Alterations in the TM6SF2 gene, which confers susceptibility to MASH and fibrosis. Genetic testing is currently not recommended, as it does not alter management. [285]

Management of MASLD in patients without obesity can be clinically challenging. Recommending weight loss may not be appropriate for lean patients with MASLD, but dietary modifications and exercise in this group may be beneficial. [285]

Table 9: Diagnostic Criteria for MASLD in Lean Individuals

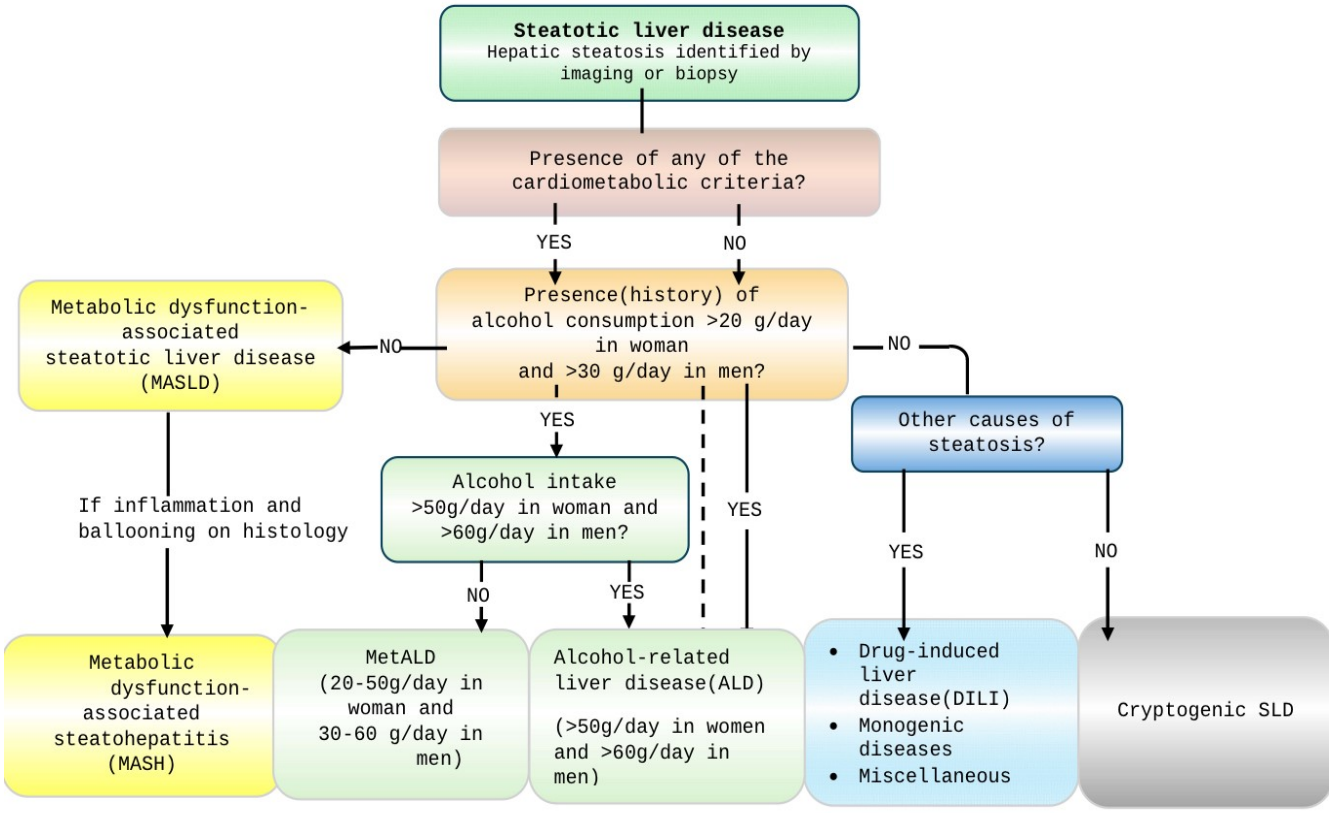
• Individuals with BMI less than 25 and 23 for the Western and Asian populations respectively
• Evidence of hepatic steatosis on imaging or liver biopsy
• Any of these cardiometabolic criteria- - an abnormal metabolic profile including waist circumference, triglyceride, fasting blood sugar, blood pressure, and high density lipoprotein or - metabolic diseases (High Lipid Profile, Hypertension, and Diabetes Mellitus) or - any medication for these diseases

Recommendation (MASLD in Lean Individuals)
56. Screening for MASLD should not solely rely on obesity as a criterion; instead, the focus should be on assessing the metabolic health of patients with lean individuals.

6. Diagnosis and Assessment of MASLD

6.1 Diagnosis of MASLD

The diagnosis of MASLD requires the presence of at least one cardiometabolic risk factor in



an individual with documented steatosis. [101]

Figure 6. Flow-chart for diagnosis of MASLD

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

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

Table 10. Cardiometabolic risk factors in the definition of MASLD

Noninvasive biomarkers are emerging as valuable tools for predicting adverse liver-related outcomes, previously an important function of liver biopsies. Although liver biopsy assessment remains the reference standard for the grading and staging of MASH, it has important limitations related to risk, cost, and resource utilization. For assessment of MASLD, the following should be done. [100]

- Noninvasive identification and quantification of hepatic steatosis
- Estimation of liver fibrosis in patients with suspected or confirmed MASLD

6.1.1 Noninvasive identification and quantification of hepatic steatosis

(a) Ultrasound

Transabdominal ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations. It is the most commonly used imaging method for the diagnosis of steatosis, since it is widely available, innocuous, cheap and

well established [289] The basic sign for steatosis is the increased echogenicity of the liver parenchyma in comparison to the cortex of the right kidney. [290]

The classification of steatosis is usually graded as follows: [290]

Grade 0: normal echogenicity of the right liver lobe in comparison with the cortex of the right kidney;

Grade 1: slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders;

Grade 2: moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm;

Grade 3: marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver.

The sensitivity of B-mode ultrasound to detect hepatic steatosis varies between 53–76%, the specificity is between 76–93%. In the presence of sonographic criteria of a higher-grade steatosis, the probability of the presence of hepatic steatosis is nearly 100%. [291] On the other hand, the sensitivity of B-mode sonography is poor in the case of mildly pronounced steatosis (<20–30%), so that hepatic steatosis cannot be ruled out with certainty if the B-mode criteria mentioned are absent. [291]

(b) Vibration-Controlled Transient Elastography (Fibroscan)

VCTE is an ultrasound-based imaging technique that allows rapid, bedside measurements of steatosis and tissue stiffness. Ultrasound-based CAP values provide a good estimate of the liver steatosis grade. [101] CAP remains the most widely used tool for first-line steatosis detection. The cutoff values of steatosis S1, S2, and S3 with the M probe were measured as 294, 310, and 331 dB/m, respectively, and the measurements made with the XL probe were similar. It was also shown that the etiology of liver damage, BMI, sex, AST level, and the presence of diabetes can affect the measurement of CAP but the use of an M probe or XL probe does not significantly affect the measurement. [292]

The sensitivity of the CAP measurement in the detection of ≥S1 was 78%, the specificity was 79%; the sensitivity in the detection of ≥S2 was 85%, the specificity was 79%; and the sensitivity in the detection of ≥S3 was 83%, the specificity was 79%. [293]

(c) MRI–proton Density Fat Fraction (PDFF)

MRI can be used to quantify the triglyceride content (usually expressed as proton density fat fraction [PDFF]) in the liver and is the non-invasive gold standard for hepatic lipid quantification in MASLD. [101] It is an accurate, reproducible, and precise MRI-based biomarker for liver fat quantification that is routinely used in clinical research. [101] Cutoffs of MRI-PDFF (6.4%, 17.4%, and 22.1%) were used for S0 to S3 steatosis grades. [309] Although MRI-PDFF is superior to CAP in the diagnosis as well as the quantification of liver fat, this advantage is tempered by cost, patient acceptance, and the disadvantage of not being a point-of-care technique. [100] Therefore, it is not recommended as a first-line tool and more suited to clinical trials. [289]

6.1.2 Estimation of Liver Fibrosis in patients with suspected or confirmed MASLD

Healthcare providers should look for MASLD with liver fibrosis either in individuals with (a) type 2 diabetes or (b) abdominal obesity and ≥ 1 additional metabolic risk factor(s) (c) abnormal liver function tests. Early diagnosis of fibrosis and subsequent appropriate management can potentially prevent progression to cirrhosis and its complications and may justify screening in these populations at risk. The risk of future liver-related events starts to increase at fibrosis stage 2. Although HCC may develop in non-cirrhotic MASLD, cirrhosis remains the key risk factor for HCC. If one can prevent MASLD from progressing to cirrhosis, theoretically most liver related events can be prevented. [101] Non-invasive methods for determining the grade of fibrosis are mainly based on the examination of blood components or on imaging methods that mostly reflect mechanical tissue properties. [101]

6.1.2.1 Laboratory-based fibrosis biomarkers

A combination of values from blood tests enables a better prediction of fibrosis than single liver enzyme values (ALT and/or AST). The following scores have been described in the literature and were tested in several studies for their predictive power for fibrosis: [101]

(a) Fibrosis-4 Index (FIB-4)

FIB-4 (Fibrosis-4 index) = age x AST/ [platelet count x √(ALT)] (age in years, ALT and AST in U/L, and platelet count in 10^9/L)

Fibrosis-4 Index (FIB-4) is a simple non-invasive tool developed to determine the presence of advanced liver fibrosis, with scores categorised into low (<1·30), indeterminate (1·30–2·67), or high (>2·67) risk of fibrosis. FIB-4 is calculated using a simple algorithm based upon age, ALT, AST, and platelet count and outperforms other calculations in its ability to identify patients with a low probability of advanced fibrosis. High values of FIB-4 and other NITs have also been associated with all-cause and liver-related outcomes in population-based studies. [294] The FIB-4 has recently been shown to perform similarly or better than a range of fibrosis biomarkers including the enhanced liver fibrosis (ELF™) test. [295]

It is consistently recommended by international guidelines as part of first-line assessments in MASLD and type 2 diabetes. Guidelines also recommend repeat FIB-4 testing every 1–3 years (depending on disease severity or presence/absence of cardiometabolic risk factors) to reassess risk of clinical events. [296] FIB-4 calculator- https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis.

(b) APRI (AST to Platelet Ratio Index)

APRI = (AST/TopNormal AST) x (100/platelet count)

Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 and cirrhosis (F4) should be based on an APRI score of >1.0. (10) In a meta-analysis by Lin et al, it was found that in patients with hepatitis C, an APRI score greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. [297] The AUC of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89, respectively in patients with chronic hepatitis C. [298]

(c) NAFLD Fibrosis Score (NFS)

NAFLD Fibrosis Score = -1.675 + 0.037 × age + 0.094 × BMI + 1.13 × impaired fasting glucose (yes = 1, no = 0) + 0.99 × AST/ALT - 0.013 × platelet count - 0.66 × albumin (age in years; BMI in kg/m2; AST and ALT in (U/L); platelet count in 10^9/L and albumin in g/dl)

NAFLD fibrosis score (NFS) is a composite score of age, hyperglycemia, body mass index, platelet count, albumin, and aspartate aminotransferase and alanine aminotransferase

(AST/ALT) ratio and was found to independently identify patients with and without advanced fibrosis at initial MASLD diagnosis. [299]

To assess the probability of fibrosis, NFS score is classified as < -1.5 for low probability, > -1.5 to < 0.67 for intermediate probability, and > 0.67 for high probability. By applying the high cutoff score (0.676), the presence of advanced fibrosis could be diagnosed with high accuracy (positive predictive value of 90% and 82% in the estimation and validation groups, respectively). [300] Tests based on components of collagen formation can provide additional evidence of fibrosis.

(d) ELF panel (Enhanced Liver Fibrosis)

The ELF panel is a proprietary blood test consisting of three elements involved in matrix turnover: hyaluronic acid, tissue inhibitor of metalloproteinase-1, and N-terminal procollagen III peptide. An ELF score of ≥ 9.8 reliably identifies patients with MASLD at increased risk of progression to cirrhosis and liver-related clinical events. [301]

The NICE guidelines recommend that the ELF test should be considered in people who have been diagnosed with MASLD to test for advanced fibrosis, suggesting an ELF score of 10.51 as the cut-off value. [302] Most clinical studies used manufacturer recommended thresholds for ruling advanced F3/4 fibrosis out (7.7) or in (9.8) respectively and reported different levels of performance of this test. [303] In a meta-analysis of 63 studies, ELF showed a relatively high performance in detecting significant fibrosis, advanced fibrosis or cirrhosis (AUROCs 0.811, 0.812 and 0.810, respectively). [101]

6.1.2.2 Imaging methods

(a) Vibration-Controlled Transient Elastography (FibroScan)

VCTE is the most commonly used method to assess liver stiffness and can be used to exclude significant hepatic fibrosis. A recent meta-analysis suggested that a VCTE-derived liver stiffness measurement (LSM) <8 kPa can be used to rule out advanced fibrosis, especially if used sequentially after FIB-4. In identifying patients with cirrhosis, a sequential approach with a FIB-4 > 3.48 and LSM by VCTE ≥ 20 kPa had a specificity of 90%. [304] LSMs by VCTE between 8 and 12 kPa may be associated with fibrotic MASH, and LSM > 12 kPa is associated with a high

likelihood of advanced fibrosis, although the positive predictive value is low (range: 0.34–0.71). [305]

Changes in liver stiffness may also be useful in identifying disease progression, such that an increase in liver stiffness of 20% on either VCTE or MRE may be associated with disease progression and long-term clinical outcomes. [306]

(b) Magnetic Resonance Elastography (MRE)

MRE is more sensitive than VCTE in the detection of fibrosis stage ≥ 2 and is considered to be the most accurate noninvasive, imaging-based biomarker of fibrosis in MASLD. Although MRE is not a first-line approach to risk stratification in a patient with MASLD, it can be an important tool if clinical uncertainty exists. An LSM by MRE ≥ 5 kPa is suggestive of cirrhosis. [100]

Among patients with cirrhosis, baseline LSM by MRE predicts future risk of incident hepatic decompensation and death. Liver stiffness assessed by MRE may also be useful to assess the risk of decompensation. In one study, MRE LSMs of 5 and 8 kPa were associated with 9% versus 20% risk of incident hepatic decompensation or death, respectively. [307] An individual patient meta-analysis provided further validation of these findings with a baseline MRE LSM stratified into three categories of <5 kPa, 5–8 kPa, and >8 kPa that were associated with 1.6%, 17%, and 19% risk of decompensation over 3 years of follow-up, respectively. [308]

6.1.2.3 Proposed strategy for non-invasive assessment of the risk for advanced fibrosis and liver-related outcomes

In adults with MASLD, a multi-step approach is recommended. First, an established non-patented blood-based score, such as FIB-4, should be used. Thereafter, established imaging techniques, such as liver elastography, are recommended as a second step to further clarify the fibrosis stage if fibrosis is still suspected or in high-risk groups.

In adults with MASLD, a multi-step approach is recommended. First, an established non-patented blood-based score, such as FIB-4, should be used. Thereafter, established imaging techniques, such as liver elastography, are recommended as a second step to further clarify the fibrosis stage if fibrosis is still suspected or in high-risk groups. [309]

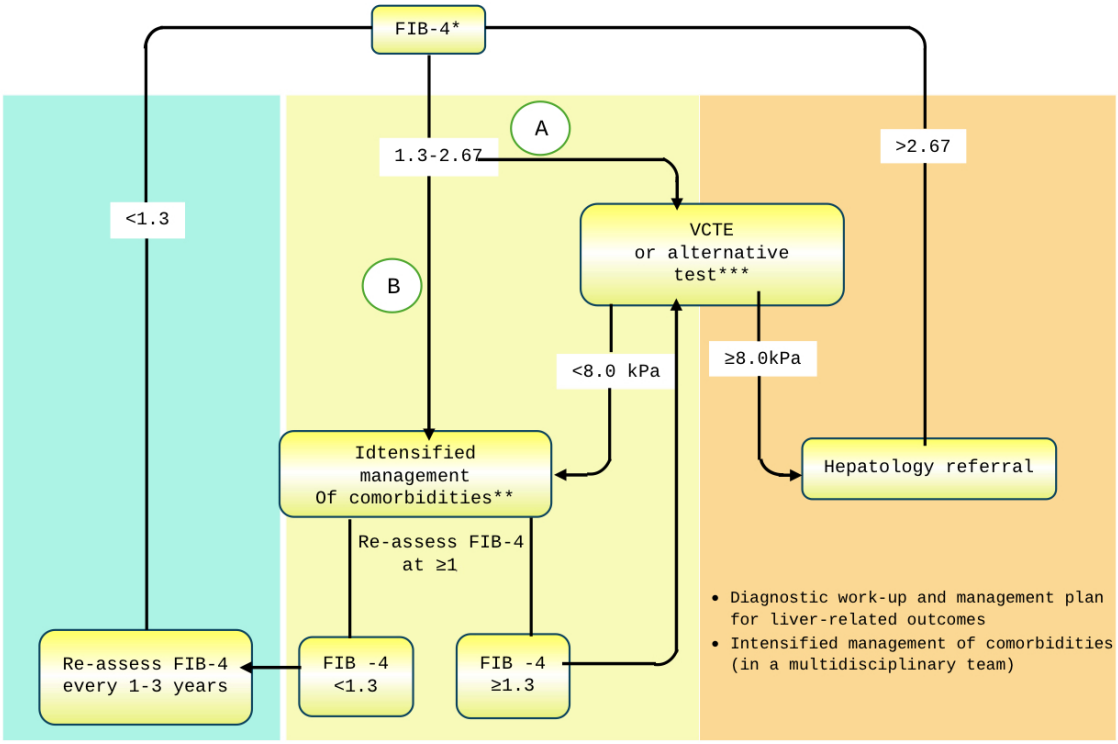


Figure 7. Proposed strategy for non-invasive assessment of the risk for advanced fibrosis

* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)

** e.g. lifestyle intervention, treatment of comorbidities (e.g. GLP1RA), bariatric procedures

*** e.g. MRE, SWE, ELF, with adapted thresholds

A and B are options, depending on medical history, clinical context and local resources

6.1.2.4 Role of liver biopsy

Although all non-invasive methods (in contrast to the limited sample by biopsy) can provide information on the entire liver, no histological characteristics of the tissue can be assessed. Only liver biopsy allows for an assessment of microscopic features (ballooning, lobular inflammation, Mallory bodies, microvesicular vs. macrovesicular steatosis, staging of fibrosis), including the presence of MASH. However, the presence of steatohepatitis (independent of fibrosis stage) may not impact treatment decisions and therefore, a liver biopsy is usually not

required for the clinical diagnosis and treatment of MASLD. Still, liver biopsies may be considered essential as part of clinical studies (e.g. to determine the MASLD activity score) or to rule out other diseases (e.g. autoimmune hepatitis). (1) In Myanmar, liver biopsy is not recommended for diagnosis and assessment of MASLD.

Recommendation (Diagnosis and Assessment of MASLD)

57. MASLD can be diagnosed by the presence of at least one cardiometabolic risk factor in an individual with documented steatosis in imaging.
58. For assessment of MASLD, noninvasive identification and quantification of hepatic steatosis and estimation of liver fibrosis should be done.
59. MASLD can be graded as grade 1, grade 2 and grade 3 with ultrasound and confirmed by transient elastography if available.
60. For assessment of fibrosis, a multi-step approach is recommended. First, an established non-patented blood-based score, such as FIB-4, should be used. Thereafter, established imaging techniques, such as liver elastography, are recommended as a second step to further clarify the fibrosis stage if fibrosis is still suspected or in high-risk groups.
61. If significant fibrosis is present, hepatology referral is recommended for further management.

7. Management of MASLD

7.1 Medical treatment

MASLD is frequently associated with metabolic diseases such as obesity, diabetes, and insulin resistance. These cardiovascular diseases as well as non- hepatic malignancies and liver related complications can lead to increased mortality in patients with MASLD. The presence of fibrosis on histology in MASLD patients is strongly linked to development of liver related outcomes and death. Therefore, the aim of treatment in MASLD patients is to reduce the incidence and mortality of cardiovascular disease and liver related complications. [100,310] The treatment of metabolic comorbidities is discussed in separate chapters. Treatment of MASLD and MASH includes non-pharmacological, pharmacological and surgical and endoscopic approaches to improve hepatic inflammation and fibrosis.

Lifestyle modifications such as weight reduction, dietary control, and exercise and treatment of comorbidities such as diabetes, obesity, hypertension, and dyslipidemia are the cornerstones of treatment for MASLD and should be applied to all MASLD patients, regardless of the degree of inflammation or fibrosis. However, pharmacologic treatments should be given MASH patients at risk of disease progression. [310]

Recommendation (Medical Treatment)
62. Lifestyle modifications and treatment for comorbidities are recommended for all patients with MASLD.
63. Patients with MASH or hepatic fibrosis need treatment for histologic improvement in addition to lifestyle modifications.

7.1.1 Non-pharmacological treatment

(a) Lifestyle Modification

Weight reduction achieved by caloric restriction, with or without increased physical activity, leads to improvements in MASLD biomarkers, including liver enzymes, steatosis, MASH, and fibrosis in clinical trials. [311,312] In an interventional trial, the evidence suggested that bodyweight reduction of ≥ 5% is required to reduce liver lipid content, 7-10% to improve

inflammation, and ≥ 10% to improve fibrosis. [313] It is also important to have sustained weight loss to have beneficial effects.

Recommendation (Lifestyle Modification)
64. Lifestyle modifications and treatment for comorbidities are recommended for all patients with MASLD.
65. Patients with MASH or hepatic fibrosis need treatment for histologic improvement in addition to lifestyle modifications.

(b) Dietary Intervention

A diet containing excess calories, particularly excess saturated fats, refined carbohydrates, and sugar-sweetened beverages, is associated with obesity and MASLD. [314-316] Excessive fructose consumption in particular increases the risk of MASLD, MASH, and advanced fibrosis independent of calorie intake. [317,318]

There are multiple beneficial dietary approaches to lose weight and improve MASLD. Hypocaloric low-carbohydrate diets and low-fat diets are found to be similarly effective in reducing liver lipid content and related biomarkers. [47,319] The Mediterranean diet has extra benefits like liver lipid reduction and improvement in cardiometabolic health. [320,321]

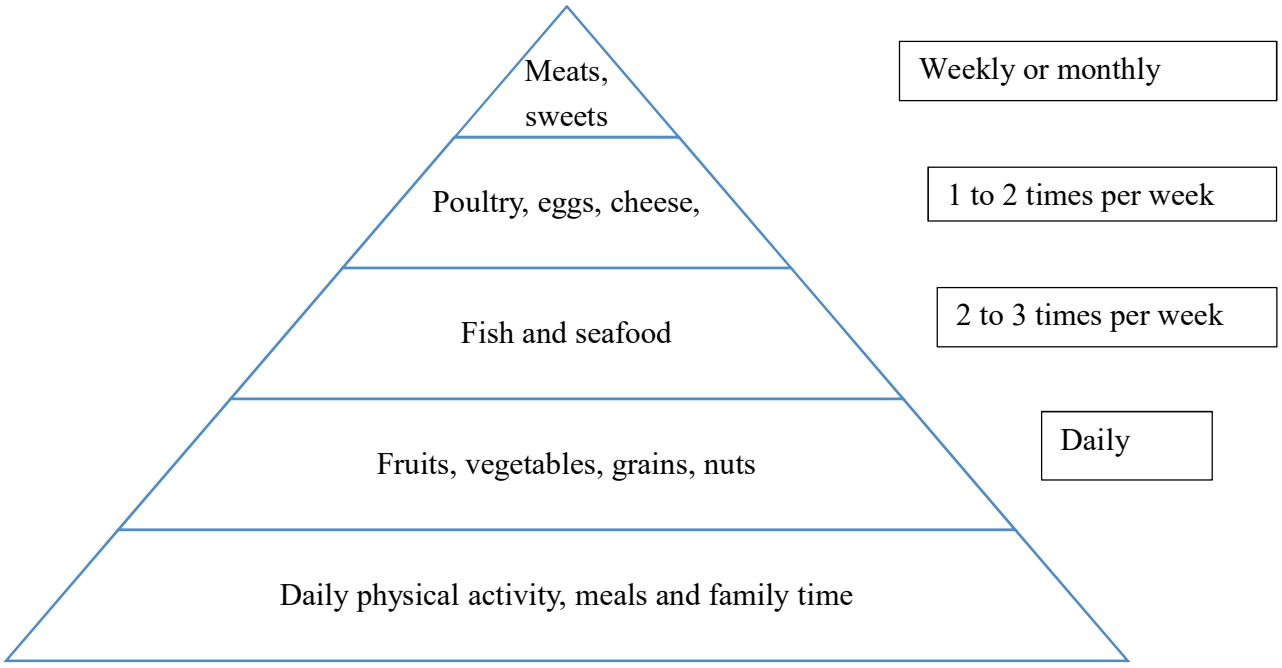


Figure 8: Mediterranean diet pyramid

Coffee consumption has been shown to have a protective effect on MASLD in several observational studies. An earlier meta-analysis showed that the intake of ≥ 3 cups of coffee per day (vs. <2 per day) was related to reduced risk of MASLD. [322] Coffee has a stronger and more consistent effect on fibrosis than for steatosis. Moreover, coffee consumption was inversely related to death from chronic liver disease and HCC. [323]

Recommendation (Dietary Intervention)
66. In adults with MASLD, improving diet quality (similar to the Mediterranean dietary pattern), limiting the consumption of ultra-processed food (rich in sugars and saturated fat) and avoiding sugar-sweetened beverages are recommended to improve liver injury.
67. Patients with MASH or hepatic fibrosis need treatment for histologic improvement in addition to lifestyle modifications.

(c) Exercise

Sedentary behaviors are independent predictors of MASLD and is associated with a greater risk of MASLD progression. Several RCTs and meta-analyses have demonstrated that exercise alone, without dietary interventions or significant weight loss, reduces liver steatosis in individuals with MASLD. [324,325]

Recommendation (Exercise)
68. Physical activity and exercise are recommended to reduce steatosis, tailored to the individual's preference and ability (preferably >150 min/week of moderate or 75 min/week of vigorous-intensity physical activity).

7.1.2 Pharmacological Treatment

Until recently, there has been no FDA-approved drugs for the treatment of MASH and treatment recommendations for persons with T2DM and MASH are centered on the dual purpose of treating hyperglycemia and/or obesity and MASH, especially if clinically significant fibrosis is present, to prevent development of cirrhosis. [99] Resmetiron, a liver-directed thyroid hormone receptor agonist, has recently been approved as MASH targeted treatment in 2024 and is recommended in EASL 2024 MASLD guideline. [101]

7.1.2.1 Liver-directed thyroid hormone receptor agonists

The incidence of clinical and subclinical hypothyroidism appears to be higher in individuals with MASLD or MASH relative to age-matched controls, and low thyroid function is associated with more severe outcomes. [326] Thyroid hormones reduce hepatic steatosis by stimulating hepatic lipophagy and mitochondrial biogenesis, and by inhibiting hepatic lipogenesis. They can also interfere with fibrogenesis by inhibiting TGF-β signaling. [327,328]

Resmetirom

Resmetirom is an orally active, liver-directed, thyroid hormone receptor agonist with high selectivity for the β1 receptor. [329] In the registrational, phase III trial of resmetirom in individuals with non- cirrhotic MASH (mostly fibrosis stages 2 and 3) of 1-year duration, Resmetirom performed better than placebo in both disease activity (resolution of steatohepatitis) and fibrosis. Progression of fibrosis in individuals with stage 2 fibrosis was lower than in the placebo arm. Liver enzymes and serum lipids were also significantly reduced while the effects

on glycaemic control and body weight were neutral. [330] Resmetirom significantly improved MRI- PDFF and liver stiffness measurements in the MAESTRO-MASLD phase III trial. [331] The recommended dosage of Resmetiron in US is 80 mg for adults less than 100 kg and 100mg for those weighing more than 100 kg. the most common side effects were diarrhoea (up to 33%), nausea (up to 22%), pruritus (up to 11%) and vomiting (up to 11%). [330] Individuals receiving resmetirom should be monitored for gastrointestinal side effects and thyroid hormone function. [99]

7.1.2.2 Vitamin E

Vitamin E is a lipid-soluble vitamin acting as a peroxyl radical scavenger with antioxidant, anti-inflammatory, and anti-apoptotic properties. It reduces de novo lipogenesis and therefore contributes to a reduction in liver lipid content. [99]

In the multicenter, randomized controlled trial (PIVENS trial), treatment with α-tocopherol (the natural form of vitamin E) 800 IU daily for 96 weeks in individuals with non-diabetic MASH resulted in improvements in both steatosis and disease activity and reduction in liver enzymes. [122] Vitamin E use was associated with lower rates of hepatic decompensation and higher transplant free survival in a retrospective study of MASH patients with advanced fibrosis. [332]

However, the results in persons with T2DM have been mixed, and vitamin E cannot be recommended with the current evidence, as benefit has been modest overall. [333] There is currently no clear data on fibrosis improvement and there is concern about the risks of vitamin E on bleeding, specifically hemorrhagic stroke and prostate cancer in men. [334,335] Such potential risks should be discussed with patients before initiation of long-term high- dose (eg, 800 IU daily) vitamin E therapy.

7.1.2.3 Peroxisome proliferator-activated receptor agonists

Thiazolidinediones are ligands for peroxisome proliferator-activated receptor γ approved for the treatment of Type 2 diabetes that improves insulin resistance, primarily targeting adipose tissue and improving lipid storage/redistribution and glucose utilization. [336] In patients with MASH with or without pre-DM or T2DM, treatment with pioglitazone improves histology and insulin resistance. [337] In the PIVENS trial, pioglitazone treatment did not significantly improve

histological features of MASH although there was reduction in hepatic steatosis and liver enzymes. [122] In another study of patients with either pre-DM or T2DM and MASH, pioglitazone treatment led to a ≥ 2-point reduction in NAS and a trend toward fibrosis improvement. [123] Pioglitazone was also demonstrated to be better than placebo in achieving MASH resolution as well as fibrosis improvement in a pool network meta-analysis. [338]

Potential side effects associated with pioglitazone include weight gain, osteoporosis in post-menopausal women, a debated risk of bladder cancer, and potential risk for worsening heart failure in those with preexisting cardiac dysfunction. [339,340] The use of pioglitazone in clinical practice has been overtaken by the increasing use of newer antidiabetic agents such as GLP-1 Receptor agonists and SGLT-2 inhibitors.

Newer drugs like lanifibranor (pan-PPAR agonist) showed dose-dependent histological improvement of steatohepatitis and fibrosis in a phase II b trial but it also associated with weight gain, pedal oedema and mild anaemia. [341] Saroglitazar, a dual PPAR α/γ agonist has been shown to improve insulin resistance, liver steatosis and liver enzymes. [342]

7.1.2.4 Incretin mimetics

Glucagon-like peptide-1 receptor agonists (GLP1RAs), single or dual (i.e., glucose-dependent insulinotropic polypeptide [GIP]-GLP1RAs), are approved for the treatment of Type 2 diabetes. Liraglutide, semaglutide and tirzepatide are also approved for obesity. These incretin mimetics have shown beneficial effects on cardiovascular and renal outcomes. [343]

Their actions include potentiation of prandial insulin secretion, as well as an inhibition of appetite and increased satiety, mediated both centrally and through reduced gastric motility, which mainly accounts for the weight-loss effects. [344]

Other hormones or their analogues potentiate the anorexigenic effects of GLP1 (GIP, glucagon, cagrilintide) or have additional peripheral effects such as increasing lipolysis, lipid oxidation and energy expenditure and are now being developed as dual or triple co- agonists that can induce a similar magnitude of weight loss as bariatric surgery. [345]

In an initial study of patients with MASH, liraglutide improved steatosis, resolved NASH, and reduced fibrosis progression compared with placebo. [346] In a phase 2b randomized controlled trial, daily SC semaglutide was given to 320 patients with MASH at 0.1, 0.2, or 0.4

mg or placebo daily for 72 weeks. MASH resolution was dose dependent and occurred in 59% in the treatment group versus 17% in the placebo group. Despite evidence of fibrosis improvement in the treatment groups, there was no statistically significant reduction in fibrosis compared with placebo. [347]

Tirzepatide (GLP1-GIP receptor agonist) has been shown to significantly reduce both liver and visceral fat in those with T2D, in association with major weight loss (comparable to bariatric surgery). [112] In the recently published phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis. [348]

7.1.2.5 SGLT-2 inhibitors

The SGLT-2inhibitors target renal glucose resorption from the glomerular filtrate and are approved for the treatment of T2DM. [349] Furthermore, they induce 2%–3% weight loss and have cardiorenal protective benefits. [350] Available studies evaluating the role of SGLT-2i in the treatment of MASLD/MASH are limited by relatively small sample sizes and lack of histological outcomes. [351,352]

7.1.2.6 Metformin

Currently, there is no evidence that metformin alone can improve histology in MASH. In people with T2D and MASLD-related advanced fibrosis or cirrhosis, metformin may improve transplant-free survival and reduce the risk of primary liver and extrahepatic cancer. [353,354] Thus, metformin should not be discontinued in those individuals with cirrhosis (unless discontinuation is required due to hepatic decompensation or renal failure), as this could increase mortality. [355]

7.1.2.7 Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is a natural hydrophobic bile acid with wide hepatoprotective effects including antioxidant, immunomodulatory and anti-apoptotic properties. UDCA use in MASH resulted in biochemical efficacy (ALT reduction) and a good safety profile, but no proof of histological efficacy. [356,357]

7.1.2.8 Obeticholic acid

Obeticholic acid (OCA) is an oral, synthetic analogue of chenodeoxycholic acid designed to have a much stronger, nano- molar, potency as a FXR (farnesoid X receptor) agonist than the native bile acid. [358] The drug was developed for MASH at a higher dose (25 mg daily). In a large phase III registrational trial of individuals with MASH and significant fibrosis (cirrhosis excluded), OCA achieved both a higher proportion of fibrosis improvement and a lower proportion of worsening than placebo. Despite improved disease activity (hepatocellular ballooning and lobular inflammation) there was no significant difference in resolution of steatohepatitis. [359] Dose-related pruritus and increases in LDL cholesterol are seen and there are additional concerns over the risk- benefit ratio (including hepatotoxicity and hepatic events).

Recommendation (Pharmacological Treatment)

69. Recently US FDA approved Resmetiron should be used whenever available in patients with non-cirrhotic MASH with significant liver fibrosis (stage ≥2).
70. Vitamin E can be considered in selected individuals as it improves MASH in some patients without diabetes after counselling potential risks of long-term use.
71. Semaglutide can be considered for type 2 diabetes and obesity in patients with MASH, as it confers a cardiovascular benefit and improves MASH.
72. Pioglitazone improves MASH and can be considered for patients with MASH in patients with T2DM.
73. Tirzepatide can be considered for patients with MASH and obesity.

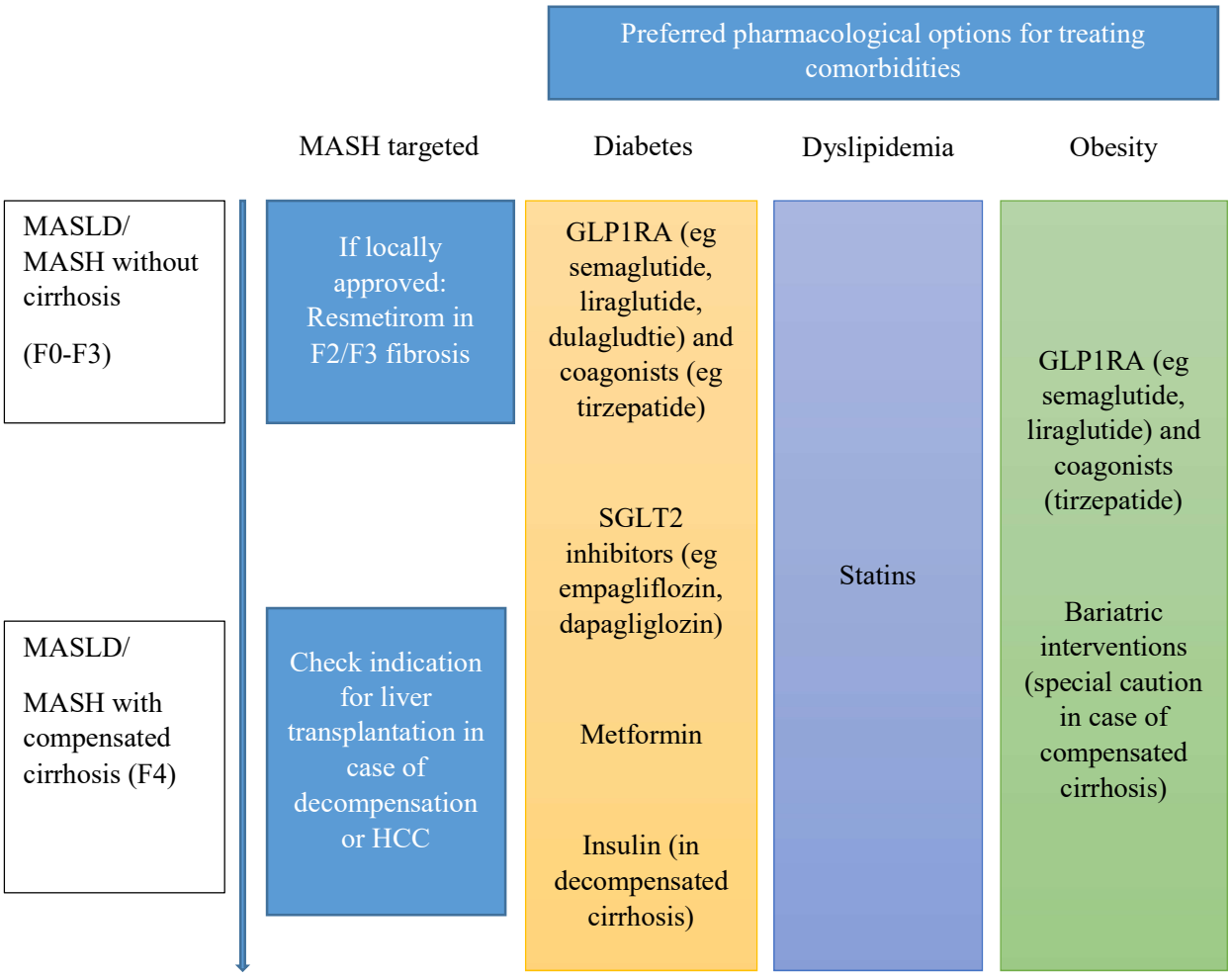


Figure 9: Treatment recommendations beyond lifestyle modification in MASLD/ MASH

7.1.3 MASH related Cirrhosis of Liver

Sarcopenic obesity, the state of decreased muscle mass in the setting of increased fat mass, occurs mainly in MASH-related cirrhosis and is found in 20–35% of individuals with cirrhosis pre-and-post liver transplant. [360,361] Obesity and sarcopenic obesity are risk factors for clinical decompensation and worsen prognosis. [361] Therefore, Evaluation for sarcopenia should be done in patients with MASH related decompensated cirrhosis.

Regarding dietary intake, in an RCT among patients with decompensated cirrhosis, a 6-month intensive high-calorie, protein-rich nutrition therapy was associated with improvement in frailty, sarcopenia, liver disease scores and survival. [362]

For patients with MASH related compensated cirrhosis, weight reduction through lifestyle intervention has been shown to reduce portal pressure and may prevent clinical decompensation. However, special attention should be given to avoid sarcopenia in this approach.

Regarding anti-diabetic drug use in cirrhotic patients, although metformin does not have effect on steatosis, inflammation and fibrosis, observational data suggest a potential protective effect against HCC. [363,364] Metformin may cause lactic acidosis through impairment of oxidative phosphorylation and the risk is increased in individuals with renal impairment and hepatic decompensation. [365]

The risk of sulfonylurea-induced hypoglycaemia is increased in individuals with advanced liver disease. Gliclazide has significant hepatic metabolism. Hepatotoxicity has also been reported for glibenclamide and is rarely seen with gliclazide.

SGLT2 inhibitors increase glycosuria. They have been shown to have beneficial cardiovascular effects, prevent progression of renal disease, and potentially even improve ALT and MRI-measured intrahepatic triglyceride content. [366] Due to increases in drug exposure in decompensated cirrhosis, SGLT2 inhibitors should be used with caution in cirrhotic patients or avoided in people with severe renal impairment.

Data on the use of GLP1RAs in advanced liver disease are limited. In a small RCT of 71 participants with compensated MASH-related cirrhosis, semaglutide at a dose of 2.4 mg weekly was well tolerated and improved steatosis, liver enzymes, bodyweight and HbA1c. [367]

Recommendation (MASH related Cirrhosis of Liver)
74. In patients with MASH cirrhosis, dietary and lifestyle recommendations should be adapted to the severity of liver disease, nutritional status and the presence of sarcopenia/sarcopenic obesity. 75. High protein diet and late evening snack are recommended for patients with sarcopenia, sarcopenic obesity or decompensated cirrhosis. 76. Moderate weight reduction is suggested in patients with compensated cirrhosis and obesity, with an emphasis on high protein intake and physical activity to maintain muscle mass and reduce the risk of sarcopenia. 77. Metformin can be used in compensated cirrhotic patients and preserved renal function but should not be used in adults with decompensated cirrhosis, especially when there is concomitant renal impairment, because of the risk of lactic acidosis. 78. Sulfonylureas should be avoided in patients with hepatic decompensation because of the risk of hypoglycemia. 79. GLP1 receptor agonists can be used in patients with Child- Pugh class A cirrhosis. 80. SGLT2 inhibitors can be used in patients with Child-Pugh class A and B cirrhosis. 81. Statins can be used in patients with chronic liver disease, including those with compensated cirrhosis; they should be used in adults according to cardiovascular risk guidelines to reduce cardiovascular events.

Summary of treatment recommendations

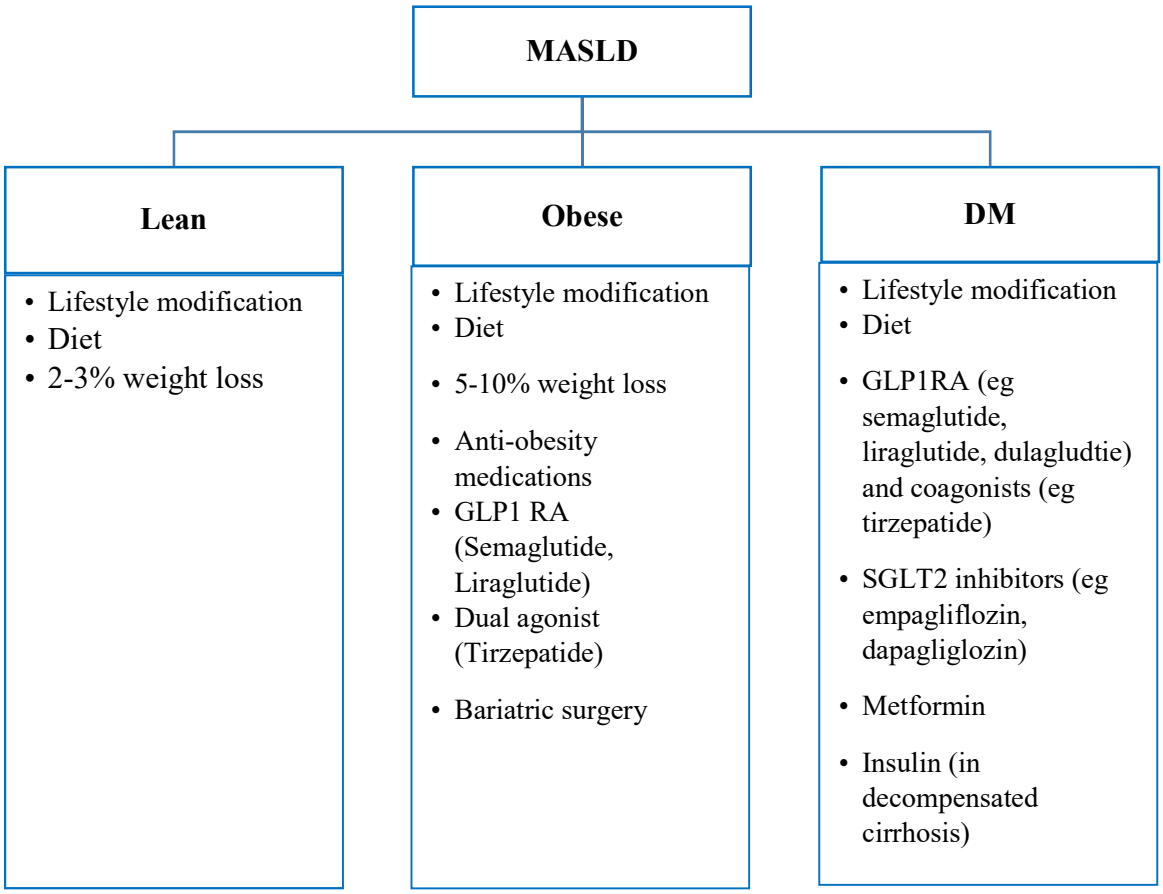


Figure 10. Treatment recommendations for MASLD

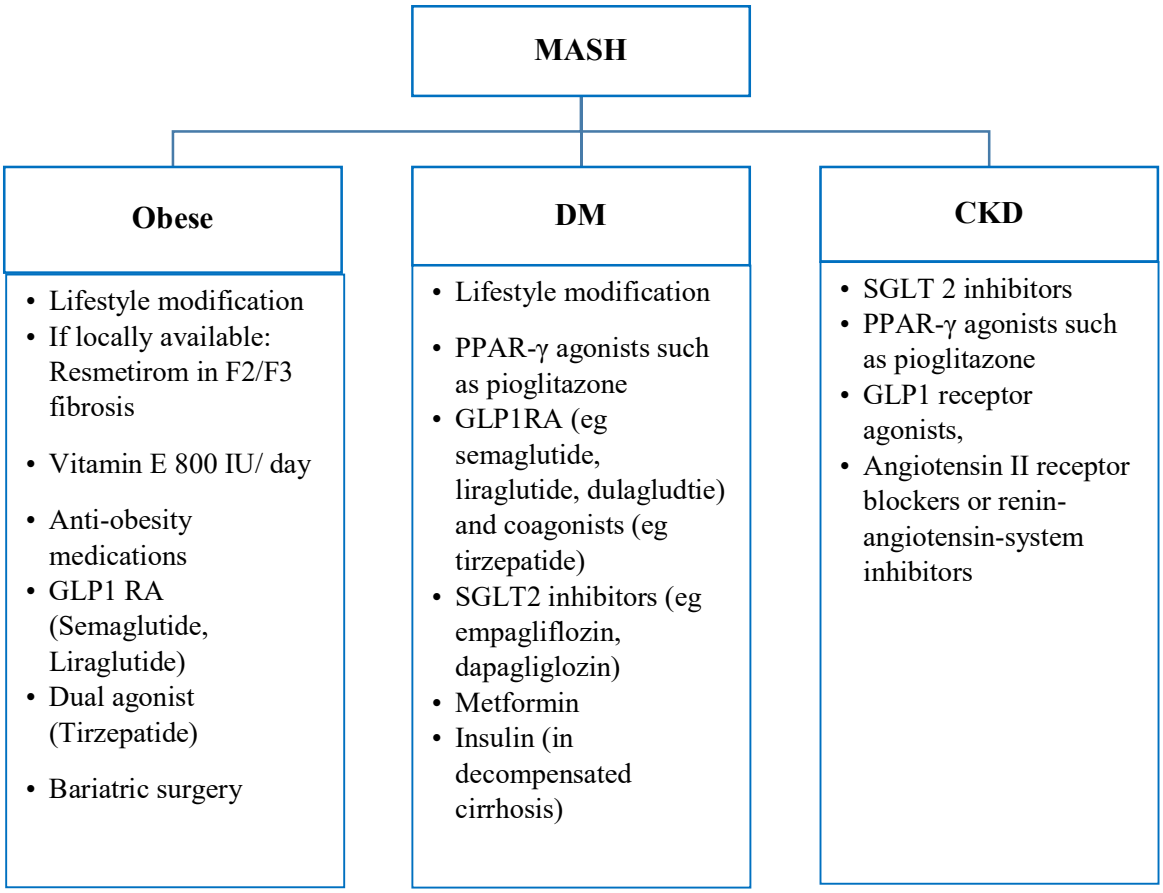


Figure 11. Treatment recommendations for MASH

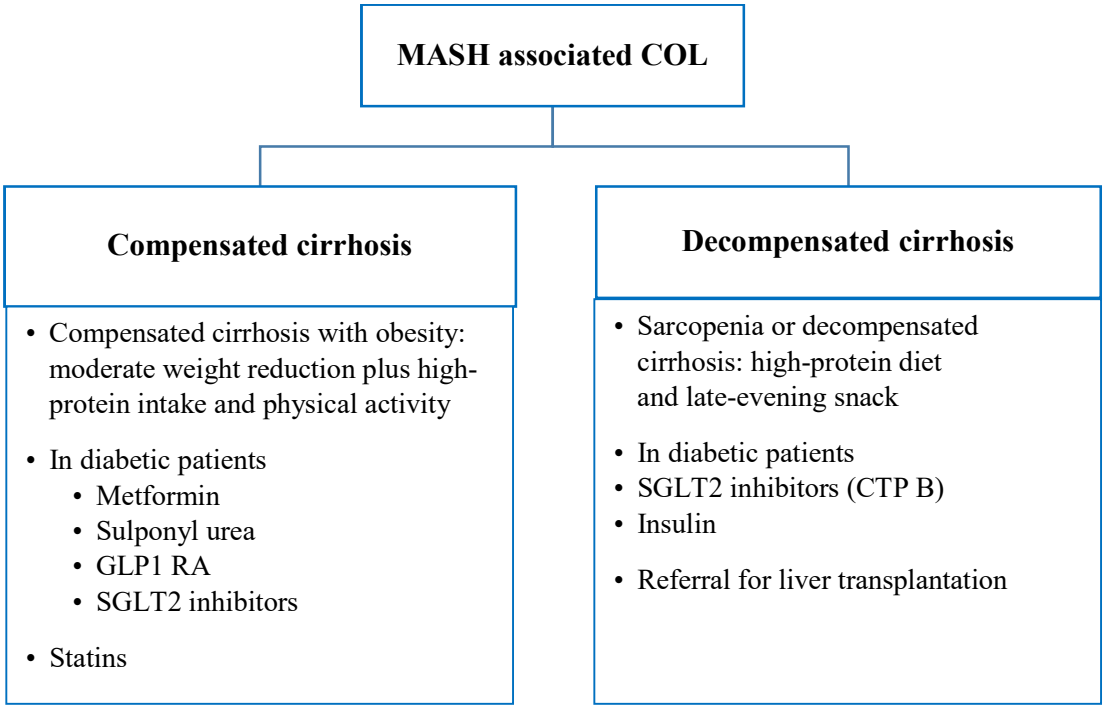


Figure 12. Treatment recommendations for MASH associated COL

8. Novel Therapeutic Agents and Future Direction

The landscape of NASH drug development has undergone significant changes in recent years. Because the underlying mechanisms of MASH are complex, new treatments are being developed to target a wide range of factors, including oxidative stress, insulin resistance, apoptosis, bile acid metabolism, lipid metabolism, and hepatic inflammation and fibrosis. [368]

Over the past 15 years, numerous compounds have been investigated for their effectiveness in treating MASH. Several trials have failed to meet prespecified primary endpoints (Table 8). Surrogate endpoints for drug approval have been clearly defined: regression of fibrosis or resolution of MASH. [369]

Despite initial disappointment due to the failure of several drugs, recent phase 2 and 3 studies have shown promising results (Table 9 and 10); resmetirom (Thyroid Hormone Receptor β (THR β) agonist [370] became the first Food and Drug Administration (FDA)–approved drug for MASH in 2024. [371] With several promising drug candidates with different mechanisms of action in phase 3 and others in the pipeline, the future of MASH therapy looks bright.

Considering the complexity of MASH pathology, several drugs and combinations of drugs should be approved in the next decade, leading to effective treatments for this serious and prevalent unmet medical need. The combinations might improve effectiveness by complementary or synergistic mechanisms of action and enhance tolerability by using lower doses of drug candidates. The ideal combination would target multiple steps in the pathogenesis, starting with energy balance to fibrogenesis, and should include drugs with significant metabolic effects and liver-directed therapy. [372]

Table 11. Main Failure in MASH Drug Development

Mechanism of Action	Drug Name
ASK1 inhibitor	Selonsertib
Dual CCR2 and CCR5 antagonist	Cenicriviroc
FGF19 agonist	Aldafermin
FXR agonist	MET642 MET409 EDP305
Monoclonal antibodies against lysyl oxidase-like 2	Simtuzumab
MPC inhibitor	MSDC-0602k
PPAR agonist	Elafibranor Seladelpar

Table 12. Drugs in Phase 2 Development (Paired Liver Biopsy Trials) [368]

Mechanism of Action	Drug Name
Cyclophilin inhibitor	Rencofilstat
Deuterium-modified thiazolindinedione	PXL065
DGAT2 inhibitor	ION224
FASN inhibitor	Denifanstat
FGF21 agonists	Efruxifermin Pegozafermin
GLP1-RA/GIP/GR	Tirzepatide BI456906 Pemvidutide Cotadutide
HSD17B13	GSK4532990
PPAR agonist	Saroglitazar
Sturcturally engineered fatty acids	Icosabutate
THR-b agonist	VK2809

Table 13. Drug in Phase 3 Development [368]

Drug Name	Obeticholic Acid	Resmetiron	Lanifibranor	Semaglutide
Class	FXR agonist	THRb agonist	Pan-PPAR agonist	GLP1-RA
Phase 3 RCT name	REGENERATE [373]	MAESTRO-NAFLD-1 [331] MAESTRO-NAFLD-OLE MAESTRO-NASH-Outcomes MAESTRO-NASH [370]	NATiV3	ESSENCE
Phase 3 histological endpoints (non cirrhotic population)	At 72 wk of Tx At least 1-point improvement of fibrosis with no worsening of NASH (OR) NASH resolution with no worsening of fibrosis	At 52 wk of Tx At least 1-point improvement of fibrosis with no worsening of NASH (OR) NASH resolution with no worsening of fibrosis	At 72 wk of Tx Resolution of NASH AND Improvement of fibrosis	At 72 wk of Tx At least 1-point improvement of fibrosis with no worsening of NASH (OR) NASH resolution with no worsening of fibrosis
Phase 3 histological Results (non cirrhotic population)	**Fibrosis improvement** **Placebo**: 11.9% (n= 311) **OCA 10 mg**: 17.6% (n=312, P=.04) **OCA 25 mg**: 23.1% (n=308, P=.0002) **NASH resolution** **Placebo**: 8.0% (n= 311) **OCA 10 mg**: 11.2% (n=312, P=0.18) **OCA 25 mg**: 11.7%	**Fibrosis improvement** **Placebo**: 14% (n=318) **Resmetirom** 80 mg: 24% (n=321, P= .0002) **Resmetirom 100** mg: 26% (n=316, P < .0001) **NASH resolution** **Placebo**: 10% (n=318) **Resmetirom 80 mg:** 26% (n=321, P < .0001) **Resmetirom 100 mg**: 30% (n=316, P<.0001)	Expected 2024	Expected 2024
Long-term outcomes (non cirrhotic population)	Expected 2025	Expected 2026	Expected 2028	Expected 2028

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