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Clinical Practice Guidelines

The African Middle East Association of Gastroenterology (AMAGE) clinical practice guidelines for the diagnosis and management of metabolic dysfunction associated fatty liver disease

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Abbreviations: ALD, Alcoholic liver disease; ALT, Alanine aminotransferase; AMAGE, African Middle East Association of Gastroenterology; AST, Aspartate transaminase; AUC, Area under the curve; BMI, Body mass index; CAP, Controlled attenuation parameter; CKD, Chronic kidney disease; CRN, Clinical Research Network; CSPH, Clinically significant portal hypertension; CT, Computed tomography; CVD, Cardiovascular diseases; DALY, Disability-adjusted life years; EGD, Esophagogastroduodenoscopy; EUS-PPG, Endoscopic ultrasound–derived portal pressure gradient; FIB-4, Fibrosis-4 Index; FLI, Fatty liver index; FLIP, Fatty Liver Inhibition of Progression; GCKR, Glucokinase regulator gene; GRADE, Grading of Recommendation, Assessment, Development, and Evaluation; HCC, Hepatocellular carcinoma; HDL, High-density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; hsCRP, High-sensitivity C-reactive protein; HSD17B13, Hydroxysteroid 17-beta dehydrogenase 13; HSI, Hepatic steatosis index; HVPG, Hepatic venous pressure gradient; LSM, Liver stiffness measurement; MAFLD, Metabolic dysfunction–associated fatty liver disease; MASH, Metabolic dysfunction–associated steatohepatitis; MBOAT7, Membrane-bound O-acyltransferase domain-containing 7; MENA, Middle East and North Africa; MRE, Magnetic resonance elastography; MRI, Magnetic resonance imaging; MRI-PDFF, Magnetic resonance imaging–proton density fat fraction; MRS, Magnetic resonance spectroscopy; NAFLD, Non-alcoholic fatty liver disease; NAS, NAFLD activity score; NITs, Non-invasive tests; PH, Portal hypertension; PNPLA3, Patatin-like phospholipase domain–containing 3; SAF, Steatosis, activity, fibrosis (score); SSM, Spleen stiffness measurement; T2DM, Type 2 diabetes mellitus; TM6SF2, Transmembrane 6 superfamily member 2; VCTE, Vibration-controlled transient elastography

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ABSTRACT

Over the past few decades, the profile of liver diseases in Africa and the Middle East has undergone significant changes. The incidence of metabolic dysfunction-associated fatty liver disease (MAFLD) has risen to alarming levels. Despite the seriousness of the situation, there is a scarcity of local or regional guidelines established to address it. This document presents the clinical practice guidelines from the African Middle East Association of Gastroenterology (AMAGE) related to the screening, diagnosis, and management of MAFLD. It addresses multiple aspects of managing this condition while taking into account local circumstances and the healthcare system's management requirements. These guidelines are intended for routine clinical use, with a specific focus on particular groups when needed.

1. Introduction

The Middle East and North Africa (MENA) region, consisting of 21 countries and a home to nearly 500 million people, faces unique demographic and socioeconomic challenges that influence health outcomes, including metabolic diseases [1]. Sub-Saharan Africa holds more than half of the world's arable land, yet less than 10% is cultivated. By 2100, it is projected that Sub-Saharan Africa will comprise 35% of the global population, currently over 1 billion individuals [2]. The region's diversity is shaped by its varied cultures, economies, social factors, histories, and political contexts.

Despite advances in managing viral hepatitis, the incidence of metabolic dysfunction associated fatty liver disease (MAFLD), previously known as non-alcoholic fatty liver disease (NAFLD), is expected to rise. This increase is due to higher rates of metabolic disorders, unhealthy diets, sedentary lifestyles, and reduced physical activity. Consequently, formulating effective strategies for managing MAFLD is crucial to lowering liver-related morbidity and mortality [3].

This document outlines clinical practice guidelines from the African Middle East Association of Gastroenterology (AMAGE) for managing MAFLD, covering diagnosis, treatment, and monitoring. The authors were invited by the AMAGE to develop this practice guideline document for managing patients with MAFLD. The recommendations presented in this document conform to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) method [4]. Briefly, separate recommendation levels (1 or 2) were assigned for each specific recommendation based on the overall strength of the recommendation and separate letter grades (A, B, C, or D) were assigned based on the overall quality of the evidence for a particular intervention and outcome. Strength of guideline recommendations was determined by the GRADE approach, as previously described [4]. These recommendations are intended to provide practical guidance for healthcare providers who care for adult patients with MAFLD, with special considerations for specific populations as needed [5]. The primary aim is to improve patient care, enhance awareness of MAFLD, and assist stakeholders in making informed choices based on evidence-backed information.

2. Epidemiology

MAFLD is the leading cause of chronic liver disease, with global prevalence rising from 25.3% (1990–2006) to 38.2% (2016–2019) and projected to exceed 55.4% in the future. In the MENA region, MAFLD prevalence is around 46%, being particularly high in Kuwait, Egypt, and Qatar [6]. At country level, estimated MAFLD prevalence is 45.37% in Kuwait, 45.0% in Egypt, 44.4% in Qatar, and 43.3% in Jordan and 33.1% in Saudi Arabia [7].

Among individuals with type 2 diabetes mellitus (T2DM), MAFLD prevalence reaches 68.71% to 77.3%, compared to 65.04% globally [8]. Although patients with obesity have a high prevalence of MAFLD, estimated at 57.5% (95% CI: 43.6–70.9%) in obese adults and 38.0% (95% CI: 31.5–44.7%) in obese children [9], MAFLD is also observed in non-obese patients, termed "lean MAFLD," affecting about 10% to 15% of the MAFLD population [10]. The prevalence of MAFLD is notably higher in men (36.6%) than women (25.5%), with peak rates in Qatar for men (69.7%) and in Iraq and Egypt for women (54.5%). Alarmingly, MAFLD affects 7% to 14% of children and adolescents [11].

3. Diagnostic criteria for MAFLD

The diagnosis of MAFLD is considered when hepatic steatosis is present alongside at least one of the following three prerequisites [12–16]: 1) a body mass index (BMI) greater than 25 kg/m^2; 2)

T2DM; or 3) a metabolic abnormality, which must include at least two out of the seven metabolic alterations listed below:

(a) Waist circumference for men ≥ 94 cm and for women ≥ 80 cm

(b) Blood pressure above 130/85 mmHg

(c) Plasma triglycerides ≥ 150 mg/dL (1.7 mmol/L)

(d) HDL Cholesterol levels < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women.

(e) Prediabetes (fasting plasma glucose ≥ 100 mg/dL [6.1 mmol/L]).

(f) Homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.

(g) Plasma high-sensitivity C-reactive protein level (hsCRP) > 2 mg/dL [14,17–20].

Recent studies have provided compelling evidence that the MAFLD criteria are superior to the NAFLD criteria for identifying individuals at risk of hepatic and extra-hepatic outcomes [21,22]. Another pivotal positive attribute of the MAFLD framework is that it enables the diagnosis of MAFLD concurrently with other liver diseases, as it is no longer regarded as a diagnosis of exclusion [23]. Instead, it is based on evidence of metabolic dysfunction, and when the criteria for MAFLD diagnosis coincide with other liver diseases such as primary biliary cholangitis, primary hemochromatosis, chronic hepatitis B and C virus infections, and alcoholic liver disease (ALD), a dual etiology diagnosis should be made. This is an aspect of particular relevance to our region given the historically high prevalence of viral hepatitis [13].

The new nomenclature, MAFLD, is simple and adaptable, garnering global attention from researchers, leading to a significant increase in related publications in our region over the past few years [24,25]. Additionally, studies from the region have indicated that the transition to the MAFLD nomenclature has contributed to improved awareness of fatty liver diseases among various specialties and primary care providers [26,27].

4. Risk factors of MAFLD

MAFLD, recognized as the hepatic manifestation of systemic metabolic dysfunction, results from a complex interplay of genetic and environmental factors. In recent decades, dietary changes in the MENA region have led to increased energy intake and higher rates of obesity. This region includes ten of the world's top fifteen countries for obesity, with over 50% of women in Kuwait, Qatar, and Libya categorized as overweight or obese. Additionally, 32.8% of the population exhibits insufficient physical activity, exceeding the global average of 27.5% [28]. Similarly, obesity is increasing in sub-Saharan Africa, with the highest incidence in South Africa where 13.5% of men and 42% of women are obese [29].

Worldwide, 537 million individuals have T2DM, with 73 million in the MENA region alone, a number projected to rise to 135.7 million by 2045. Sub-Saharan Africa also faces this issue, with around 19.4 million adults living with T2DM [30,31]. The MENA region recorded the highest disability-adjusted life years (DALYs) due to metabolic factors, with metabolic risk factors accounting for approximately 23% of all-cause DALYs [32].

Recent studies highlight the significant role of gut microbiota in MAFLD, indicating reduced microbial diversity and varying patterns corresponding to different disease stages [33]. Key genetic variants, particularly patatin-like phospholipase domain-containing 3 (*PNPLA3*), alongside other genes like transmembrane 6 superfamily member 2 (*TM6SF2*), Membrane-bound O-acyltransferase 7 (*MBOAT7*), Glucokinase regulator gene (*GCKR*) and 17-beta hydroxysteroid dehydrogenase 13 (*HSD17B13*), have been identified as significant risk factors [34–37].

5. Natural history of MAFLD

Many studies have shown that within a span of 8 to 13 years, between 12% and 40% of individuals with MAFLD progress to metabolic dysfunction-associated steatohepatitis (MASH). Additionally, around 15% of patients with MASH who develop early fibrosis may progress to cirrhosis within a similar timeframe. Among patients with cirrhosis, the rate of progression to clinical decompensation varies between 3% and 20% per year [38,39]. Various risk factors have been identified as being associated with fibrosis progression, including genetic variations, visceral obesity, T2DM, gut dysbiosis, unhealthy diets, and alcohol consumption [40–43].

The transition to steatohepatitis accelerates fibrosis progression. Specifically, it takes about 7 years for MASH to progress one stage in fibrosis compared to 14 years for those with steatosis [44]. MASH is currently recognized as one of the most important causes of hepatocellular carcinoma (HCC) [45]. Data indicates that even non-cirrhotic MAFLD may present an increased risk for HCC [46]. Additionally, obesity and T2DM have been identified as significant risk factors for HCC, even in non-cirrhotic patients. Individuals with a PNPLA3 polymorphism have been found to exhibit a threefold higher risk for HCC. Approximately 7% of patients with compensated cirrhosis due to MAFLD develop HCC within 10 years, and half of these patients may require liver transplantation [47]. On the other hand, fibrosis may regress, with a meta-analysis including 54 studies and 26,738 patients showing that after a median follow-up of 4.6 years, 21% of patients with fatty liver experienced a resolution of steatosis, while 11% reported a resolution of MASH after a median of 1.4 years [39].

Moreover, MAFLD is linked to increased severity of comorbidities, including cardiovascular diseases, T2DM, chronic kidney disease (CKD), and reduced health-related quality of life. Cardiovascular diseases diseases (CVD) continue to be the foremost cause of mortality [48–50].

6. Recommended pathway for referral from primary care to tertiary hospital

A structured referral pathway from primary care to a specialized hospital is pivotal for effectively categorizing patients requiring expert evaluation and distinguishing from those with mild conditions who can be treated in primary care [51].

Elevated levels of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) should trigger an investigation into the cause of liver damage. Nonetheless, normal serum ALT and AST levels do not completely rule out the possibility of underlying liver conditions. Individuals with MAFLD, steatohepatitis, and/or significant hepatic fibrosis or cirrhosis may present with normal serum ALT and AST values [52]. Current risk stratification algorithms employ non-invasive tests (NITs) sequentially to detect subjects with advanced liver fibrosis (F3–4), a group that constitutes less than 5% of the primary care population [53] (Fig. 1).

The Fibrosis-4 Index (FIB-4) is the primary test recommended for assessing fibrosis in primary care. With moderate accuracy (AUC of 0.76), a FIB-4 score of < 1.3 indicates low risk for advanced fibrosis, allowing monitoring every 2-3 years. Conversely, a FIB-4 score >2.67 suggests advanced fibrosis, warranting referral for specialist evaluation, although the positive predictive value of this score in primary care is only 24% - 40%. Around 30% of patients will have indeterminate FIB-4 scores, which require additional testing [54].

FIB-4 has limitations when it comes to screening for advanced liver fibrosis, especially in those with T2DM. Moreover, the FIB-4 score is influenced by age, which reduces its reliability for individuals younger than 35 or older than 65 years of age. While the suggestion to use age-specific thresholds emerged, it results in a significant decrease in sensitivity. Nevertheless, considering the general prevalence of MAFLD, applying a cutoff of < 1.3 in conjunction with other clinical indicators is reasonable to exclude most individuals with advanced fibrosis [55,56].

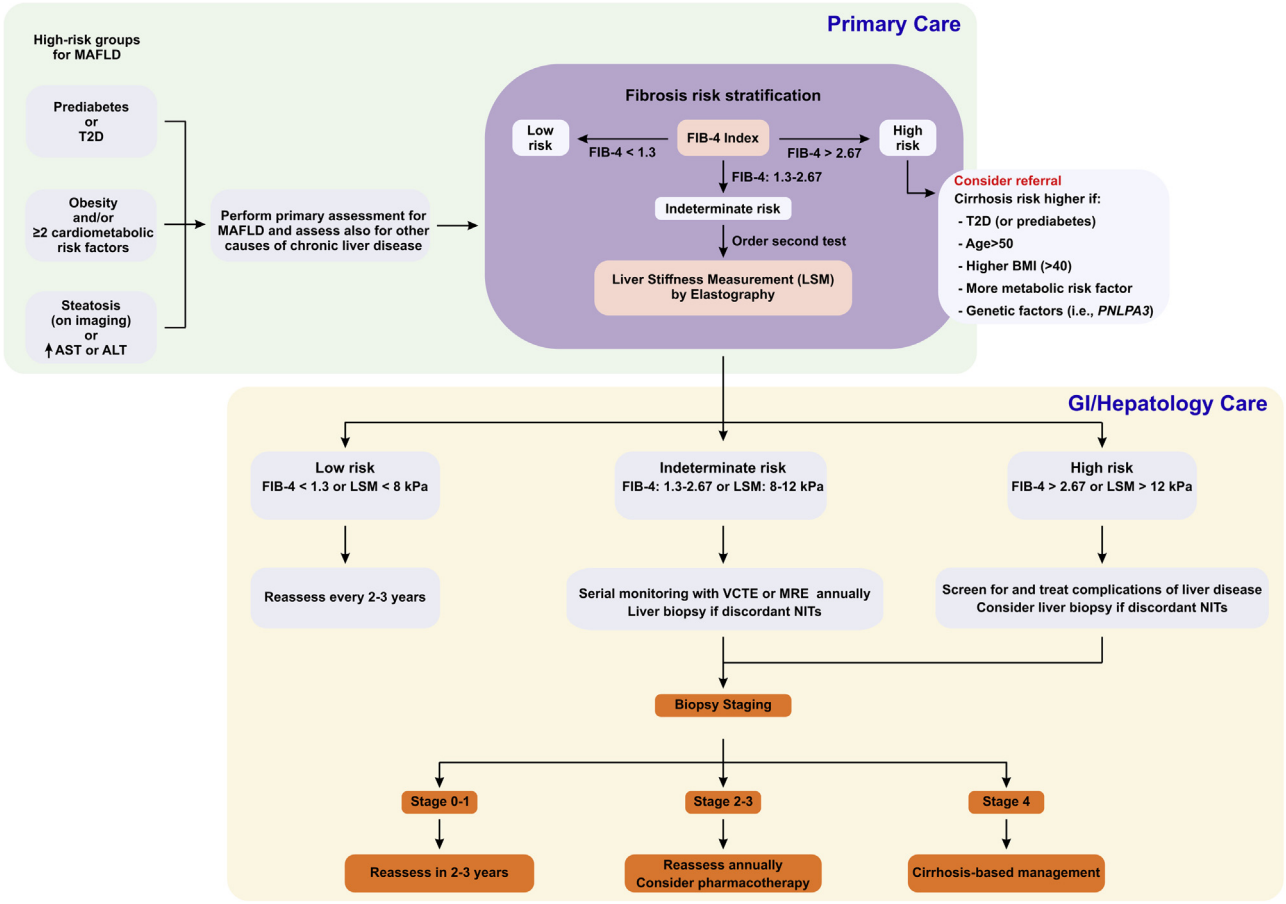

Fig. 1. The recommended algorithm for the diagnosis and management of MAFLD.

Second-line testing options can help clarify indeterminate FIB-4 results, including liver stiffness measurement (LSM) by transient elastography, acoustic radiation force impulse (ARFI)-based techniques such as point shear wave elastography (pSWE), two-dimensional shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE). Among these options, VCTE is the most widely validated and cost-effective for advanced fibrosis detection [16,57]. Individuals with an indeterminate FIB-4 and subsequent LSM < 8 kPa can be managed in primary care, and possess a similar risk of future liver-related events as patients with a FIB-4 < 1.3 [58]. MR elastography is the most accurate but is less accessible, and as such is not recommended as the primary method for risk stratification in patients with MAFLD [59].

To improve referral rates, primary care should incorporate educational initiatives and decision support tools, such as liver fibrosis calculators. A further adjustment of referral pathways might be needed, especially given potential advancements in treatment for those in the at-risk-MASH category (F2–F3 stage).

Recommendations

- The FIB-4 index is recommended as the principal evaluation tool for evaluating the risk of individuals with MAFLD in primary care settings. Patients with a score below 1.3 may receive treatment in primary care, accompanied by follow-up testing every 2 to 3 years. (B1)
- Individuals with a FIB-4 score between 1.3 and 2.67 should undergo further testing using a more accurate non-invasive test such as LSM, MRE, or maybe a liver biopsy (B1).
- Patients with a FIB-4 score more than 2.67 should be sent to the relevant expert (B1).

7. Assessment of disease severity

MAFLD affects a significant portion of the population, but only a small fraction progresses to advanced liver fibrosis (≥F3 stage). Individuals with advanced fibrosis face increased risks of complications and mortality, yet many are asymptomatic until severe issues arise, missing preventive opportunities [60,61]. While universal screening for MAFLD is not recommended, screening is advised for high-risk patients such as those with obesity, T2DM, or metabolic dysfunction [62]. Those diagnosed with MAFLD should be assessed for other components of metabolic dysfunction and receive appropriate treatment.

In particular, T2DM significantly increases the risk of steatohepatitis and advanced liver fibrosis and is an independent risk factor for hepatic decompensation and HCC in patients with MAFLD. [63] Therefore, identifying MAFLD in individuals with metabolic comorbidities is crucial, and liver assessment can be integrated into the evaluation of these patients. This can involve simple blood tests (e.g., serum ALT, AST, platelet count) and scores.

Ultrasonography is commonly used for diagnosing hepatic steatosis but has limitations in sensitivity and quantification [64]. The Controlled Attenuation Parameter (CAP), measured via transient elastography, correlates with histological steatosis, however, there are still variabilities in quantification, particularly in obese individuals. According to a meta-analysis based on biopsy studies, optimal cut-off values of 248, 268, and 280 dB/m have been identified for mild, moderate, and severe histological steatosis, respectively, with area under the curves ranging from 0.82 to 0.89 . [65] To enhance diagnostic performance, the obesity-specific XL probe has been introduced [66]. The magnetic resonance (MR)-proton density fat fraction (PDFF) is recognized as the most precise non-invasive technique for quantifying steatosis, albeit it is less readily available. Blood biomarkers such as the fatty liver index (FLI) are valuable for conducting epidemiological studies.

Histological steatohepatitis correlates with a higher rate of disease progression and complications. Serum ALT alone is an unreliable indicator of the presence of steatohepatitis. [67] The FAST score, which integrates LSM and CAP along with serum AST, demonstrates high sensitivity and specificity in identifying steatohepatitis [68]. Non-invasive assessments such as FIB-4 and LSM are viable alternatives to liver biopsy for predicting outcomes, effectively forecasting clinical results [58].

Recommendations

- Abdominal ultrasonography is currently the preferred initial technique for detecting and grading liver steatosis (A1).
- When accessible, VCTE with CAP may offer better sensitivity than ultrasonography. In large-scale clinical and epidemiological studies, serum biomarkers and liver indices like the fatty liver index (FLI) and hepatic steatosis index (HSI) can be utilized (B2).
- MRI techniques (MRI-PDFF, MRS) remain the gold standard and the most accurate method for hepatic fat quantification but are not recommended for daily clinical practice; they are mainly for early-phase trials (A1).
- No reliable biomarker for steatohepatitis exists; liver biopsy remains the standard evaluation method (A1).
- Non-invasive methods like VCTE and blood biomarkers can rule out significant fibrosis, though their accuracy in confirming significant or advanced fibrosis is limited. Combinations of biomarkers or liver biopsy are recommended for definitive confirmation (A2).
- Subjects with MAFLD should be evaluated for additional metabolic comorbidities such as T2DM, hypertension, and dyslipidemia and treated accordingly (A1).

8. Who should undergo a liver biopsy?

A liver biopsy is recommended for diagnosing MAFLD in several specific situations. It is beneficial for patients with atypical symptoms, those who fall into a grey area regarding their diagnosis, and to assess prognosis. Additionally, it helps identify individuals with other underlying causes of liver disease [16]. The histological evaluation of MAFLD should provide three essential pieces of information: the diagnosis, the grading of necro-inflammatory activity, and the staging of fibrosis severity. However, liver biopsy has several limitations, including inter-observer variability, sampling errors, high costs, and a low but definite risk of complications [60].

9. Pathological recommendation

A proper liver sample can be collected via percutaneous biopsy using a needle that is 16 G or larger, conducted under ultrasound guidance. To guarantee a sufficient specimen for histological analysis, it should include ten or more portal tracts and have a minimum length of 2 cm. [16,61]

Multiple scoring systems are commonly used to assess liver biopsies concerning MAFLD: the Fatty Liver Inhibition of Progression (FLIP) algorithm, the Brunt score, the NAFLD Activity Score (NAS), and the Steatosis, Activity, and Fibrosis (SAF) score. The NAS score is calculated by adding the scores for steatosis, ballooning, and lobular inflammation. Cases with a NAS score of 5 or above are classified as definite MASH, whereas scores of 3 and 4 are seen as borderline. Cases with a NAS score between 0 and 2 are classified as not having MASH [69]. A four-tier grading system for fibrosis has been defined by the SAF score from (0-4). Emerging evidence suggests that the SAF score offers a more reliable histological evaluation, and the inter-observer variability is improved when the SAF score is utilized [70].

Recommendations

- Indications for liver biopsy in patients with MAFLD (A1)
  - ➢ A typical set of features with non-invasive tests, showing inconclusive or unreliable outcomes.
  - ➢Evaluation of dual etiologies in liver diseases.
  - ➢Research that has received ethical approval or clinical trials, including biopsy obtaining during bariatric or cholecystectomy surgery.
- The reporting of liver biopsies should adhere to standardized methods through the implementation of either the FLIP algorithm and SAF score or the MASH CRN system. (B1)

10. MAFLD-related cirrhosis, including portal hypertension and screening for varices

MAFLD is increasingly recognized as a significant contributor to cirrhosis and doubles the risk of liver-related mortality, especially with multiple metabolic risk factors. Furthermore, when MAFLD coexists with other liver diseases, the probability of cirrhosis is more significant compared to cases attributed to a single etiology [71].

MAFLD-related cirrhosis should be suspected even when there are low or undetectable levels of steatosis, as long as the diagnostic criteria for MAFLD are met, replacing the outdated term “cryptogenic cirrhosis.” These criteria include documentation of steatosis from liver biopsy or imaging, with previous or current evidence of metabolic risk factors consistent with MAFLD [13,15].

LSM through transient elastography is effective for diagnosing MAFLD-related cirrhosis, especially when combined with serum markers, providing superior results compared to either method alone. Advanced liver disease could be ruled out with an LSM under 10 kPa, while values over 15 kPa indicate it, and those over 20-25 kPa, particularly with thrombocytopenia, suggest clinically significant portal hypertension requiring variceal screening via endoscopy [72]. In concordance with the Baveno VII consensus, patients with LSM under 20 kPa and platelet counts over 150 $\times$ 10^9 cells/μL have a very low likelihood of high-risk varices and can skip screening [73]. Spleen stiffness measurement (SSM) is helpful for borderline cases, accurately categorizing risk for variceal bleeding and clinically significant portal hypertension (CSPH), as it reflects portal blood flow resistance and is not affected by liver steatosis [74]. An SSM over 50 kPa can confirm CSPH, while below 21 kPa can exclude it [75–78]. High-risk varices, like medium to large ones or small varices with red signs, require therapeutic intervention [79].

Although magnetic resonance elastography (MRE) offers higher accuracy than LSM by transient elastography, its use is limited by cost and availability [80]. In certain cases, mainly when patient scores fall within an indeterminate (grey) range, a liver biopsy may be required [81].

Portal hypertension (PH) is typically diagnosed and treated through esophagogastroduodenoscopy (EGD), with the hepatic venous pressure gradient (HVPG) as the standard assessment tool. However, this test is costly, invasive, and not easily accessible in some medical centers [82]. Alternative methods like endoscopic ultrasound-derived portal pressure gradient (EUS-PPG) are being explored but require sedation and further validation [82]. Non-invasive techniques like ultrasound, which assess indicators like splenomegaly, are already in use and aim to identify clinically significant portal hypertension early, with transient elastography being particularly useful. This can also be evaluated through computed tomography (CT) or magnetic resonance imaging (MRI).

Recommendations

- Patients with cirrhosis who currently show no signs of steatosis meet specific criteria and should still be considered to have MAFLD-related cirrhosis:
  there should be historical or current evidence of meeting the diagnostic criteria for MAFLD, alongside documented evidence of hepatic steatosis from a previous liver biopsy or earlier imaging (B2).
  * *The history of prior viral hepatitis must be considered, as patients might have a combination of disease etiologies.*
- It is recommended to undertake endoscopic screening for gastroesophageal varices in individuals with MAFLD-related cirrhosis unless they have already been identified and treated.
- The exact frequency for EGD screening in individuals without gastroesophageal varices is not well established. For patients with multiple causes and/or those experiencing continuous decompensation, EGD screening should be performed annually. In other cases, the screening intervals can be prolonged up to a maximum of 2 years. (C2)
- The utilization of non-invasive methods for diagnosing gastroesophageal varices is discouraged due to their low reliability (A1)
- Ultrasound is recommended for identifying patients with cirrhosis. Transient elastography, which assesses liver stiffness, may be useful for ruling out high-risk varices in patients with compensated cirrhosis. (B2)

11. Extrahepatic manifestations of MAFLD

MAFLD is a multisystem disorder with implications beyond the liver. Existing research has established that MAFLD is linked to dysfunction across various organ systems, which include CVD, CKD, T2DM, and extrahepatic cancers [48]. Furthermore, MAFLD is associated with conditions such as sarcopenia, chronic obstructive pulmonary disease, SARS-CoV2 infection-related morbidity, ischemic stroke, and cognitive impairments [48,83–85]. In one particular study, MAFLD was found to be associated with 10 out of the 24 cancers investigated, affecting organs such as the uterus, gallbladder, liver, kidney, thyroid, esophagus, pancreas, bladder, breast, colorectum, and anal canal when compared to non-MAFLD individuals [86]. Associations of MAFLD with liver, kidney, and thyroid cancers remained statistically significant after adjusting various components of metabolic syndrome [76].

Numerous studies have indicated that MAFLD serves as an independent risk factor for CKD, with its severity correlating to an approximately 1.3-fold heightened risk of developing CKD [83]. CVD is a significant outcome of concern for those with MAFLD [85]. Previous studies show that patients with MAFLD face a 1.5 times greater likelihood of experiencing both fatal and non-fatal CVD events compared to those without MAFLD. This finding has been corroborated by a recent meta-analysis involving seven cohort studies [48].

The underlying molecular mechanisms responsible for these systemic impacts are intricate. Suggested explanations include genetic susceptibility, common environmental risk factors, interrelated metabolic disorders, the gut-liver axis, bile acids, endotoxins, and adipokines within a dysmetabolic environment [87,88]. Collectively, these factors contribute, to varying extents, to the progression of MAFLD.

Recommendations

Patients with MAFLD need to be assessed for CVD, risks for CVD, and chronic renal disease. It is advisable to consult the appropriate specialists as needed. (A1)

- Dyslipidemia, hypertension, and T2DM must be correctly diagnosed and managed to lower the risk of diseases affecting the renal, CVD, and other organ systems. (A1)

12. MAFLD in the setting of other liver diseases

12.1. Viral hepatitis B and C

As MAFLD can now be identified alongside other liver conditions such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and is not considered merely a diagnosis of exclusion; a patient who fulfills the criteria for MAFLD in addition to one or more other chronic liver disease diagnoses at the initial assessment or during follow-up should be classified as having dual etiology liver disease. In contrast to individuals with liver disease caused by a "single" etiology, these patients are likely to experience a diverse natural history and treatment response [13].

Due to the high prevalence of viral hepatitis and MAFLD in our region, it is expected that these two conditions will frequently occur together [89]. A recent investigation involving over 10,000 consecutive chronic hepatitis C (CHC) patients in Egypt found that nearly 50% of these patients also had MAFLD. Those with MAFLD were at a higher risk of developing hepatic fibrosis compared to HCV patients without MAFLD [90,91].

The MAFLD-CHB dual etiology incidence rate is rising quickly. There are still debates regarding whether MAFLD impacts the effectiveness of antiviral therapy in CHB patients, if nucleos(t)ide analogues (NAs) affect the body's metabolism, and whether patients with MAFLD and CHB should begin antiviral therapy right away. Patients with chronic hepatitis B who also have MAFLD are at an increased risk of developing HCC, according to a recent study [92,93]. The WHO 2024 guideline recommends initiation of antiviral therapy in all patients with MAFLD irrespective of the HBV DNA and ALT levels [94].

The positive results linked to significant viral suppression or a sustained virological response are being compromised by MAFLD. This issue is particularly concerning for individuals suffering from CHB and/or HCV infections, as they face increased risks of end-stage liver disease, higher prevalence of HCC, and elevated dropout rates from the liver transplant waiting list [95,96]. Various studies have shown that the sustained virological response achieved through direct-acting antivirals is affected by hepatic steatosis, elevated serum lipid levels, and weight gain [95]. Consequently, these patients may face an increased risk of complications related to MAFLD.

12.2. Autoimmune liver disease

A serious and even lethal liver illness that affects both adults and children, autoimmune hepatitis (AIH) is becoming more common. As a result, it should come as no surprise that MAFLD and AIH can often coexist, possibly synergistically affecting how the disease progresses and how both entities respond to treatment. Numerous circumstances, most notably the prior diagnosis of exclusion for fatty liver disease linked to metabolic dysfunction, made it challenging to clarify the nature of the intricate relationship between the two disorders. The idea behind the recent redefining of fatty liver disease, which resulted in the creation of positive diagnostic criteria for MAFLD, is to assist in overcoming some of these obstacles [97].

According to a recent study, AIH patients with MAFLD exhibited the following traits at the time of diagnosis compared to those without MAFLD: a greater body mass index, a higher incidence of hypertension, a slight increase in total bilirubin and hepatobiliary enzymes, and histologically progressing fibrosis. The features of AIH patients with MAFLD were distinct from those of AIH patients without MAFLD, as they tended to have a more severe liver condition. These results may contribute to a better understanding of AIH patients with MAFLD [98].

12.3. Alcohol abuse

The diagnosis of MAFLD is not determined by alcohol consumption; instead, it relies on the presence of metabolic factors. In a recent study, approximately 29% of individuals with NAFLD and 25% of those with MAFLD reported a history of hazardous alcohol use, which may lead to underreporting of alcohol intake in these patients. Urinary ethyl glucuronide, hair analysis, and the Alcohol Use Disorders Identification Test-consumption (AUDIT-C) are effective screening methods for identifying and managing alcohol-related liver disease (ARLD) [99].

Regardless of the assessment approach used, even moderate alcohol intake was associated with severe fibrosis, particularly in patients with MAFLD and T2DM [18,99,100]. As a result, dual-etiology fatty liver disease, characterized by the presence of both MAFLD and ARLD, is defined as a person who meets the criteria for MAFLD and engages in significant alcohol consumption (more than three drinks per day for men and over two for women) or binge drinking (consuming more than five drinks for men and over four for women within two hours) [22].

Recommendations

- Patients suffering from liver diseases, such as alcohol-related liver disease (ALD) and viral hepatitis, require a comprehensive evaluation for possible concurrent MAFLD and vice versa. (A1)
- Patients diagnosed with MAFLD should be counselled to abstain from alcohol or, if abstinence is unfeasible, to limit consumption to the minimal quantity practicable. (B1)
- Management of MAFLD and associated conditions should adhere to the established criteria for each respective disease. (B1)

(continued)

- Patients who have been cured of CHC or have significant suppression of hepatitis B virus (HBV) with MAFLD should be monitored due to the increased risk of advancing to cirrhosis, HCC, and other extrahepatic issues. (B1)
- While a specific monitoring schedule has not been determined, these patients may be observed following the guidelines intended for MAFLD with a single underlying etiology. (B2)
- Deterioration of lipid profiles, weight gain, and hepatic steatosis are often neglected during sustained virologic response (SVR). Clinicians must proactively identify, monitor these factors, and intervene as necessary to mitigate the risk of cardio-cerebral vascular disease. (B1)

12.4. Patient-reported outcomes in MAFLD

MAFLD is linked to a low health-related quality of life (HRQoL), independent of other comorbidities [101]. Patients with MAFLD experience lower health utility scores, which worsen as the disease progresses, but these scores can improve if the disease regresses [101].

Evaluating the disease burden from the patient's perspective enhances the assessment of patient-centered outcomes and provides valuable insights for the healthcare community. This information can help develop strategic approaches to managing the disease and create interventions to improve clinical and psychosocial outcomes [101]. Patient-reported outcome measures (PROMs) are standardized questionnaires designed to capture patients' feelings about their HRQoL without assistance from clinicians or family members [102]. The most effective way to assess patient-reported outcomes involves using both general and disease-specific tools. General assessment tools include the Short Form-36 (SF-36) and the European Quality of Life-5 Dimensions (EQ-5D), while disease-specific tools include the Chronic Liver Disease Questionnaire for Nonalcoholic Steatohepatitis (CLDQ-MASH) (Table 1) [101].

Recommendations

- Individuals with MAFLD experience a lower health-related quality of life (HRQoL), particularly in terms of physical functioning and fatigue as well as deterioration of mental domains of HRQOL, compared to those with other chronic liver diseases. (B2)
- Creating a comprehensive patient-centered treatment approach for MAFLD requires the inclusion of patients' perspectives on (quality of life, satisfaction with treatment, and adherence) through patient-reported outcomes. (B2)

13. Dietary and exercise recommendations for the management of MAFLD

The primary treatment for MAFLD is changing one's lifestyle through dietary and exercise interventions. Age, gender, dietary practices, and nutrient intake are the most significant contributing factors to the onset and progression of MAFLD [103].

13.1. Role of caloric restriction

Caloric restriction is a key focus of dietary intervention for MAFLD. Sufficient weight loss can improve the histological features of the disease. Gradual weight loss of over 7% is necessary to alleviate steatosis and steatohepatitis, while more than 10% weight reduction may be required to improve fibrosis [104,105]. However, some patients may experience regression of fibrosis or steatohepatitis without significant weight loss, while others may not show improvement in liver histology despite considerable weight reduction. It is important to note that dietary interventions beyond simple calorie restriction may still benefit liver health. Additionally, increased physical activity can enhance muscle mass, sometimes masking weight loss, yet contributing to an overall improvement in liver condition.

Table 1
Patient-reported outcomes measurement tools.

Type	Tool Name	Key Areas Assessed
General	**SF-36v2**	Physical functioning, mental health, vitality, etc.
	EQ-5D	Mobility, self-care, pain/discomfort, anxiety/depression
Disease-Specific	**CLDQ-MASH**	Abdominal symptoms, emotional health, fatigue
	LDQOL/SF-LDQOL	Liver disease symptoms, daily living effects
Fatigue	**FACIT-F**	Physical, emotional, social well-being

13.2. Role of diet type

A hypercaloric diet high in trans fats, saturated fats, cholesterol, and fructose-sweetened beverages increases visceral fat and promotes liver lipid accumulation, leading to steatohepatitis and fibrosis. Reducing calorie intake from these foods and incorporating monounsaturated fatty acid (MUFA) supplements can offer preventive and therapeutic benefits. Lower saturated fat intake alongside weight loss improves MAFLD, as MAFLD patients have a lower polyunsaturated fatty acid (PUFA) to saturated fatty acid (SFA) ratio than healthy individuals. [106] SFAs enhance fat storage and can worsen insulin response in MAFLD. In contrast, MUFAs improve lipid profiles, reducing oxidized LDL, triglycerides, and improving the HDL to cholesterol ratio [106].

Extra virgin olive oil (EVOO), rich in MUFAs and phenolic compounds, is beneficial for cooking, promotes insulin sensitivity, and decreases lipogenic gene expression. Increasing fiber, coffee, and green tea intake may also protect against steatohepatitis. Long-term adherence to these dietary changes is essential. [92]

13.3. Role of micronutrients

While oxidative stress is linked to fatty liver, the effectiveness of antioxidants in humans remains inconclusive, aside from high-dose vitamin E [107,108]. Vitamin D may provide anti-inflammatory benefits and may be involved in MAFLD pathogenesis, though evidence supporting its supplementation in improving steatohepatitis-related conditions is lacking [109]. Future studies are needed to determine the best dietary recommendations for reversing steatohepatitis and liver fibrosis relative to the magnitude of weight loss.

13.4. Role of physical activity

There is strong evidence that engaging in regular physical activity benefits heart health and provides various advantages for musculoskeletal function and mental well-being, independent of weight loss. Exercise influences hepatic steatosis by modifying the movement of free fatty acids (FFA) to and from the liver through alterations in substrate metabolism in muscle, adipose tissue, and the liver [110]. This process may be partially facilitated by enhancements in peripheral insulin sensitivity and glucose uptake, which subsequently improve hepatic metabolic response.

Individuals with MAFLD who aim to reduce hepatic steatosis should strive to engage in at least 135 minutes of moderate-intensity aerobic activity each week, with an ideal target of 150 to 240 minutes [111]. Currently, there is no definitive evidence indicating that the exercise intensity significantly affects the reduction of steatosis, provided the recommended volume is met. This exercise guideline also aids in enhancing cardiorespiratory fitness and is likely to have a positive impact on various cardiometabolic risk factors, including visceral adipose tissue (VAT). Nonetheless, high-quality evidence specifically related to MAFLD is still lacking.

Recommendations

- Lifestyle interventions, including a healthy, balanced diet and regular physical exercise, have been shown to improve liver histology and normalize liver enzyme levels (A1).
- Weight reduction is advantageous and advised for people with MAFLD, irrespective of BMI. The objective weight reduction is 7–10% for overweight/obese individuals and 5% for nonobese people with MAFLD. (B1)
- Physical exercise alone is sufficient for MAFLD patients who do not have steatohepatitis or fibrosis. (B1)
- There are no specific recommendations for a particular dietary regimen; dietary guidance should be personalized to each individual. Energy restriction, adherence to a Mediterranean diet, frequent coffee intake, and the avoidance of processed foods and sugar are recommended. (B1)
- Both vigorous and moderate aerobic exercises, along with strength training, can effectively decrease hepatic steatosis in MAFLD; however, resistance training may be a more appropriate option for those with limited fitness abilities. Recommendations should be customised to individual patient preferences to improve long-term compliance. (B2)

14. Pharmacological therapy

Currently, the only approved medication for MAFLD/MASH is the thyroid hormone receptor β (THR-β) agonist resmetirom (Rezdiffra^{TM}), approved in March 2024 for non-cirrhotic MASH patients [112]. Fig. 2 depicts the recommendation for the initiation and follow-up of treatment using resmetirom. Other agents, including antidiabetic drugs, farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptors (PPAR) agonists, and thyroid hormone receptor (THR) agonists, are in advanced clinical development.

15. Evidence for current potential pharmacological therapy

PPARs, such as pioglitazone, have shown benefits in hepatic histology for diabetic and prediabetic patients but have limited impact on liver fibrosis. Its use is restricted due to side effects like weight gain, fluid retention, increased bladder cancer risk, and heightened susceptibility to bone loss and distal bone fractures in postmenopausal women [108,113–116].

Sodium-glucose co-transporter-2 inhibitors (SGLT2i), such as dapagliflozin, empagliflozin, ipragliflozin, and canagliflozin, are approved oral antidiabetic therapies that may improve hepatic steatosis, though more trials are needed to clarify their effects on liver histology [117–119].

Incretins and glucagon receptor agonists, including glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and glucose-dependent insulinotropic polypeptides (GIP) have also been approved for managing T2DM and obesity. Semaglutide has shown potential benefits for hepatic inflammation and fibrosis and is expected to be approved. Dual agonists (GLP-1/GIP) like Tirzepatide have also shown promise in reducing liver and visceral fat and have shown promising results in a phase II clinical trial for treating MAFLD/MASH [120,121].

Evidence for metformin efficacy in MASH is inconclusive, with no solid backing from randomized trials [122,123]. Vitamin E has shown promising results in improving liver enzymes and histology in MASH patients in some studies, but findings are inconsistent. Long-term use may benefit patients with advanced fibrosis, although concerns about prostate cancer risk warrant caution [15,81]. Statins have shown CVD benefits but do not directly improve liver histology in MAFLD patients. They may be considered for those with hyperlipidemia, since a case-control study suggested statin use could reduce the risk of hepatic fibrosis and decompensation. However, without significant RCTs on histological endpoints, their effectiveness for MAFLD/MASH remains unproven [124,125].

While Obeticholic acid (OCA), an FXR agonist, has shown efficacy in clinical trials in reducing hepatic fibrosis, concerns about adverse effects, particularly pruritus and changes in LDL and HDL levels, led to its discontinuation from trials and development for MASH [126–128].

Recommendations

- Resmetirom is recommended for patients with MASH who have significant fibrosis, but its prescription must be supported by a thorough evaluation from a liver specialist (B1).
- Metformin, statins, and sodium-glucose co-transporter 2 inhibitors (SGLT2i) are not recommended for improving liver histology because there is insufficient evidence regarding their effectiveness. Additionally, vitamin E is not advised due to safety concerns associated with long-term use. However, metformin may reduce the risk of HCC, and statins can decrease CVD morbidity and mortality, so they should be considered for these specific indications (B2).
- GLP-1 receptor agonists (GLP-1RAs) are effective in addressing hepatic steatosis and inflammation and should be considered for MAFLD patients who also have diabetes (B2).

16. Bariatric and metabolic therapies (endoscopic approaches and surgery) for MAFLD

Lifestyle modification and weight loss are the primary strategies for managing MAFLD and MASH [129]. When lifestyle changes—such as diet and exercise—fail to produce significant weight loss, bariatric surgery becomes a viable alternative [129]. This surgical option has shown promising results for MAFLD patients, leading to postoperatively histological improvements including decreasing hepatic steatosis and inflammation. It has also demonstrated control over T2DM and a reduction in CVD events and cancer risk [130,131]. However, the evidence regarding its impact on hepatic fibrosis has been less consistent. Additionally, all-cause mortality was substantially reduced among those who had bariatric surgery, with outcomes remaining consistent over nearly seven years of follow-up [132]. However, some patients may experience worsening fibrosis after bariatric surgery, and as such all patients must be monitored closely for liver function tests after surgery, as there is a potential risk of progressive liver fibrosis in some individuals [133]. Additionally, liver biopsy during bariatric surgery could be considered, as it may provide additional benefits in determining liver histopathology. Those with cirrhosis should be monitored monthly for signs of hepatic decompensation which can develop following surgery [129].

A variety of endoscopic procedures have emerged as more accessible methods for weight loss, typically offering lower costs and fewer complications. These include intragastric balloons, endoscopic sleeve gastroplasty, aspiration devices, transpyloric shuttles, Botox injections, duodenal-jejunal bypass liners, duodenal mucosa resurfacing, incision-less magnetic anastomosis systems, primary obesity surgery endoluminal, and gastric banding [134]. While these treatments may be appealing for patients with MAFLD, there is currently a lack of studies providing histological evidence for superiority of a particular method for MASH resolution and fibrosis improvement.

Recommendations

- Bariatric or metabolic surgery is a treatment option for patients with MAFLD if the following two conditions are met:
  1) The patient has morbid obesity, defined as a BMI greater than 40 kg/m^2 or a BMI over 35 kg/m^2, accompanied by metabolic comorbidities that have not been effectively managed through lifestyle changes.
  2) There is no evidence of clinically significant portal hypertension or decompensated cirrhosis. (B1)
- The effectiveness and practicality of bariatric surgery in patients with MAFLD and a BMI of 35 kg/m^2 or lower should be carefully assessed before it can be recommended for routine clinical practice. (C2)
- Bariatric/metabolic surgery can improve the entire spectrum of MAFLD, facilitating the reduction and resolution of hepatic steatosis and steatohepatitis, as well as the regression of fibrosis. (B1)
- When considering bariatric or metabolic surgery for cirrhotic patients, clinical decisions should be individualized, taking into account the increased risk of postoperative complications. (C1)

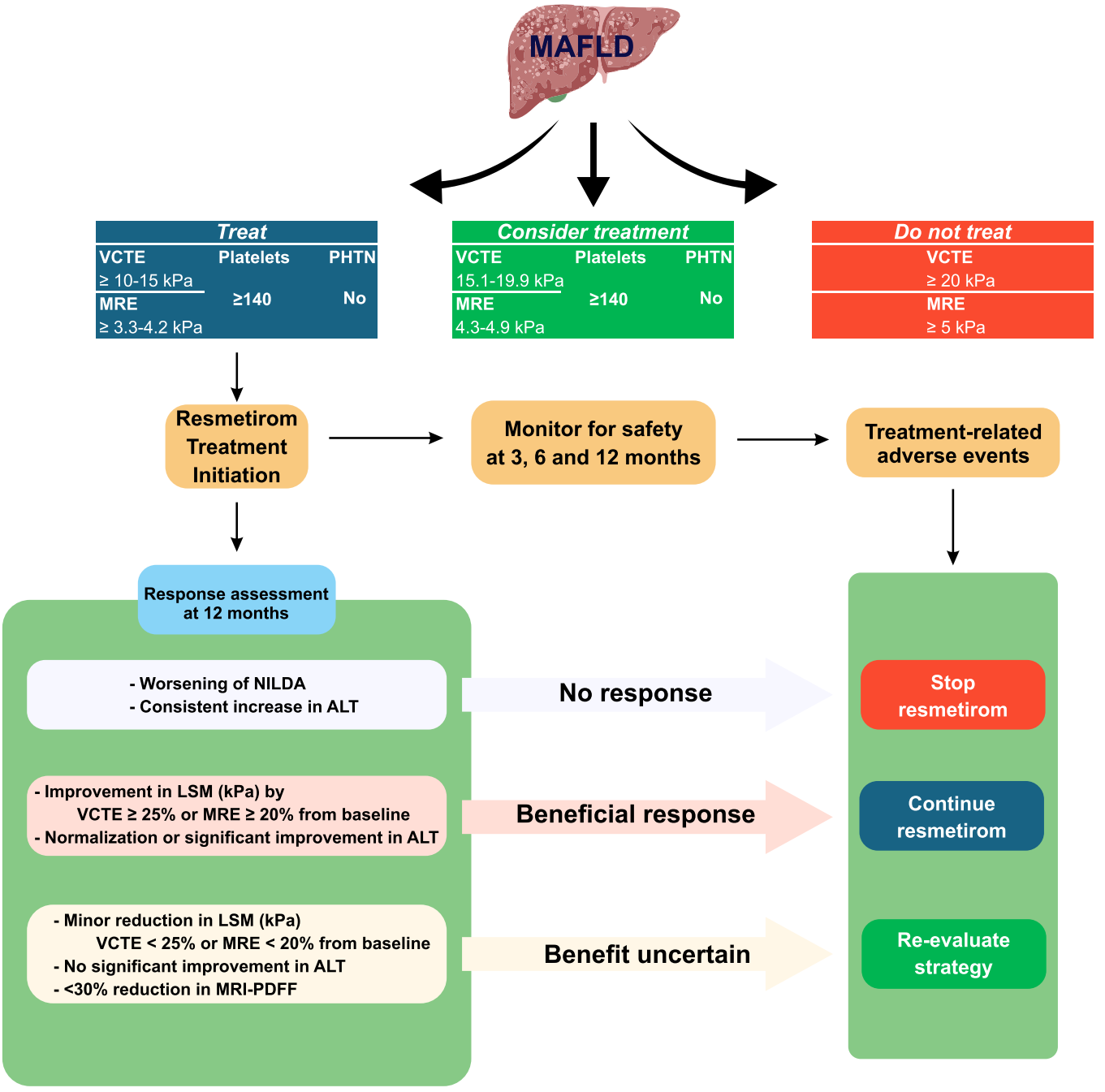

Fig. 2. The recommended algorithm for initiating and following up on treatment with Resmetirom.

17. Monitoring progress and treatment response

Individuals with severe fibrosis necessitate the most vigilant monitoring and care, as the intensity of their condition significantly impacts both liver-related outcomes and mortality [135].

Individuals with no fibrosis or early-stage fibrosis can have follow-ups every two to three years if there are no coexisting metabolic risk factors. Patients with fibrosis or those presenting uncontrolled metabolic risk factors should undergo annual monitoring. Those diagnosed with cirrhosis require surveillance every six months, which should include screening for HCC. It is recommended to utilize non-invasive scores (NFS, FIB-4) to monitor liver fibrosis progression in clinical settings, ideally alongside liver stiffness assessments, since there is no current optimal biomarker with high predictive capability for differentiating between various disease stages, which enhances prediction accuracy and reduces uncertainty.

Recommendations

- Individuals without significant fibrosis or extra metabolic risk factors can be monitored every two to three years. (C2)
- Those with significant fibrosis or other metabolic risk factors should be monitored annually, using a mix of non-invasive scores and/or liver stiffness evaluations. (C2)
- Patients with cirrhosis need to be monitored every six months, which should include assessments for HCC. (A2)

18. HCC surveillance in MAFLD

There is no substantial evidence to screen for HCC in non-cirrhotic patients, as the risk factors and natural history of HCC in MAFLD are still lacking [136]. Non-invasive tests (NITs) help identify patients without cirrhosis at the highest risk of HCC development, as an FIB-4 score > 2.67 indicates advanced fibrosis (F3/F4) and is linked to a higher risk of HCC in the absence of cirrhosis [136].

Surveillance for MAFLD cirrhosis is organized by risk stratification. Cirrhotic individuals are categorized into three groups: the high-risk group requires surveillance, the low-risk group may not need it, and the intermediate-risk group should be considered for surveillance. Nonetheless, effective performance in risk stratification remains challenging. LSM above 15 kPa should be taken into account for surveillance for HCC [15].

Although the sensitivity of abdominal ultrasound in MAFLD-related cirrhosis is lower compared to other etiologies, ultrasound is still helpful for HCC surveillance due to its availability, safety and cost-effectiveness [123]. MRI showed high sensitivity (85.7%) and specificity (97.0%). However, due to its high cost and limited availability, it is reserved for selected cases where ultrasound is inadequate, and the estimated risk of HCC development is high [137].

In combination with ultrasound, alpha-fetoprotein (AFP) is the biomarker with sufficient evidence to increase the sensitivity for detecting early HCC from 45% to 63% [138]. Six-month interval surveillance had better HCC detection rates and prognosis than 12-month intervals, while no significant difference was noted between 3-month intervals [139].

Recommendations

- Screening for HCC in patients with cirrhosis due to MAFLD is recommended every six months, as this can improve overall survival rates. The preferred screening method is abdominal ultrasonography, which can be combined with alpha-fetoprotein (AFP) testing to enhance sensitivity. However, for non-cirrhotic patients, this screening practice is not recommended due to insufficient evidence supporting its cost-effectiveness (A1).
- If the quality of the ultrasound is lacking, CT or MRI may be required. (B2)

19. Liver Transplantation for MAFLD

MASH-related decompensated cirrhosis has recently surpassed hepatitis C as an indication for liver transplantation (LT) due to the sharp rise in the incidence and prevalence of MASH and metabolic syndrome. Many differences distinguish liver transplantation (LT) due to MAFLD from other causes of liver diseases [140]. Predictors of LT in MAFLD patients include higher incidence of HCC, obesity and increased age. The most common mortality causes in non-HCC MAFLD patients include infections, and CVD and cerebrovascular complications [140]. Nonetheless, there are no differences in the outcome post-LT between MAFLD and other causes of liver diseases despite the overall higher proportion of risk factors in individuals with MAFLD [141]. The risk of CVD complications following LT is higher [142]. Therefore, MAFLD patients need a specific approach to evaluating and managing these complications. This strategy will improve the outcome after LT [143]. ECG, echocardiography, and stress thallium are used for routine evaluation of CVD status pre-liver transplantation. In contrast, coronary angiography and coronary CT angiography are used to evaluate patients with ischemic heart diseases.

Compared to de novo MAFLD, recurrent MAFLD following transplantation is more prevalent [144]. Fibrosis evaluation instruments like MRE and transient elastography are among the non-invasive techniques useful for determining the course of the illness post-LT [145]. Numerous components of metabolic syndrome are associated with immunosuppressants. For example, post-OLT corticosteroid medication has been shown to raise the risk of obesity, exacerbate pre-existing T2DM, and increase the chance of developing new-onset T2DM, hypertension, and hyperlipidemia. Consequently, early tapers should reduce the use of corticosteroids [146]. The adverse effects of calcineurin inhibitors (CNIs) are well-known and include insulin resistance, hypertension, and hyperlipidemia.

Recommendations

- Liver transplantation is a viable option for patients with MAFLD who have been carefully evaluated and selected, particularly those experiencing decompensated liver disease or HCC (B1).
- Patients with MAFLD face a heightened risk of postoperative complications due to pre-existing heart disease and metabolic comorbidities. Therefore, they undergo a comprehensive evaluation before being placed on the transplant list. Additionally, ongoing monitoring is essential after transplantation (B1).

20. Management of MAFLD-related HCC

As is the case with other liver diseases that lead to cirrhosis, the optimal management of MAFLD-related HCC must involve a multidisciplinary team, which includes hepatologists, oncologists, hepatobiliary surgeons, diagnostic and interventional radiologists, clinical pathologists, and palliative care specialists. Treatment should be individualized based on several factors, such as liver disease stage, tumor size, number of lesions, presence of portal hypertension, the patient's performance status, and any lymph node or distant spread of the disease, as well as other comorbidities.

Since MAFLD is a multisystemic disease, it is crucial to consider comorbidities when assessing patients with MAFLD-related HCC. Controlling metabolic risk factors can significantly improve HCC management outcomes in patients with MAFLD. Physical activity has been shown to positively impact the survival of patients with HCC [147]. However, it is crucial to take body composition into account—specifically skeletal muscle mass and body fat—since sarcopenia, or the loss of muscle mass, is a known predictor of outcomes for patients with HCC. This consideration is particularly important when recommending treatment options, especially concerning physical activity [148].

T2DM is also a risk factor for HCC. Research has demonstrated that metformin significantly reduces the risk of hepatic decompensation and HCC in individuals with NASH-related Child-Pugh A cirrhosis and an HbA1c level greater than 7.0% [149] Additionally, metformin can enhance survival after curative therapy in those with T2DM [150]. Therefore, combining metformin with lifestyle modifications may be advisable for MAFLD-related HCC patients with T2DM. However, before drawing firm conclusions and making strong recommendations, further rigorous, prospective randomized trials with appropriate comparison groups and validated outcome measures are needed, particularly including patients from our region.

Recommendations:

- Metformin along with lifestyle modifications may be advantageous for patients with MAFLD-related HCC, especially those with T2DM. (B1)
- It is advised to carefully consider sarcopenia as a prognostic indicator and to provide appropriate nutritional support and correct any deficiencies (C2)

21. Special MAFLD groups

21.1. Lean MAFLD

MAFLD has traditionally been associated with obesity and metabolic syndrome. However, there is a significant subset of individuals with a normal BMI, often referred to as "lean" or "non-obese," who also develop MAFLD [81]. Individuals with lean MAFLD typically exhibit

fewer components of metabolic syndrome and have a more favourable histological profile compared to those with obese MAFLD. Despite this, they tend to experience worse long-term outcomes [151–153]. A recent study suggests that differing telomere lengths, influenced by varying metabolic adaptations, may help explain this paradox [154].

Currently, there are no specific recommendations for managing MAFLD in lean individuals, and lifestyle modification remains the cornerstone of treatment, similar to that for their obese counterparts. Additionally, apart from overall caloric restriction, improving dietary patterns has shown beneficial effects in reducing the risk of developing MAFLD, even among non-obese individuals [155].

Recommendations
- MAFLD in individuals with a lean body type is recognized as a unique clinical condition that requires increased awareness and proactive management.
- Independent of their initial BMI, lifestyle changes and consistent physical activity play a crucial role in managing lean MAFLD and its related metabolic complications.

2.1.2. Pediatric MAFLD

The global rise in pediatric obesity incidence has coincided with a surge in the diagnosis of pediatric MAFLD that ranges between 5-10% globally [156]. The pathogenesis of pediatric MAFLD is multifactorial, including genetic predisposition, insulin resistance, and gut microbiota. Children remain asymptomatic and may have elevated liver enzymes, though normal levels do not exclude the diagnosis [12].

Management of pediatric MAFLD involves lifestyle modification, dietary changes, and regular exercise [157]. Vitamin E is recommended for investigation in non-diabetic children with biopsy-proven MASH [81]. Long-term outcomes in pediatric MAFLD may be associated with an increased risk of T2DM and CVD [158].

Recommendations
- Pediatric MAFLD poses a significant public health issue, indicating a worldwide rise in obesity and metabolic syndrome.
- Timely detection and ongoing monitoring are essential to prevent long-term complications.
- Further research is needed to gain deeper insights into the pathogenesis and to develop effective treatments.

21.3. Ramadan fasting and MAFLD

21.3.1. MAFLD without cirrhosis

Lifestyle modifications, such as dietary changes, weight loss, and exercise, are essential for managing MAFLD. Ramadan fasting may improve metabolic parameters, with a systematic review of 397 MAFLD patients indicating benefits in weight loss, body composition, cardiometabolic risk factors (lipid profiles, blood pressure), and glycemic parameters. It may enhance liver function (ALP, AST, bilirubin) and reduce inflammatory markers like CRP and IL-6 [159]. Additionally, studies have shown improvements in steatosis and fibrosis indices [160]. However, caution is necessary at the time of breaking the fast, as unhealthy meals high in sugar and fat can worsen MAFLD.

21.3.2. Ramadan fasting in cirrhotic patients

Cirrhotic patients are generally advised against fasting due to potential health risks. Child-Pugh A compensated cirrhosis patients may fast safely, while Child-Pugh B decompensated patients should avoid fasting due to complications. End-stage Child-Pugh C patients, especially those who are diabetic, should not fast due to severe risks such as gastrointestinal bleeding and encephalopathy. Increased gastric acid secretion and heavy meals post fasting also elevate the risk of peptic ulcer and variceal bleeding [161]. It is recommended that physicians perform upper EGD for cirrhotic patients considering fasting to detect and manage potential issues [161].

Recommendations:
- Fasting during Ramadan is highly recommended for patients with MAFLD who do not have cirrhosis, due to various positive effects on metabolic parameters.
- At risk of cirrhotic patients, those classified as Child-Pugh A can fast safely. However, fasting is not advisable for Child-Pugh B patients and is prohibited for Child-Pugh C patients.
- For any cirrhotic patients planning to fast, it is recommended to undergo screening upper endoscopy beforehand and to implement appropriate prophylactic measures.

22. Defining preventive strategies for MAFLD

MAFLD is an increasing public health concern with a high incidence and prevalence worldwide. Therefore, it is essential to establish preventive measures for MAFLD. These strategies should focus on three main areas. First, there should be an effort to raise awareness among healthcare providers and patients about the magnitude of the issue related to MAFLD. Second, simple tests should be implemented to screen and diagnose individuals who are at risk for the condition. Third, patient education is critical for the prevention and management of MAFLD. It is important to emphasize the significance of lifestyle modifications that contribute to preventing and managing MAFLD, as well as improving cardiometabolic health. These lifestyle changes will remain fundamental, even with the emergence of new treatments.

Future studies should also explore whether individualized approaches are needed and determine the precise thresholds to reverse steatohepatitis and liver fibrosis. General recommendations for prevention include avoiding alcohol altogether, vaccination against HBV, and managing cardiovascular disease risk factors such as hypertension and hyperlipidemia.

23. Climate change and MAFLD

Climate change, marked by rising temperatures and increasing pollutants, negatively impacts the environment, leading to reduced biodiversity, poor access to clean water and nutrition, and threats to infrastructure essential for human survival. Its effects can contribute to liver disorders, notably MAFLD, exacerbated by food insecurity and obesity [162].

Global warming threatens agriculture and infrastructure, heightening food insecurity, which in turn leads to obesity—a contributing factor to MAFLD. High temperatures may also promote sedentary lifestyles, worsening obesity and associated health issues, while increasing greenhouse gas emissions linked to healthcare use and food production. The prevalence of cyanobacteria in water due to climate change introduces hepatotoxic compounds that may accelerate MAFLD [163].

Addressing the root causes of these interrelated issues is crucial for preserving liver health and the environment. Promoting plant-based diets can reduce greenhouse gas emissions significantly, and encouraging exercise can diminish obesity rates. Shifting mindsets to view obesity and MAFLD as social issues rather than individual failures can lead to stronger public policies. The healthcare sector must acknowledge its role in climate change and adopt sustainable practices, focusing on prevention, patient empowerment, and reducing unnecessary emissions through improved service delivery [163].

Recommendations
- Hepatologists ought to emphasize the connection between liver disease and climate change within medical education. (C3)
- Hepatology organizations should promote lifestyle modifications that lower liver disease risks and environmental effects, reduce unnecessary healthcare visits, and incorporate these concepts into training programs. (C3)

(continued)

- They need to support government initiatives such as prohibiting junk food advertisements, subsidizing healthy options, and providing access to exercise. Furthermore, they should disseminate sustainable hepatology practices through virtual and small in-person events to enhance education and morale. (C3)

24. Conclusions

The prevalence of MAFLD is swiftly rising in Africa and the Middle East, and is becoming a major cause of chronic liver disease, HCC, and liver transplantation. Moreover, it is closely linked to the risk of developing multiple extrahepatic complications including T2DM, CVD, CKD, and various types of extrahepatic malignancies. In this region, dual etiology, especially in conjunction with viral hepatitis, is common and poses significant challenges.

The AMAGE guideline document for MAFLD aims to provide clear and practical guidance for assessing and managing both general and specific populations affected by MAFLD. Fibrosis is the primary risk factor for all hepatic and extrahepatic consequences of MAFLD, and a variety of non-invasive fibrosis assessment methods are becoming increasingly available and widely used. A thorough, interdisciplinary, and patient-centered approach is essential to provide the best treatment for MAFLD patients. This model should focus on patient-reported outcomes and address the entire spectrum of the disease, which includes not only the resolution of liver damage and hepatic steatosis but also the improvement of the associated systemic metabolic environment and the management of comorbidities that elevate the risk of cardiovascular disease (CVD) and other extrahepatic complications. Although a range of therapeutic options is expected to become available in the coming years, lifestyle changes, including dietary improvements and structured physical exercise, remain the cornerstone of effective management. Bariatric (metabolic) surgery could be necessary in refractory cases. Patients with MAFLD who have developed cirrhosis should be monitored for HCC and varices. Numerous information gaps around MAFLD have been found, and a concerted effort across diverse stakeholders to obtain further data is critical to fully implement these suggestions and to tackle this developing issue.

Author contributions

Yasser Fouad, Reda Elwakil and Mohammed Eslam designed the work and developed the study plan. All authors collected the data, participated in drafting and revising the manuscript, and approved the final version. Yasser Fouad is responsible for the integrity of the work as a whole.

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References

[1] Pan Z, Fouad Y, Abaalkhail F, Al Hassani A, Altarrah MY, Derbala M, et al. The burden of metabolic diseases in the Arab region, 1990-2021. Ther Adv Endocrinol Metab 2025;16:20420188251406531. https://doi.org/10.1177/20420188251406531.

[2] Spearman CW, Desalegn H, Ocama P, Awuku YA, Ojo O, Elsahhar M, et al. The Sub-Saharan Africa position statement on the redefinition of fatty liver disease: from NAFLD to MAFLD. J Hepatol 2021;74(5):1256–8. https://doi.org/10.1016/j.jhep.2021.01.015.

[3] Fouad Y, Ghazinyan H, Alboraie M, Al Khatry M, Desalegn H, Al-Ali F, et al. Joint position statement from the Middle East and North Africa and Sub-Saharan Africa on continuing to endorse the MAFLD definition. J Hepatol 2024;80(5):e194–e7. https://doi.org/10.1016/j.jhep.2024.01.033.

[4] Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323(7308):334–6. https://doi.org/10.1136/bmj.323.7308.334.

[5] Pan Z, Alqahtani SA, Al-Busafi SA, Al Awadhi S, Elwakil R, Fouad Y, et al. Underrepresentation of Arabs in functional genetics studies: opportunities and obstacles for advancing biology and Human health. Liver Int 2025;45(5):e70088. https://doi.org/10.1111/liv.70088.

[6] Chan KE, Koh TJL, Tang ASP, Quek J, Yong JN, Tay P, et al. Global prevalence and clinical characteristics of metabolic-associated fatty liver disease: a meta-analysis and systematic review of 10 739 607 individuals. J Clin Endocrinol Metab 2022;107(9):2691–700. https://doi.org/10.1210/clinem/dgac321.

[7] Younossi ZM, Golabi P, Paik J, Owrangi S, Yilmaz Y, El-Kassas M, et al. Prevalence of metabolic dysfunction-associated steatotic liver disease in the Middle East and North Africa. Liver Int 2024;44(4):1061–70. https://doi.org/10.1111/liv.15852.

[8] Feng G, Targher G, Byrne CD, Yilmaz Y, Wong VW-S, Lesmana CRA, et al. Global burden of metabolic dysfunction-associated liver disease, 2010 to 2021☆. JHEP Rep 2024;7(3):101271. https://doi.org/10.1016/j.jhepr.2024.101271.

[9] Amini-Salehi E, Letafatkar N, Norouzi N, Joukar F, Habibi A, Javid M, et al. Global prevalence of nonalcoholic fatty liver disease: an updated review meta-analysis comprising a population of 78 million from 38 countries. Arch Med Res 2024;55(6):103043. https://doi.org/10.1016/j.arcmed.2024.103043.

[10] Eslam M, El-Serag HB, Francque S, Sarin SK, Wei L, Bugianesi E, George J. Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight. Nat Rev Gastroenterol Hepatol 2022;19(10):638–51. https://doi.org/10.1038/s41575-022-00635-5.

[11] Li J, Ha A, Rui F, Zou B, Yang H, Xue Q, et al. Meta-analysis: global prevalence, trend and forecasting of non-alcoholic fatty liver disease in children and adolescents, 2000–2021. Aliment Pharmacol Ther 2022;56(3):396–406. https://doi.org/10.1111/apt.17096.

[12] Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, et al. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6(10):864–73. https://doi.org/10.1016/S2468-1253(21)00183-7.

[13] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73(1):202–9. https://doi.org/10.1016/j.jhep.2020.03.039.

[14] Eslam M, Sanyal AJ, George J, Sanyal A, Neuschwander-Tetri B, Tiribelli C, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999–2014 e1. https://doi.org/10.1053/j.gastro.2019.11.312.

[15] Eslam M, Sarin SK, Wong VW-S, Fan J-G, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14(6):889–919. https://doi.org/10.1007/s12072-020-10094-2.

[16] Eslam M, Fan J-G, Yu M-L, Wong VW-S, Cua IH, Liu C-J, et al. The Asian Pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic dysfunction-associated fatty liver disease. Hepatol Int 2025;19(2):1–41. https://doi.org/10.1007/s12072-024-10774-3.

[17] Fouad Y, Elwakil R, Elsahhar M, Said E, Bazeed S, Ali Gomaa A, et al. The NAFLD-MAFLD debate: eminence vs evidence. Liver Int 2021;41(2):255–60. https://doi.org/10.1111/liv.14739.

[18] Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int 2020;40(12):3018–30. https://doi.org/10.1111/liv.14675.

[19] Lee H, Lee Y-h, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. Clin Gastroenterol Hepatol 2021;19(10):2138–47 e10. https://doi.org/10.1016/j.cgh.2020.12.022.

[20] Tsutsumi T, Eslam M, Kawaguchi T, Yamamura S, Kawaguchi A, Nakano D, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: generalized estimating equation approach. Hepatol Res 2021;51(11):1115–28. https://doi.org/10.1111/hepr.13685.

[21] Alharthi J, Gastaldelli A, Cua IH, Ghazinian H, Eslam M. Metabolic dysfunction-associated fatty liver disease: a year in review. Curr Opin Gastroenterol 2022;38(3):251–60. https://doi.org/10.1097/MOG.0000000000000823.

[22] Eslam M, George J. Two years on, a perspective on MAFLD. eGastroenterology 2023;1(2):e100019. https://doi.org/10.1136/egastro-2023-100019.

[23] Jiang M, Butt AS, Cua IH, Pan Z, Al-Busafi SA, Mendez-Sanchez N, vs Eslam MMAFLD. MASLD: a year in review. Expert Rev Endocrinol Metab 2025;20(4):267–78. https://doi.org/10.1080/17446651.2025.2492767.

[24] Alboraie MA, Tanwandee T, Xu X, Nikolova D, Estupiñan EC, Ghazinyan HL, et al. Global multi-societies endorsement of the MAFLD definition. Ann Hepatol 2024;29(6):1–4. https://doi.org/10.1016/j.aohep.2024.101573.

[25] Méndez-Sánchez N, Bugianesi E, Gish RG, Lammert F, Tilg H, Nguyen MH, et al. Global multi-stakeholder endorsement of the MAFLD definition. Lancet Gastroenterol Hepatol 2022;7(5):388–90. https://doi.org/10.1016/S2468-1253(22)00062-0.

[26] Alem SA, Fouad Y, AbdAllah M, Attia D, Kamal I, Said E, et al. Hepatologists' awareness and knowledge of NAFLD and the familiarity with renaming NAFLD to MAFLD. Endocrine, Metab Immune Disord-Drug Targets (Formerly Curr Drug Targets-Immune, Endocr Metab Disord) 2024;24(12):1445–53. https://doi.org/10.2174/1871530323666221028154159.

[27] Fouad Y, Gomaa A, Semida N, Ghany WA, Attia D. Change from NAFLD to MAFLD increases the awareness of fatty liver disease in primary care physicians and specialists. J Hepatol 2021;74(5):1254–6. https://doi.org/10.1016/j.jhep.2020.12.035.

[28] Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob Health 2018;6(10):e1077–e86. https://doi.org/10.1016/S2214-109X(18)30357-7.
[29] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. Lancet 2014;384(9945):766–81. https://doi.org/10.1016/S0140-6736(14)60460-8.
[30] Hegazi R, El-Gamal M, Abdel-Hady N, Hamdy O. Epidemiology of and risk factors for type 2 diabetes in Egypt. Ann Glob Health 2015;81(6):814–20. https://doi.org/10.1016/j.aogh.2015.12.011.
[31] Federation ID. IDF Diabetes Atlas Brussels. Belgium: International diabetes federation; 2021 https://www.ncbi.nlm.nih.gov/pubmed/35914061.
[32] Azizi F, Hadaegh F, Hosseinpanah F, Mirmiran P, Amouzegar A, Abdi H, et al. Metabolic health in the Middle East and north Africa. Lancet Diabetes Endocrinol 2019;7(11):866–79. https://doi.org/10.1016/S2213-8587(19)30179-2.
[33] Chen F, Esmaili S, Rogers GB, Bugianesi E, Petta S, Marchesini G, et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. Hepatology 2020;71(4):1213–27. https://doi.org/10.1002/hep.30908.
[34] Eslam M, George J. Genetic and epigenetic mechanisms of NASH. Hepatol Int 2016;10(3):394–406. https://doi.org/10.1007/s12072-015-9689-y.
[35] Eslam M, George J. Genetic contributions to NAFLD: leveraging shared genetics to uncover systems biology. Nat Rev Gastroenterol Hepatol 2020;17(1):40–52. https://doi.org/10.1038/s41575-019-0212-0.
[36] Eslam M, Mangia A, Berg T, Chan HLY, Irving WL, Dore GJ, et al. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. Hepatology 2016;64(1):34–46. https://doi.org/10.1002/hep.28475.
[37] Alharthi J, Bayoumi A, Thabet K, Pan Z, Gloss BS, Latchoumanin O, et al. A metabolic associated fatty liver disease risk variant in MBOAT7 regulates toll like receptor induced outcomes. Nat Commun 2022;13(1):7430. https://doi.org/10.1038/s41467-022-35158-9.
[38] Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 2009;7(2):234–8. https://doi.org/10.1016/j.cgh.2008.11.005.
[39] Le P, Payne JY, Zhang L, Deshpande A, Rothberg MB, Alkhouri N, et al. Disease state transition probabilities across the spectrum of NAFLD: a systematic review and meta-analysis of paired biopsy or imaging studies. Clin Gastroenterol Hepatol 2023;21(5):1154–68. https://doi.org/10.1016/j.cgh.2022.07.033.
[40] Alharthi J, Latchoumanin O, George J, Eslam M. Macrophages in metabolic associated fatty liver disease. World J Gastroenterol 2020;26(16):1861. https://doi.org/10.3748/wjg.v26.i16.1861.
[41] Rice BA, Naimi TS, Long MT. Nonheavy alcohol use associates with liver fibrosis and nonalcoholic steatohepatitis in the framingham heart study. Clin Gastroenterol Hepatol 2023;21(11):2854–63 e2. https://doi.org/10.1016/j.cgh.2022.10.039.
[42] Pan Z, El Sharkway R, Bayoumi A, Metwally M, Gloss BS, Brink R, et al. Inhibition of MERTK reduces organ fibrosis in mouse models of fibrotic disease. Sci Transl Med 2024;16(741):eadj0133. https://doi.org/10.1126/scitranslmed.adj0133.
[43] Pan Z, Al-Busafi SA, Abdulla M, Fouad Y, Sebastiani G, Eslam M. MAFLD identifies patients with significant hepatic fibrosis better than MASLD. Hepatol Int 2024;18(3):964–72. https://doi.org/10.1007/s12072-024-10673-7.
[44] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13(4):643–54 e9. https://doi.org/10.1016/j.cgh.2014.04.014.
[45] Pan Z, Al Hassani A, Ismail MH, AlNaamani KM, Altarrah MY, Derbala M, et al. Changing profile and burden of hepatocellular carcinoma in Arab Countries in 1990-2021. Ann Hepatol 2025;30(2):102104. https://doi.org/10.1016/j.aohep.2025.102104.
[46] Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. Ann Transl Med 2017;5(13):270. https://doi.org/10.21037/atm.2017.04.41.
[47] Liu Y-L, Patman G, Leathart J, Piguet A-C, Burt A, Dufour J-F, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 2014;61(1):75–81. https://doi.org/10.1016/j.jhep.2014.02.030.
[48] Pipitone RM, Ciccioli C, Infantino G, La Mantia C, Parisi S, Tulone A, et al. MAFLD: a multisystem disease. Ther Adv Endocrinol Metab 2023;14:20420188221145549. https://doi.org/10.1177/20420188221145549.
[49] Eslam M, Ahmed A, Després J-P, Jha V, Halford JC, Chieh JTW, et al. Incorporating fatty liver disease in multidisciplinary care and novel clinical trial designs for patients with metabolic diseases. Lancet Gastroenterol Hepatol 2021;6(9):743–53. https://doi.org/10.1016/S2468-1253(21)00132-1.
[50] Mostafa AM, Pan Z, Yu ML, Örmeci N, Fouad Y, Eslam M. MAFLD: a comprehensive review of the link between metabolic dysfunction and cardiovascular risk. Hepat Med 2025;17:75–90. https://doi.org/10.2147/hmer.S506402.
[51] Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol 2019;71(2):371–8. https://doi.org/10.1016/j.jhep.2019.03.033.
[52] Alharthi J, Eslam M. Biomarkers of metabolic (dysfunction)-associated fatty liver disease: an update. J Clin Transl Hepatol 2021;10(1):134. https://doi.org/10.14218/JCTH.2021.00248.
[53] Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol 2012;56(1):234–40. https://doi.org/10.1016/j.jhep.2011.03.020.
[54] Mozes FE, Lee JA, Selvaraj EA, Jayaswal ANA, Trauner M, Boursier J, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut 2022;71(5):1006–19. https://doi.org/10.1136/gutjnl-2021-324243.
[55] Filozof CM, Jones S, Goldstein BJ. Liver fibrosis as assessed by the FIB-4 index in patients with type 2 diabetes (T2DM). Diabetes 2018;67(Supplement_1). https://doi.org/10.2337/db18-1570-P.
[56] McPherson S, Hardy T, Dufour J-F, Petta S, Romero-Gomez M, Allison M, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. Off J Am Coll Gastroenterol| ACG 2017;112(5):740–51. https://doi.org/10.1038/ajg.2016.453.
[57] Wilson MP, Singh R, Mehta S, Murad MH, Fung C, Low G. Comparing FIB-4, VCTE, pSWE, 2D-SWE, and MRE thresholds and diagnostic accuracies for detecting hepatic fibrosis in patients with MASLD: a systematic review and Meta-analysis. Diagnostics (Basel) 2025;15(13). https://doi.org/10.3390/diagnostics15131598.
[58] Boursier J, Hagstrom H, Ekstedt M, Moreau C, Bonacci M, Cure S, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. J Hepatol 2022;76(5):1013–20. https://doi.org/10.1016/j.jhep.2021.12.031.
[59] Lin H, Lee HW, Yip TC, Tsochatzis E, Petta S, Bugianesi E, et al. Vibration-controlled transient elastography scores to predict liver-related events in steatotic liver disease. JAMA 2024;331(15):1287–97. https://doi.org/10.1001/jama.2024.1447.
[60] Mozes FE, Lee JA, Vali Y, Alzoubi O, Staufer K, Trauner M, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol 2023;8(8):704–13. https://doi.org/10.1016/S2468-1253(23)00141-3.
[61] Chan WL, Chong SE, Chang F, Lai LL, Chuah KH, Nik Mustapha NR, et al. Long-term clinical outcomes of adults with metabolic dysfunction-associated fatty liver disease: a single-centre prospective cohort study with baseline liver biopsy. Hepatol Int 2023;17(4):870–81. https://doi.org/10.1007/s12072-023-10550-9.
[62] Abeysekera KWM, Valenti L, Younossi Z, Dillon JF, Allen AM, Nourredin M, et al. Implementation of a liver health check in people with type 2 diabetes. Lancet Gastroenterol Hepatol 2024;9(1):83–91. https://doi.org/10.1016/S2468-1253(23)00270-4.
[63] Huang DQ, Noureddin N, Ajmera V, Amangurbanova M, Bettencourt R, Truong E, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis. Lancet Gastroenterol Hepatol 2023;8(9):829–36. https://doi.org/10.1016/S2468-1253(23)00157-7.
[64] Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009;51(6):1061–7. https://doi.org/10.1016/j.jhep.2009.09.001.
[65] Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Ledinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66(5):1022–30. https://doi.org/10.1016/j.jhep.2016.12.022.
[66] Caussy C, Brissot J, Singh S, Bassirian S, Hernandez C, Bettencourt R, et al. Prospective, same-day, direct comparison of controlled attenuation parameter with the M vs the XL probe in patients with nonalcoholic fatty liver disease, using magnetic resonance imaging-proton density fat fraction as the standard. Clin Gastroenterol Hepatol 2020;18(8):1842–50 e6. https://doi.org/10.1016/j.cgh.2019.11.060.
[67] Verma S, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). Liver Int 2013;33(9):1398–405. https://doi.org/10.1111/liv.12226.
[68] Ravaioli F, Dajti E, Mantovani A, Newsome PN, Targher G, Colecchia A. Diagnostic accuracy of FibroScan-AST (FAST) score for the non-invasive identification of patients with fibrotic non-alcoholic steatohepatitis: a systematic review and meta-analysis. Gut 2023;72(7):1399–409. https://doi.org/10.1136/gutjnl-2022-328689.
[69] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6):1313–21. https://doi.org/10.1002/hep.20701.
[70] Bedossa P, Consortium FP. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014;60(2):565–75. https://doi.org/10.1002/hep.27173.
[71] Wang X, Wei S, Wei Y, Wang X, Xiao F, Feng Y, Zhu Q. The impact of concomitant metabolic dysfunction-associated fatty liver disease on adverse outcomes in patients with hepatitis B cirrhosis: A propensity score matching study. Eur J Gastroenterol Hepatol 2023;35(8):889–98. https://doi.org/10.1097/MEG.0000000000002583.
[72] Petta S, Vanni E, Bugianesi E, Di Marco V, Cammà C, Cabibi D, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the non-invasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2015;35(5):1566–73. https://doi.org/10.1111/liv.12584.
[73] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF. Baveno VII - renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–74. https://doi.org/10.1016/j.jhep.2021.12.022.
[74] Eslam M, Ampuero J, Jover M, Abd-Elhalim H, Rincon D, Shatat M, et al. Predicting portal hypertension and variceal bleeding using non-invasive measurements

of metabolic variables. Ann Hepatol 2013;12(4):588–98. https://doi.org/10.1016/S1665-2681(19)31343-2.
[75] Colecchia A, Montrone L, Scaioli E, Bacchi–Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143(3):646–54. https://doi.org/10.1053/j.gastro.2012.05.035.
[76] Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol 2014;60(6):1158–64. https://doi.org/10.1097/MPG.0000000000000400.
[77] Elkrief L, Rautou P-E, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015;275(2):589–98. https://doi.org/10.1148/radiol.14141210.
[78] Song J, Huang J, Huang H, Liu S, Luo Y. Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: a meta-analysis. Clin Res Hepatol Gastroenterol 2018;42(3):216–26. https://doi.org/10.1016/j.clinre.2017.11.002.
[79] Zheng KI, Liu C, Li J, Zhao L, Zheng M-H, Wang F, Qi X. Validation of Baveno VI and expanded Baveno VI criteria to identify high-risk varices in patients with MAFLD-related compensated cirrhosis. J Hepatol 2020;73(6):1571–3. https://doi.org/10.1016/j.jhep.2020.06.042.
[80] Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. Gastroenterology 2017;152(3):598–607 e2. https://doi.org/10.1053/j.gastro.2016.10.026.
[81] Fouad Y, Esmat G, Elwakil R, Zakaria S, Yosry A, Waked I, et al. The egyptian clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Saudi J Gastroenterol 2022;28(1):3–20. https://doi.org/10.4103/sjg.sjg_357_21.
[82] Ryou M, Stylopoulos N, Baffy G. Nonalcoholic fatty liver disease and portal hypertension. Explor Med 2020;1:149. https://doi.org/10.37349/emed.2020.00011.
[83] Pan Z, Alqahtani SA, Eslam M. MAFLD and chronic kidney disease: two sides of the same coin? Hepatol Int 2023;17(3):519–21. https://doi.org/10.1007/s12072-023-10526-9.
[84] Pan Z, Derbala M, AlNaamani K, Ghazinian H, Fan J-G, Eslam M. MAFLD criteria are better than MASLD criteria at predicting the risk of chronic kidney disease. Ann Hepatol 2024;29(5):101512. https://doi.org/10.1016/j.aohep.2024.101512.
[85] Pan Z, Shiha G, Esmat G, Mendez-Sanchez N, Eslam M. MAFLD predicts cardiovascular disease risk better than MASLD. Liver Int 2024;44(7):1567–74. https://doi.org/10.1111/liv.15931.
[86] Liu Z, Lin C, Suo C, Zhao R, Jin L, Zhang T, Chen X. Metabolic dysfunction-associated fatty liver disease and the risk of 24 specific cancers. Metabolism 2022;127:154955. https://doi.org/10.1016/j.metabol.2021.154955.
[87] Pal SC, Eslam M, Mendez-Sanchez N. Detangling the interrelations between MAFLD, insulin resistance, and key hormones. Hormones 2022;21(4):573–89. https://doi.org/10.1007/s42000-022-00391-w.
[88] Ramírez-Mejía MM, Qi X, Abenavoli L, Romero-Gómez M, Eslam M, Méndez-Sánchez N. Metabolic dysfunction: the silenced connection with fatty liver disease. Ann Hepatol 2023;28(6):101138. https://doi.org/10.1016/j.aohep.2023.101138.
[89] Khattab MA, Eslam M, Sharwae MA, Hamdy L. Seroprevalence of hepatitis C and B among blood donors in Egypt: Minya Governorate, 2000-2008. Am J Infect Control 2010;38(8):640–1. https://doi.org/10.1016/j.ajic.2009.12.016.
[90] Attia D, Abdel Alem S, El-Akel W, Abdel-Razek W, Eslam M, Fouad Y, Waked I. Prevalence and clinical characteristics of patients with metabolic dysfunction-associated fatty liver disease with hepatitis C virus infection—a population-based study. Aliment Pharmacol Ther 2022;56(11-12):1581–90. https://doi.org/10.1111/apt.17233.
[91] Khattab MA, Eslam M, Alavian SM. Hepatitis C Virus as a multifaceted disease: a simple and updated approach for extrahepatic manifestations of Hepatitis C Virus infection. Hepat Mon 2010;10(4):258–69 https://www.ncbi.nlm.nih.gov/pubmed/22312391.
[92] Chen Y, Gao W, Ye J, Yang L. Research progress of antiviral treatment for patients with chronic hepatitis B combined with metabolic fatty liver disease. Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chin J Hepatol 2024;32(10):955–60. https://doi.org/10.3760/cma.j.cn501113-20231228-00305.
[93] Huang S-C, Su T-H, Tseng T-C, Chen C-L, Hsu S-J, Liao S-H, et al. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. Hepatol Int 2023;17(5):1139–49. https://doi.org/10.1007/s12072-023-10545-6.
[94] Organization WH. Global hepatitis report2024: action for access in low-and middle-income countries. World Health Organization; 2024.
[95] Fouad Y, Lazarus JV, Negro F, Peck-Radosavljevic M, Sarin SK, Ferenci P, et al. MAFLD considerations as a part of the global hepatitis C elimination effort: an international perspective. Aliment Pharmacol Ther 2021;53(10):1080–9. https://doi.org/10.1111/apt.16346.
[96] Shiha G, Waked I, Soliman R, Elbasiony M, Gomaa A, Mikhail NNH, Eslam M. GES: A validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals. Liver Int 2020;40(11):2828–33. https://doi.org/10.1111/liv.14666.
[97] Gaber Y, AbdAllah M, Salama A, Sayed M, Abdel Alem S, Nafady S. Metabolic-associated fatty liver disease and autoimmune hepatitis: an overlooked interaction. Expert Rev Gastroenterol Hepatol 2021;15(10):1181–9. https://doi.org/10.1080/17474124.2021.1952867.
[98] Takahashi A, Ohira H, Abe K, Zeniya M, Abe M, Arinaga-Hino T, et al. Autoimmune hepatitis with metabolic dysfunction-associated fatty liver disease. Internal Med 2025;64(3):337–42. https://doi.org/10.2169/internalmedicine.3112-23.
[99] Staufer K, Huber-Schönauer U, Strebinger G, Pimingstorfer P, Suesse S, Scherzer T-M, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. J Hepatol 2022;77(4):918–30. https://doi.org/10.1016/j.jhep.2022.04.040.
[100] Idalsoaga F, Kulkarni AV, Mousa OY, Arrese M, Arab JP. Non-alcoholic fatty liver disease and alcohol-related liver disease: two intertwined entities. Front Med (Lausanne) 2020;7:448. https://doi.org/10.3389/fmed.2020.00448.
[101] Aybuke S, Annette P, Linda H, Zobair MY. A comprehensive review of patient-reported outcomes in metabolic dysfunction-associated steatotic liver disease. Metab Target Organ Damage 2024;4(4):42 https://www.oaepublish.com/articles/mtod.2024.70.
[102] Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas 2018;9:353–67. https://doi.org/10.2147/PROM.S156279.
[103] Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67(4):829–46. https://doi.org/10.1016/j.jhep.2017.05.016.
[104] Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51(1):121–9. https://doi.org/10.1002/hep.23276.
[105] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367–78 e5. https://doi.org/10.1053/j.gastro.2015.04.005.
[106] Musso G, Gambino R, Pacini G, De Michieli F, Cassader M. Prolonged saturated fat–induced, glucose-dependent insulinotropic polypeptide elevation is associated with adipokine imbalance and liver injury in nonalcoholic steatohepatitis: dysregulated enteroadipocyte axis as a novel feature of fatty liver. Am J Clin Nutr 2009;89(2):558–67. https://doi.org/10.3945/ajcn.2008.26720.
[107] Lirussi F, Azzalini L, Orando S, Orlando R, Angelico F. Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Datab System Rev 2007;2007(1):CD004996. https://doi.org/10.1002/14651858.CD004996.pub3.
[108] Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–85. https://doi.org/10.1056/NEJMoa0907929.
[109] Barchetta I, Del Ben M, Angelico F, Di Martino M, Fraioli A, La Torre G, et al. No effects of oral vitamin D supplementation on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. BMC Med 2016;14:1–10. https://doi.org/10.1186/s12916-016-0638-y.
[110] Solomon TP, Haus JM, Marchetti CM, Stanley WC, Kirwan JP. Effects of exercise training and diet on lipid kinetics during free fatty acid-induced insulin resistance in older obese humans with impaired glucose tolerance. Am J Physiol-Endocrinol Metab 2009;297(2):E552–E9. https://doi.org/10.1152/ajpendo.00220.2009.
[111] Keating SE, Sabag A, Hallsworth K, Hickman IJ, Macdonald GA, Stine JG, et al. Exercise in the management of metabolic-associated fatty liver disease (MAFLD) in adults: A position statement from exercise and sport science Australia. Sports Med 2023;53(12):2347–71. https://doi.org/10.1007/s40279-023-01918-w.
[112] Kokkorakis M, Boutari C, Hill MA, Kotsis V, Loomba R, Sanyal AJ, Mantzoros CS. Resmetirom, the first approved drug for the management of metabolic dysfunction-associated steatohepatitis: trials, opportunities, and challenges. Metab-Clin Exp 2024;154:155835. https://doi.org/10.1016/j.metabol.2024.155835.
[113] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165(5):305–15. https://doi.org/10.7326/M15-1774.
[114] Viscoli CM, Inzucchi SE, Young LH, Insogna KL, Conwit R, Furie KL, et al. Pioglitazone and risk for bone fracture: safety data from a randomized clinical trial. J Clin Endocrinol Metab 2017;102(3):914–22. https://doi.org/10.1210/jc.2016-3237.
[115] Huang J-F, Dai C-Y, Huang C-F, Tsai P-C, Yeh M-L, Hsu P-Y, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in nonalcoholic steatohepatitis patients. Hepatol Int 2021;15(5):1136–47. https://doi.org/10.1007/s12072-021-10242-2.
[116] Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: a meta-analysis. Front Endocrinol (Lausanne) 2021;12:615409. https://doi.org/10.3389/fendo.2021.615409.
[117] Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. Lancet Diabetes Endocrinol 2013;1(2):140–51. https://doi.org/10.1016/S2213-8587(13)70050-0.
[118] Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014;2(9):691–700. https://doi.org/10.1016/S2213-8587(14)70120-2.
[119] Brown E, Heerspink HJ, Cuthbertson DJ, Wilding JP. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet 2021;398(10296):262–76. https://doi.org/10.1016/S0140-6736(21)00536-5.

[120] Gastaldelli A, Cusi K, Landó LF, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 2022;10(6):393–406. https://doi.org/10.1016/S2213-8587(22)00070-5.
[121] Liarakos AL, Koliaki C. Novel dual incretin receptor agonists in the spectrum of metabolic diseases with a focus on tirzepatide: real game-changers or great expectations? A narrative review. Biomedicines 2023;11(7):1875. https://doi.org/10.3390/biomedicines11071875.
[122] Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann HL, Raschpichler G, Bjøro K, et al. Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. Scand J Gastroenterol 2009;44(7):853–60. https://doi.org/10.1080/00365520902845268.
[123] Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomed Rep 2013;1(1):57–64. https://doi.org/10.3892/br.2012.18.
[124] Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study: a post-hoc analysis. Lancet 2010;376(9756):1916–22. https://doi.org/10.1016/S0140-6736(10)61272-X.
[125] Eslami L, Merat S, Malekzadeh R, Nasseri-Moghaddam S, Aramin H. Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Cochrane Datab System Rev 2013;2013(12):CD008623. https://doi.org/10.1002/14651858.CD008623.pub2.
[126] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385(9972):956–65. https://doi.org/10.1016/S0140-6736(14)61933-4.
[127] Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394(10215):2184–96. https://doi.org/10.1016/S0140-6736(19)33041-7.
[128] Sanyal AJ, Ratziu V, Loomba R, Anstee QM, Kowdley KV, Rinella ME, et al. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis. J Hepatol 2023;79(5):1110–20. https://doi.org/10.1016/j.jhep.2023.07.014.
[129] Hafeez S, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: a future treatment by choice or by chance? J Obes 2013;2013(1):839275. https://doi.org/10.1155/2013/839275.
[130] Mazzini GS, Augustin T, Noria S, Romero-Marrero C, Li N, Hameed B, et al. ASMBS position statement on the impact of metabolic and bariatric surgery on nonalcoholic steatohepatitis. Surg Obes Relat Dis 2022;18(3):314–25. https://doi.org/10.1016/j.soard.2021.11.015.
[131] Lee Y, Doumouras AG, Yu J, Brar K, Banfield L, Gmora S, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17(6):1040–60 e11. https://doi.org/10.1016/j.cgh.2018.10.017.
[132] Krishnan A, Hadi Y, Alqahtani SA, Woreta TA, Fang W, Abunnaja S, et al. Cardiovascular outcomes and mortality after bariatric surgery in patients with nonalcoholic fatty liver disease and obesity. JAMA Netw Open 2023;6(4) e237188-e. https://doi.org/10.1001/jamanetworkopen.2023.7188.
[133] Wirth KM, Sheka AC, Kizy S, Irey R, Benner A, Sieger G, et al. Bariatric surgery is associated with decreased progression of nonalcoholic fatty liver disease to cirrhosis: a retrospective cohort analysis. Ann Surg 2020;272(1):32–9. https://doi.org/10.1097/SLA.0000000000003871.
[134] Salomone F, Sharaiha RZ, Boškoski I. Endoscopic bariatric and metabolic therapies for non-alcoholic fatty liver disease: evidence and perspectives. Liver Int 2020;40(6):1262–8. https://doi.org/10.1111/liv.14441.
[135] Eslam M, Alvani R, Shiha G. Obeticholic acid: towards first approval for NASH. Lancet 2019;394(10215):2131–3. https://doi.org/10.1016/S0140-6736(19)32963-0.
[136] Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, Argo CK. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018;48(7):696–703. https://doi.org/10.1111/apt.14937.
[137] Kim SY, An J, Lim Y-S, Han S, Lee J-Y, Byun JH, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. JAMA Oncol 2017;3(4):456–63. https://doi.org/10.1001/jamaoncol.2016.3147.
[138] Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154(6) 1706-18. e1. https://doi.org/10.1053/j.gastro.2018.01.064.
[139] Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53(2):291–7. https://doi.org/10.1016/j.jhep.2010.03.010.
[140] Kwong A, Kim W, Lake J, Smith J, Schladt D, Skeans M, et al. OPTN/SRTR 2018 annual data report: liver. Am J Transpl 2020;20:193–299. https://doi.org/10.1111/ajt.15674.
[141] Verna EC, Phipps MM, Halazun KJ, Markovic D, Florman SS, Haydel BM, et al. Outcomes in liver transplant recipients with nonalcoholic fatty liver disease-related HCC: results from the US multicenter HCC transplant consortium. Liver Transpl 2023;29(1):34–47. https://doi.org/10.1097/LVT.0000000000000007.
[142] VanWagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology 2012;56(5):1741–50. https://doi.org/10.1002/hep.25855.
[143] Tsochatzis E, Coilly A, Nadalin S, Levistky J, Tokat Y, Ghobrial M, et al. International liver transplantation consensus statement on end-stage liver disease due to nonalcoholic steatohepatitis and liver transplantation. Transplantation 2019;103(1):45–56. https://doi.org/10.1097/TP.0000000000002433.
[144] Finkenstedt A, Auer C, Glodny B, Posch U, Steitzer H, Lanzer G, et al. Patatin-like phospholipase domain-containing protein 3 rs738409-G in recipients of liver transplants is a risk factor for graft steatosis. Clin Gastroenterol Hepatol 2013;11(12):1667–72. https://doi.org/10.1016/j.cgh.2013.06.025.
[145] Shetty A, Giron F, Divatia MK, Ahmad MI, Kodali S, Victor D. Nonalcoholic fatty liver disease after liver transplant. J Clin Transl Hepatol 2021;9(3):428. https://doi.org/10.14218/JCTH.2020.00072.
[146] Hanouneh I, Macaron C, Lopez R, Feldstein A, Yerian L, Eghtesad B, Zein N. Recurrence of disease following liver transplantation: nonalcoholic steatohepatitis vs hepatitis C virus infection. Int J Organ Transplant Med 2011;2(2):57 https://www.ncbi.nlm.nih.gov/pubmed/25013596.
[147] Hashida R, Kawaguchi T, Koya S, Hirota K, Goshima N, Yoshiyama T, et al. Impact of cancer rehabilitation on the prognosis of patients with hepatocellular carcinoma. Oncol Lett 2020;19(3):2355–67. https://doi.org/10.3892/ol.2020.11345.
[148] Ha Y, Kim D, Han S, Chon YE, Lee YB, Kim MN, et al. Sarcopenia predicts prognosis in patients with newly diagnosed hepatocellular carcinoma, independent of tumor stage and liver function. Cancer Res Treatment: Off J Korean Cancer Assoc 2018;50(3):843–51. https://doi.org/10.4143/crt.2017.232.
[149] Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Eslam M, et al. Type 2 diabetes and metformin use associate with outcomes of patients with non-alcoholic steatohepatitis-related, child-pugh A cirrhosis. Clin Gastroenterol Hepatol 2020;19(1):136–45 e6. https://doi.org/10.1016/j.cgh.2020.04.083.
[150] Zhou J, Ke Y, Lei X, Wu T, Li Y, Bao T, et al. Meta-analysis: the efficacy of metformin and other anti-hyperglycemic agents in prolonging the survival of hepatocellular carcinoma patients with type 2 diabetes. Ann Hepatol 2020;19(3):320–8. https://doi.org/10.1016/j.aohep.2019.11.008.
[151] Alharthi J, Pan Z, Gloss BS, McLeod D, Weltman M, George J, Eslam M. Loss of metabolic adaptation in lean MAFLD is driven by endotoxemia leading to epigenetic reprogramming. Metabolism 2023;144:155583. https://doi.org/10.1016/j.metabol.2023.155583.
[152] Pan Z, Khatry MA, Yu M-L, Choudhury A, Sebastiani G, Alqahtani SA, Eslam M. MAFLD: an ideal framework for understanding disease phenotype in individuals of normal weight. Ther Adv Endocrinol Metab 2024;15:20420188241252543. https://doi.org/10.1177/20420188241252543.
[153] Eslam M, Fan J-G, Mendez-Sanchez N. Non-alcoholic fatty liver disease in non-obese individuals: the impact of metabolic health. Lancet Gastroenterol Hepatol 2020;5(8):713–5. https://doi.org/10.1016/S2468-1253(20)30090-X.
[154] Alarabi M, Pan Z, Romero-Gómez M, George J, Eslam M. Telomere length and mortality in lean MAFLD: the other face of metabolic adaptation. Hepatol Int 2024;18(5):1–11. https://doi.org/10.1007/s12072-024-10701-6.
[155] Li S, Chen J, Zhang Y, Huang S, Pan Q, Tang D, et al. Identifying the most critical behavioral lifestyles associated with MAFLD: evidence from the NHANES 2017−2020. Front Endocrinol (Lausanne) 2024;15:1375374. https://doi.org/10.3389/fendo.2024.1375374.
[156] Lee EJ, Choi M, Ahn SB, Yoo J-J, Kang SH, Cho Y, et al. Prevalence of nonalcoholic fatty liver disease in pediatrics and adolescents: a systematic review and meta-analysis. World J Pediatr 2024;20(6):569–80. https://doi.org/10.1007/s12519-024-00814-1.
[157] Vimalesvaran S, Vajro P, Dhawan A. Pediatric metabolic (dysfunction)-associated fatty liver disease: current insights and future perspectives. Hepatol Int 2024;18(Suppl 2):873–83. https://doi.org/10.1007/s12072-024-10691-5.
[158] Lin Y-C, Wu C-C, Ni Y-H. New perspectives on genetic prediction for pediatric metabolic associated fatty liver disease. Front Pediatr 2020;8:603654. https://doi.org/10.3389/fped.2020.603654.
[159] Lin X, Wu G, Huang J. The impacts of Ramadan fasting for patients with non-alcoholic fatty liver disease (NAFLD): a systematic review. Front Nutr 2024;10:1315408. https://doi.org/10.3389/fnut.2023.1315408.
[160] Gad AI, Abdel-Ghani HA, Barakat AA-eA. Effect of Ramadan fasting on hepatic steatosis as quantified by controlled attenuation parameter (CAP): a prospective observational study. Egypt Liver J 2022;12(1):22. https://doi.org/10.1186/s43066-022-00187-y.
[161] Sakr AH. Fasting in Islam. J Am Diet Assoc 1975;67(1):17–21 https://www.ncbi.nlm.nih.gov/pubmed/1141609.
[162] Leddin D. The impact of climate change, pollution and biodiversity loss on digestive health and disease. Gastro Hep Adv 2024;3(4):519–34. https://doi.org/10.1016/j.gastha.2024.01.018.
[163] Lelieveld J, Proestos Y, Hadjinicolaou P, Tanarhte M, Tyrlis E, Zittis G. Strongly increasing heat extremes in the Middle East and North Africa (MENA) in the 21st century. Clim Change 2016;137(1):245–60. https://doi.org/10.1007/s10584-016-1665-6.