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GUIDELINES

The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease

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Abstract

Metabolic associated fatty liver disease (MAFLD) is the principal worldwide cause of liver disease and affects nearly a quarter of the global population. The objective of this work was to present the clinical practice guidelines of the Asian Pacific Association for the Study of the Liver (APASL) on MAFLD. The guidelines cover various aspects of MAFLD including its

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epidemiology, diagnosis, screening, assessment, and treatment. The document is intended for practical use and for setting the stage for advancing clinical practice, knowledge, and research of MAFLD in adults, with specific reference to special groups as necessary. The guidelines also seek to improve patient care and awareness of the disease and assist stakeholders in the decision-making process by providing evidence-based data. The guidelines take into consideration the burden of clinical management for the healthcare sector.

Introduction

The Asia–Pacific region with at least 55 countries is home to more than half of the world's population and accounted for 62.6% of liver-related deaths in 2015 [1]. Though there are substantial disparities in rates of development within the political, economic, and educational spheres, the entire region is moving towards urbanisation, shifting from an agrarian diet towards increased consumption of energy dense, nutrient poor foods, a sedentary lifestyle, and reduced physical activity. Similar to other affluent nations, this change has led to an increase in prevalence of disorders related to poor metabolic health. As would be expected from this, metabolic associated fatty liver disease (MAFLD) (formerly known as non-alcoholic fatty liver disease (NAFLD)) has risen in prevalence to alarming levels, placing an enormous burden on individuals and health-care systems [2]. This document presents the clinical practice guidelines of the Asian Pacific Association for the Study of the Liver (APASL) on MAFLD. The authors performed a systematic review of the literature retrieved after an extensive PubMed search up to April 2020 on specified domains of interest and translated this scientific evidence into practice guidelines with recommendations to improve the assessment and management of patients with MAFLD.

These guidelines cover various aspects in the management of MAFLD including epidemiology, diagnosis, screening, assessment, and treatment. The statements in this document follow the Grading of Recommendation Assessment, Development, and Evaluation approach (Table 1).

The document was intended for practical use and for setting the stage for advancing knowledge and research of MAFLD in adults, with specific reference to special groups whenever necessary. The final purpose was to improve patient care and awareness of MAFLD and to assist stakeholders in the decision-making process by providing evidence-based data. The guidelines take into consideration the burden of clinical management for the healthcare sector. A summary of all the recommendations is provided in Supplementary Table 1. Since it is expected that new evidence will emerge on the implications of adopting the MAFLD criteria, updates to these guidelines might be required in future.

Epidemiology

Emerging evidence based on several large population-based studies has demonstrated an exponential increase in MAFLD burden in the Asia–Pacific region over the past three decades [1]. A recent systematic review and meta-analysis of MAFLD prevalence from an Asian context and comprising > 13,044,518 individuals suggested that the prevalence of MAFLD in this region is 29.62% (95% CI 28.13–31.15) [4]. Within the Asia–Pacific region, MAFLD prevalence varies widely as would be predicted from tremendous variations in genetic background, nutrition, physical activity, lifestyle, and sedentary behavior. As expected, there is a bias in reported studies towards those that emanate from more affluent countries with more developed healthcare systems in the region [1].

Though there are no nationwide epidemiological surveys even within a single country such as China, there are substantial differences according to regions and over time in the prevalence of MAFLD. For instance, MAFLD prevalence in the populations from Shanghai (East China) was estimated to have increased from 15% before 2005 to 38.17% in 2012 [5, 6]. The prevalence in Xinxiang, Henan Province (Central China) was 29.85% in 2017 [7]. Similarly, in other regions of China, Chengdu (Southwest China) and Guangdong (South China), MAFLD prevalence rates were 12.5% and 17%, respectively [8, 9]. In Taiwan, the prevalence of MAFLD was estimated to be 11.4% in the general population [10] but was even higher in sub-populations such as the elderly (50.1%) [11] and among Taxi drivers, who typically have

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Table 1 Evidence grade used for the APASL Clinical Practice Guidelines on MAFLD (adapted from the GRADE system [3])

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain	C
Grading of recommendations	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2

inactive lifestyles (66.4%) [12]. In Hong Kong, a community proton-magnetic resonance spectroscopy (MRS)-based study suggested the prevalence of 28.8%; 19.3% in non-obese subjects, and 60.5% among the obese [13].

In the Far East, the community prevalence of MAFLD was found to be 23–26% while 27.3% of subjects undergoing routine health screening demonstrated fatty liver by abdominal ultrasonography in Japan and Korea, respectively [14, 15]. Notably, in Japan, the prevalence of MAFLD has increased from 12.6% before 1990 to 30.3% in 1998 [16].

In rural India, a region characterized by traditional lifestyles and diets, the prevalence of MAFLD is remarkably low (~9%), while it mimics other Asian country prevalence rates in urban populations (16–32%) [17–19]. A nationwide community ultrasound-based study from Bangladesh of 2782 participants observed that the overall prevalence of MAFLD was 33.86% with no difference between urban and rural populations suggesting that Bangladesh has one of the highest rates of MAFLD in South Asia [20]. A similar dramatic variation in MAFLD prevalence (5–30%) was observed in smaller reports from Singapore, Malaysia, Sri Lanka, and Indonesia [21–24]. Differences in the prevalence of MAFLD was also observed among Asians of different ethnicities; for example, in multi-ethnic studies from Malaysia, the prevalence of MAFLD is consistently higher among ethnic Malays and Indians compared with ethnic Chinese; this ethnic predilection is observed as early as young adulthood [23, 25, 26].

Thus, while MAFLD rates are varied, there is a common trend to increasing prevalence with time. This has meant that the prevalence of MAFLD between the East and West is more similar than different and is beginning to approximate each other and in some cases, to exceed that in the West (e.g., in Pacific Island nations). Given the high prevalence of viral hepatitis in the region and as previous diagnostic criteria are based on the exclusion of other liver diseases, it may result in under-reporting of the true burden of MAFLD. This further highlights the urgent need for "positive criteria" for disease diagnosis.

Few studies have examined the incidence of MAFLD in Asia. A recent meta-analysis (18 studies) suggested that the annual MAFLD incidence rate in Asian countries was 50.9 cases per 1000 person-years (95% CI 44.8–57.4) [4]. In a population study in Hong Kong using paired MRS, 13.5% (95% CI 10.6–16.3%) of the studied cohort developed MAFLD over an interval of 3–5 years, with an annual incidence of MAFLD estimated at 3.4%[27].

Definition and diagnosis of MAFLD

Interest in fatty liver diseases not due to alcohol has risen dramatically, in large part driven by its increased global prevalence. However, this disease is highly heterogeneous and thus placing all patients with a diverse and differential array of disease drivers under the acronym NAFLD can negatively impact clinical decision-making. Further, NAFLD is a diagnosis of exclusion rather than one of inclusion.

To address these issues, APASL endorses the proposal of a consensus panel of leading experts who proposed that a more appropriate nomenclature for the disease would be "metabolic associated fatty liver disease" or MAFLD [28]. The major benefit of this new nomenclature is a shift towards a diagnosis of inclusion based on the presence of metabolic dysfunction, the key driver of the disease. The new algorithm is developed from "positive criteria" regardless of alcohol consumption or other concomitant liver diseases (Fig. 1) [29]. In addition, this new nomenclature helps to identify a homogenous group of patients and will guide efforts for stratification of patients with MAFLD. As summarized in the paper, the diagnosis of MAFLD is based on the detection of liver steatosis (liver histology, non-invasive biomarkers or imaging) together with the presence of at least one of three criteria that includes overweight or obesity, type 2 diabetes mellitus (T2DM) or clinical evidence of

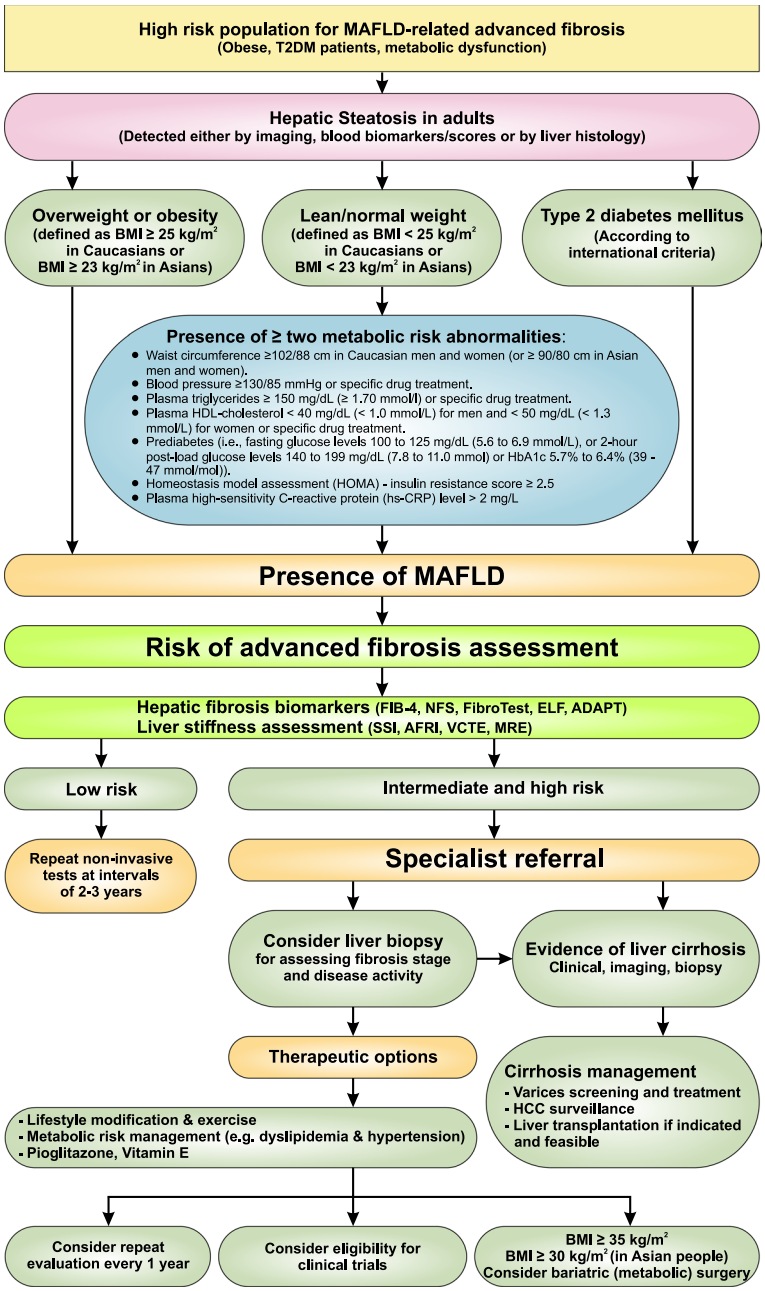

Fig. 1 Recommended algorithm to diagnose, evaluate, and monitor disease severity in suspected patients with MAFLD and management approach for confirmed cases. *HDL-C* high-density lipoprotein (HDL) cholesterol; *APRI* aspartate aminotransferase (AST)-to-platelet ratio index, *FIB-4* Fibrosis-4 index, *NFS* MAFLD fibrosis score; *ELF* enhanced liver fibrosis; *ADAPT* A PRO-C3-based fibrosis algorithm that included age, presence of diabetes, *PRO-C3* and platelet count, SSI, supersonic shear imaging; *AFRI* acoustic radiation force impulse; *VCTE* vibration-controlled transient elastography; *MRE* magnetic resonance elastography. Individuals can be defined as having low, intermediate, or high risk for advanced fibrosis for each score as per the following cut-offs: APRI (0.5 and 1.5), FIB-4 (1.30 and 2.67),, NFS (lower cutoff < − 1.455 and > 0.67611)

metabolic dysfunction, such as an increased waist circumference and an abnormal lipid or glycemic profile. Situations including cirrhosis cases where liver fat is no longer present are recognized as a special category within the new criteria. A recent study on a cohort of 13,083 patients from the NHANES III (National Health and Nutrition Examination Surveys) database showed that the MAFLD criteria are more practical and have higher ability for identifying at-high risk patients than the previous NAFLD criteria [30].

Diagnosis and impact of MAFLD in the setting of other liver disease

Since MAFLD is no longer a diagnosis of exclusion and is based on the presence of metabolic dysfunction, it is now possible to diagnose its coexistence with other liver diseases such as alcoholic liver disease (ALD), chronic hepatitis B virus infection (CHB), and chronic hepatitis C virus infection (CHC), primary biliary cholangitis, and primary hemochromatosis, especially in Asian populations. Moreover, meeting the criteria for a diagnosis of MAFLD plus one and more other less frequent alternative causes of fatty liver

Table 2 Etiology of fatty liver disease

Etiology classification	Specific causes
Metabolic associated fatty liver disease	Overweight/obese, type 2 diabetes mellitus, metabolically unhealthy normal weight subjects
Alcohol associated fatty liver disease	Significant alcohol consumption (> 21 standard drinks per week in men and > 14 standard drinks per week in women over a 2-year period), binge drinking (> 5 standard drinks in men and > 4 standard drinks in women over a 2- h period), and lifetime alcohol intake > 100 kg [31]
Alternative causes of fatty liver disease	Long-term use of steatogenic medications (corticosteroids, valproic acid, tamoxifen, methotrexate, amiodarone, etc.), exposure to some chemicals, HCV genotype 3 infection, Wilson's disease, coeliac disease, starvation, total parenteral nutrition, severe surgical weight loss, disorders of lipid metabolism (abetalipoproteinemia, hypobeta lipoproteinemia, lysosomal acid lipase deficiency, familial combined hyperlipidaemia, lipodystrophy and Mauriac syndrome), Weber–Christian syndrome, glycogen storage disease, Cushing's syndrome, etc

either at baseline or at follow-up, e.g., long-term use of steatogenic medications, HCV genotype 3 infection, or Wilson disease should also be diagnosed as mixed or dual etiology liver disease as the case may be (Table 2).

These individuals likely have a different natural history and response to therapy than those with liver disease of a "single" etiology [29]. Notably, MAFLD may accelerate the progression of liver disease in patients with ALD and CHB, and synergistically induce liver cirrhosis or even HCC development [32, 33]. Therefore, patients with MAFLD should be carefully evaluated for possible concurrent liver diseases such as ALD and viral hepatitis. Conversely, MAFLD and underlying metabolic dysfunction may increase the risk of metabolic and cardiovascular events in patients with other liver diseases.

MAFLD patients with ALD represent a large and important group that requires further investigation and characterisation with respect to natural history, outcomes and response to treatment. Meticulous history taking for lifetime and current alcohol intake through patient interview aid in diagnosis of dual etiology fatty liver disease. Recently, there has been mounting evidence against the so-called "safe limits" for alcohol intake in the setting of MAFLD [28, 34, 35], as even low alcohol intake is associated with an increased risk for cirrhosis and cancer, and decreased rates of improvement in steatohepatitis [28, 36, 37]. The effect of alcohol intake on the progression of liver disease and outcomes likely has a dose–response with a synergistic negative effect in the presence of metabolic syndrome and the "cut-off" values of alcohol intake in MAFLD should be set lower than the apparent "threshold levels". Therefore, patients with MAFLD should be advised to avoid alcohol and if that is not possible, to consume the lowest amount possible.

Table 3 Risk factors for MAFLD

Major risk factor	Common and uncommon risk factor
Overweight/obesity	Gut microbiota
Central obesity	Hyperuricemia
Type 2 diabetes mellitus	Hypothyroidism
Dyslipidemia	Sleep apnoea syndrome
Arterial hypertension	Polycystic ovary syndrome
Metabolic syndrome	Polycythaemia
Insulin resistance	Hypopituitarism
Dietary factors: high-calorie diets rich in saturated fats and cholesterol, soft drinks high in fructose, highly processed foods	Genetic variations: *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7*, and *HSD17B13*
Sedentary lifestyle or sedentary occupation, low level of physical activity	Epigenetic factors: microRNAs (miR), DNA methylation, histone modification, and ubiquitination alterations
Sarcopenia	A personal or family history of T2DM, premature vascular disease, atherogenic dyslipidemia and high blood pressure (metabolic syndrome), fatty liver

Notably, many of these factors could be association, it is hard to ascertain the causality

PNPLA3 patatin-like phospholipase domain-containing protein 3; *TM6SF2* transmembrane 6 superfamily member 2, *GCKR* glucokinase regulator, *MBOAT7* membrane bound O-acyltransferase domain containing 7 HSD17B13: hydroxysteroid 17-beta dehydrogenase-13

With the high prevalence rates of MAFLD and CHC, it is expected that these two disease entities will occur together and their concomitant existence is estimated to be approximately 38% [38]. MAFLD significantly impacts the entire natural course of CHC including progression of the liver disease, therapeutic responses, and the development of some extrahepatic complications [39–44]. Viral eradication by direct-acting anti-viral therapy or previously by interferon therapy was demonstrated to reduce insulin resistance, liver steatosis, and fibrosis in patients with CHC, especially in genotype 3 HCV infection [45, 46].

Although CHB infection is negatively associated with hepatic steatosis in some reports [47], the number of patients with coexisting CHB and MAFLD is growing rapidly [48]. Notably, MAFLD may accelerate the progression of liver disease in patients with CHB; a recent study from Thailand suggested that MAFLD was independently associated with increased risk of significant liver fibrosis (OR, 10.0; 95% CI 2.08–48.5) and advanced liver fibrosis (OR, 3.45; 95% CI 1.11–10.7) in CHB patients [49]. Similarly, another study demonstrated that MAFLD independently increased the risk of HCC development by 7.3-fold (OR: 7.3, 95%CI 1.52–34.76) in patients with CHB[50].

MAFLD is becoming a major reason for persistently abnormal liver tests and poor outcomes in individuals with CHB and/or CHC infection after profound virological suppression or sustained virological response [51, 52]. Treatment of MAFLD in this group should be considered as for non-infected patients.

Should MAFLD be considered with other liver diseases?

Recommendations

- MAFLD can and frequently does coexist with other liver diseases (A1).
- MAFLD treatment and that of concomitant diseases should be as per the recommendations for each of the diseases (B1).

Table 4 Working definition of overweight/obesity and central obesity for Asian adults

Lean (normal range): BMI 18.5–22.9 kg/m^2
Overweight: BMI 23.0–24.9 kg/m^2
Obesity: BMI > 25.0 kg/m^2
Central obesity: Waist circumference (measured at the top of the iliac crest) > 90 cm for males and > 80 cm for females

BMI body mass index

Risk factors for MAFLD

MAFLD is a public health challenge in many parts of Asia–Pacific region due to socioeconomic changes and the rapid transition from undernutrition to overnutrition. In turn, excess energy intake relative to expenditure with nutritionally imbalanced and unhealthy diets contribute to an accumulation of triglyceride in adipose tissue and the liver. Risk factors for MAFLD in Asians are similar to that in Westerners (Table 3). However, Asians are more likely to have central fat deposition despite having a lower body mass index (BMI). In detailed metabolic studies, south Asians in the USA had higher insulin resistance (IR) compared to Caucasians in spite of having an equal or lower BMI [53]. Likewise, Asian-Indian men have greater liver fat content and higher IR than age- and BMI-matched European individuals [54, 55]. A greater waist circumference and visceral adipose tissue (VAT) has a more significant correlation with IR and MAFLD than a high BMI [56, 57]. Similarly, abdominal and visceral adiposity is greater among Asians compared with Caucasians and lower in Africans, for the same BMI [58–61]. Modified cut-off points for BMI and waist circumference have thus been recommended for the Asian population [62, 63] (Table 4). Consistent with this phenotype, rates of T2DM are also markedly increased in Asian Indian populations [6, 64]. Even, non-obese and lean Asian people with MAFLD are at a high risk of metabolic syndrome and T2DM [65].

Although overweight/obesity is closely associated with the development and progression of MAFLD, subtle weight gain that has not led to overweight is an important determinant of incident metabolic disease and MAFLD. Within the MAFLD population, 19.2% of people are lean and 40.8% are non-obese, without differences in the histological severity of disease between lean and obese patients [66, 67]. Up to one-third of patients with MAFLD and a normal BMI meet the criteria for metabolic syndrome [67].

Metabolic syndrome and its components also increase the risk of developing MAFLD. As would be expected from these data, the global prevalence of MAFLD among patients with T2DM is 55.5% and up to 10–20% have advanced fibrosis [68]. The bidirectional causal relationship of components of metabolic syndrome with MAFLD has been well established [69]. Thus, patients with MAFLD benefit from lifestyle intervention and weight loss [70] as well as assessment for, and treatment of, other components of the metabolic syndrome. Such an approach will reduce the risk of liver and non-liver related comorbidities, while screening for MAFLD by ultrasonography should be considered in at-risk populations including those with overweight/obesity, T2DM or metabolic syndrome.

A functional role for microbiota in MAFLD-pathogenesis is increasingly appreciated [71]. This is best illustrated by

differences in the impact of gut bacteria from obese and lean humans on the risk of fat accumulation in germ-free mice. Transplantation of fecal bacteria from obese adult humans led to a higher percentage of body fat in the mice compared to those from lean adults [72]. However, human data on the role of gut microbiota in MAFLD and its therapeutic use are in their early stage.

There is strong evidence in support of racial and socioeconomic-disparity-based differences in gut microbiota. In humans, greater fecal bacterial diversity is seen in less affluent populations such as those from Bangladesh, when compared to urbanized European or American children [73]. Similarly, greater fecal bacterial diversity was noted in children from rural South Thailand compared to urbanized children from Singapore [74]. This diversity is obvious even within ethnic groups with a relatively narrow range of socioeconomic discrepancy. For example, a recent study compared pre-adolescents from three distinct Malaysian ethnic groups [Malays, Chinese and Orang Asli (indigenous)], with a relatively narrow range of socioeconomic discrepancy. The study demonstrated that the highest bacterial diversity was in indigenous children who are relatively economically deprived compared to their Chinese counterparts [75].

The role of factors such as genetics, epigenetics, and sarcopenia have also been recognized and are the subject of recent reviews [76–79]. Incorporation of genetic variant testing in routine clinical practice is not recommended currently due to the lack of certainty on cost-effectiveness and utility.

Should the high-risk population be screened for MAFLD?

Recommendations

- Screening for MAFLD by ultrasonography should be considered in at-risk populations such as patients with overweight/obesity, T2DM and metabolic syndrome (A1).
- Patients with MAFLD should be assessed for other components of metabolic syndrome and be treated accordingly (A1).
- Patients with MAFLD should receive advice and support for lifestyle interventions to reduce the risk of events from metabolic and cardiovascular disease, and to resolve fatty liver disease (A1).

Natural history of MAFLD

Globally, 54.3% of deaths due to cirrhosis and 72.7% of deaths due to hepatocellular carcinoma (HCC) occurred in the Asia–Pacific region in 2015[1]. However, the true burden of MAFLD in Asia is not fully understood. Cardiovascular disease (CVD) followed by cancer and liver failure are the main causes of death in MAFLD. There is clear evidence for ethnic differences in prevalence of MAFLD, with highest prevalence among Latinos and least among African Americans, with Caucasian and Asian ethnicities having an intermediate prevalence [80–82]. In contrast, less is known regarding the consequences of hepatic steatosis, liver inflammation, and fibrosis according to ethnicity. While data are scant, cross-sectional studies suggested that Asian subjects are more likely to have worse histologic injury. In a recent study, despite having a lower BMI than other groups, Asians (included patients of Korean, Filipino, Chinese and Indian origin) had more lobular inflammation and higher grades of ballooning compared to other ethnicities (Caucasian, Hispanics and African Americans) [80]. In another report, Asians living in the US showed a trend toward an association with more severe steatosis and inflammation compared to Caucasians [83]. If liver tests are used as a surrogate for hepatic inflammation, a large cross-sectional multiethnic cohort from the United Kingdom suggested that the highest prevalence of abnormal liver tests is among Asians (Bangladeshi (18.4%), Pakistani (17.6%), and Indian (14.8%)), compared with Caucasians (13.5%), Africans (11.8%), and Caribbean islanders (10.2%). In a subsequent multivariate analysis, Bangladeshi ethnicity was an independent risk factor for MAFLD and for elevated liver tests [84]. Similarly, scant data are available regarding liver fibrosis. Asians tended to have a higher risk for fibrosis, while Africans were at lower risk compared to Caucasians. This, however, did not reach statistical significance possibly due to sample size limitations [80, 83]. Notably, these biopsy-based studies might be subject to selection bias. A population-based study in Hong Kong suggested that while MAFLD is prevalent and detected in about 25% of the population, the prevalence of advanced fibrosis is low [85].

In the Asia–pacific region there is a paucity of data on MAFLD-HCC and is likely confounded by the higher prevalence of viral hepatitis, a major risk factor for HCC in Asia. Viral hepatitis increases the risk of oncogenic transformation, viral hepatitis can also contribute to HCC development even in the absence of serological clues of previous infection [86], which is most likely to occur in the context of CHB [86].

The available data suggest that 2% of all HCC in Japan was due to MAFLD; the median age of patients was 72 years, and 62% were males [87]. Similarly, a large retrospective cohort study of 6,508 Japanese with MAFLD suggested that the rate of new HCC was 0.043% during a median follow-up of 5.6 years. In this study, 184 patients with significant fibrosis were identified using the AST-to-platelet ratio index; 6/184 (3.26%) developed HCC during the follow-up period [88]. Similar trends have been noted from other countries in Asia. In South Korea, a study of 329 patients has shown that the proportion with MAFLD-related HCC rose from 3.8% in 2001–2005 to 12.2% in 2006–2010; by contrast, HBV-related HCC declined from

86.6% to 67.4% [89]. In India, despite the high prevalence of MAFLD and T2DM, there is a lack of data on the prevalence of MAFLD-HCC. A recent estimate suggested that a potential staggering 930,000 people in India might have MAFLD-HCC [90].

Notably, in a recent modelling study of eight countries, the MAFLD population in China is projected to increase by 29.1% to 314.58 million cases from 2016 to 2030 [91]. Decompensated cirrhosis and liver-related deaths secondary to MAFLD are expected to double during the same period. Similarly, in another study looking at fibrosis progression among the MAFLD populations of Hong Kong, Singapore, South Korea and Taiwan [92]. Prevalent MAFLD cases were projected to increase from 6 to 20%, incident decompensated cirrhosis from 65 to 100% and incident cases of HCC from 65 to 85%, over the period 2019–2030.

In regard to comparisons with other liver diseases, in a prospective cohort study, the yearly cumulative incidence of HCC was 2.6% in MAFLD-cirrhosis during a median follow-up of 3.2 years. This was comparable with a reported 4% incidence in a CHC cirrhotic population over the same time period [93]. A recent multicentre study suggested that MAFLD-HCC is more often detected at a later tumor stage compared to HCV-HCC, and could arise in the absence of cirrhosis with a similar survival rate compared to HCV infection, after patient matching [94]. Another prospective cohort multi-centre study from Australia, the US, and Europe reported that patients with MAFLD and advanced fibrosis have lower rates of HCC and liver-related complications compared to those with HCV infection, but similar overall mortality [95]. Large prospective studies from Asia are required to corroborate these data.

Overall, these figures are likely to be underestimated as a significant number will have had dual etiology liver disease with MAFLD and viral hepatitis or ALD but would have been identified as viral hepatitis- or ALD-associated HCC. In addition, another important consideration is that the prevalence figures of MAFLD-HCC may be an underestimate if cryptogenic cirrhosis attributable to MAFLD is considered. In a recent study of 105 patients with HCC, 29% were found to have cryptogenic cirrhosis; half of these had histological or clinical features consistent with MAFLD [96]. Similar observations have been reported from Asia. In a Japanese report, clinical features of MAFLD were more frequent in cryptogenic cirrhosis than with virus-related cirrhosis [97], while in India, two thirds of patients with a pre-transplant diagnosis of cryptogenic cirrhosis were ultimately diagnosed with MAFLD on their explants [98]. Thus, with current recommendations for abandoning the term "cryptogenic cirrhosis" to describe cirrhotic patients with low or undetectable levels of steatosis but who meet the diagnostic criteria for MAFLD, many would fit under the umbrella of "MAFLD-related cirrhosis" [99].

Extrahepatic manifestations of MAFLD

MAFLD is one aspect of a multi-system disease and it is therefore not surprising that cardiovascular disease (CVD) is its most important complication, followed by cancer and others diseases including obstructive sleep apnea, chronic kidney disease (CKD), polycystic ovarian syndrome, and osteoporosis.

MAFLD is associated with subclinical atherosclerosis as evidenced by increased carotid intima media thickness, coronary artery calcification score, arterial stiffness, and endothelial dysfunction [100]. In a longitudinal study of 8020 subjects without subclinical carotid atherosclerosis at baseline, those with regression of MAFLD were less likely to develop subclinical carotid atherosclerosis compared to those with persistent MAFLD. Furthermore, the risk of developing subclinical carotid atherosclerosis was higher among subjects with more severe liver fibrosis [101]. Importantly, MAFLD is associated with an increased risk of fatal and/or non-fatal cardiovascular events and the risk is higher among patients with more severe liver disease [102, 103]. Furthermore, those with more severe fatty liver disease had a higher in-hospital and 3-year mortality following an episode of myocardial infarction [104]. Overall, CVD is the leading cause of mortality in patients with MAFLD and baseline liver fibrosis is the strongest predictor [105]. Therefore, patients with MAFLD should be evaluated for CVD risk.

Francque et al., have proposed an algorithm for screening MAFLD patients for cardiovascular disease. MAFLD patients with clinically active CVD or a history of a cardiovascular event should be under the care of a cardiologist. Otherwise, patients with more severe disease (i.e. steatohepatitis or significant fibrosis), T2DM, or increased risk of CVD should undergo further evaluation (e.g. electrocardiogram, echocardiogram and/or subclinical CVD screening, where available) and be considered for referral to a cardiologist. Patients who are negative on further evaluation can be re-evaluated every 2–3 years [106]. CVD risk can be estimated using risk scores (e.g. Atherosclerotic Cardiovascular Disease Risk Estimator Plus, available at https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/content/about/).

Similarly, a strong association between MAFLD and CKD has been established, independent of the presence of potential confounding factors such as obesity, T2DM, and hypertension [107]. An independent association between MAFLD and sarcopenia has also been suggested.

Dyslipidemia, if present, should be treated to reduce the risk of cardiovascular events and mortality. A study on 428 MAFLD patients across four Asian countries found disproportionately low statin use compared with the prevalence

of dyslipidemia; 59% of patients who were not on a statin should have been on one, while the majority (74%) of patients who were on a statin were not treated to target [108]. A post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation study found statin therapy to not only be safe but it resulted in improved liver tests and reduced cardiovascular morbidity in patients with mild to moderately abnormal liver tests,likely due to MAFLD [109].

A blood pressure target of < 130/80 mmHg is appropriate for most patients and HbA1c level of ≤ 6.5% is considered optimal if it can be achieved in a safe and cost-effective manner [110]. The types and choice of medications for treatment of dyslipidemia, hypertension, and T2DM are beyond the scope of this paper. However, newer medications for T2DM, i.e. glucagon-like peptide-1 analogue (GLP-1a) and sodium glucose cotransporter 2 inhibitors (SGLT2i) have been shown to improve metabolic syndrome and cardiovascular outcomes and may be useful for treatment of steatohepatitis. Empagliflozin, for example, significantly reduced overall and cardiovascular-specific morality and hospitalization for heart failure compared with placebo [111]. Likewise, liraglutide significantly reduces death from cerebro-cardiovascular causes compared with placebo [112]. Risk factor modification to target is typically undertaken in primary care; however, specialists treating patients with MAFLD should be encouraged to assess and undertake risk factor management as part of a holistic approach to patient care.

How to manage the extra-hepatic manifestations of MAFLD?

Recommendations

- MAFLD patients should be evaluated for cardiovascular disease and cardiovascular risk, and referred to a cardiologist, if necessary (A1).
- Dyslipidemia, hypertension, and diabetes mellitus should be identified and treated accordingly to reduce the risk of cardiovascular and kidney disease (A1).

Non-invasive tests

The purpose of non-invasive tests (NITs) includes establishing a diagnosis of MAFLD, assessing disease severity, and monitoring disease progression and treatment response [113]. The detection of hepatic steatosis by histology or imaging is key to a diagnosis of MAFLD. In clinical practice, routine imaging such as abdominal ultrasonography is usually sufficient for the detection of hepatic steatosis [114]. Controlled attenuation parameter (CAP) measurement by vibration-controlled transient elastography (VCTE) is more sensitive than ultrasonography [115]. As a continuous variable it can theoretically be used to monitor changes in hepatic steatosis over time, though this needs to be confirmed by studies using paired liver biopsies or other quantifiable methods for assessing steatosis such as with MRS or MRI proton density fat fraction (MRI-PDFF). An interquartile range > 30–40 dB/m has been associated with less reliable CAP measurements [116, 117] but its role requires further validation.

MRI-based techniques such as MRI-PDFF and proton-MRS are considered the gold standard to quantify liver fat. In some clinical trials, a > 30% relative reduction in liver fat fraction correlated with histological improvements in the activity score or resolution of steatohepatitis [118], though the same has not been reported in other studies [119], and the association is probably drug-specific. Currently, liver fat fraction by MRI is often used in early phase clinical trials to determine potential benefits of the investigational drug treatment.

The fatty liver index (FLI) is a simple algorithm based on BMI, waist circumference, triglycerides, and GGT for detecting fatty liver and may be used as an alternative method for the diagnosis of steatosis, particularly in large population studies [120]. Ultrasonographic Fatty Liver Indicator (US -FLI) is another scoring system used to rule out steatohepatitis. The score ranges from 2 to 8 based on ultrasonographic features, including the intensity of liver/kidney contrast [121].

Among the various histological features of MAFLD, the degree of liver fibrosis has the strongest correlation with future liver-related morbidity and mortality [122]. NITs of fibrosis can be classified into simple fibrosis scores, specific fibrosis biomarkers, and imaging biomarkers [123]. Simple fibrosis scores such as the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) [124], Fibrosis-4 index (FIB-4) [125], and NAFLD fibrosis score (NFS) [126] only involve clinical and routine laboratory parameters and are inexpensive. Although the accuracy is modest, these scores have good negative predictive values to exclude advanced fibrosis and is the primary clinical utility of these scores [127, 128]. This is particularly important in primary care or resource poor settings where the pre-test probability of advanced fibrosis is low [129]. Individuals can be defined as being at low, intermediate, or high risk for advanced fibrosis for each score according to the following cut-offs: APRI (0.5 and 1.5), FIB-4 (1.30 and 2.67), NFS (< -1.455 and > 0.67611). People with low fibrosis scores are also at low risk of developing hepatic complications [130]. Therefore, it is reasonable to use simple fibrosis scores as an initial assessment in primary care. A limitation of these scores is that they incorporate liver enzymes in the models. As patients with liver enzymes in the normal range can have the full spectrum of liver fibrosis stages, it remains a shortcoming. Furthermore, liver enzymes are sensitive to age, which can lead to false positive results [131].

In contrast, more specific fibrosis markers are needed in specialist settings to guide the management of patients [132, 133]. Among them, the enhanced liver fibrosis panel has been tested in multiple observational studies and clinical trials with good overall accuracy [134]. Another biomarker, called Pro-C3, reflects the formation of type III collagen in hepatocytes. The ADAPT algorithm includes age, T2DM, Pro-C3, and platelet count and has an area under the receiver-operating characteristics curve of 0.87 for advanced fibrosis [135].

Liver stiffness measurement (LSM) by VCTE is widely used in the Asia–Pacific region, in part because of patient preference against biopsy. Although the success rate of VCTE is lower in obese subjects, the majority of MAFLD patients can achieve successful liver stiffness measurement with the XL probe [136, 137], and the same cut-offs can be used for both the M and XL probes if the probes are used according to the body habitus or guided by the automated probe selection tool [138]. The diagnostic performance for advanced hepatic fibrosis of shear wave elastography is similar to that of VCTE [139]. Although the quality criteria for fibrosis assessment is limited, shear wave elastography is an option for liver stiffness measurement.

Non-obese MAFLD is more often described in Asia; commonly used fibrosis tests do not appear to be affected in this special group [140]. The combination of LSM and simple fibrosis scores has the advantage of improving the positive predictive value and reducing the proportion of patients with indeterminate results [141]. In head-to-head comparisons, magnetic resonance elastography has higher success rates and an even higher accuracy than VCTE, but its wider application is limited by cost and availability [142, 143].

On the other hand, there has not been any robust biomarker for steatohepatitis. Their development is in part limited by the substantial intra-and inter-observer variability in the assessment of histological lobular inflammation and hepatocyte ballooning and the fact that inflammation can resolve even over relatively short periods. Serum keratin-18 fragments (also known as cytokeratin-18 fragments) reflect hepatocyte apoptosis and were proposed as a steatohepatitis biomarker. However, subsequent studies suggested that its overall accuracy is modest [144]. In a recent multi-centre study, the combination of AST with CAP and liver stiffness measurement by VCTE (the FAST score) achieved a c-statistic of 0.74–0.95 for the detection of fibrotic steatohepatitis (NAS score ≥ 4 and fibrosis score ≥ 2) [145].

How and what non-invasive scores to use in MAFLD?

- Abdominal ultrasonography is the recommended first-line diagnostic modality for imaging of MAFLD and is usually sufficient for the detection of hepatic steatosis (A1).
- If available, controlled attenuation parameter (CAP) measurement by vibration-controlled transient elastography (VCTE) may be used as a more sensitive tool than ultrasonography. If imaging modalities are not available or feasible such as in very large epidemiological studies, serum biomarkers and scores such as the fatty liver index (FLI) may be used as an alternative method for the diagnosis of steatosis (B2).
- Magnetic resonance imaging-based techniques such as MRI-PDFF and proton-MRS are considered the gold standard to quantify liver fat but it is not recommended for routine clinical practice useful tool in early phase clinical trials (A1).
- There is no robust biomarker for steatohepatitis and liver biopsy remains the test of choice for assessment of steatohepatitis (A1).
- The exclusion of high risk of significant or advanced fibrosis is acceptable using non-invasive tools, liver stiffness measurement by VCTE or shear wave elastography and blood biomarkers and scores of fibrosis or their sequential combination (A2).
- The confirmation of significant or advanced fibrosis by liver stiffness measurement and/or serum biomarkers/scores is less accurate and would require further confirmation by liver biopsy as per the clinical context (B2).

Liver biopsy

With the development of NITs of hepatic steatosis and fibrosis, routine liver biopsy to assess the severity of MAFLD cannot be justified. However, liver biopsy remains an important diagnostic test to rule out other liver diseases, especially when the clinical picture is atypical. Some examples of atypical features include very high aminotransferase level and the presence of severe hepatic steatosis in patients with no or little metabolic burden. Although non-invasive tests are sufficient to guide clinical management in the majority, some cases may fall into the grey zone when dual cut-offs are used (i.e. low cut-off to rule out and high cut-off to rule in a certain fibrosis stage) [141], and others may have unreliable results (e.g. high interquartile range-to-median ratio in case of liver stiffness measurement) [146]. In some patients, NITs results may not fit the clinical picture (e.g. normal fibrosis tests in patients with radiological features of cirrhosis and/or thrombocytopaenia). Liver biopsy can be performed in such instances to clarify the situation.

MAFLD is common in patients with gallstones and morbid obesity [147, 148]. Because liver biopsy during laparoscopic or open surgery is safe, it is reasonable to offer this procedure in patients at risk of MAFLD.

Table 5 Comparisons of grading and staging of histological lesions in MAFLD

	Brunt et al.	Kleiner et al.	Bedossa et al.
Steatosis	0: None 1: Up to 33% 2: 33–66% 3: > 66%	0: < 5% 1: 5–33% 2: 33–66% 3: > 66%	0: < 5% 1: 5%–33% 2: 34–66% 3: > 67%
Lobular inflammation	0: None 1: 1–2 foci per 20× 2: Up to 4 foci per 20× 3: > 4 foci per 20× Portal inflammation was graded as follows: 0: None 1: Mild 2: Moderate 3: Severe	0: No foci 1: < 2 foci per 20× 2: 2–4 foci per 20× 3: > 4 foci per 20×	0: None 1: ≤ 2 foci per 20× 2: > 2 foci per 20×
Hepatocyte ballooning	Mild Marked	0: None 1: Few 2: Many	0: Normal hepatocytes with cuboidal shape and pink eosinophilic cytoplasm 1: Presence of clusters of hepatocytes with a rounded shape and pale cytoplasm usually reticulated; although shape is different, size is quite similar to that of normal hepatocytes 2: Same as grade 1 with some enlarged hepatocytes, at least two that of normal cells
Fibrosis	0: None 1: Perisinusoidal 2: Perisinusoidal and periportal 3: Bridging 4: Cirrhosis	0: None 1a: Delicate perisinusoidal 1b: Dense perisinusoidal 1c: Portal only 2: Perisinusoidal and periportal 3: Bridging 4: Cirrhosis	0: None 1a: Delicate perisinusoidal 1b: Dense perisinusoidal 1c: Portal only 2: Perisinusoidal and periportal 3: Bridging 4: Cirrhosis

Finally, resolution of steatohepatitis and improvement in fibrosis remain key surrogate endpoints in phase 2b/3 MAFLD trials. Achieving these short-term histological endpoints may allow drug approval under the United States Food and Drug Administration (FDA)'s subpart H pathway [149]. Besides, liver biopsy is an important tool to enhance our understanding of MAFLD through not only careful histological assessment but also molecular and "omic" tools.

When would liver biopsy be indicated in MAFLD?

Recommendations: Indications for liver biopsy in patients with suspected MAFLD (A1)

- Uncertain diagnosis and evaluation for dual etiologies.
- Non-invasive tests showing indeterminate or non-concordant results.
- During cholecystectomy and bariatric surgery.
- Approved research

Pathological recommendations

The term non-alcoholic steatohepatitis (NASH) was coined by Ludwig et al. to describe a cohort of patients with a liver disease that histologically mimicked alcoholic steatohepatitis in patients without a history of significant alcohol intake and has been in use [150] till recently [29].

The minimum required staining includes hematoxylin and eosin (for detection of morphological features), picrosirius red or Mallory's stain (for the detection of fibrosis), and Perl's staining (for the detection of hemosiderosis). Whenever possible and ethically approved, the storage of non-processed fresh frozen tissue for other kinds of staining such as lipid staining and research is advisable. Grading and staging of histological lesions in steatohepatitis was first proposed by Brunt et al. Necroinflammation was graded as mild, moderate, or severe, based on the combination of steatosis, lobular and portal inflammation, and hepatocyte ballooning (Table 5) [151]. In 2005, Kleiner et al. developed and validated a histological evaluation system that encompassed

the spectrum of MAFLD and allowed for assessment of changes with therapy for the NASH Clinical Research Network (Table 5). The activity score (NAS) included only features of active injury and that are potentially reversible in the short term. The NAS was defined as the unweighted sum of scores for steatosis, lobular inflammation, and ballooning. Cases with NAS of 0 to 2 were largely considered not-NASH, while most cases with scores ≥ 5 were diagnosed as NASH. Cases with scores of 3 and 4 were divided almost evenly between the three diagnostic categories of NASH, borderline, and not-NASH. Importantly, the authors noted that the primary purpose of the NAS was to assess overall histological change and numeric values were not intended to replace the pathologist's diagnosis of steatohepatitis [152].

In 2012, Bedossa et al. developed and validated an algorithm for categorization (subsequently called the fatty liver inhibition of progression or FLIP algorithm) and scoring (called the SAF score) for MAFLD (Table 5). NAFLD (now MAFLD) was defined as the presence of steatosis in > 5% of hepatocytes and NASH by the addition of hepatocyte ballooning and lobular inflammation of any degree. The SAF score summarized the main histological lesions. Lobular inflammation was graded 0–2, unlike the NAS which graded lobular inflammation 0 to 3. However, grade 2 of the SAF score does encompass grade 2 and 3 of the NAS. The authors also noted that they did not change the definition of hepatocyte ballooning proposed by the NASH CRN, but added reference to the size and shape of hepatocytes for clarity. The activity score was the unweighted sum of lobular inflammation and hepatocyte ballooning. Among the 204 patients with NAS 3 to 4, 116 (57%) had no steatohepatitis, whereas 88 (43%) had steatohepatitis. On the other hand, among the 249 patients with A ≥ 2, 230 (92%) had steatohepatitis, whereas all patients with A < 2 did not have steatohepatitis. Furthermore, there was a strong correlation between activity score and the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. In other words, the activity score provided a more robust histological approach that clearly distinguished most patients with steatohepatitis and associated with transaminase levels. Moreover, the authors found no significant differences in ALT and AST levels between patients with normal liver and patients with pure steatosis supporting the exclusion of steatosis as a marker of activity [153]. The NASH CRN system and FLIP algorithm and SAF score improved interobserver variability [154] and has been validated clinically [152, 155]. Further studies are needed to determine how the NAS relates to the SAF score. This will have important implications, particularly for studies of the natural history of MAFLD using previous histological data.

What is the recommended pathological reporting?

Recommendations

- A standardized reporting of histological lesions in MAFLD patients is important for the study of natural history, enrolment in clinical trials, and evaluation of response to treatment and comparison of data from different geographic locations (A1).
- Histological evaluation should include at least hematoxylin and eosin stains, and either Masson's trichrome stain or picrosirius red stain (A1).
- Reporting should be standardised using either the FLIP algorithm and SAF score or the NASH CRN system for reporting of histological lesions in MAFLD (B1).

MAFLD-related cirrhosis

At the outset, patients with cirrhosis, even if they are without significant hepatic steatosis, but meet the diagnostic criteria for MAFLD, should be considered as having MAFLD-related cirrhosis. This is because multiple lines of evidence indicate that hepatic steatosis may diminish with progression to cirrhosis [156]. Equally important is that there is a substantial proportion of MAFLD patients with cirrhosis who were previously undiagnosed and present for the first time with decompensated cirrhosis, variceal bleeding, or HCC.

Cirrhosis can be diagnosed by typical findings on ultrasonography, but the diagnosis may be missed when this is obscured by liver fat. In this sense, assessment of MAFLD patients beyond ultrasonography is necessary. LSM provides a reliable assessment of the severity of liver fibrosis and can be used to diagnose cirrhosis in MAFLD patients in the correct clinical context [157].

Liver fibrosis is the most important predictor of mortality in MAFLD patients, with the highest risk among those with cirrhosis [158]. The spectrum from severe fibrosis to cirrhosis is a continuum in asymptomatic patients and distinguishing the two is often not possible on clinical grounds. Hence, the term "compensated advanced chronic liver disease" has been introduced. LSM < 10 kPa in the absence of other known clinical signs rules out, whereas a LSM of 10–15 kPa is suggestive, and > 15 kPa is highly suggestive of compensated advanced chronic liver disease [159]. As mentioned previously, the same LSM cut-offs can be used with the M probe or XL probe when probe choice is based on a computer recommendation or BMI [138].

MAFLD patients with liver stiffness measurement > 15 kPa should be considered for surveillance for HCC [138], whereas those with LSM > 20–25 kPa and/or thrombocytopenia are likely to have clinically significant portal hypertension and should undergo endoscopy for

variceal screening [159]. LSM is also useful for prognostication in patients with MAFLD, with mortality rate being higher with increasing LSM [160]. LSM may not be readily available in many places. In such settings, fibrosis scores can be a first step to identify patients who are more likely to have severe liver fibrosis and for referral for LSM [161]. It is unclear whether MAFLD cirrhotics should be biopsied for activity assessment and further studies would be required to clarify this aspect.

How to diagnose MAFLD-cirrhosis?

Recommendations

- Patients with cirrhosis in the absence of typical histology who meet the following criteria should be considered as having MAFLD-related cirrhosis:

Past or present evidence of metabolic risk factors that meet the criteria to diagnose MAFLD, as described in Fig. 1, with at least one of the following:

(1) Documentation of MAFLD on a previous liver biopsy*.

(2) Historical documentation of steatosis by hepatic imaging* (B2).

**History of past alcohol intake should be considered as patients may have dual disease etiology with alcohol use disorder*

Diagnosis and monitoring for clinically significant portal hypertension and varices

Classification of cirrhosis is based on prognostic staging: compensated and decompensated cirrhosis [162, 163]. Such classification depends on the presence or absence of clinically evident decompensating events such as ascites, variceal hemorrhage, encephalopathy, jaundice, or spontaneous bacterial peritonitis.

The initial sequelae of MAFLD-cirrhosis or liver cirrhosis in general is portal hypertension, which contributes to most of the complications seen in cirrhotic patients. In MAFLD, this process classically starts close to the central vein (zone 3), where lipid droplet formation is most active [164]. Therefore, correctly monitoring for the development of clinically significant portal hypertension, defined by hepatic venous pressure gradient (HVPG) of 10 mm Hg is important. The measurement of HVPG is considered the gold standard for monitoring clinically significant portal hypertension and is superior to liver biopsy for predicting complications in MAFLD patients, though it is invasive. Ultrasound is a safe technique for detecting morphological abnormalities associated with cirrhosis and portal hypertension. The identification of porto-collateral circulation on ultrasound, computed tomography (CT), or MRI or the evidence of a reversal of flow within the portal system is a specific and indicative measure of clinically significant portal hypertension and is associated with variceal development and growth [165]. Therefore, periodic screening by imaging methods is recommended in these patients. Notably, though by definition all patients with gastroesophageal varices have significant portal hypertension, clinically significant portal hypertension is present in approximately 50%–60% of patients with cirrhosis but without gastroesophageal varices.[166–168].

The prognosis is worse in patients with cirrhosis and gastroesophageal varices compared to those without gastroesophageal varices. Therefore, patients with MAFLD-cirrhosis should be screened for gastroesophageal varices according to Baveno VI Criteria.[169] A recent meta-analysis of 30 studies (8469 participants) suggested that Baveno VI criteria have high diagnostic accuracy as a triage test for screening for high-risk varices and varices in patients with compensated advanced chronic liver disease (sensitivity: 0.90 (95% CI 0.85–0.93) [170]. The criteria have recently been validated in 224 Chinese patients with MAFLD related compensated cirrhosis [171].

Diagnosis of the existence and size of varices and the presence of red wale marks at esophagogastroduodenoscopy (EGD) is required before the treatment of varices. However, EGD and variceal treatment are invasive procedures associated with the risk of bleeding [172]. As a result, there has been research into noninvasive methods for determining the presence of high-risk varices (i.e. medium/large varices) in order to avoid using endoscopy as a screening tool. Currently, the use of noninvasive tests to diagnose gastroesophageal varices is not recommended as the discriminative accuracy is limited. However, the assessment of LSM by transient elastography is accepted as an accurate technique to rule out high-risk varices in patients with compensated cirrhosis as described in the previous section. Patients with LSM < 20 kPa and platelet count > 150,000/mm^3 have a very low probability (< 5%) of having high-risk varices [173]. The use of EGD can be avoided in these patients. Those with LSM > 20–25 kPa are considered to have clinically significant portal hypertension. In cirrhotic patients without clinically significant portal hypertension, or LSM value between 10–15 kPa, monitoring of its onset is needed, although data on the specific time interval for monitoring are lacking.

Screening for HCC

Though hepatic steatosis associates with "risk factors for HCC" such as obesity, T2DM, and metabolic dysfunction, in the absence of cirrhosis the risk of HCC is low [156, 174–176]. Therefore, till we have more validated prediction biomarkers or algorithms for non-cirrhotic patients at high risk of HCC, surveillance for HCC is only recommended in patients with MAFLD-related cirrhosis. Similarly, patients with LSM > 15 kPa should be considered for surveillance for HCC.

Ultrasound is useful for HCC surveillance from the perspective of the safety, availability, and cost-effectiveness [177–182]. However, its sensitivity for detection of early stage HCC is reported to be only 47% [183], and simultaneous measurement of serum biomarker such as AFP is recommended [183, 184]. In addition, contrast-enhanced ultrasonography has been reported to be useful for the early detection of HCC, but is not widely available [185, 186]. When the ultrasound quality is inadequate due to obesity or excessive gas in the alimentary tract, or when confirmation is required, CT or MRI may be utilised as a surveillance modality [177–182]. Recently, non-enhanced MRI has been reported to have higher screening efficacy for HCC than ultrasonography in high-risk patients [187]. However, the availability and high cost are unsolved issues.

A randomized controlled trial showed that there is no significant difference in the detection rate of early HCC and in prognosis, when surveillance intervals are 3- or 6-monthly. The Italian Liver Cancer (ITA.LI.CA) group has shown that a 6-month surveillance interval has better rates of early HCC detection and prognosis than a 12-month interval [188]. Furthermore, 3-monthly surveillance led to a higher number of unnecessary recall procedures. Thus, based on the tumor volume doubling-time of HCC [189], a 6-month screening interval is recommended.

Treatment

Ideally, an effective therapy should not only reduce steatosis and liver injury, but also improve the metabolic sequelae and cardiovascular risk that is intimately linked to MAFLD. Hence, lifestyle modification including dietary change, weight loss, and structured exercise intervention remains the first-line and cornerstone therapy for this condition.

Diet and lifestyle changes

Lifestyle intervention programmes and weight loss can achieve reductions in liver fat content, resolution of steatohepatitis and fibrosis and improve a patients' quality of life in a dose-dependent manner. A recent study ($n = 293$) showed an improvement in liver histology (steatohepatitis) in 58% of those achieving > 5% and in 90% of those achieving weight loss of > 10%, respectively; only the latter demonstrated an improvement in fibrosis stage (in 45%) [190]. Similarly, studies in Asian populations support the dose–response effect of weight loss with a 7–10% weight loss target; ~ 40% of those with MAFLD have some improvement even with 3–5% weight reduction [191, 192].

The overall aim of lifestyle intervention should be for gradual weight loss (up to 1 kg/week) with a hypocaloric diet (500–1000 kcal deficit). There is no strong evidence to support a particular dietary approach for the resolution of MAFLD. A recent meta-analysis of controlled isocaloric feeding with constant dietary protein and varying ratios of carbohydrate to fat suggests that the differences are too small, implying that "a calorie is a calorie" [193].

Patients with MAFLD tend to consume energy-dense foods rich in sugar-sweetened beverages and saturated fat and cholesterol, but deficient in micronutrients found in fresh fruit, fibre, green vegetables, and omega-3 polyunsaturated fatty acids (n-3 PUFA) [194]. Therefore, dietary plans should encourage low-carbohydrate, low-fat, and Mediterranean-type diets. In particular, adopting a Mediterranean-type diet has been shown to reduce CVD as primary prevention [195] and aids in fat mobilization from specific fat depots including hepatic, cardiac, and pancreatic fat deposits [196]. Isocaloric diets that are high in animal or plant protein were recently demonstrated to reduce hepatic steatosis and inflammation in patients with T2DM [197]. However, the differences between these different diet protocols on long-term outcomes is questionable [198]. A systematic review and meta-analysis showed a significantly decreased risk of MAFLD and liver fibrosis among regular coffee drinkers [199].

Weight loss and more importantly sustaining this effect is challenging. A multidisciplinary approach to management is pivotal to ensure motivation and continued participation in intervention programmes. Increasing clinic visit frequency [200] and utilising an internet-based approach for lifestyle changes [201] have been suggested to maximize the efficacy of weight loss in patients with MAFLD. Therefore, collaboration between different stakeholders, including government/policy makers, physicians, patients association and researchers can effectively promote healthy lifestyles and benefit patients with MAFLD.

Exercise

The optimal exercise dose for hepatic benefit, including type, intensity, volume, and effect size without weight loss is still subject to debate. For the general adult population, physical activity guidelines recommend 30 min/day of moderate-intensity exercise for ≥ 5 days/week or a total of ≥ 150 min/week or vigorous-intensity exercise for ≥ 20 min/day on ≥ 3 days/week (≥ 75 min/week). Resistance exercise on 2–3 days/week and flexibility exercises > 2 days/week are also recommended [202]. Specific data in patients with MAFLD are relatively limited, while exercise intervention with histological improvement

overtime as the primary outcome is difficult to undertake. A recent systematic review and meta-analysis suggested that exercise can reduce hepatic steatosis independent of diet change [203]. Exercise and life style intervention were also found to be able to reduce liver stiffness [204], HCC [205], and portal hypertension in patients with cirrhosis and obesity [206] A randomized clinical trial that included 220 individuals showed that both vigorous and moderate exercise were equally effective in reducing intrahepatic triglycerides and the effect appeared to be largely mediated by weight loss [207]. In another study of an occupational health screening program that included 233,676 subjects between 2002 and 2014, moderate-vigorous exercise was demonstrated to be beneficial in decreasing the risk of development of new fatty liver or improving resolution of existing fatty liver during 5 years' follow-up [208]. In another study, a dose–response relationship between exercise volume and reduction in hepatic steatosis was demonstrated with higher responses observed in individuals exercising over 250 min/week as compared to those exercising for less than 150 min/week [209]. A recent systematic review suggested that both aerobic and resistance exercise reduces hepatic steatosis equally in MAFLD, while resistance exercise does this with less energy consumption. Thus, resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor fitness or for those who cannot tolerate or participate in aerobic exercise [210]. Overall, the selection of the type and duration of exercise must be based on patients' preference and the likelihood of long-term adherence. Notably, combined diet/exercise strategies are more effective in normalisation of liver enzymes levels, reducing hepatic steatosis and for improving histology than either modality alone [211].

What are practical recommendations for lifestyle intervention in MAFLD?

Recommendations

- Lifestyle change towards a healthy diet and physical activity norms via structured programmes are recommended for MAFLD (C2).
- Patients without steatohepatitis or fibrosis should receive counselling for a healthy diet and physical activity and no pharmacotherapy for their liver disease (B2).
- Both overweight/obese and nonobese MAFLD can benefit from weight loss. In the former, a 7–10% weight loss is the target of most lifestyle interventions and results in improvement of liver enzymes and histology (B1).
- Dietary recommendations should consider energy restriction and exclusion of MAFLD-mediating components (processed food, food and beverages high in added fructose). A Mediterranean type diet is advisable (B1).
- Combined diet/exercise strategies are more effective in normalisation of liver enzymes levels and reducing liver fat and improving histology (B1).
- Both aerobic exercise and resistance training effectively reduce liver fat and should be tailored based on patient preferences to ensure long-term adherence. Resistance exercise may be more feasible than aerobic exercise for MAFLD patients with poor fitness (B2).

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

It is currently premature to consider foregut bariatric surgery as an established option to treat MAFLD [212]. Bariatric operations are traditionally offered to patients with MAFLD only if they qualify because of other obesity-related comorbidities [213]. While not an indication per se, MAFLD is present in 65 – 90% of all patients who undergo weight loss surgery [214, 215]. Under these circumstances, numerous retrospective and prospective observational cohort studies have investigated the potential utility of bariatric surgery on MAFLD parameters. According to recent systematic reviews and meta-analyses [216–218], resolution of hepatic steatosis was demonstrated in > 75% of patients. With respect to steatohepatitis, improvements in ballooning and lobular inflammation are consistently observed [216]. Remarkably, regression of fibrosis has been reported in 16 of the 18 studies that investigated postoperative fibrosis scores on liver biopsy [216]. A recent prospective study also suggested resolution of steatohepatitis and fibrosis in liver biopsies from 84% and 70.2% of patients 5 years later, respectivtely. Notably, the reduction in fibrosis commenced in the first year and continued over the 5-year follow-up [219]. However, the lack of randomized controlled trials comparing bariatric surgery (and the various surgical procedures) with other interventions prevents definitive assessment of the benefits and harms of this approach as a therapeutic option for MAFLD [214]. Patients with MAFLD-related cirrhosis merit special consideration as candidates for bariatric surgery because of their high perioperative risk with a reported operative mortality as high as 16.3% in patients with decompensated disease [220].

In light of the above evidence, bariatric surgery can be considered for MAFLD only if the following two criteria are met: (1) presence of other indications [e.g., BMI > 35 kg/m^2 [> 30 kg/m^2 in Asian people)] and (2) absence of liver cirrhosis or evidence of compensated cirrhosis without concomitant portal hypertension. The feasibility of weight

loss surgery for patients with MAFLD and BMI ≤ 35 kg/m^2 [≤ 30 kg/m^2 in Asian people] is presently unclear and more results are needed to support this practice.

It is noteworthy that steatohepatitis and liver fibrosis have been reported as potential complications of jejunoileal bypass surgery [221]. Besides traditional bariatric operations, research in the field of MAFLD has begun to focus on the potential utility of endoscopic bariatric and metabolic therapies (EBMT) including intragastric balloons (IGBs) and endoscopic sleeve gastroplasty (ESG) [222]. EMBT are safer and less invasive than bariatric surgery, ultimately representing an attractive option for patients with MAFLD who qualify because of other obesity-related comorbidities. IGBs have been shown to improve MAFLD-related parameters in short-term studies, whereas ESG may potentially lead to resolution of MAFLD in the long term [222]. However, the purported benefits of EMBT in MAFLD warrant further evaluation in randomized controlled trials.

What are the recommendations for bariatric (metabolic) surgery in MAFLD?

Recommendations

- Bariatric (metabolic) surgery reduces liver fat and improves the histological lesions of MAFLD, including fibrosis (B1).
- Due to the high risk of post-operative complications from bariatric (metabolic) surgery in patients with cirrhosis, the decision should be individualised (C1).

Evidence for current drug therapies

Several anti-diabetic medications are reported to be beneficial for patients with MAFLD [212, 223]. Belfort et al. conducted a RCT of pioglitazone and demonstrated that 6-month treatment with pioglitazone improved hepatic steatosis, ballooning necrosis, and inflammation in steatohepatitis patients with prediabetes or T2DM [224]. Furthermore, 18-month treatment with pioglitazone significantly improved hepatic fibrosis in steatohepatitis patients with prediabetes or T2DM [225]. The beneficial effects of pioglitazone on hepatic histology has been reported in steatohepatitis patients with and without T2DM [226–229]. Weight gain, edema, the development of bladder cancer, and a decrease in bone mineral density are possible concerns with pioglitazone, and this therapy is not widely used [230, 231].

GLP-1a has been reported to improve hepatic histology including fibrosis in a RCT and meta-analyses [232–235]. GLP-1a also reduces body weight. However, GLP-1a causes gastrointestinal adverse effects including loss of appetite which can result in poor patient-reported outcomes [236]. SGLT2i has been reported to reduce hepatic fat content [237–239]. A pilot study on a small number of biopsy-proven steatohepatitis patients showed significant improvements in steatosis, ballooning, and fibrosis, which remained significant when compared with a historical placebo [240]. The effects of SGLT2i on hepatic fibrosis require further studies. Metformin does not improve hepatic histology in patients with MAFLD [241–244]. However, metformin improves IR [241, 243, 244] and reduces the risk of HCC in patients with MAFLD, though the studies have not been

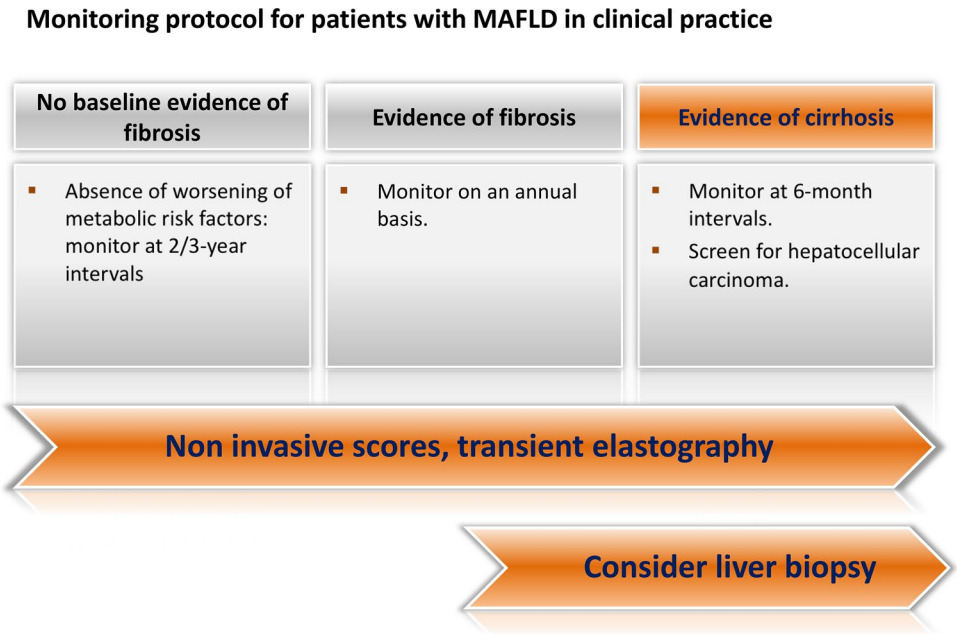

Fig. 2 Monitoring protocol for patients with MAFLD in clinical practice

prospective or randomized [245, 246]. Importantly, both GLP-1a and SGLT2i have been shown to be beneficial in cardiovascular outcome in patients with T2DM.

Vitamin E has been reported to be effective in improving hepatic histology in patients with steatohepatitis [229, 247–249]. However, several studies have failed to demonstrate its beneficial effects and level 1 evidence is thus lacking [243, 250–252]. Recently, a propensity score matching analysis demonstrated that vitamin E decreases the risk of death or transplant and hepatic decompensation in patients with metabolic steatohepatitis with bridging fibrosis or cirrhosis [253]. The development of prostate cancer is a possible concern of vitamin E [254].

Statins did not show any beneficial effects on hepatic histology [255]. However, statins reduced cardiovascular morbidity in patients with MAFLD [255, 256]. Thus, statins should be considered in all patients with MAFLD with hyperlipidemia. However, the treatment of hyperlipidemia in patients with MAFLD appears suboptimal. In a multicentre study, 58.9% of patients who were on a statin did not achieve their treatment target while 74.1% of patients who were not on statin should have been receiving therapy [257].

Pentoxifylline, a phosphodiesterase inhibitor with anti-inflammatory effects has been demonstrated in a meta-analysis to improve lobular inflammation and NAS without affecting lipid profiles. However, there was no significant improvement in other histological features, such as steatosis, ballooning or fibrosis [258].

Patients with MAFLD are at a high risk of hepatic fibrosis, HCC, cardiovascular events, and cancer. Thus, for any physician treating these patients, metabolic risk factor modification to improve long-term outcomes is an essential part of holistic management.

Monitoring progress and response to treatment

There is no accepted consensus on the optimal strategy for monitoring patients with MAFLD and their response to treatment [259]. Ideally, an optimal surveillance schedule should include routine biochemistry, assessment of comorbidities, and monitoring of hepatic fibrosis [260]. By taking into account that the severity of fibrosis is the main prognostic determinant in terms of both liver-related outcomes and mortality [261], those with advanced fibrosis merit the closest monitoring. Because patients with MAFLD are expected to progress at a mean of 0.12 (range: 0.07–0.18) fibrosis stage per year [262], the following schedule can be proposed as a general guidance (Fig. 2): (1) patients without fibrosis can be monitored at 2- or 3-year interval if there has been no worsening of concomitant metabolic risk factors; (2) patients with fibrosis should be monitored on an annual basis, and (3) patients with cirrhosis should undergo monitoring at 6-month intervals including surveillance for HCC. In selected patients at high risk of liver disease progression, monitoring should include a repeat liver biopsy every 5 years, unless they have established cirrhosis [260]. Notably, a recent study showed that while the prevalence and incidence of MAFLD in patients with T2DM are high, few patients progress to advanced fibrosis in 3 years [136].

Although liver histology remains the primary endpoint in clinical trials, its routine use over time for serial surveillance of fibrosis progression is unfeasible owing to its known limitations (cost, invasiveness, risk of complications, subjective interpretation). However, no easily applicable method for use in daily practice with a high predictive value for differentiating different stages of liver fibrosis has been identified. Monitoring of fibrosis progression in the clinic might rely on a combination of noninvasive scores (NFS, FIB-4 and ADAPT) and LSM [263, 264] although this strategy requires further validation. Growing evidence supports the utility of magnetic resonance elastography for the non-invasive detection of fibrosis in early-phase trials of MAFLD [265]. However, this technique is expensive and cannot be recommended for routine clinical use.

How to monitor the progress of treatment in MAFLD?

Recommendations

- Patients without fibrosis can be monitored at intervals of 2 or 3 years in the absence of worsening of metabolic risk factors using a combination of non-invasive scores and liver stiffness mesaurment (C2).
- Patients with fibrosis should be monitored on an annual basis using a combination of non-invasive scores and liver stiffness mesaurment (C2).
- Patients with cirrhosis should undergo monitoring at 6-month intervals including surveillance for hepatocellular carcinoma (A2).
- In subgroup of patients at high risk of fibrosis progression, monitoring may include a repeated liver biopsy every 5 years' follow-up, unless they have established cirrhosis (C2).

Patient-reported outcomes in MAFLD

The multi-dimensional complexity of MAFLD management has highlighted the importance of understanding the disease from a patient perspective through Patient Reported Outcomes (PRO). This is particularly important as new drugs in development may have significant side effects, and economic and cost-effectiveness modelling are needed to identify the ideal target subpopulation for treatment.

Instruments assessing general health-related quality of life (HRQoL) questionnaires such as the Short Form-36 (SF-36), EuroQoL 5-Dimensions 5-Level (EQ-5D-5L), the Chronic Liver Disease Questionnaire (CLDQ) and more recently, disease-specific questionnaires such as CLDQ-NASH and NASH-CHECK have been validated in MAFLD [266–268]. These questionnaires have been translated into various languages and validated internationally. Other instruments looking more specifically at fatigue and work productivity have also been applied to MAFLD [266].

Patients with MAFLD appear to have worse HRQoL, physical, mental as well as fatigue scores compared to other causes of chronic liver disease such as chronic viral Hepatitis B and C [269–271]. Demographics or metabolic comorbidities that have been associated with these low HRQoL scores include age, female gender, depression, smoking, T2DM, and BMI, although MAFLD by itself is an independent risk factor [272, 273]. When referenced against the severity of liver disease, several studies using a variety of instruments have reported cirrhosis as an independent risk factor for lower HRQoL and physical health scores [269, 270, 272]. However, a European study which controlled for features of steatohepatitis found only lobular inflammation, but not histologic ballooning or cirrhosis, to be associated with poorer HRQoL scores [273]. Regardless, there is a dearth of MAFLD PRO data in the Asian context and how cultural variation may nuance the PROs is not known.

Patient perspectives on quality of life, satisfaction, and compliance with lifestyle advice are critical to developing and evolving to a patient-centred approach to impact MAFLD outcomes. This is all the more important because of the integral role of lifestyle in disease pathogenesis. Studies in Asian populations evaluating the improvement of PROs and the trade-off thresholds for side effects during therapy are needed to better guide and strategize approaches to this disease.

What is the role of patient reported outcomes in MAFLD?

Recommendations

- Patient perspectives on quality of life, satisfaction, and compliance are critical to developing a patient-centred approach to impact MAFLD outcomes (B2).
- Patients with MAFLD appear to have worse HRQoL, physical, mental, and fatigue scores compared to patients with other causes of chronic liver disease such as hepatitis B and C (B2).

The pipeline of new treatments

The past few years have witnessed a steady increase in the number of drug targets for MAFLD as new information about its molecular pathogenesis unfolds. At the end of 2019, it was estimated that there were 196 investigational candidate drugs for MAFLD in various stages of development [274]. The drugs that have so far progressed to phase 3 development include obeticholic acid (OCA), elafibranor, selonsertib, cenicriviroc, resmetirom, and aramchol [275]. Several challenges remain for having a drug approved for MAFLD treatment. This includes the tremendous heterogeneity of the disease, and as well, performance bias or the Hawthorne effect where the placebo group provided with lifestyle and regular medical advice in a clinical trial setting impacts on histological and biochemical responses.

OCA is a farnesoid X receptor agonist whose potential actions include decreasing hepatic steatosis, inflammation, and fibrosis and an increase of insulin sensitivity [276]. OCA is being tested at two different doses (10 mg/day and 25 mg/day) in the ongoing phase 3 Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment (REGENERATE) trial. This RCT is being conducted in ~ 2400 patients. The study has a dual primary endpoint consisting of resolution of steatohepatitis with no worsening of fibrosis and improvement of fibrosis by ≥ 1 stage with no worsening of steatohepatitis. An interim analysis of the REGENERATE trial has shown that treatment with OCA 25 mg/day resulted in an improvement of fibrosis without worsening of steatohepatitis in 21.0% ($p < 0.001$) of participants, whereas resolution of steatohepatitis without worsening of fibrosis was observed in 14.9% of patients ($p = 0.001$) [275, 277]. The main adverse event of OCA was pruritus which occurred in 51% of patients in the 25-mg group, 28% in the 10-mg group, and 19% in the placebo group. Notably, 9% of patients in the 25-mg group discontinued the drug because of pruritus. Over the 18-month trial duration, cholelithiasis or cholecystitis was observed in 3% ($n = 19$) of patients in the 25-mg group, 1% ($n = 7$) in the 10-mg group, and < 1% ($n = 2$) in the placebo group [277]. A caveat to the use of OCA is increases in serum low-density lipidprotein (LDL) and decreases in high-density lipidprotein (HDL), which may be partially countered by statin therapy [275, 278]. Although cirrhosis was an exclusion criterion for the REGENERATE trial [279], an ongoing

study (NCT03439254) is focusing on the dosing of OCA in patients with steatohepatitis and concomitant compensated cirrhosis. Recently, the FDA determined that the predicted benefit of OCA remains uncertain and did not warrant accelerated approval under subpart H.

Elafibranor, a dual peroxisome proliferator-activated receptor alpha/delta agonist (PPARα/δ) agonist was found to induce resolution of steatohepatitis without worsening of fibrosis in the GOLDEN Study 2b Trial [280]. The same endpoint is used as the primary outcome measure in the ongoing phase 3 clinical trial of elafibranor (RESOLVE-IT). Unfortunately, the study did not meet the predefined surrogate primary endpoint of steatohepatitis resolution without worsening of fibrosis, though the trial is ongoing. The study will also provide data on long-term outcomes including all-cause mortality, cirrhosis, and liver-related clinical endpoints.

Selonsertib, an inhibitor of apoptosis signal-regulating kinase-1 (ASK-1) showed promise in improving hepatic inflammation and fibrosis in animal models and advanced to phase 3 (STELLAR-3 and -4) but was discontinued because it was not superior to placebo in both trials [281]. Cenicriviroc, a CCR2/CCR5 chemokine receptor blocker aims to reduce the drivers of inflammation and fibrosis [282]. A multicentre, randomised, double-blind, placebo-controlled study of cenicriviroc for the treatment of fibrosis in MAFLD (AURORA) is currently underway. The primary outcome is improvement of fibrosis without worsening of steatohepatitis. Resmetirom is a liver-directed, orally active, selective thyroid hormone receptor-β agonist designed to improve steatohepatitis by increasing hepatic fat metabolism and reducing lipotoxicity [283]. A phase 3 study in patients with advanced liver fibrosis, MAESTRO-NASH is ongoing with the primary endpoint being resolution of steatohepatitis after 1 year. Aramchol, a cholic-arachidic acid conjugate that inhibits stearoyl-CoA desaturase was initially produced for treatment of gallstones [284]. Aramchol 600 mg is currently being tested in a phase 3/4 study (ARMOR) to assess its efficacy and safety in subjects with steatohepatitis and fibrosis stages 2–3 who are overweight or obese and have prediabetes or T2DM. In addition to these phase 3 clinical trials, a number of early phase trials are underway. While target-based therapeutic agents are being developed based on new pathophysiological knowledge and the drug discovery pipeline in MAFLD has been promising, the results have been below expectations. A combination drug treatment strategy wherein several drivers of disease are simultaneously engaged could be more effective than targeting individual drivers, since redundancy is common in biological systems.

Future clinical trials should consider the mechanism of action of the drug, and as well better stratification of patients and standardization of lifestyle interventions, exercise, and diet between treatment arms. Further trials should consider innovative designs such as basket, adaptive or umbrella trials [28].

Special groups

Lean subjects with MAFLD often have visceral obesity, sarcopenia, and recent weight gain. They also have a higher prevalence of features of the metabolic syndrome compared to lean controls and can develop steatohepatitis and advanced fibrosis [285, 286]. A recent RCT from Hong Kong suggested that lifestyle intervention is effective in treating MAFLD even in non-obese patients. The amount of weight reduction needed to achieve remission was less than that for non-obese patients. By 6 years, non-obese patients remained more likely to maintain weight reduction and have ALT normalization [287]. Similar findings were observed in a study from Turkey where 5% body weight loss induced MAFLD remission in both obese and lean patients with MAFLD [288]. Similarly, a small biopsy-based study revealed that 5% weight reduction is associated with improvement of steatohepatitis in non-obese patients, similar to that which is observed in obese patients [289]. Larger biopsy-based studies are required to confirm the findings. Non-obese subjects are more likely than obese subjects to maintain weight reduction and normal liver enzymes in the long term [287]. Therefore, lifestyle intervention with regular exercise is effective in treating MAFLD and in improving overall fitness and metabolic co-morbidities irrespective of baseline BMI. A 3–5% weight reduction may be sufficient in lean MAFLD.

Pediatric MAFLD is the most common cause of liver disease in children and may represent a more severe phenotype that will benefit from early intervention. The management of MAFLD in children consists of treating the liver disease itself, but more importantly addressing the underlying obesity and the related comorbidities. The overall goal is to improve a child's quality of life and reduce long-term metabolic, cardiovascular, and liver complications. Lifestyle changes (dietary interventions, physical activity, and nutritional and psychologic counselling) lead to significant improvements in BMI, aminotransferase levels, and hepatic steatosis in children with MAFLD [290]. While the efficacy of several medications including metformin, vitamin E, omega-3 fatty acid supplementation and probiotics has been investigated in children, intensive lifestyle modification remains the only prevention and treatment strategy for pediatric MAFLD at this stage.

What is the approach for management of special groups (non-obese and pediatric) with MAFLD?

Recommendations

- Lifestyle intervention with regular exercise is effective in treating MAFLD and in improving overall fitness and metabolic co-morbidities irrespective of baseline BMI (B1).
- Lifestyle change (dietary interventions, physical activity, and nutritional and psychologic counselling) is the only prevention and treatment strategy for pediatric MAFLD, though beneficial effects on fibrosis are yet to be demonstrated. No effective and safe drug treatment for fibrosis in pediatric MAFLD has been proven (B1).

Management of MAFLD-related HCC

The survival rate of patients with MAFLD-related HCC is similar to that from other etiologies [94, 291–294]. While a high prevalence of non-cirrhosis is a feature of MAFLD-related HCC, patients with non-cirrhotic MAFLD-related HCC have a similar risk of mortality as cirrhotic patients with disease from other etiologies [94, 293–295]. Accordingly, metabolic risk factor modification significantly contributes to their optimum management.

High BMI is one of three criteria for MAFLD diagnosis and its negative impact on HCC-related mortality has been reported in western cohorts [296]. However, there is no association between high BMI and HCC-related mortality in Asian patients in a meta-analysis or in cohort studies [296–298]. The reason(s) for this discrepancy remain(s) unclear but sarcopenia could be a possible explanation. Sarcopenia is a prognostic factor for Asian patients with HCC [297, 299–305], while physical activity is reported to be associated with better survival in patients with HCC [306]. Thus, an important aspect of management is by considering body composition that includes body fat and skeletal muscle mass, when treating patients with HCC.

T2DM is another criteria for MAFLD in the context of hepatic steatosis. In this regard, an international cohort study demonstrated that metformin significantly reduced the risk of HCC in MAFLD patients with HbA1c levels above 7.0% [245]. A meta-analysis has also shown that metformin prolongs the survival of HCC patients with T2DM after the curative treatment of the cancer [246]. Thus, metformin may be a beneficial treatment along with life-style intervention, in MAFLD-related HCC patients with T2DM. Again, however, there are no prospective, randomized data to support this contention and thus no strong recommendation can be made.

The Japan Study Group for MAFLD has performed a nationwide study and created a data mining-based prognostic algorithm for patients with MAFLD-related HCC [307]. The decision-tree revealed that the best profile comprised treatment with hepatectomy or radiofrequency ablation and a serum albumin level ≥ 3.7 g/dL [307]. However, these need confirmation in other international cohorts.

What is the approach to management of MAFLD-HCC?

Recommendations

- Control of diabetes and obesity could be beneficial in MAFLD-related HCC patients (B1).
- Metformin may be a beneficial treatment in MAFLD-related HCC patients with T2DM (C2).
- Serum albumin level is a prognostic factor and nutritional therapy focusing on protein metabolism is important for the management of patients with MAFLD-related HCC (C2).

Liver transplantation for MAFLD

MAFLD has become an increasingly frequent indication for liver transplantation (LT) in the Asia–Pacific region over the past decade, both as a sole etiologies or co-existing with other conditions [308–310]. With increasingly effective vaccination programs and anti-viral medication, it is likely that MAFLD will continue to increase as a LT indication. MAFLD transplant recipients are typically older, with a higher BMI and are more likely to have T2DM and hypertension than non-MAFLD recipients [311, 312]. Not surprisingly, MAFLD patients have a higher likelihood of underlying cardiovascular disease (CVD) which was up to 53% in one North American series of patients undergoing pre-LT coronary angiography [313]. Thus a careful CVD evaluation is mandatory as pre-existing CVD along with age predicts post-LT cardiovascular events [314].

MAFLD patients have a 60% higher risk of developing a major adverse cardiovascular event (MACE) within 30 days post-LT, and this predicts a lower post-LT survival [315]. Consequently, the United Network for Organ Sharing data suggests CVD-specific mortality is increased in transplanted MAFLD patients relative to other etiologies, and relates to pre-existing risk factors for T2DM, renal impairment, and prior CVD [316]. MAFLD may also be associated with a pro-coagulant state with reports of an increased risk of portal vein thrombosis complicating transplantation [317, 318].

Importantly, post-LT survival in MAFLD patients is equivalent to that from other etiologies, with 5-year overall survival rates of 73–79% [311, 319]. Infection (22–25%), and CVD (5–22%) were identified as the commonest causes of post-LT death [311, 320]. Older age (> 60 years), female gender,higher MELD (> 23), and extremes of BMI (< 18.5 and > 40 kg/m2) were reported to predict post-LT death in the the European Liver Transplant Registry[311].

Recurrence of MAFLD in the graft is common, occurring in up to 90% of recipients [321]. A minority of patients have an accelerated disease course with graft cirrhosis developing in 2–4% of patients in less than a decade; however, death from graft cirrhosis is uncommon (0.2–3% of patients) [320, 321]. Corticosteroids and calcineurin antagonists are well-established immunosuppressive regime in LT with known risks to exacerbate hyperglycemia, hypertension, and dyslipidemia; hence the optimal regime in MAFLD recipients is unclear. Statins should be encouraged post-LT in those with dyslipidemia and/or pre-existing CVD and may be associated with a survival benefit [322].

What are the recommendations for liver transplantation in MAFLD?

Recommendations

- Post-transplant survival for MAFLD patients is equivalent to that of other liver diseases in appropriately selected patients. Liver transplantation should be considered for MAFLD patients with decompensated liver disease or hepatocellular carcinoma (B1).
- Patients with MAFLD cirrhosis have a high prevalence of pre-existing cardiovascular disease and should be thoroughly evaluated prior to listing for transplantation (B1).

Conclusion

The APASL guidelines document for MAFLD (along with the criteria for diagnosis) is intended to provide assessment and management advice for the general as well as special populations with the disease. The burden of MAFLD is rapidly increasing in the Asia–Pacific; in this region dual etiology disease particularly with viral hepatitis and alcohol is common. MAFLD is a leading cause of chronic liver disease and increasingly of HCC on the one hand and is a contributor to the various associated systemic complications such as T2DM, CVD, and CKD. Fibrosis is the major determinant of all the complications of MAFLD and liver biopsy remains the reference standard. However, various biomarkers and imaging modalities are available (and are being increasingly used) for the non-invasive assessment of fibrosis. Patients with cirrhosis should be considered for surveillance for varices and HCC. Lifestyle intervention remains the cornerstone of management but it is expected that over the next decade, drug treatments will be approved and added to the armamentarium of therapeutic choices. Holistic patient-centred and multidisciplinary management approaches are required that focus on the amelioration of liver injury, treating the associated systemic metabolic dysfunction, while being aware of the importance of patient-reported outcomes.

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Compliance with ethical standards

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