Malaysian Society of Gastroenterology and Hepatology consensus statement on metabolic dysfunction-associated fatty liver disease

Wah-Kheong Chan, †Soek-Siam Tan, ‡Siew-Pheng Chan, ‡‡Yeong-Yeh Lee, •Hoi-Poh Tee, ¶Sanjiv Mahadeva, *Khean-Lee Goh, *‡Anis Safura Ramli, *†‡Feisul Mustapha, ‡‡Nik Ritza Kosai and Raja Affendi Raja Ali

*Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, §§Upper Gastrointestinal, Metabolic and Bariatric Surgery Unit, Department of Surgery, ¶¶Gastroenterology Unit, Department of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, †Disease Control Division, Ministry of Health, Malaysia, Putrajaya, ‡Department of Hepatology, Selangor Hospital, **Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Selangor Campus, Batu Caves, ††Subang Jaya Medical Centre, Subang Jaya, ‡‡Institute of Pathology, Laboratory and Forensic Medicine, Centre of Excellence for Research on Atherosclerosis and CVD Prevention, Universiti Teknologi MARA, Sungai Buloh Campus, Sungai Buloh, Selangor, *School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, ‡‡KPJ Pahang Specialist Centre, Kuantan, Pahang, Malaysia

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consensus, MAFLD, Malaysia, Malaysian Society of Gastroenterology and Hepatology, metabolic dysfunction-associated fatty liver disease, MSGH, multi-disciplinary, NAFLD, non-alcoholic fatty liver disease.

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Correspondence
Dr Wah-Kheong Chan, Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.
Email: wahkheong2003@hotmail.com

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Abstract
The Malaysian Society of Gastroenterology and Hepatology saw the need for a consensus statement on metabolic dysfunction-associated fatty liver disease (MAFLD). The consensus panel consisted of experts in the field of gastroenterology/hepatology, endocrinology, bariatric surgery, family medicine, and public health. A modified Delphi process was used to prepare the consensus statements. The panel recognized the high and increasing prevalence of the disease and the consequent anticipated increase in liver-related complications and mortality. Cardiovascular disease is the leading cause of mortality in MAFLD patients; therefore, cardiovascular disease risk assessment and management is important. A simple and clear liver assessment and referral pathway was agreed upon, so that patients with more severe MAFLD can be linked to gastroenterology/hepatology care, while patients with less severe MAFLD can remain in primary care or endocrinology, where they are best managed. Lifestyle intervention is the cornerstone in the management of MAFLD. The panel provided a consensus on the use of statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, sodium–glucose cotransporter-2 inhibitor, glucagon-like peptide-1 agonist, pioglitazone, vitamin E, and metformin, as well as recommendations on bariatric surgery, screening for gastroesophageal varices and hepatocellular carcinoma, and liver transplantation in MAFLD patients. Increasing the awareness and knowledge of the various stakeholders on MAFLD and incorporating MAFLD into existing noncommunicable disease-related programs and activities are important steps to tackle the disease. These consensus statements will serve as a guide on MAFLD for clinicians and other stakeholders.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common cause of chronic liver disease affecting an estimated 20–30% of the world population. There have been advancements in various aspects of the disease in recent years. In fact, a new term, metabolic dysfunction-associated fatty liver disease (MAFLD), was introduced in 2020 as a more appropriate term for fatty liver associated with the metabolic syndrome. There is now a better understanding on the epidemiology and natural history of the disease, and it is becoming increasingly clear that gastroenterologist/hepatologist cannot work in silo to tackle this disease. Integration of MAFLD into the national response to noncommunicable diseases (NCDs) and co-localizing a simple and clear assessment and referral pathway in clinics seeing patients with metabolic syndrome including diabetes mellitus are important public health strategies. There have also been advancements in noninvasive tests and in the management of the disease. In view of these developments, the Malaysian Society of Gastroenterology and Hepatology saw the need to review the literature and provide a consensus statement that can be used as a guide by clinicians and other stakeholders in the local setting.

Methods

The consensus panel consisted of experts in the field of gastroenterology and hepatology, endocrinology, bariatric surgery, family medicine, and public health, who demonstrated knowledge and expertise in MAFLD and/or the metabolic syndrome through their research work and publications, presentation at conferences and workshops, participation in the preparation of national guidelines, and vast experience in the management of patients with these conditions. There were representatives from universities and both the public and private healthcare sectors. Among them were the Immediate Past Presidents and President of the Malaysian Society of Gastroenterology and Hepatology, the President of the Malaysian Endocrine and Metabolic Society and Chairperson of the 6th Edition of the Clinical Practice Guidelines on the Management of Type 2 Diabetes Mellitus, and the Deputy Director (Non-Communicable Diseases) of the Diseases Control Division, Ministry of Health, Malaysia. Each member of the panel was assigned to draft, based on comprehensive literature review, a section of the paper and to prepare consensus statements for the assigned section. The literature review was performed independently by each of the panel members for their assigned section(s). Panel members were not made compulsory to follow any specific guidelines when performing their literature review. Relevant articles were identified using the PubMed database up to March 2021. A standardized guide was provided to all panel members for grading of level of evidence and recommendation (Table 1). The preparation of the consensus document did not include an expert in consensus process. However, it followed the well-described modified Delphi process. The work of each of the members was compiled, and the draft full paper along with the references was circulated to all members of the panel for review and comment. The panel members were asked to vote online for each of the consensus statements using a Likert scale of 1–5 (Table 1). Consensus was considered as achieved for a statement when > 80% of the panel members voted “accept completely” or “accept with some reservation.” A statement was considered as rejected if > 80% of the panel members voted “reject completely” or “reject with reservation.” When a consensus could not be achieved, the statement was modified based on comments from the panel members, and a second round of voting was conducted. When a consensus was still not achieved after that, the statement was modified again based on comments from the panel members, and the process concluded after the third or last round of voting. Each statement was graded to indicate the level of evidence and the strength of recommendation (Table 1). The final paper, consisting of the consensus statements, the accompanying commentary and the references, was circulated and approved by all panel members. The term NAFLD was used in this paper whenever the cited reference is an original paper that had used the term NAFLD.

Results

All invited experts accepted the invitation and participated in the preparation of the consensus document. A total of 27 statements
were prepared. During the first round of voting, consensus was achieved for 25 statements. The two statements that did not achieve consensus were the statement on pioglitazone and the statement on vitamin E. The statements were revised based on comments from the panel members, and consensus was achieved during the second round of voting. The consensus statements are presented in Table 2.

**Definition and natural history.** Metabolic dysfunction-associated fatty liver disease is diagnosed in a person with fatty liver based on imaging, noninvasive score, or histology, if the person is overweight or obese, has type 2 diabetes mellitus (T2DM), or has at least two metabolic risk abnormalities (Fig. 1). There have been strong debates about this nomenclature change. Unlike NAFLD, MAFLD is diagnosed based on a set of positive criteria, does not require exclusion of other causes of chronic liver disease, and clearly attributes the disease to its underlying etiology. While ≥80% of patients meeting the criteria for one definition would also meet the criteria for the other definition, an estimated 5–8% would meet the criteria for NAFLD but not MAFLD and vice versa. The former consists of NAFLD patients with mild or no metabolic disorders, while the latter consists of MAFLD patients with significant alcohol intake or other causes of chronic liver disease. The term MAFLD has been shown to have better clinical utility and has been endorsed by the Asia Pacific Association for the Study of Liver and the Malaysian Society of Gastroenterology and Hepatology. Because of its close association with the metabolic syndrome, patients with NAFLD or MAFLD are at increased risk of cardiovascular disease (CVD). It has long been recognized that CVD is the leading cause of mortality in NAFLD patients. Interestingly, recent data suggest that MAFLD, but not NAFLD, was associated with increased cardiovascular mortality. Furthermore, MAFLD was associated with an increased risk of all-cause mortality, while NAFLD, after adjusting for metabolic risk factors, was not. Another study found that MAFLD patients who did not fulfill the criteria for NAFLD had significantly greater incident cardiovascular events compared with NAFLD patients who did not fulfill the criteria for MAFLD. In addition, NAFLD or MAFLD patients may develop fibrosis and progressive liver disease over time, which is more likely in patients with steatohepatitis than in those with simple steatosis. Based on studies on NAFLD patients, fibrosis stage progresses by an average of one stage in 7 years in patients with steatohepatitis and by an average of one stage in 14 years in patients with simple steatosis. The risk of liver-related complications and mortality increases exponentially with increase in fibrosis stage. NAFLD patients with cirrhosis may develop hepatocellular carcinoma (HCC) at 1–4% per year, and although non-cirrhotic NAFLD patients may also develop HCC, the absolute risk is <0.1% per year. A study has found that persons with hepatic steatosis but not fulfilling the criteria for MAFLD were unlikely to have significant liver disease, further supporting the use of the new term. Besides CVD and liver-related complications, NAFLD has been associated with increased risk of extrahepatic malignancies, especially gastrointestinal, breast, and gynecological malignancies, and incident chronic kidney disease.

**Epidemiology.** The local prevalence of MAFLD is estimated to be 20–40% based on two studies published to date. Both were health screening studies on healthy individuals that used ultrasonography to diagnose fatty liver. In the earlier study with 1621 subjects, an overall prevalence of NAFLD of 22.7% was reported. In the second study with 628 subjects, a prevalence rate of 37.4% was reported. In one of the largest population-based study in Asia that used highly accurate magnetic resonance spectroscopy for the diagnosis of significant hepatic steatosis, the prevalence of NAFLD was clearly shown to increase with increasing number of components of the metabolic syndrome, from 5% among those without any components of the metabolic syndrome to 80% among those with all five components. In a follow-up study of subjects who did not have NAFLD at baseline, incident NAFLD was found in 13.5% after a median interval of 47 months; older age, increasing waist circumference, increasing serum triglyceride level, and decreasing serum high-density lipoprotein cholesterol level were identified as independent factors associated with incident NAFLD. According to the National Health and Morbidity Survey, which provides the best nationwide population-based data on NCDs, the prevalence of overweight or obesity in Malaysian adults has increased from 29.4% in 2011 to 30.0% in 2015 and 50.1% in 2019, while the prevalence of diabetes mellitus has risen from 11.2% in 2011 to 13.4% in 2015 and 18.3% in 2019. While there has not been any such large-scale study on MAFLD locally, the increasing prevalence of obesity and obesity-related diseases points toward an increasing prevalence of MAFLD. A modeling study has projected an increasing incidence of HCC, decompensated cirrhosis, and liver-related mortality as a result of the increasing prevalence of obesity and NAFLD in Asian countries. The term lean NAFLD has been used to refer to NAFLD in patients with normal body mass index, which is most observed in middle-aged Asian populations, which are known to have more visceral adiposity for the same body mass index compared with other ethnicities.

**Assessment.** Metabolic dysfunction-associated fatty liver disease patients may present with elevated serum aminotransferase level that is detected either during health screening or as part of the investigation for another illness. Other common causes of elevated serum aminotransferase level are drug-induced liver injury, alcohol-related liver disease, and viral hepatitis B and C infection, which should be considered during the assessment. Investigations for other less common liver diseases will depend on clinical findings. Ultrasonography should be performed to diagnose fatty liver and exclude focal liver lesion in patients with elevated serum aminotransferase level. However, ultrasonography is operator dependent and may not detect fatty liver, especially when the fatty liver is mild.

The severity of liver fibrosis is the single most important predictor of liver-related complications and mortality. Therefore, assessing the severity of liver fibrosis is important. Noninvasive tests for liver fibrosis can be divided into blood or imaging-based tests. Simple blood-based tests utilize readily available clinical and laboratory parameters for the diagnosis of advanced liver fibrosis. The fibrosis-4 (FIB-4) score uses age, aspartate aminotransferase, alanine aminotransferase, and platelet count. It has modest accuracy but high negative predictive...
### Table 2  Consensus statements

| Definition and natural history |
|--------------------------------|
| **Statement 1**: Metabolic dysfunction-associated fatty liver disease (MAFLD) is diagnosed in a person with fatty liver based on imaging, noninvasive score, or histology, if the person is either overweight or obese, has type 2 diabetes mellitus, or has at least two metabolic risk abnormalities  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 100%, B = 0%, C = 0%, D = 0%, E = 0% |
| **Statement 2**: Cardiovascular disease is the leading cause of mortality in MAFLD patients. MAFLD patients with more severe liver fibrosis are at increased risk of liver-related complications and mortality  
Level of evidence: I  
Strength of recommendation: A  
Level of agreement: A = 100%, B = 0%, C = 0%, D = 0%, E = 0% |

### Epidemiology

| Statement 3: MAFLD is commonly seen in the local Malaysian population, and its prevalence is increasing because of increasing prevalence of obesity and obesity-related diseases  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 91%, B = 0%, C = 0%, D = 9%, E = 0% |
| Statement 4: The high and increasing prevalence of MAFLD will lead to increasing incidence of HCC, decompensated cirrhosis, and liver-related mortality from the disease  
Level of evidence: III  
Strength of recommendation: B  
Level of agreement: A = 82%, B = 18%, C = 0%, D = 0%, E = 0% |

### Assessment

| Statement 5: MAFLD patients with elevated serum aminotransaminase level should be evaluated by a thorough history of intake of medications, supplements, herbal therapies, and alcohol and screened for viral hepatitis B and C infection  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 91%, B = 9%, C = 0%, D = 0%, E = 0% |
| Statement 6: Ultrasonography should be performed to diagnose fatty liver and exclude focal liver lesion in patients with elevated serum aminotransferase level  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 64%, B = 36%, C = 0%, D = 0%, E = 0% |
| Statement 7: MAFLD patients should have liver fibrosis assessment using FIB-4 and stratified as having low risk of advanced liver fibrosis if FIB-4 is < 1.3. MAFLD patients with FIB-4 ≥ 1.3 have increased risk of advanced liver fibrosis and should undergo further assessment by liver stiffness measurement  
Level of evidence: I  
Strength of recommendation: A  
Level of agreement: A = 73%, B = 18%, C = 9%, D = 0%, E = 0% |
| Statement 8: Liver biopsy can be considered for MAFLD patients with discordant noninvasive tests for liver fibrosis, when another liver pathology is suspected or needs be excluded, when the diagnosis of steatohepatitis is uncertain or needs to be confirmed, and when required for therapeutic trials  
Level of evidence: II  
Strength of recommendation: A  
Level of agreement: A = 91%, B = 9%, C = 0%, D = 0%, E = 0% |

#### Screening for more severe metabolic dysfunction-associated fatty liver disease

Statement 9: Patients with T2DM are an important target group to screen for more severe MAFLD. The FIB-4 can be used as a screening tool. Patients with intermediate or high FIB-4 score may have advanced liver fibrosis and should be considered for liver stiffness measurement  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 82%, B = 18%, C = 0%, D = 0%, E = 0% |
| Statement 10: MAFLD patients with liver stiffness ≥ 10 kPa may have advanced liver fibrosis and should be considered for referral to gastroenterology/hepatology. MAFLD patients with liver stiffness ≥ 15 kPa should be considered for HCC screening. MAFLD patients with liver stiffness ≥ 20–25 kPa are likely to have clinically significant portal hypertension and should be referred to gastroenterology/hepatology and be considered for variceal screening  
Level of evidence: III  
Strength of recommendation: A  
Level of agreement: A = 82%, B = 18%, C = 0%, D = 0%, E = 0% |
Lifestyle intervention is the cornerstone of management of metabolic dysfunction-associated fatty liver disease

Statement 11: Dietary intervention is beneficial in controlling disease activity and cardiovascular risk and should be prescribed to MAFLD patients
Level of evidence: I
Strength of recommendation: B
Level of agreement: A = 100%, B = 0%, C = 0%, D = 0%, E = 0%

Statement 12: Exercise can reduce liver fat irrespective of weight loss and should be prescribed to MAFLD patients
Level of evidence: I
Strength of recommendation: B
Level of agreement: A = 73%, B = 27%, C = 0%, D = 0%, E = 0%

Statement 13: Regardless of obesity state, weight loss through lifestyle intervention is associated with improvement in MAFLD
Level of evidence: I
Strength of recommendation: A
Level of agreement: A = 100%, B = 0%, C = 0%, D = 0%, E = 0%

Management of metabolic risk factors to reduce cardiovascular disease risk

Statement 14: Standard detailed cardiometabolic risk screening and aggressive modification of CVD risk factors is mandatory in all MAFLD patients
Level of evidence: I
Strength of recommendation: A
Level of agreement: A = 73%, B = 27%, C = 0%, D = 0%, E = 0%

Statement 15: Statin should be initiated in patients with MAFLD who meet criteria based on current recommendations
Level of evidence: I
Strength of recommendation: A
Level of agreement: A = 73%, B = 27%, C = 0%, D = 0%, E = 0%

Statement 16: ACE-i and angiotensin receptor blockers are the preferred first-line antihypertensive agents in MAFLD patients
Level of evidence: I
Strength of recommendation: A
Level of agreement: A = 91%, B = 9%, C = 0%, D = 0%, E = 0%

Statement 17: SGLT2-i should be considered for MAFLD patients with diabetes mellitus
Level of evidence: II
Strength of recommendation: B
Level of agreement: A = 55%, B = 45%, C = 0%, D = 0%, E = 0%

Statement 18: GLP1-RA should be considered for MAFLD patients with diabetes mellitus and/or obesity
Level of evidence: I
Strength of recommendation: A
Level of agreement: A = 91%, B = 9%, C = 0%, D = 0%, E = 0%

Pharmacological treatment for metabolic dysfunction-associated fatty liver disease

Statement 20: Pioglitazone at a dose of 30–45 mg/day may be considered for the treatment of steatohepatitis, but it has weight gain as an adverse effect, and may be associated with increased risk of bone fracture and bladder cancer
Level of evidence: II
Strength of recommendation: C
Level of agreement: A = 36%, B = 55%, C = 0%, D = 9%, E = 0%

Statement 21: Vitamin E at a dose of 800 IU/day may be considered for the treatment of steatohepatitis, but it may be associated with increased risk of prostate cancer and hemorrhagic stroke
Level of evidence: II
Strength of recommendation: C
Level of agreement: A = 45%, B = 45%, C = 9%, D = 0%, E = 0%

Bariatric surgery for metabolic dysfunction-associated fatty liver disease

Statement 22: MAFLD as a comorbidity should prompt consideration for bariatric surgery in patients with BMI ≥ 35 kg/m² who have failed lifestyle intervention
Level of evidence: II
Strength of recommendation: B
Level of agreement: A = 54%, B = 27%, C = 9%, D = 9%, E = 0%

(Continues)
values for advanced liver fibrosis. A FIB-4 score of \(<1.3\) can be used to exclude advanced liver fibrosis, while a score of \(1.3-2.67\) and \(>2.67\) indicates intermediate and high risk of advanced liver fibrosis, respectively.\(^{27}\) The specificity of the FIB-4 score is lower in patients \(\geq 65\) years old, resulting in a higher false positive rate. Therefore, a higher cutoff for low risk (i.e. FIB-4 \(<2.0\)) may be used to exclude advanced liver fibrosis for patients \(\geq 65\) years old.\(^{28}\) There are some proprietary blood-based tests for diagnosis of liver fibrosis, but these are more costly and not widely available.

The imaging-based tests include transient elastography (TE) and magnetic resonance elastography. Although magnetic resonance elastography has higher success rates and higher accuracy compared with TE, its application is limited by cost and availability.\(^{29}\) A comparison of the characteristics of FIB-4 and TE is shown in Table 3.\(^{30,31}\) Most noninvasive tests for liver fibrosis use two diagnostic thresholds and have a gray zone whereby the results are indeterminate. By performing sequential testing using two different noninvasive tests, the proportion of patients within the gray zone can be reduced. FIB-4 followed by TE has been shown to have high diagnostic accuracy, avoiding unnecessary referral to specialist and/or liver biopsy.\(^{32,33}\) Liver biopsy is considered the gold standard for the assessment of MAFLD, but it is limited by sampling variability, intra-observer and inter-observer variability, and a small risk of serious complications. Liver biopsy is best reserved for patients with discordant noninvasive tests for liver fibrosis, when another liver pathology is suspected or needs to be excluded, and when the diagnosis of steatohepatitis is uncertain or needs to be confirmed. Non-alcoholic steatohepatitis (NASH) is the more severe form of NAFLD that is defined histologically by the presence of significant hepatic steatosis, lobular inflammation, and hepatocyte ballooning. Liver biopsy is usually required in therapeutic trials for NASH.

In recent years, many novel scoring systems have been developed for NAFLD or MAFLD, with different diagnostic goals, including NASH,\(^{34}\) fibrotic NASH,\(^{35,39}\) significant fibrosis,\(^{40,41}\) advanced fibrosis or compensated advanced chronic liver disease,\(^{42,43}\) and high-risk varices.\(^{44,46}\) These scoring systems have different requirements (including the need for markers that are not be routinely performed and/or the use of online calculators) and diagnostic accuracies, and the position of these tests in day-to-day clinical practice is not yet well defined.\(^{47}\)
Metabolic dysfunction-associated fatty liver disease (MAFLD)

**Hepatic steatosis**
Based on imaging, noninvasive score, or histology

**Plus**

**Overweight or obese**
Defined as BMI ≥ 23 kg/m² in Asians

**Or**

**Type 2 diabetes mellitus**
According to widely accepted international criteria

**Or**

**Presence of ≥ 2 metabolic risk abnormalities**
- Waist circumference ≥ 90 cm in Asian men and ≥ 80 cm in Asian women.
- Blood pressure ≥ 130/85 mmHg or specific drug treatment.
- Plasma triglycerides ≥ 1.70 mmol/L or specific drug treatment.
- Plasma HDL cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women or specific drug treatment.
- Prediabetes (i.e. fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h post-load glucose levels 7.8 to 11.0 mmol/L, or HbA1c 5.7% to 6.4%).
- HOMA-IR ≥ 2.5.
- Plasma hs-CRP level > 2 mg/L.

**Figure 1** Definition of metabolic dysfunction-associated fatty liver disease (MAFLD). BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein.

**Table 3** Comparison of the characteristics of the fibrosis-4 score and transient elastography

|                        | Fibrosis-4 score | Transient elastography |
|------------------------|------------------|------------------------|
| Acceptability to patients | High             | High                   |
| Reproducibility         | Excellent        | Good                   |
| Availability            | Widely available | Limited                |
| Cost                    | +                | ++                     |
| Cutoffs for advanced liver fibrosis |                |                       |
| < 1.3: low risk         |                  | < 10 kPa: unlikely to have advanced liver fibrosis |
| 1.3–2.67: intermediate risk | 10–15 kPa: may have advanced liver fibrosis |
| > 2.67: high risk       | > 15 kPa: likely to have advanced liver fibrosis |
| Accuracy                | +++              | ++++                   |
| Failure/unreliable rates | < 1%             | 20%                    |
| Confounders             | High serum aminotransferase level, age, thrombocytopenia not related to liver cirrhosis | High serum aminotransferase level, cholestasis, focal liver lesion, obesity |

**Screening for more severe metabolic dysfunction-associated fatty liver disease.** The prevalence of steatohepatitis among NAFLD patients has been estimated to be 7%. Among consecutive NAFLD patients who underwent liver biopsy at a tertiary hospital, advanced liver fibrosis was found to be 21%. Because MAFLD is highly prevalent and only a small (but significant) proportion of MAFLD patients have more severe liver disease, it is essential that strategies are in place to ensure MAFLD patients receive appropriate triaging and management at all levels of the health system and within the constraints of resources. Integrating MAFLD into the broader NCD agenda and targeting high-risk groups to identify MAFLD patients with more severe liver disease who require specialist care are important strategies to achieve this. In this context, patients with T2DM represent an important target group. The prevalence of NAFLD in patients with T2DM has been estimated to be 50–72%. Moreover, T2DM is a risk factor for more severe NAFLD. In a study on T2DM patients using liver stiffness
measurement, the prevalence of advanced liver fibrosis was found to be 21%. Furthermore, among patients with liver stiffness measurement $\geq 8$ kPa who underwent a liver biopsy, majority were found to have steatohepatitis (83%) and some degree of liver fibrosis (87%).

A simple and clear assessment and referral pathway for MAFLD in patients with T2DM can be found in the 6th Edition of the Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus. Patients with T2DM can be screened for more severe liver disease using the FIB-4 score. A low score indicates that advanced liver fibrosis is unlikely, and the patient can remain in primary care or endocrinology, where they are best managed. On the other hand, a patient with intermediate or high score can be referred for liver stiffness measurement (Fig. 2). In a study on all patients age $> 35$ years with T2DM attending annual review at two primary care practices, the use of two-tier assessment of liver fibrosis, that is, FIB-4 followed by liver stiffness measurement in those with elevated FIB-4, significantly improved identification of advanced liver fibrosis. In another study to evaluate the performance of FIB-4-based screening strategy for the diagnosis of advanced liver fibrosis in patients with diabetes or prediabetes, the presence of cirrhosis and HCC was found to be significantly higher among patients with high FIB-4 than among patients with intermediate or low FIB-4. MAFLD patients with liver stiffness $\geq 10$ kPa may have advanced liver fibrosis and should be considered for referral to gastroenterology/hepatology. MAFLD patients with liver stiffness $\geq 15$ kPa should be considered for HCC screening (see section on Screening for hepatocellular carcinoma). The refined Baveno VI criteria used liver stiffness $< 8$ and $> 12$ kPa, instead of $< 10$ and $> 15$ kPa, for excluding and diagnosing compensated advanced chronic liver disease, and additional risk models were proposed for the larger proportion of unclassified patients using the lower cutoffs. However, the value of using the lower cutoffs is not entirely clear, and the use of an additional risk model would add complexity to the assessment. Furthermore, the diagnostic performance of the refined Baveno VI criteria as a second step for patients with indeterminate or high FIB-4 is unclear. Because of these considerations, the original Baveno criteria of $< 10$ and $> 15$ kPa have been used, although this may be revised when more data in support of the refined Baveno criteria become available. MAFLD patients with liver stiffness $\geq 20–25$ kPa are likely to have clinically significant portal hypertension and should be referred to gastroenterology/hepatology and be considered for variceal screening (see section on Screening for gastroesophageal varices).

**Lifestyle intervention is the cornerstone of management of metabolic dysfunction-associated fatty liver disease.** Westernized diet, characterized by highly processed foods, red meat, and soft drinks among others, has been associated with a greater risk of NAFLD. Instead, Mediterranean

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**Figure 2** Algorithm for screening for more severe metabolic dysfunction-associated fatty liver disease among patients with type 2 diabetes mellitus. HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.
diet, characterized by high fiber, seafood, and olive oil, reduces the disease activity and cardiovascular risk associated with NAFLD.58 Thus, studies have focused on low-fat diet, low-carbohydrate or very-low-carbohydrate diet, hypocaloric diet, and high-protein diet as dietary measures to control disease activity and risk factors of NAFLD.59,60 Such studies achieved variable successes in clinical outcomes due to heterogeneity in methodology. More recently, small-scale randomized studies have demonstrated beneficial effects of intermittent fasting and Ramadan fasting in NAFLD.61–63

An earlier meta-analysis has reported liver benefits of exercise as a stand-alone intervention, with reduction in liver fat, but not liver enzymes, irrespective of weight loss.64 A later meta-analysis supported the same findings.65 Mechanisms that underlie benefits of exercise on liver fats are not exactly known, but cardiorespiratory fitness is important.66 Moreover, resistance exercise is preferred to aerobic exercise in the presence of poor cardiorespiratory fitness.67 If exercise is combined with dietary therapy as lifestyle intervention, a network meta-analysis found aerobic exercise plus diet to be the most effective, although diet works better for liver enzymes, while exercise works better in improving insulin sensitivity and reducing body mass index.68 Similar benefits are seen in children and adolescents.69 Weight loss through lifestyle intervention (diet and exercise) has been found to improve histology, including a greater reduction in inflammation and fibrosis. For example, weight loss of ≥ 10% led to NASH resolution in 90% and fibrosis improvement in 45–81% of subjects enrolled in a comprehensive lifestyle program.70 Weight loss works for both obese and nonobese individuals, and the amount of weight loss needed to achieve liver benefits is less in the nonobese patients.71 While clinical benefits can be seen with any amount of weight loss, greater weight loss is associated with a greater disease improvement.72

Management of metabolic risk factors to reduce cardiovascular disease risk. Both MAFLD and CVD share common risk factors.73 NAFLD is associated with a twofold to threefold increased risk of prediabetes and diabetes,74 and hypertension.75 NAFLD is also associated with a proatherogenic dyslipidemic profile, that is, hypertriglyceridemia, low high-density lipoprotein cholesterol, increased small, dense low-density lipoprotein particles, and a state of subclinical inflammation.76 Meta-analyses have shown an association between NAFLD and subclinical atherosclerosis and increased cardiovascular events including in-stent restenosis,77–80 and the CVD risk is proportionate to the severity of NAFLD.81 Therefore, cardiovascular surveillance that includes early identification of cardiometabolic risk factors and institution of appropriate management is mandatory.12 Optimizing control of CVD risk factors remains the main strategy for treatment; these include a healthy and active lifestyle, smoking cessation, blood pressure management, diabetes optimization, and lipid lowering with statin therapy according to targets as outlined in guidelines for primary prevention of CVD.82 Statins reduce CVD risk and favorably impact mortality and should be initiated in MAFLD patients based on current recommendations.82 MAFLD does not increase the risk of serious liver injury from statins, and they are generally safe. However, statin therapy remains under-prescribed in this high-risk population.83 Statins should, however, be avoided in patients with decompensated cirrhosis. Blood pressure control to standard targets is recommended based on current guidelines. In general, angiotensin-converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) is the preferred first-line antihypertensive agent in patients with T2DM and in patients without T2DM who are < 55 years old; calcium channel blocker is the preferred first-line antihypertensive agent in patients without T2DM who are ≥ 55 years old.84 However, renin–angiotensin system activation is involved in the pathogenesis of cardiovascular pathologies in T2DM and MAFLD. Moreover, targeting the renin–angiotensin system may be beneficial in patients with NAFLD based on preclinical and preliminary clinical data.85,86 Furthermore, a meta-analysis has shown significant reduction in incidence of T2DM with the use of ACE-i or ARB, which may be of special clinical benefit for patients with hypertension and prediabetes or the metabolic syndrome.87 Therefore, ACE-i and ARB should be the preferred first-line antihypertensive agents in MAFLD patients.88,89 However, the use of ACE-i or ARB is relatively contraindicated in patients with decompensated cirrhosis.90

Weight loss, either by lifestyle alone or in combination with glucose-lowering drugs, by reversing insulin resistance and hyperglycemia, will result in decreased cardiometabolic risk while slowing or halting steatohepatitis disease activity, and hopefully, fibrosis.91 Two new classes of glucose-lowering agents, that is, sodium–glucose cotransporter-2 inhibitor (SGLT2-i) and glucagon-like peptide-1 receptor agonist (GLP1-RA), have proven cardiovascular benefits beyond glucose-lowering, with the added advantage of weight reduction. Current evidence with SGLT2-i in NAFLD has shown improvements in hepatic steatosis. In a randomized controlled trial of patients with NAFLD and T2DM, empagliflozin 10 mg daily for 20 weeks resulted in significantly greater reduction in hepatic steatosis as measured by magnetic resonance imaging proton density fat fraction compared with placebo.92 This reduction in steatosis was more than expected for the modest weight loss, suggesting additional weight-independent mechanisms at play. SGLT2-i has also been shown to result in improvements in steatosis and fibrosis based on TE.93 However, to date, there is no randomized control trial assessing the histological response to SGLT2-i, which is required for drug development for NASH, with evidence coming from only small, single-arm, open-label studies.94,95 Treatment with GLP1-RAs is associated with a reduction in hepatic steatosis and serum aminotransferase levels; this effect is proportionate to the degree of weight loss.96,97 Importantly, GLP1-RAs show promise in improving histological features of NASH and lesser fibrosis progression.98,99

Pharmacological treatment for metabolic dysfunction-associated fatty liver disease. No drug has been approved for use in NAFLD or MAFLD by regulatory bodies. However, several drugs have been endorsed by international liver societies and expert working parties. Pioglitazone at a dose of 30–45 mg/day has been found to improve the serum aminotransferases level and liver histology.100–104 Pioglitazone caused weight gain as a common adverse effect in these studies,100–103 and may be associated with increased risk of bone fracture.105 There has also been concern about bladder cancer, but this remained controversial.106–111 Vitamin E at a dose of 800 IU/day demonstrated improvement in serum

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Although vitamin E has not been consistently shown to result in overall improvement in the NAFLD activity score, it has been consistently shown to improve liver steatosis. However, vitamin E may be associated with increased incidence of hemorrhagic stroke and prostate cancer. Obeticholic acid, a farnesoid X receptor agonist, improved liver fibrosis in the interim analysis of a phase 3 trial. However, it was not granted temporary approval by regulatory body, citing that the benefit of the drug remained uncertain and did not sufficiently outweigh the potential risks. Pruritus and increased serum low-density lipoprotein cholesterol level were the most common adverse effects associated with the use of obeticholic acid. Metformin can lead to improvements in metabolic parameters and serum aminotransferase level, but failed to improve any pooled outcome in steatohepatitis. There is lack of large, well-designed, randomized control trial on the use of pentoxifylline, silymarin, and other compounds such as curcumin, ursodeoxycholic acid, and n-3 polyunsaturated fatty acids in the treatment of NAFLD. A meta-analysis of five randomized controlled trials found that pentoxifylline resulted in significantly greater reductions in serum aminotransferase levels and improvements in liver histology in NAFLD patients. A randomized controlled trial found that silymarin resulted in significantly greater fibrosis improvement in biopsy-proven NASH patients. However, further studies are needed. There are currently multiple other novel classes of drug being developed for the treatment of NASH, including peroxisome proliferator-activated receptor agonists, thyroid hormone receptor β agonists, dual glucagon-like peptide-1 and glucagon receptor agonists, and fibroblast growth factor 21, but the studies are ongoing, and the results are awaited.

**Bariatric surgery for metabolic dysfunction-associated fatty liver disease.** In a systematic review and meta-analysis of 32 cohort studies comprising 3093 liver biopsy specimens, bariatric surgery was found to be associated with resolution of steatosis, lobular inflammation, and hepatocyte ballooning in 66%, 50%, and 76%, respectively. However, 12% of patients developed new or worsening features of NAFLD, such as fibrosis. The occasional worsening of NAFLD may be related to the type of bariatric procedures (e.g. jejunal–ileal bypass and biliopancreatic diversion), malnutrition, and malabsorption. Despite this, there appear to be a clear net advantage of bariatric surgery for patients with NAFLD. This study also supports Roux-en-Y gastric bypass (RYGB) as the gold standard of bariatric procedures with most data showing safety for the liver. In another systematic review and meta-analysis that included 21 studies consisting of 2374 patients, bariatric surgery resulted in improvement of steatosis in 88% and improvement or resolution of steatohepatitis and fibrosis in 59% and 30%, respectively. Once again, the study revealed that the number of patients who had improvement in NAFLD after RYGB was higher than the average of all pooled studies. These strongly suggest that bariatric surgery should be considered as a treatment of NAFLD in patients with body mass index ≥ 35 kg/m² who have failed lifestyle intervention, with RYGB providing a greater positive impact on NAFLD histology.

**Screening for gastroesophageal varices.** Portal hypertension is a well-recognized sequelae of all chronic liver disease when they progress to cirrhosis. Observational clinical studies have shown that while most NAFLD patients who develop gastroesophageal varices have F3 or F4 fibrosis, a minority (approximately 20%) can develop portal hypertension with only F1 or F2 fibrosis. Studies using both Doppler ultrasound scanning and invasive hepatic vein portal gradient measurements in patients with NAFLD have demonstrated increased portal hypertension in cases with severe steatosis without or with only mild fibrosis. Factors predictive of clinically significant portal hypertension in NAFLD patients have been suggested to include a low platelet count (< 150 × 10^9/L) and splenomegaly on imaging. The Baveno VI Consensus Workshop reported that patients with a liver stiffness < 20 kPa and with a platelet count > 150 000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy, and that these patients can be followed up by yearly repetition of TE and platelet count. The Expanded-Baveno VI criteria using platelet count > 110 000 and liver stiffness < 25 kPa were found to increase the proportion of patients avoiding screening endoscopy without increasing the proportion of patients with missed varices needing treatment. This was confirmed in a subsequent meta-analysis; however, a slightly higher number of high-risk varices were missed.

**Screening for hepatocellular carcinoma.** The link between MAFLD-related cirrhosis and HCC is well-established globally. A retrospective study of NASH cirrhosis in the USA showed that HCC had a cumulative incident rate of 2.6% per year among 195 patients who were followed for a median of 3.2 years. In Japan, HCC was found to develop among 69 adults with NASH cirrhosis at an annual incidence rate of 2.3%. Based on cost-effectiveness considerations, the threshold benefit for screening for HCC has been estimated at a risk of > 1.5% per year. As such, patients with MAFLD-related cirrhosis clearly meet this threshold and would appear to benefit from the early detection of HCC via screening. When deciding to enter a MAFLD patient with cirrhosis into an HCC screening program, however, the clinician should take into account the patient’s age, overall health, functional status, and willingness to comply with screening assessment. Furthermore, if a patient with MAFLD-related cirrhosis is found to have HCC at screening, they should be an appropriate candidate for treatment. The modality and interval for HCC screening in MAFLD-related cirrhosis should be the same as for cirrhosis due to other etiologies.

Hepatocellular carcinoma has been recognized to develop in non-cirrhotic MAFLD patients. A systematic review and meta-analysis of 19 studies with 168 571 participants showed that non-cirrhotic NASH subjects were at greater odds of developing HCC than non-cirrhotic subjects with chronic liver disease due to other etiologies (odds ratio 2.61, 95% confidence interval 1.27–5.35, P = 0.009). However, the annual incidence rate of HCC was found to be only 0.04% in a large-scale study of Japanese MAFLD subjects. Similarly, a US-based community study calculated a low HCC annual risk of 0.02% among all subjects with NAFLD. Hence, experts have concluded that the risk...
estimate is likely to be too low to justify routine screening in MAFLD patients without cirrhosis. Noninvasive modalities for assessing liver fibrosis, such as TE, have become increasingly available in routine clinical practice. With the availability of noninvasive modalities, and the recognized association between advanced fibrosis and HCC in MAFLD patients, it would be reasonable to consider HCC screening in non-cirrhotic MAFLD patients who have been detected to have advanced fibrosis. The Baveno VI Consensus Workshop reported that liver stiffness > 15 kPa is highly suggestive of compensated advanced chronic liver disease, and these patients may be considered for HCC screening. The cost-effectiveness of this strategy however is unproven and will require further study.

Liver transplantation. End-stage liver disease due to cirrhosis (i.e. Child–Pugh score > 12) has a poor prognosis regardless of its etiology, with a median survival of < 6 months. Cirrhosis occurs in approximately 12% of patients with MAFLD and is a leading cause of liver-related mortality in this condition. Furthermore, HCC develops with advancing fibrosis and cirrhosis in NAFLD and is an additional cause for liver-related mortality in NAFLD. Liver transplantation provides an opportunity to reduce or even eradicate liver-related mortality in MAFLD. In many Western countries with an established transplantation service, NAFLD-related cirrhosis and HCC have now become the most common indication for liver transplantation. However, NAFLD patients requiring liver transplantation have been observed to have more morbidity after transplantation compared with other etiologies of liver disease. Despite the increased comorbidities in NAFLD, a meta-analysis showed that the 1- and 5-year survival rate after liver transplantation, at 85–90% and 70–80%, respectively, was similar between NASH and non-NASH patients. However, this meta-analysis reported a higher rate of death from CVD events or sepsis in posttransplant NASH versus non-NASH patients.

The important role of primary care in the management of metabolic dysfunction-associated fatty liver disease. Metabolic dysfunction-associated fatty liver disease and CVD are both manifestations of end-organ damage of the metabolic syndrome. A meta-analysis of 16 observational studies consisting of 34,043 patients with a median 7-year follow-up showed that patients with NAFLD had a higher risk of fatal and/or nonfatal CVD events than those without NAFLD. Patients with more severe NAFLD were also more likely to develop fatal and nonfatal CVD events. The strong association of MAFLD with the metabolic syndrome and CVD underscores the need for early identification and adequate management of cardiometabolic risk factors in patients with MAFLD in primary care. Patients aged ≥ 30 years old attending a primary care clinic should be assessed for the presence of metabolic syndrome components and they should be risk stratified using the 10-year general CVD Framingham Risk Score. The cutoff age of ≥ 30 years is recommended as the prevalence of cardiometabolic risk factors rises exponentially in Malaysian adults aged ≥ 30 years. If these patients are found to have obesity or T2DM or ≥ 2 metabolic syndrome components or elevated alanine aminotransferase (≥ 34 U/L) or in the high Framingham Risk Score category, they are recommended to have ultrasonography to screen for MAFLD. If they are found to have MAFLD, then the severity of the condition should be assessed using FIB-4 scoring (see section on Assessment). Patients with MAFLD and coexisting cardiometabolic risk factors should be targeted for aggressive lifestyle intervention and risk factor management. The ultimate management goals for these patients are to prevent the progression of MAFLD and to improve their cardiovascular outcomes. Only patients with more severe MAFLD (see sections on Assessment and Screening for more severe metabolic dysfunction-associated fatty liver disease) require referral to gastroenterology/hepatology, while MAFLD patients with less severe liver disease should remain in primary care or endocrinology where they are best managed. A comparison of screening and assessment strategies, as well as other aspects in the management of NAFLD, by five international or national organizations can be found elsewhere.

The important role of public health in metabolic dysfunction-associated fatty liver disease. The main risk factors for NCDs are tobacco use, unhealthy diet, harmful use of alcohol, and lack of physical activity. Although the major NCDs (diabetes, CVDs, and cancer) are often associated with older age groups, people from all age groups are vulnerable to NCD risk factors. Throughout all stages of life, there are ways in which these risk factors may be targeted to help prevent the development of NCDs later in life. A set of cost-effective and affordable policy options (best buys) already exist to tackle NCDs. MAFLD and T2DM could be considered two sides of the same coin. Nevertheless, several recent studies and reviews have found that the level of awareness among patients, healthcare providers, and health-related policymakers is low on MAFLD, contributing to overall low public health response to MAFLD globally. Like many low-income and middle-income countries, the prevalence of obesity and diabetes continues to increase in Malaysia. Rather than focusing on modifying the individuals’ behavior by increasing awareness and knowledge, we must now focus on systems and structural approach, incorporating policy and regulatory interventions, to strengthen the national response to the prevention and control of NCDs, including obesity and diabetes. Based on the pathophysiology of MAFLD, interventions to prevent obesity and diabetes in the population will have the co-benefit of reducing the burden of MAFLD. Increasing the awareness and knowledge of the various stakeholders on MAFLD would be the first logical step in advocating for this important health issue. The first target group would be healthcare professionals of two main groups, that is, healthcare professionals in primary care involved...
in managing patients living with NCDs, and healthcare professionals involved in creating clinical practice guidelines and policies related to the prevention and management of NCDs, particularly those outside of the hepatology community. The primary strategy is to incorporate MAFLD into existing NCD-related programs and activities rather than taking a silo approach. The second target group will be the general population. The overall level of health literacy among Malaysians is low. There is broadly consistent evidence that comprehension of health information and advice among individuals with low health literacy can be improved through communication modifications and other mixed-strategy interventions. However, there is paucity of evidence in such interventions in Malaysia, particularly for MAFLD. Recently, the Economic Intelligence Unit and the European Association for the Study of Liver International Liver Foundation have worked together to launch a report as a global call to action and to highlight priorities in shaping and delivering more comprehensive responses to MAFLD.

**Figure 3** Algorithm for screening for metabolic dysfunction-associated fatty liver disease (MAFLD) among adults ≥ 30 years old in primary care. Refer to relevant sections of the text, including "Lifestyle intervention is the cornerstone of management of metabolic dysfunction-associated fatty liver disease," "Management of metabolic risk factors to reduce cardiovascular disease risk," and "Pharmacological treatment for metabolic dysfunction-associated fatty liver disease" for details on the management of patients diagnosed with MAFLD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; US, ultrasound.

**Conclusion**

The panel recognized the high and increasing prevalence of the MAFLD and the consequent anticipated increase in liver-related complications and mortality from the disease. Nevertheless, CVD is the leading cause of mortality in MAFLD patients; therefore, CVD risk assessment and management is important and should be incorporated into the management of MAFLD patients. A simple and clear liver assessment and referral pathway was agreed upon, so that patients with more severe MAFLD can be linked to gastroenterologist/hepatologist care, while patients with less severe MAFLD can remain in primary care or endocrinology, where they are best managed. Lifestyle intervention is the cornerstone in the management of MAFLD, and its importance cannot be overemphasized. The panel provided a consensus on the use of statin, ACE-i, or ARB, SGLT2-i, glucagon-like peptide-1 agonist, pioglitazone, vitamin E, and metformin, as well as recommendations on bariatric surgery, screening for gastroesophageal varices and HCC, and liver transplantation in MAFLD patients. The panel concurred that increasing the awareness and knowledge of the various stakeholders on MAFLD and incorporating MAFLD into existing NCD-related programs and activities are important steps. The input from a multidisciplinary panel reflects the need for a concerted multidisciplinary approach to tackle the disease. This consensus document represents early steps, but an important milestone, for pushing the MAFLD agenda forward to achieve more widespread engagement of all stakeholders.

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