Changing clinical management of NAFLD in Asia

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Abstract
Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease, affecting approximately 25% of the world’s population. Recently, because of the sedentary lifestyle and overnutrition resulting from urbanisation, the burden of NAFLD has rapidly increased in many Asian countries. Currently, the prevalence of NAFLD in Asia is approximately 30%, as is the case in many Western countries. In Asia, the prevalence and presentation of NAFLD vary widely across regions because of the substantial diversity in race, socioeconomic status and living environment. Furthermore, the dual aetiology of fatty liver, particularly with viral hepatitis in Asia, makes it complex and challenging to manage. Because Asians are likely to have central adiposity and insulin resistance, approximately 7%-20% of non-obese Asians with body mass indexes of less than 25 kg/m² are estimated to have NAFLD. Accumulating evidence indicates that NAFLD is associated with various extrahepatic comorbidities such as cardiovascular disease, chronic kidney disease, malignancy, in addition to liver-specific complications. Therefore, NAFLD should be managed as a multisystem disease in conjunction with metabolic syndrome. Lifestyle modification remains the basis of NAFLD management, but few patients can achieve adequate weight loss and maintain it long term. While various pharmacological agents are in phase 3 trials for steatohepatitis, Asian patients are underrepresented in most trials. This article reviews the epidemiological trends, clinical features, optimal assessment and current management practices for NAFLD in Asia.

Keywords
FIB-4, hepatocellular carcinoma, liver fibrosis, metabolic syndrome, non-alcoholic steatohepatitis, non-obese NAFLD
Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide. The clinical spectrum of NAFLD ranges from the benign form of simple steatosis to the more active form of non-alcoholic steatohepatitis (NASH), eventually leading to cirrhosis and hepatocellular carcinoma. NASH has become the second leading indication of liver transplantation and the third leading cause of hepatocellular carcinoma in the United States, and its incidence has increased substantially globally.

Asia is the largest continent with 4.5 billion people, which constitutes approximately 60% of the total world population. The region is a heterogeneous area with substantial variations in race, socioeconomic status and living conditions. It consists of approximately 50 countries, including the most populous countries, China and India, as well as less populated island nations. Recently, this diversity has been accompanied by rapid urbanisation and transition from agrarian diets to more energy-dense foods, resulting in an increased prevalence of metabolic disorders. A recent systematic review estimated that the overall prevalence of NAFLD in Asia was 29.6%, which increased significantly over time. According to the World Health Organisation (WHO) Global Health Estimates in 2015, 63% of global deaths because of liver disease occur in the Asia-Pacific region. While viral hepatitis is prevalent in Asia, the burden of NAFLD is gradually increasing. For example the incidence of non-viral hepatocellular carcinoma (HCC), which is related to lifestyle factors including obesity and diabetes, is increasing in Japan. Thus, NAFLD is the major aetiology of chronic liver disease after the control of viral hepatitis in Asia.

NAFLD is a liver phenotype of the metabolic syndrome and is closely associated with various metabolic abnormalities and obesity. Accumulating evidence indicates that NAFLD should be viewed as a systemic disease that may affect extrahepatic organs, such as cardiovascular diseases, chronic kidney diseases and malignancy, and should not be treated as a liver-specific disease. Notably, cardiovascular diseases and extrahepatic malignancy outweighed all liver-related morbidities as the leading mortality in NAFLD patients. The severity of liver fibrosis has been identified as the most important predictor of morbidity and mortality in patients with NAFLD. In addition, a recent nationwide study in Sweden has demonstrated that the accumulation of hepatic fat per se may increase mortality.

There are several Asia-specific issues related to NAFLD. Because Asians are more likely to have central fat deposition despite having a lower body mass index (BMI), NAFLD can often be diagnosed in non-obese individuals. The prevalence of NAFLD among non-obese individuals (BMI < 25 kg/m²) is estimated to be 7%-20% in Asia. In addition, chronic viral hepatitis is highly prevalent in Asian countries, and the co-occurrence of fatty liver and viral hepatitis is often problematic. Recent studies have demonstrated that fatty liver is the most common cause of abnormal liver function in patients with viral hepatitis, especially among those with virus under control.

Given the increasing medical and socioeconomic impact of NAFLD on Asians, we now have to develop strategies to address this emerging health issue. In this review, the characteristics and changing impact of NAFLD in Asia was introduced and appropriate management strategies were discussed.

## 2 | CLINICAL FEATURES OF NAFLD IN ASIA

### 2.1 | Definitions

NAFLD is the excessive fat accumulation in the liver, which is associated with insulin resistance, and is defined by the presence of steatosis in >5% of hepatocytes according to histological analysis. Its diagnosis requires the exclusion of secondary causes of fat accumulation in the liver such as excessive alcohol consumption.

The American Association for the Study of Liver Disease (AASLD) defined significant alcohol consumption as 210 g weekly for men and 140 g weekly for women, and the European Association for the Study of the Liver (EASL) similarly defined it as a daily alcohol consumption of ≥30 g for men and ≥20 g for women. Most Asian countries have strict criteria for significant alcohol consumption (≥140 g weekly for men, ≥70 g weekly for women) to avoid overlap with alcohol-related liver disease (ALD), while recommended daily limits of ≥30 g for men and ≥20 g for women are used in Japan. Although the acceptable alcohol consumption varies by region, there is no intrinsic meaning in determining the amount of consumed that distinguishes NAFLD from ALD, given the differences in sex or individual ability to metabolise alcohol.

To address the above issues, a clear and reproducible definition of NAFLD is necessary for clinical practice and epidemiological studies. The current established exclusive definition of NAFLD requires evidence of hepatic steatosis by either imaging or histology and absence of other causes of hepatic fat accumulation. A consensus among international experts recently proposed changing the name of NAFLD to metabolic (dysfunction)-associated fatty liver disease.
(MAFLD). The proposed criteria for MAFLD diagnosis are based on the evidence of hepatic steatosis in addition to one of the following: overweight/obesity, presence of type 2 diabetes mellitus (T2DM) and components of metabolic syndrome, which is independent of alcohol consumption or other concomitant liver diseases. The concept of MAFLD reflects the underlying pathogenesis, eliminates the exclusive nomenclature of NAFLD and allows for the coexistence of other chronic liver diseases. MAFLD is more practical for identifying patients with fatty liver disease with a high risk of disease progression. The Asian Pacific Association for the Study of the Liver (APASL) provides guidelines for the treatment of ‘MAFLD’ ahead of others.

2.2 | Epidemiology

Trends of overall prevalence

The prevalence of obesity (BMI ≥30 kg/m²) in Asian countries, based on the WHO Global Health Observatory in 2016, is shown in Figure 1. Given that the global prevalence of obesity is 13.1%, the prevalence tends to be higher in Western Asia and lower in Eastern Asia. There is clear evidence of ethnic differences in terms of NAFLD prevalence, with the highest among Latinos and lowest among African Americans, and Caucasian and Asian ethnicities having an intermediate prevalence. In a recent meta-analysis, the prevalence of NAFLD was reported as follows: global, 25.2%; Asia, 27.4%; the Middle East, 31.8%; North America, 24.1%; South America, 30.5%; Europe, 23.7% and Africa, 13.5%. In relation to Asia, the prevalence of NAFLD was reported as follows: global, 25.2%; Asia, 27.4%; the Middle East, 31.8%; North America, 24.1%; South America, 30.5%; Europe, 23.7% and Africa, 13.5%. In relation to the high obesity rates in Western Asia (Figure 1), the prevalence of NAFLD is highest in the Middle East. In addition, the estimated global prevalence of NAFLD has increased from 20.1% in 2000-2005 to 23.8% in 2006-2010 and 26.8% in 2011-2015. As in Western countries, because of the growing cases of obesity, T2DM and other components of metabolic syndrome, the prevalence of NAFLD in Asian countries is rising. A recent systematic review and meta-analysis revealed that the prevalence of NAFLD in Asia has also increased significantly over time: 25.3% in 1999-2005, 28.5% in 2006-2011 and 33.9% in 2012-2017. The overall NAFLD incidence rate in Asia was 50.9 per 1000 person-years, with the highest rate in mainland China (63.0 per 1000 person-years) and lowest rate in Japan (29.0 per 1000 person-years). A recent modelling analysis of eight countries using a Markov model to forecast NAFLD disease burden projected that total NAFLD cases will grow modestly (0%-30%) and that NASH prevalence will increase more (15%-56%), while liver mortality and advanced liver disease will more than double as a result of an aging or increasing population between 2016 and 2030, with the highest growth in China as a result of urbanisation. Figure 2 shows the prediction of the prevalence of NAFLD in Asia–Pacific and Western countries based on a Markov model. While the prevalence of NAFLD in the United States is outstanding, the prevalence in Asian and Western countries is not much different and is expected to increase by 2030.

Regional differences in prevalence

The prevalence of NAFLD varies substantially according to ethnicity, region, target group, or overtine because of the tremendous variations in genetic background, nutritional status, physical activity and lifestyle in Asian countries. For instance the national prevalence of NAFLD in China was 29.2%, with a heavier disease burden among the Uygur (46.6%) and Hui (53.8%) ethnic groups. In addition, the prevalence is higher in the northwest region of mainland China (33.8%) and in Taiwan (39.9%), which are regions with relatively high gross domestic products per capita, and lower in the southwest region (19.3%). Meanwhile, the overall NAFLD prevalence in South Korea was 30.3%, with a slight increase from 29.0% to 31.0% over an approximately 10-year period. In a longitudinal study from Japan, the prevalence of NAFLD has increased from 12.6% before 1990 to 30.3% in 1998. According to a systematic review from Japan, the overall NAFLD prevalence was 25.5%, which varied by region and increased over time, and is forecasted to reach 39.3% in 2030 and 44.8% in 2040.

In some countries, the prevalence varies greatly by region. In rural India, characterised by traditional lifestyles and diets, the prevalence of NAFLD is substantially low at 10%, while it is similar to that in other Asian countries in urban areas as 16%-32%. Furthermore, reports from Sri Lanka indicated a higher proportion of affected people in urban areas (up to 34.5%) than in rural areas (17.9%). In contrast, a nationwide study from Bangladesh reported that the overall prevalence of NAFLD was 33.9%, with no difference between urban and rural populations. Differences in the prevalence of NAFLD have also been found among different ethnic groups. A multi-ethnic study in Malaysia found that the prevalence of NAFLD among Malays and Indians was consistently higher than that among Chinese individuals.

2.3 | Risk factors

Metabolism

Risk factors for NAFLD in Asians are similar to those in Westerners, which include overweight, T2DM, components of metabolic syndrome, insulin resistance, dietary factors, sedentary lifestyle and sarcopenia. In detailed metabolic studies, Asians tend to have higher insulin resistance and greater liver fat content and visceral adiposity than Caucasians, despite having an equal or lower BMI. These studies indicated that Asians are likely to have central fat deposition, metabolic disorders and NAFLD despite having a lower BMI.

Genetic background

In addition to lifestyle, genetic predisposition is known to have an important influence on the development and progression of NAFLD. A genome-wide association study reported that the 1148M single nucleotide polymorphism (rs738409 C > G) of the patatin-like phospholipase domain containing 3 protein (PNPLA3) as a susceptibility gene...
involved in the development of NAFLD. The PNPLA3 minor allele contributes to the development of NAFLD, fibrosis progression and hepatocarcinogenesis, regardless of racial differences. The percentage of the G risk allele carriers is higher in East Asia than in the Western countries, which may confer much susceptibility to NAFLD especially in East Asian individuals. In addition to PNPLA3, several other genetic polymorphisms have been shown to be involved in NAFLD pathogenesis. For example, a meta-analysis revealed that phosphatidylethanolamine N-methyltransferase (PEMT) rs7496A (V175M) is involved in the development of NAFLD in East Asians. The pathogenesis of NAFLD involves a complex combination of common genetic variants that are either dependent or independent of race.

Others

In recent years, genetic analysis of the gut microbiota has progressed, and its relationship with various diseases has become clear.
than 30 kg/m² resistance is higher in Asians than in Westerners, despite a BMI of less than 25 kg/m². The prevalence of visceral obesity and insulin resistance is higher in Asians than in Westerners, despite a BMI of less than 25 kg/m². The prevalence of NAFLD in non-obese subjects is particularly high in Asian countries (7%-20%), which tends to be higher than that in some countries, including Japan and Korea. It is necessary to educate Asians that a small amount of weight gain can cause metabolic disorders and eventually worsen NAFLD in some non-obese individuals.

In a recent study, despite having a lower BMI than other groups, Asians had more severe steatosis and lobular inflammation and higher grades of ballooning compared to other ethnicities. Furthermore, NAFLD in non-obese individuals is associated with higher mortality than in obese individuals. In contrast, another histological study from Hong Kong did not suggest a higher incidence of severe NAFLD or adverse clinical events in the non-obese population. The severity of NAFLD in non-obese patients is a matter of debate and further study is needed.

### 2.5 Co-occurrence with viral hepatitis

#### Chronic hepatitis C

Abnormalities in lipid metabolism in the liver are well-known features of chronic hepatitis C (CHC). Indeed, hepatic steatosis usually occurs in approximately 50% of patients with HCV infection, and steatohepatitis has been documented in 4%-10% of HCV-infected individuals. For example pathological findings of the liver biopsy in Taiwanese patients with HCV genotype 1 or 2 infection revealed that approximately 30% of patients had hepatic steatosis, which was significantly associated with the degree of liver fibrosis. For most patients with CHC, steatosis is usually associated with the presence of metabolic derangement and insulin resistance, whereas HCV genotype 3 is known to have a direct impact on hepatic steatosis. HCV-associated hepatic steatosis contributes to the progression of underlying liver fibrosis and the development of HCC by accelerating liver necroinflammation and oxidative stress. Mechanistically, the core protein of the virus promotes insulin resistance by inducing the degradation of insulin receptor substrate-1. Epidemiological and in vitro studies have demonstrated that HCV directly promotes insulin resistance, steatosis, fibrosis progression, and the clearance of the virus is associated with the improvement or disappearance of insulin resistance. Viral eradication with new oral direct antiviral agents (DAAs) in CHC patients who originally have significant steatosis reduces hepatic fat deposition as defined by the controlled attenuation parameter (CAP). On the other hand, genotype 3-associated viral steatosis was found to decrease the response to DAAs. In summary, hepatic steatosis commonly occurs in CHC patients and significantly affects the progression of liver disease and the therapeutic response.

#### Chronic hepatitis B

The number of patients with chronic hepatitis B (CHB) and fatty liver is increasing rapidly, with a reported rate of 14%-59%. A meta-analysis has shown that the prevalence of hepatic steatosis in CHB is similar to that in the general population (29.6%) and lower than...
that in CHC patients.\textsuperscript{72} Although numerous cross-links have been found between HBV infection and fatty liver, the impact of hepatic steatosis on the natural history of CHB remains debatable. An inverse relationship between serum HBV DNA and hepatic steatosis was observed,\textsuperscript{73} and moderate to severe hepatic steatosis was associated with a higher likelihood of HBsAg seroclearance.\textsuperscript{74} On the other hand, severe hepatic steatosis has been linked with severe liver fibrosis in patients with CHB,\textsuperscript{75} and any degree of hepatic steatosis was associated with fibrosis progression in patients with CHB.\textsuperscript{76} Accordingly, obesity, diabetes and metabolic syndrome may accelerate the progression of liver disease in CHB and synergistically induce the development of cirrhosis or hepatocellular carcinoma.\textsuperscript{77} Thus, although the relationship between hepatic steatosis and CHB is complex and unresolved, HBV infection itself seems to protect against steatosis, metabolic syndrome and insulin resistance, while the presence of hepatic steatosis is associated with increased risk of disease progression of CHB. A recent review demonstrated that coexisting fatty liver did not influence the response to oral nucleos(t)ide analogues or interferon therapy.\textsuperscript{78}

### 3 ASSESSMENT AND MANAGEMENT OF NAFLD

#### 3.1 Detection of NAFLD and high-risk patients

**Screening for fatty liver**

The detection of hepatic steatosis is key to the diagnosis of NAFLD. In clinical settings, abdominal ultrasonography (US), a non-invasive and inexpensive method, is usually used to detect hepatic steatosis. Given the close relationship between NAFLD and metabolic syndrome, screening for NAFLD using US should be considered in at-risk populations, such as patients with overweight/obesity, T2DM and metabolic syndrome. According to a meta-analysis comparing US findings with histopathological findings, abdominal US has a sensitivity of 85% and specificity of 94% for the diagnosis of moderate to severe fatty liver.\textsuperscript{79} However, characteristic US findings in patients with NAFLD, such as bright liver, vascular blurring and deep attenuation, are operator-dependent; moreover, their diagnostic accuracy is lower in patients with morbid obesity or hepatic steatosis of less than 20%.\textsuperscript{80} Therefore, a significant number of NAFLD patients with 5%-20% hepatic fat content in the liver can be missed on US imaging alone.

The CAP measurement by transient elastography (TE) for quantifying liver fat via evaluation of US attenuation in the liver is more sensitive than US alone and is able to detect histopathological grade 1 steatosis (5%-33% fat content in the liver) with sensitivity/specificity ratio of 69%/82%.\textsuperscript{81} In addition, as a continuous variable, it has the advantage of being used in monitoring changes in hepatic steatosis over time. Several Asian studies demonstrated that CAP and liver stiffness measurements (LSM) are useful method for NAFLD screening in T2DM patients; the prevalence of significant hepatic steatosis and advanced fibrosis based on TE were 60%-70% and 20% respectively.\textsuperscript{82,84} MRI-based techniques such as MRI proton density fat fraction (MRI-PDFF) and proton magnetic resonance spectroscopy (MRS) are considered the gold standard for quantifying liver fat.\textsuperscript{85} However, CAP and MRI-based techniques often lack availability owing to the need for expensive equipment. New diagnostic methods for B-mode imaging, such as attenuation imaging (ATI), attenuation coefficient (ATT) and ultrasound-guided attenuation parameter (UGAP), which can be installed on the US, have recently been introduced and validated mainly in Asian countries.\textsuperscript{86-88}

Fundamentally, it is still controversial whether there is a need to detect NAFLD patients with hepatic steatosis of as low as 5% because fibrosis is the most important factor in NAFLD progression.\textsuperscript{10-12} Recently, however, it has been reported that even simple fatty liver without fibrosis is associated with increased total mortality.\textsuperscript{73} In addition, reports in health check-up cohorts from South Korea have shown that elevated CAP is associated with metabolic disorders.\textsuperscript{89} Therefore, in terms of detecting metabolic abnormalities and early intervention, it may be worthwhile to detect mild fatty liver, and further validation is needed.

**Enclosing high-risk populations**

Because it is costly to conduct surveillance for hepatic complications in all NAFLD patients, it is necessary to include NASH patients who are at risk for disease progression. Among the various histological features of NAFLD, the degree of liver fibrosis has the strongest correlation with future liver-related morbidity and mortality.\textsuperscript{10-12} Liver biopsy is still the gold standard for assessing the stage of liver fibrosis and establishing the histological diagnosis of steatohepatitis; however, it is limited by its invasiveness and intra-/inter-observer variability in pathological interpretations. Furthermore, given the global epidemic of NAFLD, routine evaluation by liver biopsy as the first method of diagnosis and staging of NASH is not appropriate and should be limited to cases that require differentiation from other diseases. Therefore, various non-invasive tests have been proposed for NASH staging, mainly focusing on the assessment of significant fibrosis.

The American College of Gastroenterology and Chronic Liver Disease Foundation panel (ACG-CLDF panel) reported that FIB-4 is probably the most studied simple non-invasive algorithm that can be used for risk stratification in clinical practice.\textsuperscript{90} FIB-4 is an index for the prediction of liver fibrosis according to age and levels of platelets, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The FIB-4 threshold values of <1.30 and >2.67 can be used to predict the absence or presence of advanced fibrosis respectively.\textsuperscript{91} There are many reports demonstrating that FIB-4 has been shown to easily stratify patients with significant liver fibrosis in NAFLD patients.\textsuperscript{92,93} Since the specificity of FIB-4 declined with age, a lower cutoff of 2.0 is recommended for those aged ≥65 years, which improves specificity to 70% without adversely affecting sensitivity.\textsuperscript{94} Other non-invasive tests such as the NAFLD Fibrosis Score (NFS)
and the Enhanced Liver Fibrosis (ELF) score have also been proposed as indicators of fibrosis in NAFLD. It is reasonable to use these simple fibrosis scores as an initial assessment in primary care.

LSM is an alternative biomarker for liver fibrosis. TE is the most evidence-based LSM device and is widely used in Asia. At a cut-off value of <8 kPa, TE had a 94%-100% negative predictive value for detecting significant fibrosis. TE is also recommended in the current guidelines for the management of NAFLD. Furthermore, a recent multicentre study revealed that the combination of AST with CAP and LSM by TE (the FAST score) achieved a c-index of 0.74-0.95 for the detection of steatohepatitis with significant fibrosis. Shear wave elastography (SWE) is another elastography technique that can be performed using a conventional ultrasound probe. The diagnostic performance of SWE for advanced liver fibrosis is similar to that of TE. Although the quality criteria for fibrosis assessment have not yet been confirmed, SWE may be an option for LSM. Magnetic resonance elastography (MRE) is also considered a clinically useful method for evaluating liver fibrosis stage. A report from Japan demonstrated that MRE showed even higher accuracy in comparison with TE, but its wider application is limited by its high cost and lack of availability.

New approaches are also being developed such as the stratification of liver fibrosis using methylation patterns of plasma cell-free DNA. In addition, machine learning-based risk stratification using blood data, LSM values and pathological images has been developed, and new diagnostic methods using artificial intelligence are expected in the future.

3.2 Surveillance for NAFLD-related complications

Liver-related complications

Recent studies have noted a rising trend in NAFLD-related HCC in Asian countries. According to a systematic review and meta-analysis conducted in Asia, the annual incidence of HCC in Asian NAFLD patients is 1.8 per 1000 person-years. A large retrospective cohort study of 6508 Japanese patients with NAFLD suggested that the incidence of new HCC was 0.043% during a median follow-up of 5.6 years, whereas the incidence rate of HCC in patients with significant fibrosis was 3.26% during the follow-up period. Compared with other liver diseases, the yearly cumulative incidence of HCC in the NAFLD-cirrhotic population is comparable to that in the CHC cirrhotic population. Thus, although the incidence of HCC is generally low in NAFLD, patients with advanced fibrosis are at high risk for HCC development and should be carefully monitored. Accordingly, the current regional guidelines recommend HCC surveillance only in NAFLD patients with cirrhosis.

Liver fibrosis is the most important predictor of mortality in patients with NAFLD, with the highest risk of hepatocarcinogenesis among those with cirrhosis. LSM provides a reliable assessment of the severity of liver fibrosis and can be used to diagnose cirrhosis in patients with NAFLD in clinical settings. Patients with LSM >15 kPa are highly suggestive of compensated advanced chronic liver disease and should be considered for HCC surveillance. LSM is also useful for determining the prognosis of NAFLD patients. However, LSM is not available in all clinics and hospitals, and it is necessary to identify patients with a high possibility of liver fibrosis.

**FIGURE 3** Screening and surveillance of NAFLD patients. Recommended algorithm for diagnosing, evaluating and managing NAFLD patients. HBV, hepatitis B virus; HCV, hepatitis C virus; NFS, NAFLD fibrosis score; TE, transient elastography; MRE, magnetic resonance elastography; SWE, shear wave elastography; HCC, hepatocellular carcinoma; BMI, body mass index.
progression by fibrosis scores such as FIB-4 or NFS and refer them to a specialised hospital. In a study from Japan comparing 239 T2DM patients with non-viral HCC and 3277 T2DM patients without HCC, the FIB-4 index was an outstanding predictor of HCC development.\textsuperscript{114} In terms of safety, availability, and cost-effectiveness, ultrasound is the most practical screening modality for HCC, and a 6-month screening interval is recommended.\textsuperscript{22,27} Because it is difficult to visualise the HCC in NAFLD patients by US because of obesity, simultaneous measurement of serum biomarker is also recommended.\textsuperscript{115} Two multi-centre Japanese study groups revealed that des-gamma-carboxy prothrombin (DCP) had a higher positive rate than alpha foetoprotein in NAFLD patients.\textsuperscript{116,117}

Although more studies are required to determine the benefit and cost-effectiveness of HCC surveillance in Asian NAFLD patients, there seems to be no disagreement that patients with NASH-related cirrhosis should undergo HCC surveillance, because screening all NAFLD patients regularly for HCC is impractical. However, a small study from Japan suggests that NAFLD-related HCC often develops in the absence of cirrhosis.\textsuperscript{118} In addition, NAFLD-related HCC is more often detected at a later tumour stage.\textsuperscript{6} Further accumulation of evidence from Asia is needed to develop an optimal surveillance method for NAFLD-related HCC.

**Extrahepatic diseases**

Because of the close association between NAFLD and metabolic syndrome, it is not surprising that cardiovascular diseases are the most important complication, followed by extrahepatic cancer.\textsuperscript{8,13} Therefore, it is important to perform cardiovascular risk assessment and screening for other metabolic syndrome components and malignancy in patients with NAFLD.

In Asian contexts, NAFLD is an independent risk factor for coronary atherosclerosis, T2DM and chronic kidney disease.\textsuperscript{119-121} In addition, the risk of colorectal adenoma and carcinoma in NAFLD patients is 1.5- and 3-fold higher, respectively, than in patients without NAFLD.\textsuperscript{122} Based on these reports, NAFLD may increase the risk of cardiovascular disease, chronic kidney disease and colorectal neoplasm in Asian patients; thus, risk assessment of patients with these diseases should be performed individually. However, there are not enough prospective data to develop optimal screening algorithms, and there is a need to define Asian patients with NAFLD who are at high risk of developing metabolic complications.

### 3.3 Management of NAFLD and related diseases

#### Lifestyle intervention

Lifestyle modification, including dietary change and structured exercise intervention, remains the first-line therapy for NAFLD. Weight loss is the most important intervention for NAFLD, and studies in Asian populations support a 7%-10% weight loss goal, although there is evidence that up to 40% of patients with NAFLD can improve with a 3%-5% weight loss.\textsuperscript{123,124} However, there are no data from Asians to support the resolution of NASH through lifestyle modification, and further research is warranted.

According to the latest expert view of the American Gastroenterological Association (AGA), clinically significant weight loss generally requires a hypocaloric diet targeting 1200-1500 kcal/day or a reduction of 500-1000 kcal/day from baseline.\textsuperscript{125} Patients with NAFLD tend to consume energy-dense foods rich in sugar-sweetened beverages, saturated fats and cholesterol, but are deficient in micronutrients found in fresh fruits, fibre, green vegetables and omega-3 polyunsaturated fatty acids.\textsuperscript{126} Thus, NAFLD patients should follow the Mediterranean diet, minimise saturated fatty acid intake specifically in red and processed meat, and limit or eliminate consumption of commercially produced fructose.\textsuperscript{125} However, there is no strong evidence to support any particular dietary approach for the improvement of NAFLD. A recent meta-analysis of controlled isocaloric feeding studies with constant dietary protein and varying ratios of carbohydrate to fat suggests that the rate of change in body fat between diets was so small that it was physiologically meaningless.\textsuperscript{127} According to a report from Hong Kong, a hypocaloric diet should also be implemented for non-obese NAFLD patients with a lower target weight-loss threshold of 3%-5%, as they experience histological benefits similar to those of obese NAFLD patients.\textsuperscript{128}

The type, intensity and amount of exercise that are optimal for improving NAFLD remains debatable. The expert panel on AGA recommended that regular physical activity should be considered for patients with NAFLD, with a target of 150-300 min of moderate-intensity, or 75-150 min of vigorous-intensity aerobic exercise per week, and that resistance training exercise can be complementary to aerobic exercise and can have independent effects on NAFLD.\textsuperscript{125} Accordingly, a randomised clinical trial of 220 Chinese individuals confirmed that vigorous and moderate exercise were equally effective in reducing intrahepatic triglyceride content, and the effect appeared to be largely mediated by weight loss.\textsuperscript{129} In addition, a recent systematic review suggested that both aerobic and resistance exercise reduce hepatic steatosis equally in NAFLD, with less energy consumption in resistance exercise.\textsuperscript{130} Thus, resistance exercise may be more feasible than aerobic exercise for NAFLD patients with poor cardiorespiratory fitness or for those who cannot tolerate or participate in aerobic exercise. Given that sarcopenia is associated with both NAFLD and NAFLD-related advanced fibrosis or hepatocarcinogenesis in Asian patients,\textsuperscript{31,132} specialised dietary and activity management will be beneficial against sarcopenic obesity.

#### Pharmacological treatment

While lifestyle management is effective and should be encouraged, not all patients are able to adhere to diet and exercise. Therefore, pharmacological therapy is necessary in some patients.
However, there are no approved drugs for the treatment of NAFLD and NASH.

Oxidative stress is an important mechanism of hepatocellular injury and disease progression in patients with NASH. Vitamin E has been reported to be effective in improving liver histology in patients with NASH.\(^{133}\) In addition, a recent propensity score matching analysis revealed that vitamin E reduces the risk of death or transplantation and liver decompensation in NASH patients with severe fibrosis.\(^{134}\) However, the development of prostate cancer in relatively healthy males aged >50 years may be a concern for vitamin E.\(^{135}\)

Several anti-diabetic agents have been reported to be beneficial for patients with NAFLD. Ligands of peroxisome proliferator-activated receptors (PPARs) improve insulin sensitivity and hepatic fatty acid oxidation and have anti-inflammatory effects. In a randomised controlled trial, pioglitazone, a PPAR\(_y\) agonist, was shown to improve hepatic steatosis, ballooning and inflammation in patients with NASH.\(^{136}\) Weight gain, oedema and the development of bladder cancer are potential concerns with pioglitazone. Glucagon-like peptide-1 (GLP-1), a peptide hormone secreted from the gut, stimulates insulin secretion and suppresses glucagon secretion. Liraglutide, a GLP-1 receptor agonist, has been reported to reduce body weight and improve hepatic histology, including fibrosis.\(^{137}\) Another GLP-1 analogue, semaglutide, has also been reported to be effective in NASH patients and is currently in phase 3 trials, including in Asian countries.\(^{138}\)

Importantly, GLP-1 receptor agonists have been shown to reduce cardiovascular deaths, myocardial infarction and stroke in diabetic patients.\(^{139}\) Sodium-glucose cotransporter 2 inhibitors (SGLT2i) attenuates glucose reabsorption in the proximal tubule, leading to plasma glucose reduction. SGLT2i has been reported to reduce hepatic fat content,\(^{140}\) and several pilot studies in Asia have found a significant reduction in transaminase activity, body weight and liver histology including steatosis and fibrosis in NAFLD patients.\(^{141,142}\) Among a variety of SGLT2i, dapagliflozin has already entered the phase 3 trial.

Statins did not show any beneficial effects on liver histology but reduced cardiovascular morbidity in patients with NAFLD.\(^{143}\) Thus, despite the poor quality of evidence, the APASL guidelines concluded that the use of statins in NAFLD may be justified because of their potential to prevent the adverse outcomes of cardiovascular conditions associated with NASH.\(^{27,144}\)

Several drugs, including obeticholic acid, cenicriviroc, elafibranor, belapetin, resmetirom, aramchol, dapagaliflozin and semaglutide are now in phase 3 trials.\(^{145}\) However, because of the marked differences between Asians and Caucasians, Asian patients have been underrepresented in NASH drug trials. In fact, obeticholic acid is now in phase 3 trial worldwide, but in phase 2 trial in Japanese NASH patients, pruritus appeared in about 50% of patients and there was no significant improvement in liver fibrosis; therefore, drug development was halted in Japan and South Korea.\(^{144}\) Thus, future studies should involve more Asian patients to inform clinical practice.

### Bariatric surgery

Obese patients who have not responded to lifestyle modification and medical intervention should be encouraged to be referred to an obesity specialist, and bariatric surgery or gastric ballooning can be considered. By improving obesity and diabetes, bariatric surgery reduces liver fat and is likely to improve all histological lesions of NASH, including fibrosis. Although there are no randomised controlled trials comparing the effects of bariatric surgery on NAFLD with any other therapies, numerous retrospective and prospective observational cohort studies have investigated the potential utility of bariatric surgery for NAFLD. According to a recent systematic review, resolution of hepatic steatosis was demonstrated in >75% of patients, and improvements in ballooning and lobular inflammation were consistently observed.\(^{146}\) In addition, a long-term follow-up study of 102 obese Japanese patients undergoing bariatric surgery demonstrated that liver fat accumulation and visceral fat areas were significantly improved at 1 year after surgery, and the decrease in BMI, body fat percentage, and basal metabolic rate prolonged for at least 5 years.\(^{147}\) In 37 Asian patients receiving annual TE following bariatric surgery, the mean LSM reduced significantly from baseline values of 9.8-6.8 kPa at 5 years after operation.\(^{148}\) The latest APASL guidelines recommend that bariatric surgery can be considered for NAFLD only if the following are met: (a) presence of other indications such as BMI >30 kg/m\(^2\) (for Asian people) and (b) absence of cirrhosis with high perioperative risk.\(^{27}\)

In addition to conventional bariatric procedures, the usefulness of endoscopic bariatric and metabolic treatments (EBMT) such as intragastric balloon and endoscopic sleeve gastroplasty is beginning to attract attention. EBMT is safer and less invasive than bariatric surgery, making it an attractive option for patients with NAFLD who have other obesity-related complications. EBMT has been shown to improve parameters associated with NAFLD in the short term and should be further evaluated in randomised controlled trials.\(^{149,150}\)

### 4 | CONCLUSION

In Asia, where urbanisation is progressing, the burden of NAFLD has rapidly increased over the past decade because of the westernisation of diets and sedentary lifestyles. Because of the great heterogeneity in ethnic groups, cultures, environments, economics and health systems, the prevalence, presentation and underlying mechanism of NAFLD vary widely across Asian countries. In addition, the dual aetiology of the disease, particularly with viral hepatitis, is common; thus, the NAFLD management has to be complex and challenging in Asia. NAFLD is a major cause of chronic liver disease and HCC, as well as a contributor to various systemic complications, such as cardiovascular disease and extrahepatic cancer, because of its close association with metabolic disorders. Therefore, NAFLD should be managed as a multisystem disease and the ultimate goal of treatment is to prevent liver-related complications and extrahepatic damage. Because fibrosis is the major determinant of all NAFLD...
complications, it is imperative to include patients with severe fibrosis using various biomarkers and imaging modalities for non-invasive assessment of fibrosis, and patients with cirrhosis should be considered for surveillance of HCC. Lifestyle modification remains the cornerstone for managing NAFLD, but it is expected that pharmacological therapy will soon be added to the treatment options. Because Asian patients have been underrepresented in current drug trials for NAFLD, it is necessary to consider the inclusion of different ethnic groups in the future. Finally, awareness of NAFLD remains poor in most Asian countries, and public education about the disease needs to be strengthened to improve its prevention and management.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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