Title: TASL-TSOC Taiwan Position Statement for the Management of Metabolic Dysfunction-Associated Fatty Liver Disease and Cardiovascular Diseases

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Short title: Taiwan position statement of MAFLD and CVD

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List of abbreviations: MAFLD, Metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; T2DM: type 2 diabetes mellitus; HCC, hepatocellular carcinoma; CVD, cardiovascular diseases; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; CAD, coronary arterial disease; VTE, venous thromboembolism; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MRE, magnetic resonance elastography; FIB-4, Fibrosis-4; LSM, liver stiffness measurement; MI, myocardial infarction; HF, heart failure; HfpEF, preserved ejection fraction HF; LV, left ventricular; AF, atrial fibrillation; EASL, European Association for the Study of the Liver; APASL, Asia-Pacific Association for the Study of the Liver; PPAR-γ, peroxisome proliferator-activated receptor gamma; EBMT,
endoscopic bariatric and metabolic therapies; GLP-1RA, glucagon-like peptide-1 receptor agonists; DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT-2i, sodium-dependent glucose cotransporter-2 inhibitors; OCA, Obeticholic acid; CHB, chronic hepatitis B; CHC, chronic hepatitis C.
Abstract

Metabolic dysfunction associated fatty liver disease (MAFLD) is an increasingly important and common liver disease worldwide. The diagnosis of MAFLD is based on the presence of steatosis on image/histology/serum markers accompanied with presence of at least one of the three metabolic features that include overweight/obesity, type II diabetes mellitus, and metabolic risk factors. MAFLD is not only a liver disease but also a contributing or related factor of cardiovascular diseases (CVD) which lead to the major etiology of morbidity and mortality in patients with MAFLD. Hence, understanding the association of MAFLD and CVD, surveillance and risk stratification of MAFLD in patients with CVD, and current status of management of MAFLD are urgently needed for both hepatologist and cardiologist. The purpose of this Taiwan position statement is to review literature and provide suggestions that cover from epidemiology, etiology, risk factors, risk stratification, non-pharmacological intervention, and potential drug treatment of MAFLD, especially focusing on association with CVD.

Keywords: MAFLD, cardiovascular diseases, position statement, Taiwan.
Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) and nonalcoholic fatty liver disease (NAFLD) are significant global health issues. In the general population, the incidence of MAFLD ranges from 15% to 30% [1]. The prevalence of NAFLD is approximately 55% in patients with type 2 diabetes mellitus (T2DM) and up to 80% in those with obesity [2, 3]. The rates of T2DM, hypertension, low high-density lipoprotein cholesterol, and hypertriglyceridemia were 9%, 8.4%, 9.6%, and 23.6%, respectively, in patients with biopsy-proven NAFLD [4].

The prognosis of hepatic outcomes in MAFLD is associated with the severity of liver fibrosis [5]. Several studies have demonstrated a significantly higher incidence of cirrhosis, hepatocellular carcinoma (HCC), and liver-related death in patients with NAFLD and fibrosis [6, 7]. Evidence has shown that cardiovascular events were increased in MAFLD patients [8]. The latest international consensus statements on the association between MAFLD and the risk of cardiovascular diseases (CVD), which developed by the experts from six continents, indicates that MAFLD increased cardiovascular events and mortality than patients without MAFLD. In addition, CVD as the leading cause of death in patients with MAFLD [9].

Metabolic comorbidities are the leading risk factors associated with a cardiovascular event and liver-related mortality in MAFLD. T2DM intensifies the risk of CVD and chronic kidney disease due to increased insulin resistance (IR) [10]. The incidence of T2DM and hypertension also increased with the severity of MAFLD [11]. A meta-analysis revealed that T2DM, low high-
density lipoprotein, hypertriglyceridemia, and hypertension were significantly associated with a high risk of severe liver diseases, including cirrhosis, HCC, and liver-related mortality [12].

**Position statement 1: MAFLD can lead to hepatic and extra-hepatic morbidity and mortality.**

**Definition and diagnosis of MAFLD**

In 2020, the international expert consensus recommended changing the term NAFLD to MAFLD. Compared to NAFLD, MAFLD adequately reflects similar pathophysiological mechanisms and cardiometabolic risk factors of fatty liver disease and cardiovascular disease, such as metabolic dysfunction, obesity, insulin resistance, and dyslipidemia [13]. MAFLD is diagnosed based on histological, imaging, or biomarker evidence of hepatic steatosis in patients with overweight/obesity, T2DM, or presence of at least two metabolic risk factors (Figure 1) [13].

**Diagnostic tools**

Liver biopsy remains the gold standard for diagnosing and assessing histological features in NAFLD. However, the invasiveness of liver biopsy limits its routine use in clinical practice [14]. Ultrasound-based modalities are widely adopted as first-line screening tools for hepatic steatosis, showing excellent performance in detecting moderate and severe steatosis, with a sensitivity and specificity of 84.8% [95% confidence interval (CI): 79.5-88.9%] and 93.6% (95% CI: 87.2-97.0%) [15]. Ultrasound-based transient elastography enables quantitative evaluation of liver stiffness and steatosis. The area under receiver operative characteristic curve (AUROC) of
Ultrasonic controlled attenuation parameter (CAP) for the detection of steatosis reached to 0.95 [16]. Magnetic resonance imaging-derived proton density fat fraction is the most sensitive noninvasive method for quantifying hepatic steatosis with a AUROC of 0.95 [17]. Several noninvasive serum biomarkers are available for hepatic steatosis evaluation, including the fatty liver index [18], hepatic steatosis index [19], NAFLD liver fat score [20], and lipid accumulation product [21], with moderate-to-good diagnostic performance (sensitivity: 86-93%, specificity: 40-71%) [22].

Position statement 2: MAFLD is defined as the presence of hepatic steatosis plus metabolic derangements.

Position statement 3: Abdominal ultrasonography is a useful and convenient tool for identifying hepatic steatosis.

MAFLD pathogenesis and risks

In 1998, the two-hit theory was proposed for NAFLD pathogenesis, involving increased fat accumulation and inflammatory cascade in the liver [23]. IR in the adipose tissue, muscle, and liver is a key factor in the first hit [24, 25], and is associated with energy imbalance caused by excessive caloric intake. Hepatic steatosis is caused by an imbalance between liver lipid storage and clearance, leading to excessive triglyceride-rich droplets in hepatocytes. As the second hit, the inflammatory cascade is overly activated by inflammatory cytokines, adipokines,
lipotoxicity, endoplasmic reticulum stress, oxidative stress, and mitochondrial dysfunction [26-31]. Unresolved liver steatosis can progress to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis and HCC in severe cases [32, 33]. Recent research has identified genetic factors, epigenetics, and gut microbiota dysbiosis as other MAFLD-associated molecular and metabolic elements [34-36], leading to the hypothesis of a “multiple-hit” patho-mechanism [37].

Figure 2 shows the pathophysiologic interaction between MAFLD and CVD. The “multiple hits” involved in MAFLD pathogenesis all converge to a vicious cycle that promotes atherosclerosis and CVD development and progression [38, 39]. In patients with MAFLD, the severity of hepatic steatosis and fibrosis correlated with the coronary atheroma burden and atherosclerosis [40, 41]. Moreover, inflammation and IR in MAFLD may increase platelets and coagulation factors, which are associated with coronary arterial disease (CAD) [42] and venous thromboembolism (VTE).

Metabolic disorders and genetic origins participate in MAFLD and CVD development [43, 44]. Multiple hits stemming from the interactions of genetic and environmental risk factors of MAFLD and CVD contribute to MAFLD and CVD concurrence [43, 44] (Fig ).

**Lifestyle factors**

In genetically susceptible individuals, sedentary lifestyle, high sugar/saturated fat diet, metabolic derangements, and gut dysbiosis initiate and advance MAFLD [44]. Lifestyle changes, including limited intake of dietary fructose, are highly recommended [43].
**Metabolic factors**

Risk factors for MAFLD development include male sex, advancing age, obesity, IR, T2DM, and hyperlipidemia, which are linked to gut dysbiosis [45]. IR is significantly involved in MAFLD pathogenesis and its progression to NASH, with T2DM strongly linking MAFLD, NASH, and CVD [46]. Cholecystectomy was reported as an independent risk factor of MAFLD, attributable to altered bile acid enterohepatic circulation [47].

**Genetic factors**

Several genetic variants (*PNPLA3*, *TM6SF2*, and *MBOAT7*) increased NAFLD susceptibility [48]. However, a Mendelian randomization analysis indicated no causal relationship between the NAFLD-associated *PNPLA3* variant and CVDs. Among NAFLD-related genetic variants, *TM6SF2* appears to be protective against VTE, whereas *MBOAT7* may be unfavorable [49].

**Others**

Other risk factors include steatogenic drugs, male sex, and infections. COVID-19, hepatitis C, acquired immunodeficiency syndrome, *Helicobacter pylori*-induced peptic ulcer, and periodontitis caused by *Bacteroidetes, Candidatus saccharibacteria, Firmicutes*, and *Proteobacteria* worsen MAFLD [50].

Position statement 4: MAFLD and CVD share similar risk factors that exacerbate the progression of both conditions. Identifying these risk factors is crucial for effective management and treatment.
Screening strategy for MAFLD in patients with CVD

Who should be screened?

Patients with MAFLD having T2DM, central obesity, sedentary lifestyle, and metabolic syndrome have a higher risk of advanced fibrosis [51], whereas fibrosis severity was associated with cardiovascular risk in patients with steatosis or steatohepatitis [52]. Thus, MAFLD surveillance should be considered in patients with CVD. For patients with subclinical atherosclerosis and multiple risk factors of CVD, MAFLD screening may be considered [53].

| Position statement 5: MAFLD should be considered in patients with CVD, irrespective of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. |

How to screen?

The screening tool should effectively identify patients with MAFLD having advanced liver fibrosis. Transient elastography is more cost-effective than magnetic resonance elastography (MRE) for detecting advanced liver fibrosis, although its sensitivity and specificity are compromised [54]. Thus, in patients suspected of advanced fibrosis or those with inconclusive sonography and transient elastography findings, MRE should be considered. Indirect serological biomarkers include AST, AST-to-platelet ratio index, Fibrosis-4 (FIB-4), NAFLD fibrosis score,
and AST-to-ALT ratio. Direct serological biomarkers include enhanced liver fibrosis test and FibroMeter NAFLD test [53].

**Fibrosis assessment**

Fibrosis assessment is crucial for patients with MAFLD. Primary care practitioners, gastroenterologists, cardiologists, and neurologists should screen for advanced fibrosis in patients with MAFLD and CVD. FIB-4 may be more practical for being a straightforward calculation based on widely available, simple, and cheaper test. Since no single measurement or threshold value has high sensitivity and specificity rates (≥80%), a sequential algorithm starting with FIB-4 as a first-line test followed by liver stiffness measurement (LSM) was recommend. Figure 4 shows the algorithm recommended for MAFLD screening and liver fibrosis assessment among patients with CVD. The recommended algorithm is based on both clinical evidence and expert consensus. A meta-analysis showed that sequential combination of FIB-4 scores of <1.3 and ≥2.67 followed by LSM of <8.0 and ≥10.0 kPa could rule-in and rule-out advanced fibrosis with sensitivity of 66% (95% CI, 63%–68%) and specificity of 86% (95% CI, 84%–87%), respectively [55]. Another study demonstrated that patients with FIB-4 <1.3 were at low risk of HCC (0.05-0.21/1000 PY), while those > 2.67 were at high risk of HCC (1.9-4.56/1000 PY) (Cholankeril G, et al. J Hepatol 2022). This sequential algorithm minimizes unnecessary tests and referrals, facilitates timely identification of advanced fibrosis, and improves cost-effectiveness [53]. Therefore, several clinical guidelines recommended similar
algorithms, such as AGA's NASH Clinical Care Pathway [56], AACE/AASLD Clinical Practice Guideline for NAFLD [57], and JSH-JSG clinical practice guidelines for NAFLD/NASH 2020 [58].

| Position statement 6: Determination of disease severity by noninvasive markers, preferably FIB-4, is recommended. |

Identification and management of cardiovascular comorbidities in patients with patients MAFLD

There is increasing scientific and clinical interest in the link between MAFLD and CVD risk, and increasingly evidence supports that patients with MAFLD have increased risk of CVD morbidity and mortality [59]. Advanced fibrosis and cirrhosis are associated with higher liver-related death rates in patients with MAFLD [60], whereas mild fibrosis predisposes patients with MAFLD to risks of cardiovascular events and non-hepatic malignancies [61]. MAFLD serves as an indicator of high cardiovascular risk and contributes to CVD development and and could be considered as an important risk factor for CVD [62-64].

**MAFLD and atherosclerotic CVD (ASCVD)**

Approximately 10% of patients with MAFLD in primary care facilities have CAD [65]. Chinese and Taiwanese studies have suggested that MAFLD is associated with a higher risk of cardiovascular events and subclinical CAD, and the ASCVD burden is substantial in patients
with MAFLD [40, 65, 67]. The extent of steatosis increases coronary atheroma burden in MAFLD [68], whereas liver fibrosis markers are associated with CAD progression [41]. MAFLD is also associated with worse outcomes in patients undergoing coronary artery bypass grafting and percutaneous coronary angioplasty [69-71]. In myocardial infarction (MI), concomitant MAFLD exacerbates the risk of cardiovascular events and deaths [72]. A large biobank analysis reported that MAFLD was associated with cardiovascular and all-cause mortality [73]. Patients with both non-ST-segment elevation MI and MAFLD have higher risk of premature ventricular complexes and ventricular tachycardia [74].

**MAFLD and arterial hypertension**

High blood pressure may predict MAFLD onset independently of conventional risk factors [75]. A recent study from Taiwan revealed that patients with fatty liver have a higher risk of prevalent and incident hypertension and/or diabetes, and the risk increased with the severity of fatty liver [12]. A study suggested that effective hypertension control reduces MAFLD risk [76].

**MAFLD and heart failure (HF)**

In patients with preserved ejection fraction HF (HFpEF), the prevalence of MAFLD is approximately 50% [77]. Among patients with MAFLD, the left ventricular (LV) filling pressure is high, along with a more fibrotic LV myocardium and worse global longitudinal strain [78]. Increased hepatic sinusoid resistance and venous return impairment can lead to
high-normal cardiac output and high LV mass, characteristic of the obstructive HFpEF.

MAFLD may affect cardiac metabolism [79, 80], and fibrosis may promote the formation of spontaneous portosystemic shunts, altering arterial blood flow and systemic vascular resistance in HFpEF associated with cirrhosis and advanced liver disease [81].

**MAFLD and cardiac arrhythmias**

The incidence of QT interval prolongation is higher in patients with MAFLD and T2DM [82]. Ventricular arrhythmias, atrioventricular blocks, and atrial fibrillation (AF) are more frequently observed in MAFLD [74, 83]. Liver fibrosis is linked to adverse atrial remodeling and recurrent AF in patients with MAFLD after catheter ablation [84]. The Rotterdam study reported an association between AF and liver stiffness but not steatosis [85, 86]. The conflicting results may be attributed to the heterogeneous patient backgrounds.

**MAFLD and thromboembolic diseases**

MAFLD is an independent risk factor for VTE [87], and 81% of patients with VTE had MAFLD [88]. The levels or activities of Von Willebrand factor, factors VII–IX, XI, and XII [89], and plasminogen activator inhibitor-1 are high in patients with MAFLD [90]. Patients with NASH have higher anti-cardiolipin immunoglobulin G levels than those with MAFLD [91], suggesting the potential association of thrombotic risks with liver fibrosis. Obesity is also a VTE-associated risk factor in MAFLD [92, 93]. However, the potential benefits of interventions such as bodyweight reduction, aerobic exercise, bariatric surgery, and
anticoagulation medications on VTE risk require further investigation [94, 95].

**Position statement 7: MAFLD increases the risk of hepatic-related and cardiovascular events, and it should be considered a risk enhancer of CVD.**

**Screening and management strategy of cardiovascular risks in patients with MAFLD**

In MAFLD, CVD risk screening and early management are recommended [96, 97]. A regional validated risk calculator can be used to stratify the 10-year ASCVD or CAD risk in these patients. In patients with high CAD or angina risk, stress or imaging tests for CAD could be considered [98]. In the presence of risk factors, such as hypertension, obesity, T2DM, and advanced age, referral for echocardiography and natriuretic peptide testing should be considered in symptomatic cases [99]. An early referral to the cardiology specialists is highly recommended in symptomatic cases or patients with MAFLD having high cardiovascular risk [98, 99].

**Position statement 8: In patients with MAFLD, cardiovascular risk screening and management are recommended. In symptomatic or high-risk cases, referral and multidisciplinary care involving cardiologists are highly recommended.**

**Linking care of MAFLD and CVD: Decrease risks of CVD and liver cancer/HCC**

*Nonpharmacological management of MAFLD/NAFLD*
**Lifestyle modification**

Lifestyle interventions that reduce bodyweight are critical for NAFLD [100]. Approximately 5% weight loss is needed to improve liver steatosis and >10% weight loss for both liver steatosis and fibrosis [101, 102]. However, sustained weight loss is challenging. Approximately 21.2% of patients with initial weight loss regained weight after a median follow-up of 32.3 months [103]. Thus, a multidisciplinary approach involving physicians, psychologists, behavioral therapists, dietician/nutritionists, patient family, patient support group, and digital support is pivotal for lifestyle interventions [104, 105].

**Diet control**

Excessive intake of calories, saturated fats, refined carbohydrates, and sugar-sweetened beverages are common in the diets of patients with NAFLD and obesity [106-109]. Dietary macronutrients are involved in NAFLD pathogenesis [110], such as fructose that promotes hepatic steatosis and inflammatory signaling [106] and polyunsaturated fatty acids that exhibit anti-inflammatory effects [111]. The current guidelines of the European Association for the Study of the Liver (EASL) and Asia-Pacific Association for the Study of the Liver (APASL) recommend a hypocaloric diet (500–1000 kcal deficit) [112, 113]. Several trials support changing the amount and type of dietary carbohydrate/fat or adopting the Mediterranean diet, as both strategies improved hepatic steatosis regardless of weight loss [114, 115]. Furthermore, the Mediterranean diet is effective in primary CVD prevention [114, 116]. Moreover, regular
coffee consumption is associated with a lower risk of NAFLD and liver fibrosis [117, 118].

Exercise

Exercise improves MALFD/NAFLD through various mechanisms, such as the upregulation of several signaling pathways, particularly pathways involving the peroxisome proliferator-activated receptor gamma (PPAR-γ) [119, 120]. Exercise may also suppress mammalian target of rapamycin complex 1 signaling, further improving MAFLD/NAFLD [121]. Exercise training is beneficial for hepatic and cardiometabolic function in patients with MAFLD/NAFLD [122], with improvements in vascular stiffness and endothelial dysfunction that lower the cardiovascular risk [123]. Vigorous exercise improved the histological findings of NASH, particularly in reducing fibrosis [124]. Regular and moderate exercise for at least 150 min per week or increasing activity levels for >60 min per week ameliorates MAFLD/NAFLD [125]. Aerobic exercise, i.e., continuous and rhythmic activities requiring the use of large muscles, is the primary training modality assessed in NAFLD exercise studies. By contrast, the benefit of resistance training remains controversial because of heterogeneity in training intensity and protocol. A combination of aerobic and resistance training is expected to outperform either exercise modality [126, 127]. Alternative activities such as yoga, Pilates, and Tai-chi have demonstrated their benefits in pilot studies [128-130]. Updated guidelines of both the American Association for Study of Liver Disease (AASLD) and EASL strongly recommend any type of sustained individualized exercise for patients with MAFLD/NAFLD [125].
Bariatric surgery

Bariatric surgery leads to a sustained weight loss of up to 30% in patients with obesity, along with improvements in T2DM, NASH/NAFLD, morbidity, and mortality [131, 132]. Patients undergoing bariatric surgery showed NASH resolution and fibrosis regression 5 years postoperatively [133]. Bariatric surgery also reduced CVD risk and CVD-associated morbidity in patients with obesity and NAFLD [134, 135]. In addition, endoscopic bariatric and metabolic therapies (EBMT) improved aminotransferases and decreased NAFLD activity score in patients with obesity and NAFLD [133, 13, 137]. However, well-designed prospective studies are warranted to assess the hepatic or cardiovascular benefits of EBMT for patients with NAFLD and obesity.

Position statement 9: Lifestyle modification constitutes the basic and important approach.

Position statement 10: Bodyweight reduction is the cornerstone of the nonpharmacological management of MAFLD; however, long-term bodyweight control remains an issue of concern.

Pharmacological intervention of MAFLD

While no drugs are approved for MAFLD, treatments of metabolic conditions closely
associated with MAFLD may potentially reverse IR, thereby ameliorating steatohepatitis and preventing fibrosis. Although lifestyle modification and weight loss are recommended as first-line interventions and effectively reduced steatosis, inflammation, and fibrosis, they are often unsuccessful [101]. Therefore, pharmacological therapy may address the gap in inhibiting MAFLD progression. Table 1 shows the summary of investigated drugs for MAFLD. The use of approved anti-diabetic drugs has been investigated in NASH, including biguanides, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-dependent glucose cotransporter-2 inhibitors (SGLT-2i), and PPAR agonists [138, 139]. Novel agents for NASH/NAFLD are being evaluated in different phases of clinical development, and their mechanism of action include participation in de novo hepatic lipogenesis, mitochondrial fatty acid oxidation, inflammation, cell injury, collagen deposition, and fibrinolysis [140].

**Vitamin E**

Oxidative stress plays a key role in NASH pathogenesis; thus, vitamin E is justifiable as a therapeutic agent for NASH. Randomized controlled trials (RCTs) have been conducted in nondiabetic adults, children, and adolescents with biopsy-proven NASH [141-143]. Pooled analyses have demonstrated that vitamin E significantly decreased aminotransferases and improved histological characteristics of NASH, except for liver fibrosis [143-145]. In an RCT in patients with co-existing T2DM and NASH, 18 months of vitamin E supplementation
improved steatosis histologically [146]. The role of vitamin E in NASH and advanced fibrosis or cirrhosis remains inconclusive.

Safety concerns of vitamin E should be considered. All-cause mortality was higher in patients taking high-dose (>800 IU/day) vitamin E [147]. In addition, vitamin E increases risk of HF in patients with vascular disease or T2DM [148] and prostate cancer in healthy men [149]. Although a high vitamin E diet was associated with a reduced stroke risk [150], it may increase hemorrhagic stroke significantly [151]. In summary, vitamin E at a daily dose of 800 IU may be considered in nondiabetic adults with biopsy-proven NASH. The associated risks and benefits should be fully discussed with each patient before initiating therapy.

**Bile acids**

AASLD or EASL does not recommend ursodeoxycholic acid, a natural dihydroxy bile acid, is for the treatment of NAFLD or NASH because of insufficient evidence showing beneficial effects on liver histology.

Obeticholic acid (OCA) is an analog of bile acid chenodeoxycholic acid and a potent farnesoid-X-receptor agonist. Despite the primary endpoints being met in OCA’s phase 2 FLINT trial and phase III REGENERATE trial, US FDA raised safety concerns regarding pruritus, high LDL levels, and limited change in cardiovascular risk [152, 153]. Consequently, OCA is not recommended for off-label use to treat NASH by AASLD, EASL, and APASL [154-156].

**Lipid-lowering agents**
Statins may lower LDL and cardiovascular risk in patients with NAFLD and NASH without liver decompensation. However, according to AASLD and EASL, the treatment does not benefit or harm liver disease [154-156]. Current studies present mixed findings on the role of PCSK9 inhibitors in managing early stages of NAFLD, emphasizing the need for extensive long-term research to ascertain their efficacy and safety profile [157].

**Glucose-lowering agents**

**Metformin**

Metformin is a biguanide with mild insulin-sensitizing effect and is traditionally the first-line therapy for T2DM. In NAFLD unresponsive to lifestyle modification, biochemical improvement was observed after metformin treatment [158]. Hepatic fat reduction with weight loss was found in a proportion of patients with NASH treated with metformin [159]. In an open-label trial, metformin in combination with rosiglitazone further improved liver histology in patients with NASH [160]. Unfortunately, a meta-analysis of metformin trials did not reveal liver disease activity or fibrosis stage improvement [161-163]. Overall, insufficient evidence supports the routine use of metformin in patients with NASH [163].

**Pioglitazone**

Pioglitazone improves liver function, decreases hepatic fat, and improves NASH characteristics in clinical trials and systemic review [164, 165], potentially regardless of diabetic status [166]. Despite this, weight gain was observed after pioglitazone therapy, whereas data on other
thiazolidinediones are limited [167]. In patients with T2DM and NASH, pioglitazone reduced CVD events [168].

**GLP-IRA**

GLP-IRA is a new class of anti-diabetic agents for T2DM that improves weight loss, glycemic control, and liver enzymes by activating the gut-derived incretin pathway [169]. GLP-1RAs also have beneficial reno- and cardiovascular effects on T2DM [170, 171]. In the phase 2 LEAN RCT, the histological findings showed that patients with T2DM receiving liraglutide for 48 weeks had a higher rate of NASH resolution and reduced progression of fibrosis compared with placebo [172]. In the phase 2 trial of semaglutide, a 72-week treatment resulted in a significantly higher percentage of NASH resolution compared with placebo in patients with biopsy-proven NASH and F1–F3 liver fibrosis. However, the semaglutide trial did not show benefits in improving the fibrosis-stage [173]. In a systematic review and meta-analysis of patients with T2DM and NAFLD, GLP-1RAs were found effective in improving intrahepatic, visceral, and subcutaneous adipose tissue fat, liver function, body mass index, waist circumference, and glucose/lipid profiles but did not improve liver fibrosis markers such as FIB-4 and NAS [174]. The main adverse events included mild-to-moderate gastrointestinal discomfort such as poor appetite, constipation, diarrhea, and hypoglycemia, which could resolve within a few weeks. Despite few small-scale studies reporting that GLP-1RAs is associated with NASH resolution and fibrosis regression, more large-scale studies are needed.
SGLT-2i

SGLT-2i are anti-diabetic agents with extended benefits and are approved for reducing adverse outcomes in nondiabetic patients with HF and chronic kidney diseases [175, 176]. An observation study revealed that add-on 50 mg ipragliflozin for 45 weeks improved glycemic control and normalized ALT levels in patients with T2DM and NAFLD unresponsive to incretin-based therapy [177]. SGLT-2i also improves glycemic control and liver function in patients with T2DM and NAFLD, and weight loss was exclusive to SGLT-2i [178, 179]. The efficacy of canagliflozin, dapagliflozin, and empagliflozin in treating NAFLD or NASH have been investigated in RCTs involving patients with T2DM with or without NAFLD and found hepatic benefits including aminotransferase, steatosis, and/or fibrosis improvements associated with SGLT-2i [174, 180-182]. Overall, SGLT-2i exhibits the positive effects on hepatic steatosis in meta-analyses; however, the effect of SGLT-2i on hepatic fibrosis requires further investigation [183-185].

DPP-4i

DPP-4 inhibition reduces glucagon levels, delays gastric emptying, stimulates insulin release, and augments pancreatic beta-cell regeneration [186]. DPP-4i was suggested to alleviate T2DM-related microvascular complications [187]. Early interventions with sitagliptin in patients with T2DM may have long-lasting reno- and islet-protective effects [188]. It remains conflicting whether sitagliptin increases the risk of
hospitalization for HF [189, 190]. Sitagliptin was favorable for lowering CVD incidence in patients with T2DM [191] A 12-week sitagliptin therapy did not reduce hepatic steatosis or fibrosis in overweight patients with T2DM [192], nor did it reduce aminotransaminase levels in patients with NASH [193]. Vildagliptin exhibited a CVD risk comparable to sitagliptin [194] and prevented the progression of T2DM-related CVD by improving LDL heterogeneity [195].

Position statement 11: Regressing hepatic steatosis/fibrosis and improving cardiovascular/metabolic outcomes are the optimal goals of pharmacological intervention of MAFLD.

MAFLD/CVD and other hepatitis

The rates of co-existing MAFLD and chronic hepatitis B (CHB) or chronic hepatitis C (CHC) is 30%–70%, and MAFLD occurs in 13.6%–59.3% of patients with CHB [196]. An inverse association was reported between hepatitis B virus replication and hepatic steatosis [197], as fat deposition in hepatocytes and related increasing inflammation status may inhibit or suppress viral replication [198, 199]. Contrarily, patients with MAFLD and CHB tend to experience accelerated liver disease progression and have more liver-related complications, and the death rate is higher than that in patients with CHB or MAFLD [200]. More studies are needed to explore the effect of co-existing CHB on CVD risk in patients with MAFLD.
Liver steatosis, a common histological feature, is found in 30%–70% patients with CHC [201-203]. The co-existence of CHC and MAFLD occurs in 9%–38% of cases [204]. Data suggested that metabolic disturbances are highly prevalent in patients with CHC, putting them at a higher risk of CVD, carotid and coronary atherosclerosis, and myocardial dysfunction [205]. Nevertheless, no direct evidence suggests that MAFLD aggravates CVD risk in patients with CHC.

Delineating the relative contributions of alcohol consumption in patients with MAFLD in the presence of metabolic risk factors is challenging. Alcohol consumption may deteriorate liver diseases and CVD in patients with MAFLD through an additive or synergistic mechanism.

**Summary**

MAFLD has become an important health issue globally. Because of underlying insulin resistance or metabolic derangement, there are now many cross-talks between hepatologists (steatosis, hepatic manifestation of metabolic syndrome) and cardiologists (CVDs, cardiac manifestation). In this positional statement, 11 important clinical issues regarding the diagnosis, screening and assessment of MAFLD, the importance of co-care of MAFLD and CVDs, and potential management strategies have been addressed and discussed by both the liver and cardiovascular experts. The benefits of various lifestyle modification and updates of different pharmacological intervention for CVD and for steatosis-associated advanced fibrosis have also been briefly reviewed. We hope these statements can help simplified the clinical practice of
both gastroenterologists/hepatologists and cardiologists in patients with MAFLD or CVDs.

These statements also aim to draw attention of the general practitioners to the importance of the emerging MAFLD and to set optimal goals of clinical management.
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**Figure Legends**

Figure 1. Definition of metabolic-dysfunction associated fatty liver disease.

- The presence of hepatic steatosis
  - Overweight/obesity
    - BMI ≥ 23 kg/m² in Asians
    - BMI ≥ 25 kg/m² in Caucasians
  - Metabolic dysregulation
  - The presence of type 2 diabetes mellitus
- At least two metabolic risk factors
  - Increased waist circumference
  - Hypertension
  - Hypertriglyceridemia
  - Low serum HDL-cholesterol levels
  - Impaired fasting plasma glucose
  - Insulin resistance (assessed by homeostatic model assessment of insulin resistance)
  - Subclinical inflammation (evaluated by high-sensitivity C-reactive protein levels)

Metabolic-dysfunction associated fatty liver disease
Figure 2. The pathophysiological mechanisms for the interaction between MAFLD and CVD. Abbreviations: MAFLD, metabolic associated fatty liver disease; CVD, cardiovascular disease
Figure 3. Illustration of the risk factors interplaying between the development of MAFLD and CVDs.
Figure 4. Algorithm for screening of MAFLD and fibrosis assessment among CVD patients.

1. **Step 1: Identify CVD patients with hepatic steatosis**
   - Steatosis on any imaging modality or non-invasive serum panels

2. **Step 2: Noninvasive testing for liver fibrosis**
   - (FIB-4 is a calculated value based on age, AST, ALT & platelet count)
   - FIB-4 < 1.3
   - FIB-4 1.3 to 2.67
   - FIB-4 > 2.67

3. **Step 3: Liver stiffness measurement (LSM)**
   - LSM < 8 kPa
   - LSM 8 to 12 kPa
   - LSM > 12 kPa

   - **Low Risk**
     - Regular monitoring every 1-2 years unless clinical circumstances change

   - **Intermediate Risk**
     - Refer to hepatologist or close monitoring with re-eval of risk every 3-6 months

   - **High Risk**
     - Refer to hepatologist
Table 1. Summary of the effects of pharmaceutical interventions on liver and CV outcomes in MAFLD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Liver effects</th>
<th>CV effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit. E</td>
<td>Improve steatosis, ballooning hepatocyte, and inflammation in non-T2DM patients; but not improve fibrosis</td>
<td>May increase risk of heart failure in T2DM patients</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>Improved liver fibrosis without worsening NASH in patients with F2/F3 fibrosis. Safety concern</td>
<td>Little in changes the risk of cardiovascular event.</td>
</tr>
<tr>
<td>Statin</td>
<td>No benefits or harm</td>
<td>Prevent cardiovascular risk</td>
</tr>
<tr>
<td>Metformin</td>
<td>Not improve fibrosis</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Decrease content of hepatic fat and improve parameters of NASH in T2DM or non-T2DM</td>
<td>Reduces event of cardiovascular disease in T2DM and NASH</td>
</tr>
<tr>
<td>Glucagon-like peptide 1 receptor agonists</td>
<td>Effective of improving hepatic steatosis and liver enzymes for NAFLD patients. Efficacy in fibrosis regression needs study.</td>
<td>Beneficial effects on renal and cardiovascular complications in T2DM patients</td>
</tr>
<tr>
<td>Sodium-glucose cotransporter 2 inhibitors</td>
<td>Positive effects on hepatic steatosis in T2DM and NAFLD Role of regression of hepatic fibrosis needs investigation</td>
<td>Offer significant cardiometabolic and renal protection</td>
</tr>
<tr>
<td>Dipeptidyl peptidase IV (DPP-IV) inhibitors</td>
<td>Not reduce hepatic steatosis or fibrosis in overweight T2DM</td>
<td>Lowering cardiovascular diseases incidence in T2DM patients</td>
</tr>
</tbody>
</table>