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Metabolic Dysfunction Associated-Steatotic Liver Disease (MASLD) and Cardiovascular Risk: Embrace All Facets of the Disease

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Abstract

Purpose of Review In recent years, the terms "metabolic associated fatty liver disease-MAFLD" and "metabolic dysfunction-associated steatotic liver disease-MASLD" were introduced to improve the encapsulation of metabolic dysregulation in this patient population, as well as to avoid the negative/stigmatizing terms "non-alcoholic" and "fatty".

Recent Findings There is evidence suggesting links between MASLD and coronary heart disease (CHD), heart failure (HF), atrial fibrillation (AF), stroke, peripheral artery disease (PAD) and chronic kidney disease (CKD), although the data for HF, AF, stroke and PAD are scarcer.

Summary Physicians should consider the associations between MASLD and CV diseases in their daily practice. Based on this knowledge and current guidelines, they should also assess and manage CV risk/co-morbidities in such patients. It is important to further investigate the impact of MASLD on CV outcomes, a knowledge that will help to elucidate the clinical implications of this "novel" liver entity.

Keywords Metabolic associated steatotic liver disease · Metabolic associated fatty liver disease · Non-alcoholic fatty liver disease · Cardiovascular disease · Coronary heart disease · Stroke

Introduction

> If we knew what it was we were doing, it would not be called research, would it?
> *Albert Einstein*

In 2020, a consensus of experts proposed to replace the term "non-alcoholic fatty liver disease-NAFLD" with "metabolic associated fatty liver disease-MAFLD" using different diagnostic criteria, i.e., the presence of hepatic steatosis (via imaging, histology, biomarkers or scores) accompanied by one of the following: (a) type 2 diabetes mellitus (T2DM), (b) overweight/obesity (cut-offs according to ethnicity) or (c) metabolic dysregulation defined as the presence of ≥ 2 features: increased waist circumference, blood pressure, triglycerides, high-sensitivity C-reactive protein (hsCRP) or Homeostatic Model Assessment of Insulin Resistance (HOMA- IR), decreased high-density lipoprotein cholesterol (HDL-C) or prediabetes [1]. The introduction of the term "MAFLD" sought to reclassify NAFLD and improve the encapsulation of metabolic dysregulation in this patient population [2]. Indeed, the definition of MAFLD focuses on the causal etiologies [such as T2DM, overweight/obesity, metabolic syndrome (MetS)], and not on chronic alcohol consumption [1]. In contrast, NAFLD is diagnosed in the presence of hepatic steatosis after excluding any secondary causality [3, 4]. Therefore, NAFLD and MAFLD may not reflect the same patient populations, e.g., the presence of metabolic disorders and liver steatosis characterizes MAFLD patients, whereas metabolic risk factors may be absent in some NAFLD patients (e.g., lean NAFLD) [5]. Furthermore, liver biopsy, the "gold standard" for NAFLD diagnosis,

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has a limited use in daily practice and thus, supervised machine learning and "omics" have been examined as a "non-invasive alternative" to liver biopsy [6]. In contrast, MAFLD diagnosis does not require liver biopsy, thus largely facilitating disease diagnosis in clinical practice [1].

In 2023, a multisociety Delphi consensus recommended a novel nomenclature for the disease, i.e., metabolic dysfunction-associated steatotic liver disease (MASLD) to replace both NAFLD (and MAFLD), since the terms "non-alcoholic" and "fatty" were regarded as stigmatizing [7]. MASLD comprises both metabolic dysfunction-associated steatotic liver (MASL) and metabolic dysfunction-associated steatohepatitis (MASH). Of note, a pathophysiology-based classification of steatotic liver disease (SLD) has been recently suggested, including different SLD subtypes according to causality: e.g., genetics (GASLD), metabolic (MASLD), obesity (O-MASLD), sarcopenia (S-MASLD), lipodystrophy (LASLD), cryptogenic (CSLD) and moderate/increased alcohol intake (MetALD) [8]. Very recently, in 2024, the European Association for the Study of Liver (EASL)-European Association for the Study of Diabetes (EASD)-European Association for the Study of Obesity (EASO) have published their guidelines on MASLD management, also recommending that clinicians should assess cardiovascular (CV) risk in MASLD patients [9]. Figure 1 shows the diagnostic algorithm for SLD and its subtypes based on the recent EASL-EASD-EASO clinical guidelines [9]. Table 1 summarizes the differences in the diagnostic criteria and sub-types of NAFLD, MAFLD and MASLD.

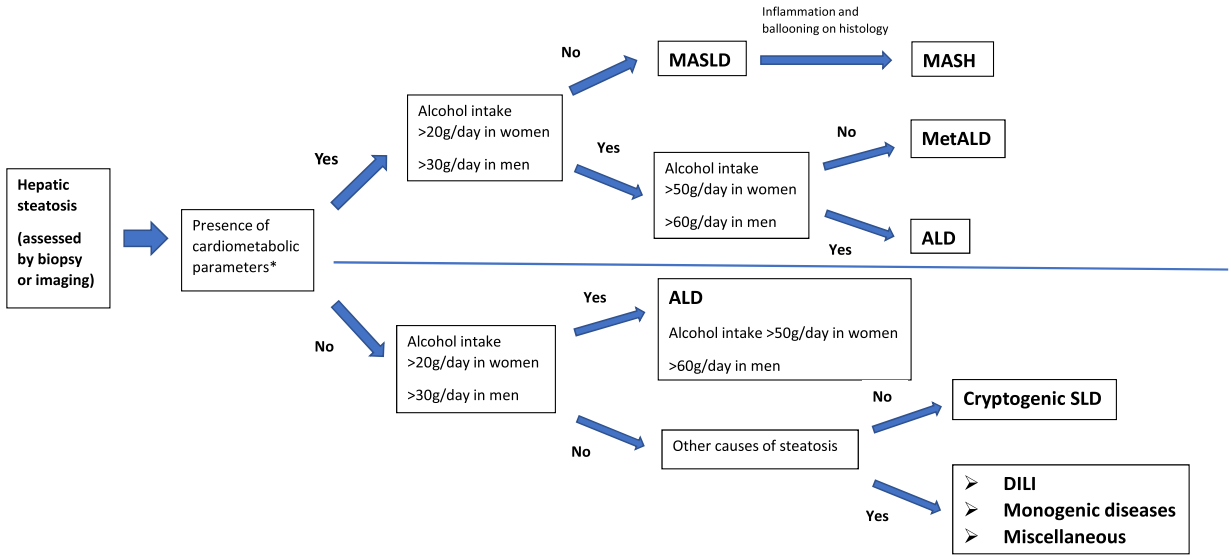
NAFLD has already been associated with increased liver and CV morbidity and mortality [10–15]. Based on the abovementioned differences between NAFLD and MASLD definitions, it is important to investigate the impact of MASLD on CV outcomes, a knowledge that will help to elucidate the clinical implication of this "novel" liver entity.

The aim of the present narrative review was to summarize the current data on the associations between MASLD and the risk of coronary heart disease (CHD), heart failure (HF), atrial fibrillation (AF), stroke, peripheral artery disease (PAD) and chronic kidney disease (CKD). We also discuss the clinical challenges rising from this "terminology" shift.

MASLD and CHD

The link between NAFLD and CHD has already been established in observational, cohort and genetic studies, with several underlying pathogenetic mechanisms being recognized (e.g., insulin resistance/hyperglycemia, oxidative stress, systemic/vascular inflammation, endothelial dysfunction, atherogenic dyslipidemia, coagulopathy and gut microbiota) [16–18]. There is some evidence for an association between MAFLD and CHD. For example, among 570,426 individuals from a nationwide claims database followed for a median of 5.2 years, MAFLD correlated with an increased risk of CHD

MASLD, metabolic dysfunction-associated steatotic liver disease; ALD, alcohol-related liver disease; DILI, drug-induced liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MetALD; MASLD with moderate (increased) alcohol consumption; SLD, steatotic liver disease



***1] Overweight or Obesity** BMI ≥25 kg/m² (≥23 kg/m² in Asians) Waist circumference ≥94 cm in men and ≥80 cm in women (Europeans) ≥90 cm in men and ≥ 80 cm in women (South Asians and Chinese) ≥85 cm in men and ≥90 cm in women (Japanese) **2] Dysglycemia or type 2 diabetes** Prediabetes: HbA1c 5.7-6.4% or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dL) or 2-h plasma glucose during OGTT 7.8-11 mmol/L (140-199 mg/dL) or Type 2 diabetes: HbA1c ≥6.5% or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) or 2-h plasma glucose during OGTT ≥11.1 mmol/L (≥200 mg/dL) or antidiabetic therapy **3] Plasma triglycerides** ≥1.7 mmol/L (≥150 mg/dL) or lipid-lowering therapy **4] HDL-cholesterol** ≤1.0 mmol/L (≤39 mg/dL) in men and ≤1.3 mmol/L (≤ 50 mg/dL) in women or lipid-lowering therapy **5] Blood pressure** ≥130/85 mmHg or antihypertensive therapy OGTT, oral glucose tolerance test; HDL, high-density lipoprotein

Fig. 1 Diagnostic algorithm for steatotic liver disease and its subtypes based on recent guidelines

Table 1 Differences in the diagnostic criteria and sub-types of NAFLD, MAFLD, and MASLD

	NAFLD[4]	MAFLD[1]	MASLD[9]
Definition	Presence of steatosis in > 5% of hepatocytes according to histological analysis or by PDFF **OR** > 5.6% volume fraction of fat in the liver assessed by 1H-MRS or quantitative fat/water selective MRI	Hepatic steatosis detected either by blood biomarkers/scores, imaging techniques or by liver histology **AND** Overweight/obesity (BMI ≥ 25 kg/m^2 in Caucasians or ≥ 23 kg/m^2 in Asians) or Type 2 diabetes or Lean/normal weight with at least two metabolic risk abnormalities #	Hepatic steatosis identified by biopsy or imaging **AND** Presence of any of cardiometabolic criteria ¥ **AND** Alcohol intake ≤ 20 g/day in women and ≤ 30 g/day in men
Sub-types	• NAFL: pure steatosis • NASH: steatosis and mild lobular inflammation • Early NASH: no or mild (F0–F1) fibrosis • Fibrotic NASH: significant (≥ F2) or advanced (≥ F3, bridging) fibrosis • NASH-cirrhosis (F4) • HCC	• MAFLD • MAFLD-related fibrosis • MAFLD-related cirrhosis • HCC	• MASLD • MASH • HCC • MetALD (in the presence of alcohol intake 20–50 g/day in women and 30–60 g/day in men) • ALD (in the presence of alcohol intake > 50 g/day in women and > 60 g/day in men)

BMI, body mass index; *PDFF*, proton density fat fraction; *1H-MRS*, proton magnetic resonance spectroscopy; *MRI*, magnetic resonance imaging; *NAFL*, non-alcoholic fatty liver; *NAFLD*, non-alcoholic fatty liver disease; *NASH*, non-alcoholic steatohepatitis; *HCC*, hepatocellular carcinoma; *MAFLD*, metabolic dysfunction-associated fatty liver disease; *MASLD*, metabolic dysfunction-associated steatotic liver disease; *MASH*, metabolic dysfunction-associated steatohepatitis; *ALD*, alcoholic liver disease; *MetALD*, MASLD with moderate (increased) alcohol consumption; *HDL*, high-density lipoprotein; *OGTT*, oral glucose tolerance test; *HDL*, high-density lipoprotein

Waist circumference ≥ 102/88 cm in Caucasian men and women (or ≥ 90/80 cm in Asian men and women); Blood pressure ≥ 130/85 mmHg or antihypertensive treatment; Plasma triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/L) or lipid-lowering treatment; Plasma HDL-cholesterol < 40 mg/dL (< 1.0 mmol/L) for men and < 50 mg/dL (< 1.3 mmol/L) for women or drug treatment; Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL [5.6 to 6.9 mmol/L], or 2-h post-load glucose levels 140 to 199 mg/dL [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol]; Homeostasis model assessment of insulin resistance score ≥ 2.5; Plasma high-sensitivity C-reactive protein level > 2 mg/L

¥ Overweight or Obesity BMI ≥ 25 kg/m^2 (≥ 23 kg/m^2 in Asians) Waist circumference ≥ 94 cm in men and ≥ 80 cm in women (Europeans) ≥ 90 cm in men and ≥ 80 cm in women (South Asians and Chinese) ≥ 85 cm in men and ≥ 90 cm in women (Japanese); Dysglycemia or type 2 diabetes Prediabetes: HbA1c 5.7–6.4% or fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dL) or 2-h plasma glucose during OGTT 7.8–11 mmol/L (140–199 mg/dL) or Type 2 diabetes: HbA1c ≥ 6.5% or fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL) or 2-h plasma glucose during OGTT ≥ 11.1 mmol/L (≥ 200 mg/dL) or antidiabetic therapy; Plasma triglycerides ≥ 1.7 mmol/L (≥ 150 mg/dL) or lipid-lowering therapy; HDL-cholesterol ≤ 1.0 mmol/L (≤ 39 mg/dL) in men and ≤ 1.3 mmol/L (≤ 50 mg/dL) in women or lipid-lowering therapy; Blood pressure ≥ 130/85 mmHg or antihypertensive therapy

compared with controls (i.e., those without T2DM/MetS/MAFLD), both in the absence (HR 1.32, 95%CI 1.17–1.50) and presence of T2DM [hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.06–1.58] [19]. In a prospective UK Biobank cohort (n = 325,129 participants, median follow-up: 12.8 years), those with MAFLD had a significantly higher likelihood to experience a myocardial infarction (HR 1.35, 95%CI 1.29–1.41; p < 0.001) [20].

In a recent observational study, among 113 CHD patients (72% had significant CHD defined as > 50% stenosis of at least one coronary artery), MASLD prevalence rate was 52%, with liver fibrosis being present in all patients with significant CHD [21]. Similarly, in a cross-sectional study on 2,038 patients undergoing coronary computed tomography angiography (CCTA), MASLD was related to a higher incidence of major adverse CV events (MACE) (i.e., 25.90% vs. 14.71% in patients without MASLD; p < 0.001) during a mean follow-up of 26.9 months [22]. In cox regression analysis, MACE was more strongly associated with MASLD compared with coronary calcium score (CCS), number of plaques and epicardial fat volume [HR 1.843 (95%CI 1.475–2.303, 1.001 (95%CI 1.000–1.001), 1.097 (95%CI 1.075–1.119) and 1.035 (95%CI 1.030–1.041), respectively; p < 0.001 for all comparisons] [22]. Integrating these parameters in a composite risk score demonstrated superior predictive value for MACE (AUC = 0.948) compared with individual variables (p < 0.0001 for all comparisons) [22]. Of note, abnormal peri-organ or intra-organ fat (APIFat) deposition (including, apart from "fatty liver", epicardial, perirenal, peripancreatic, perivascular and intramuscular fat) has been linked to increased CV risk [23–28]. The above-mentioned cross-sectional study is the first to investigate the associations between MASLD and epicardial fat [22]. Further research is needed to elucidate the links between

MASLD and other fat depots. Interestingly, a recent systematic review (n = 21 studies reporting CV outcomes in adults with histologically confirmed MASH and MASLD or other liver diseases) reported an increased prevalence or incidence of CV disease (CVD) in patients with MASH vs. other liver conditions with odds ratios (OR) ranging from 3.12 (95%CI 1.33–5.32) to 4.12 (95%CI 1.91–8.90) [29].

MAFLD has also been related to subclinical atherosclerosis. In this context, among 1,164 patients undergoing CCTA, MAFLD correlated with the presence of noncalcified plaques (OR 1.67, 95%CI 1.15–2.43; p = 0.007) and mixed plaques (OR 1.54; 95%CI 1.10–2.16; p = 0.011) [30]. A recent meta-analysis (24 observational studies) reported that MASLD was related to a higher prevalence of critical coronary stenosis (> 50% diameter of stenosis) compared with controls (OR 1.54, 95%CI 1.23–1.93), as well as to increased CAC scores (OR 1.35, 95%CI 1.02–1.78 for CAC score 0–100 and OR 2.26, 95%CI 1.57–3.23 for CAC score > 100) [31]. In the same meta-analysis, MASLD patients were more likely to have 'high-risk' coronary plaques (OR 2.13, 95%CI 1.42–3.19) with a higher prevalence of spotty calcification and positive remodelling (OR 2.96, 95%CI 1.22–7.20 and OR 2.92, 95%CI 1.79–4.77, respectively) [31].

Hepatic fibrosis has also been linked to CHD in the presence of MAFLD. For example, among 1,346 MAFLD patients, increased liver fibrosis scores were significantly associated with the presence of coronary artery disease-CAD (assessed via CCTA and defined as coronary artery stenosis ≥ 50%): ORs were 1.345 (95%CI 1.142–1.583; p < 0.001) for the Fibrosis-4 (FIB-4) score and 1.191 (95%CI 1.080–1.313; p < 0.001) for the NAFLD Fibrosis Score (NFS); these associations remained significant even after adjusting for several CV risk factors [32]. Of note, both scores were significantly higher in CAD patients compared with the non-obstructive group (defined as the presence of 1–49% coronary artery stenosis) and normal controls (defined as absence of coronary artery stenosis): for FIB-4 score 1.45 ± 0.89 vs. 1.28 ± 0.75 vs. 1.06 ± 0.78 (p < 0.05 for all comparisons), for NFS −0.93 ± 2.13 vs. −1.33 ± 1.58 vs. −1.92 ± 1.24 (p < 0.05 for all comparisons) [32]. Similarly, in another cross-sectional study with 1,664 MAFLD patients, FIB-4 score was associated with CAD (defined as a history of MI, acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft or angioplasty); the upper tertile of FIB-4 had an OR of 3.28 to predict CAD (95%CI 1.621–6.638; p = 0.002) [33].

MAFLD has also been linked to HF incidence. For example, among 98,685 participants of the Kailuan cohort, followed for a median of 14.01 years, MAFLD patients had an increased risk of HF development compared with non-MAFLD ones (HR 1.40, 95%CI 1.30–1.50) [34]. Of note, among different MAFLD groups, those with T2DM had an even higher HF risk (HR 1.95, 95%CI 1.73–2.20) [34]. Furthermore, among 1,189,113 Korean T2DM patients included in the Korean National Health Insurance Service database and followed for an average of 6.6 years, MAFLD presence increased HF risk by 1.4-fold (HR 1.41, 95%CI 1.31–1.52) in patients without diabetic kidney disease (DKD), whereas it did not affect HF incidence in patients with DKD [35]. Of note, a link between NAFLD and new-onset HF has also been described; underlying pathophysiological mechanisms include cardiac remodeling, autonomic dysfunction, CHD, AF and microvascular dysfunction [36]. Indeed, several trials reported a significantly higher HF prevalence, and especially HF with preserved ejection fraction (HFpEF), in NAFLD patients, with advanced fibrosis further increasing HF incidence [37–39]. With regard to MASLD, among 46,322 hospitalized cirrhotic patients, those with MASLD had a significantly higher HF risk (OR 1.14, 95%CI 1.10–1.21; p < 0.001) [40]. Furthermore, in a sample of 413,860 participants from the general population (using UK Biobank data), 12,527 HF incident cases occurred during a median of 10.7 years, with liver fibrosis being linked to a significant higher risk of HF hospitalization or death (HR ranging from 1.59 to 1.90 according to fibrosis score used) [41].

NAFLD has also been related to a significantly increased AF incidence [42, 43] and AF recurrence after ablation [44]. With regard to MAFLD, among 245 patients undergoing AF ablation (median follow-up 418 days), those with MAFLD/severe fibrosis presented a higher rate of AF recurrence than those with MAFLD/indeterminate fibrosis and those with MAFLD but without fibrosis (77 vs. 32.5 vs 17.5%, respectively; p = 0.0179) [45]. With regard to MASLD, a population-based cohort (including 11,206 Swedish adults with histologically-confirmed MASLD without prior cardiac arrhythmias and 51,856 controls matched by sex, age, county and calendar year) with a median follow-up of 10.8 years, found that the rate of incident AF was significantly higher in MASLD patients compared with controls (adjusted HR 1.26, 95%CI 1.18–1.35); the corresponding HRs for patients with simple steatosis, non-fibrotic MASH, non-cirrhotic fibrosis and cirrhosis were: 1.24 (95%CI 1.14–1.35), 1.34 (95%CI 1.07–1.68), 1.24 (95%CI 1.03–1.50) and 1.59 (95%CI 1.15–2.19) [46]. MASLD was also associated with significantly greater rates of incident bradyarrhythmias (adjusted HR = 1.26, 95%CI 1.06–1.48), ventricular arrhythmias/cardiac arrest (adjusted HR = 1.53, 95%CI 1.30–1.80) and other supraventricular arrhythmias (adjusted HR = 1.27, 95%CI 1.00–1.62) compared with controls [46].

MASLD and Stroke

There are only a few published data on the association between MAFLD and stroke. A data-driven cluster analysis included 1,038 MAFLD patients from the First Affiliated

Hospital of Sun Yat-sen University to develop a model for MAFLD classification that was then validated in 10,451 cases from a Chinese cohort (33.4% of MAFLD) and 304,141 cases (34.9% of MAFLD) from UK Biobank database [46]. Overall, 5 clusters of MAFLD patients were identified related to: i) mild obesity and dyslipidemia (Cluster 1), ii) age (Cluster 2), iii) severe insulin resistance (Cluster 3), iv) high Lp(a) (Cluster 4), and v) severe mixed hyperlipidemia (Cluster 5) [47]. In multivariate analysis, Cluster 3 and Cluster 4 were significantly associated with an increased risk of stroke (HR 1.52, 95%CI 1.24–1.86; $p < 0.0001$ for Cluster 3 and 1.19, 95%CI 1.01–1.40; $p = 0.033$ for Cluster 4, respectively) [47]. This finding highlights the importance of accurate MAFLD classification in relation to clinical outcomes.

With regard to MASLD, a prospective UK Biobank cohort (n = 325,129 participants, median follow-up: 12.8 years) found that MASLD was associated with a significantly higher risk of stroke incidence (HR 1.26, 95%CI 1.18–1.33; $p < 0.001$) [20]. In a nationwide Korean study (n = 8,808,494 participants without prior CVD, followed up for a median of 12.3 years) reported that CVD incidence was significantly higher in MASLD/SLD patients than in those without (adjusted HR 1.38; 95%CI 1.37–1.39); the corresponding HRs for MASLD, MetALD and MASLD with other etiology were: 1.39 (95%CI 1.38–1.40), 1.28 (95%CI 1.26–1.30) and 1.30 (95%CI 1.26–1.34) [48]. Interestingly, among 8,962,813 Korean individuals without prior CVD, followed for a median of 10.1 years, adjusted HRs for CVD events were 1.09 (95%CI 1.03–1.15) in the NAFLD-only group, 1.43 (95%CI 1.41–1.45) in the MAFLD-only group, and 1.56 (95%CI 1.54–1.58) in the both-FLD group [49].

More evidence exists for a link between NAFLD and stroke. In a pooled analysis of 25,839 NAFLD patients (diagnosed by ultrasonography, liver biopsy or CT), stroke prevalence was 5.04% (95%CI 2.74–9.09%); the incidence of ischemic stroke was 6.05% (95%CI 2.93–12.07), whereas of hemorrhagic stroke 2.22% (95%CI 0.22–18.77) [50]. The OR of stroke prevalence in NAFLD patients was 1.88 (95%CI 1.23–2.88; $p = 0.02$) compared with non-NAFLD individuals [50]. Furthermore, the analysis of a nationwide Swedish cohort including 10,422 histologically confirmed NAFLD patients and 10,648 controls, followed up for a median of 13.6 years, reported that the incidence of major adverse cardiovascular events (MACE) was significantly higher in NAFLD patients compared with controls (adjusted HR 1.63, 95%CI 1.56–1.70); the corresponding value for stroke was adjusted HR 1.58 (95%ci 1.46–1.71) [51]. Similarly, in a Chinese cohort of 79,905 participants followed up for a median of 10.34 years, NAFLD was diagnosed (and categorized in severity) by ultrasonography in 24,874 individuals; the risk of developing ischemic stroke was 16% higher (95%CI 1.07–1.26) in NAFLD vs non-NAFLD patients [52]. This risk gradually increased in patients with mild (HR 1.15, 95%CI 1.05–1.25), moderate (HR 1.19, 95%CI 1.06–1.34) and severe NAFLD (HR 1.21, 95%CI 1.08–1.50), respectively [52].

A recent meta-analysis including 33 studies (n = 10,592,851 individuals of the general population; mean age 53 ± 8 years; 50% men; mean follow-up 10 ± 6 years) reported that NAFLD correlated with an increased risk of ischemic stroke (OR 1.6, 95%CI 1.2–2.1) [53]. Interestingly, a Mendelian Randomization (MR) study found potential causal effects of NAFLD on certain ischemic stroke subtypes, i.e., large artery atherosclerosis (LAA) (OR 1.065, 95%CI 1.004–1.129; $p = 0.037$) and small vessel occlusion (SVO) (OR 1.058, 95%CI 1.003–1.116; $p = 0.037$), whereas no causal inference was observed for cardioembolic stroke (OR 1.026, 95%CI 0.983–1.071; $p = 0.243$) [54]. However, conflicting results exist. For example, another MR study did not find causal association between NAFLD and any stroke subtype [55].

MASLD and PAD

A recent observational study involving 101,465 Chinese adults undergoing a health check (mean age 49.8 ± 10.0 years; 65.3% men) reported that 51.0% of the total population had MAFLD (diagnosed by abdominal ultrasound) [56]. The prevalence of PAD (diagnosed by ankle-brachial index, ABI) was higher in the MAFLD vs non-MAFLD group (2.7 vs 2.2%), leading to an increased adjusted OR of 1.30 (95%CI 1.19–1.42, $p < 0.001$) [56]. Furthermore, in the same study, 6,833 participants were followed up for 2.76 ± 1.36 years; MAFLD at baseline was related to a higher risk of PAD incidence (adjusted HR 1.67, 95%CI 1.17–2.38, $p = 0.005$). Of note, this risk was greater in patients with three metabolic disorders (adjusted HR 2.27, 95%CI 1.39–3.71, $p = 0.001$) compared with those with two metabolic disorders (adjusted HR 1.64, 95%CI 1.13–2.38, $p = 0.009$) [56].

With regard to NAFLD, in a study involving 2,646 T2DM patients aged ≥ 40 years, NAFLD (defined by ultrasound) was related to a 75% increased risk of PAD (diagnosed by ABI) after adjustment for several metabolic factors (OR 1.49, 95%CI 1.12–2.00) [57]. Furthermore, among 51,645 T2DM patients (aged 18–75 years) from 501 Diabetes Prospective Follow-up (DPV) centers, those with elevated liver enzymes had a higher prevalence of PAD compared with those with normal liver tests ($p = 0.0029$) [58]. Ciardullo et al. reported that, among 3.094 NAFLD patients from the NHANES (1999–2004), followed up for a median of 13 years, PAD was associated with a significantly greater incidence of all-cause death (adjusted HR 1.8, 95%CI

1.4–2.4) and CVD mortality (adjusted HR 2.5, 95%CI 1.5–4.3) [59].

MASLD and CKD

Several studies reported a significant association between MAFLD and CKD. In this context, in a longitudinal cohort study of 41,246 Chinese individuals followed up for a median of 10 years, MAFLD correlated with CKD incidence (HR 1.18, 95%CI 1.11–1.26); the corresponding HR for men and women were: 1.16 (95%CI 1.07–1.26) and 1.32 (95%CI 1.18–1.48), respectively [60]. In subgroup analyses, the MAFLD-related CKD risk was higher in men aged < 60 years and in those with combined dyslipidemia [60]. Similarly, in a cohort of 3,627 T2DM patients followed up for a median of 10.0 years, MAFLD-related CKD risk was greater in those aged < 60 years (HR 1.58, 95%CI 1.28–1.95) compared with those aged ≥ 60 years (HR 1.03, 95%CI 0.79–1.33) [61]. In the total population, MAFLD was an independent predictor of CKD development even after adjusting for several confounding factors (HR 1.30, 95%CI 1.11–1.53; p < 0.001) [61]. The association between MAFLD and CKD development has also been reported in other studies [62–66]. Similarly, a recent meta-analysis, involving 355,886 patients with NAFLD or MAFLD, followed up for 4.6–6.5 years, showed that MAFLD was significantly related to a higher CKD prevalence (OR 1.50, 95%CI 1.02–2.23; p = 0.04) and incidence (adjusted HR 1.35, 95%CI 1.18–1.52; p < 0.001) [67]. In the past, NAFLD presence and severity has also been linked to CKD development, as supported in meta-analyses [68, 69].

Interestingly, in a cross-sectional study involving 27,371 Japanese individuals undergoing a medical health checkup, MAFLD was associated with CKD risk (adjusted OR 1.83, 95%CI 1.66–2.01; p < 0.001), whereas NAFLD without metabolic dysfunction was not [70]. Among the 27,371 participants, 16,938 were followed up for a median 4.6 years: again, MAFLD correlated with CKD incidence (adjusted HR 1.24, 95%CI 1.14–1.36; p < 0.001), whereas NAFLD without metabolic dysfunction was not [70]. Similarly, a retrospective cohort study involving 21,713 Korean adults (median follow up: 5.3 years; range 2.8–8.3 years) reported an increased CKD risk in MAFLD patients (HR 1.97, 95%CI 1.49–2.60), as well as those with metabolic dysfunction but without fatty liver (HR 1.23, 95%CI 1.00–1.53), but not in NAFLD only group (HR 1.06, 95%CI 0.63–1.79) [71]. Another cohort of 28,890 Japanese individuals followed up for 10 years, found that only MAFLD (but not fatty liver or NAFLD) was an independent predictor of CKD onset (HR 1.12, 95%CI 1.02–1.26; p = 0.027) [72]. However, conflicting results exist. In a cohort study of 6,873 Chinese individuals followed up for an average of 4.6 years, the rates of CKD incidence were similar for NAFLD (22.7%, 95%CI 21.3–24.0) and MAFLD patients (27.0%, 95%CI 25.5–28.4) [73]. In the study by Kwon et al., all MAFLD subgroups were significantly associated with CKD incidence, i.e., those with overweight/obesity (HR 2.94, 95%CI 1.91–4.55), excessive alcohol intake (HR 2.71, 95%CI 2.11–3.47), viral hepatitis (HR 2.38, 95%CI 1.48–3.84), T2DM (HR 2.20, 95%CI 1.67–2.90) and metabolic dysfunction only (HR 1.50, 95%CI 1.19–1.89) [71].

MAFLD has been linked to worse CKD prognosis. In this context, analysis of data from 337,783 UK Biobank participants over a median follow up of 12.8 years found that MAFLD patients were twice more prone to develop end-stage renal disease (ESRD) (HR 2.03, 95%CI 1.68–2.46; p < 0.001); this association remained significant in both CKD and non-CKD patients [74]. With respect to liver fibrosis severity, the adjusted HRs for ESKD incidence in MAFLD patients with increasing NFS were 1.23 (95%CI 0.96–1.58), 2.45 (95%CI 1.98–3.03) and 7.67 (95%CI 5.48–10.73), respectively, thus highlighting the link between hepatic fibrosis and CKD severity [74]. In this context, in a community-based prospective study involving 4,042 participants followed up for a mean of 4.4 years, fibrosis progression from low to intermediate and high NFS was related to a significantly higher risk of CKD incidence compared with stable fibrosis with low NFS (OR 2.82, 95%CI 1.22–6.56; p = 0.016) [75]. Similarly, a greater NFS correlated with impaired estimated glomerular filtration rate-eGFR (standard coefficient: −0.067 l; p < 0.001) among 11,376 Taiwanese subjects [76]. Overall, liver fibrosis (but not steatosis) and more severe MAFLD forms have higher odds of developing CKD, as reported in a recent meta-analysis [67]. In contrast, liver steatosis (defined by transient elastography with a Controlled Attenuated Parameter-CAP) was a better predictor of CKD prevalence (r = 0.89; p < 0.0001) than fibrosis (defined by liver stiffness measurements) in a study involving 335 MAFLD patients (r = 0.52; p = 0.12) [77]. Of note, liver fibrosis has also been suggested to represent a potential clinical marker of erythropoietin stimulating agent (ESA) hypo-responsiveness [78].

Furthermore, the co-existence of MAFLD and CKD (but not either disease alone) was an independent predictor for ischemic heart disease (HR 1.51, 95%CI 1.02–2.22) among 28,990 Japanese individuals receiving annual health examinations that were followed up for a mean of 6.9 years [79]. In a prospective cohort study using data from 18,073 UK Biobank participants with CKD (median follow-up 13 years), NAFLD was linked to an increased risk of CV events (HR 1.20, 95%CI 1.11–1.30; p < 0.0001) in multivariate analysis [80]. NFS was also associated with a higher incidence of CV events (HR 1.19, 95%CI 1.01–1.40) and total mortality (HR 1.31, 95%CI 1.13–1.52) [80].

According to a recent international Delphi-based consensus statement: i) CKD prevalence is higher in MAFLD patients compared with non-MAFLD individuals, ii) MAFLD is an independent predictor of CKD in patients with or without T2DM, iii) MAFLD is related to a higher risk of CKD compared with patients with liver steatosis in the absence of systemic metabolic dysregulation, iv) increased severity of MAFLD is linked to more advanced CKD stages, and vice versa, v) CKD and MAFLD share common pathophysiological mechanisms, and vi) management of both CKD and MAFLD include lifestyle interventions and drug treatment of cardiometabolic disorders such as hypertension, dyslipidemia and hyperglycemia [81].

With regard to MASLD, among 12,138 Japanese receiving annual health examinations followed up for 10 years, the rate of CKD development (defined as eGFR < 60 mL/min/1.73 m^2 or positive for urinary protein) was significantly increased in subjects with MASLD (adjusted HR 1.20, 95%CI 1.08–1.33; p = 0.001), but not in those with MetALD (adjusted HR 1.11, 95%CI 0.90–1.36; p = 0.332) compared with subjects with non-SLD [82]. In another observational study among 2,046 adults who underwent routine liver function testing, 1,448 individuals had MASLD without fibrosis (161 of them also had CKD), whereas 598 had MASLD with fibrosis (117 of them also had CKD); liver fibrosis was significantly related to increased CKD risk [adjusted risk ratio (RR) 1.31, 95%CI 1.04–1.64; p = 0.021] [82]. Of note, mortality risk was higher in subjects with liver fibrosis (adjusted HR 2.30, 95%CI 1.49–3.56; p < 0.001), being even greater in those with both liver fibrosis and CKD (adjusted HR 5.07, 95%CI 3.07–8.39; p < 0.014) [83]. The link between MASLD and CKD has been recently discussed by others [84].

Clinical Challenges Following the "Terminology" Shift from NAFLD to MAFLD/MASLD

Growing evidence supports a significantly higher CV morbidity (including CHD, stroke, HF, PAD and CKD) (Fig. 2), as well as total and CV mortality in MAFLD patients. In this context, according to a recent meta-analysis including 2,620,736 individuals, MAFLD was linked to a greater overall mortality (HR 1.24, 95%CI 1.13–1.34), CV death (HR 1.28, 95%CI 1.03–1.53), liver-related mortality (HR 2.76, 95%CI 1.07–7.13), PAD (OR 1.32, 95%CI 1.05–1.68), CKD (HR 1.53, 95%CI 1.38–1.68), HF (HR 1.67, 95%CI 1.58–1.76), CV events (HR 1.49, 95%CI 1.34–1.64) and stroke (HR 1.55, 95%CI 1.37–1.73) [2]. Similar results

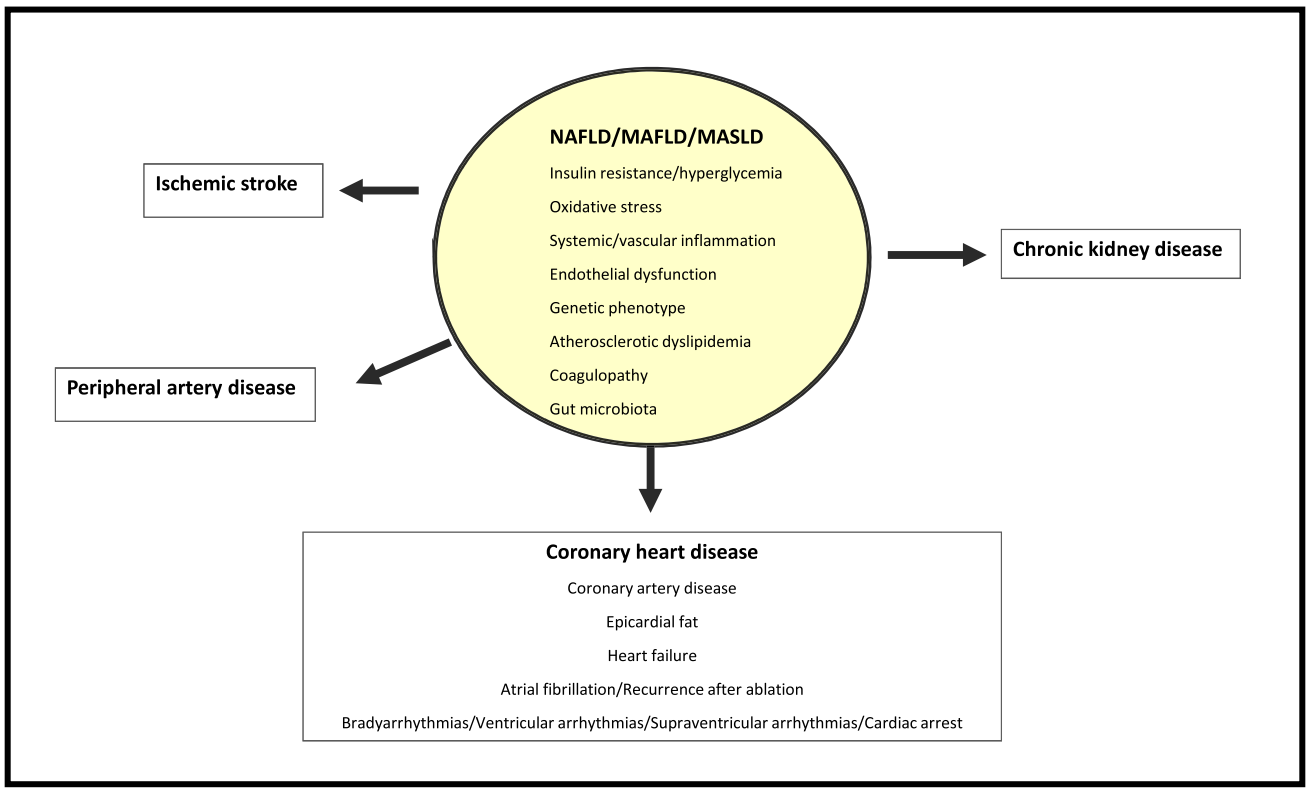


Fig. 2 Associations between nonalcoholic fatty liver disease (NAFLD), metabolic associated fatty liver disease (MAFLD) and metabolic associated steatotic liver disease (MASLD) with cardiovascular diseases and chronic kidney disease

have been published, since the introduction of the 'MAFLD/MASLD' terminology, as discussed in the previous sections of this review.

However, there are certain issues that should be considered in relation to this transition from NAFLD to MAFLD and MASLD. First of all, NAFLD and MAFLD/MASLD may represent distinct steatotic liver entities (according to their definition and comorbidities) and thus, it is vital to establish whether they also differ in terms of clinical outcomes. Of note, a recent observational data meta-analysis (involving 379,801 patients with NAFLD or MAFLD) found that MAFLD definition accounted for 81.59% (95%CI 66.51–90.82) of NAFLD diagnosed cases, thus leading to a significantly higher likelihood of being diagnosed as MAFLD than NAFLD (OR 1.37, 95%CI 1.16–1.63; $p < 0.001$) [85]. Furthermore, there is some evidence that MAFLD is associated with advanced fibrosis (i.e., a more progressive form of the disease) to a greater extent than NAFLD [86]. This finding could be attributed to the harmful effects of chronic alcohol abuse and viral hepatitis, that can be present in MAFLD (but not in NAFLD) patients. The same applies for the observed higher all-cause mortality in MAFLD vs. NAFLD patients (HR 1.66, 95%CI 1.19–2.32) among 7,761 participants of the Third National Health and Nutrition Examination Survey (NHANES III) that were followed for a median of 23 years [87]. Similar results of a greater overall mortality risk in MAFLD than NAFLD patients have been published in another analysis of 12,480 NHANES III participants [88]. In the same context, among 3,306 MAFLD patients with chronic coronary syndrome, the risk for major adverse cardiac events (MACEs) during an average follow-up of 55 months, was higher in those with MAFLD-only (2.32-fold) than those with MAFLD overlapping with NAFLD (1.33-fold) both compared with controls (i.e., those without MAFLD) [89]. In terms of subclinical atherosclerosis, a cross-sectional study ($n = 162,180$ participants) found that the MAFLD-only group had the strongest relationship with coronary artery calcification prevalence (adjusted OR 1.60, 95%CI 1.52–1.69), whereas the NAFLD-only group was associated with a lower risk (adjusted OR 0.76, 95%CI 0.66–0.87) [90]. Similarly, in longitudinal analyses ($n = 34,233$ participants), the MAFLD-only group had the strongest correlation with coronary artery calcification incidence (adjusted HR 2.03, 95%CI 1.62–2.55), followed by the both MAFLD/NAFLD group (adjusted HR 1.73, 95%CI 1.47–2.05), whereas the NAFLD-only group did not significantly predict incident CAC (adjusted HR 0.88,95%CI 0.44–1.78) [90].

MASLD has distinct subtypes and thus, it is important to elucidate the associations between CV risk and the different MAFLD subgroups. This knowledge will facilitate the selection of the most appropriate therapeutic strategy for each individual case. For example, among 8,412,730 Korean adults aged 40–64 years (3,087,640 had MAFLD) from a nationwide health screening database, who were followed for a median of 10.0 years, adjusted HRs for CVD (including MI, ischemic stroke, HF or CVD death) were 1.16 (95%CI 1.15–1.18) for the overweight/obese-MAFLD group, 1.23 (95%CI 1.20–1.27) for the lean-MAFLD group and 1.82 (95%CI 1.80–1.85) for the T2DM-MAFLD group compared with the non-MAFLD group [91]. In the same study, CVD risk was greater in lean- and T2DM-MAFLD patients compared with the overweight/obese-MAFLD individuals, regardless of metabolic comorbidities [91]. Advanced liver fibrosis significantly increased this risk in each MAFLD subtype [91]. These findings highlight the importance of screening CVD risk even in lean MASLD patients.

Although this innovation in SLD nomenclature has revealed clinical challenges, it also empowered the awareness of metabolic dysregulation as an important outcome factor in this patient population that should be individually managed for better prognosis.

In conclusion, there is growing evidence on the significant associations between MASLD and increased CVD risk. The latter refers to CHD, HF, AF, stroke, PAD and CKD. Physicians should consider these associations in their daily practice and assess/manage CV risk/co-morbidities in MASLD patients, according to current guidelines.

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  These are the latest joint EASL-EASD-EASO clinical guidelines for MASLD management.

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