MASLD: a systemic metabolic disorder with cardiovascular and malignant complications

Giovanni Targher, Christopher D Byrne, Herbert Tilg

ABSTRACT
Non-alcoholic fatty liver disease (NAFLD) has rapidly become the most common chronic liver disease globally and is currently estimated to affect up to 38% of the global adult population. NAFLD is a multisystem disease where systemic insulin resistance and related metabolic dysfunction play a pathogenic role in the development of NAFLD and its most relevant liver-related morbidities (cirrhosis, liver failure and hepatocellular carcinoma) and extrahepatic complications, such as cardiovascular disease (CVD), type 2 diabetes mellitus, chronic kidney disease, and certain types of extrahepatic cancers. In 2023, three large multinational liver associations proposed that metabolic dysfunction-associated steatotic liver disease (MASLD) should replace the term NAFLD; the name chosen to replace non-alcoholic steatohepatitis was metabolic dysfunction-associated steatohepatitis (MASH). Emerging epidemiological evidence suggests an excellent concordance rate between NAFLD and MASLD definitions—that is, 99% of individuals with NAFLD meet MASLD criteria. However, this nomenclature change better reflects the pathophysiology and cardiometabolic implications of this common and burdensome liver disease.

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease globally and is currently estimated to affect up to 38% of the global adult population. The worldwide prevalence of NAFLD is projected to increase further within the next decade, in parallel with the increasing global epidemics of obesity and type 2 diabetes mellitus (T2DM). In the last 10–15 years, important conceptual advances have been made in understanding the complex pathophysiological mechanisms of this highly prevalent liver condition. In particular, it has been progressively recognised that NAFLD is a multisystem disease, where insulin resistance and related metabolic dysfunction play a pathogenic role in the development of NAFLD and its most relevant liver-related morbidities (cirrhosis, liver failure and hepatocellular carcinoma (HCC)) and extrahepatic complications, such as cardiovascular disease (CVD), T2DM, chronic kidney disease (CKD) and certain types of extrahepatic cancers. Consequently, in 2020, a panel of international experts proposed a change of terminology and definition for NAFLD in adult individuals—that is, metabolic dysfunction-associated fatty liver disease (MAFLD). Subsequently, in 2023, three large multinational liver associations proposed that metabolic dysfunction-associated steatotic liver disease (MASLD) should replace the term NAFLD; the name chosen to replace non-alcoholic steatohepatitis was metabolic dysfunction-associated steatohepatitis (MASH). Emerging evidence suggests an excellent concordance rate between NAFLD and MASLD definitions—that is, 99% of individuals with NAFLD meet MASLD criteria. However, this nomenclature change better reflects the pathophysiology and cardiometabolic implications of this common and burdensome liver disease.

Epidemiological data on MASLD and the risk of CVD complications
MASLD is recognised as a risk factor for major adverse cardiovascular events, which are the leading cause of mortality in adults with MASLD. A recent systematic review and meta-analysis of population-based studies published between 1990 and 2019 provided further evidence that among the MASLD population, the pooled mortality rate was 12.6 per 1000 person-years (95% CI 6.7 to 23.7) for all-cause mortality; 4.2 per 1000 person-years (95% CI 1.3 to 7.0) for cardiome-chronic conditions; 2.8 per 1000 person-years (95% CI 0.8 to 4.9) for extrahepatic cancer-specific mortality and 0.92 per 1000 person-years (95% CI 0.0 to 2.2) for liver-specific mortality, respectively. Substantial epidemiological evidence from large cohort studies indicates that MASLD is an independent risk factor for CVD morbidity and mortality. In a nationwide cohort study of 10422 Swedish middle-aged individuals with historically confirmed MASLD and −50 000 population controls matched by age, sex, calendar year and county, Simon et al showed that MASLD was associated with an increased risk of developing...
CVD outcomes (defined as nonfatal coronary heart disease, stroke, heart failure or cardiovascular death) over a median of 13.6 years. This risk was independent of common cardiometabolic risk factors and increased progressively with worsening severity of MASLD histology, with the highest incidence rates observed with noncirrhotic fibrosis (adjusted HR 1.67, 95% CI 1.47 to 1.89) and cirrhosis (adjusted HR 2.15, 95% CI 1.77 to 2.61).14

Many of the published cohort studies were included in an updated meta-analysis that incorporated 36 studies (published until July 2021) with ~5.8 million middle-aged individuals from different countries and captured nearly 100,000 fatal and nonfatal CVD events over a median of 6.9-year follow-up. This meta-analysis concluded that MASLD (diagnosed by liver imaging, International Classification of Diseases codes or liver histology) conferred a pooled HR of 1.45 (95% CI 1.31 to 1.61) for fatal and nonfatal CVD events, a risk that appeared to increase further with more advanced liver disease, especially MASH with higher fibrosis stages (random-effects HR 2.50, 95% CI 1.68 to 3.72) and remained statistically significant in those studies where analysis was adjusted for common cardiometabolic risk factors.15

After the publication of this comprehensive meta-analysis, these findings have been further supported by other cohort studies. For instance, using a nationwide health screening database of ~8.8 million South Korean adults followed up for a median of 12.3 years, Lee et al reported that MASLD (assessed by fatty liver index ≥30) was independently associated with an increased risk of incident CVD events defined as a composite of myocardial infarction, ischaemic stroke, heart failure or cardiovascular death (adjusted HR 1.39, 95% CI 1.38 to 1.40).16 In the UK Biobank cohort study involving 330751 individuals without baseline CVD, Chen et al confirmed that MASLD was significantly associated with an increased risk of incident CVD events over a median of 11.8 years.17 Subsequently, in the UK Biobank imaging substudy (33,616 participants) where liver disease activity (measured by iron-corrected T1 mapping) and liver fat (by proton density fat fraction) were assessed by MRI using LiverMultScan, Roca-Fernandez et al found that liver disease activity was associated with a higher risk of major CVD events, cardiac hospitalisations and all-cause mortality, independent of pre-existing metabolic syndrome features and liver fat.18

Data from the Rancho Bernardo study (including 1523 elderly participants from the USA followed up for a mean of 15.2 years) confirmed that MASLD was independently associated with a ~35% higher risk of CVD mortality.19

To date, convincing epidemiological evidence indicates that MASLD promotes not only accelerated coronary atherosclerosis but also affects all other anatomical structures of the heart, conferring an increased risk of left ventricular diastolic dysfunction and hypertrophy, cardiac valvular calcification and arrhythmias (mainly permanent atrial fibrillation).20-24 Furthermore, a recent meta-analysis of 11 longitudinal cohort studies with aggregate data on more than 11 million middle-aged individuals reported that MASLD was associated with a 1.5-fold higher long-term risk of new-onset heart failure (pooled random-effects HR 1.50, 95% CI 1.34 to 1.67), regardless of the presence of hypertension, T2DM and other common cardiometabolic risk factors.25 These findings have been confirmed in two cohorts of ~175,000 outpatients with and without MASLD who were propensity score matched for sex, age, index year and known risk factors for heart failure.26 In this cohort study, the authors found that MASLD was significantly associated with a 10-year higher cumulative incidence of heart failure (HR 1.34, 95% CI 1.28 to 1.39), in both men and women and across different age strata.26

Meta-analyses of the excess of fatal and nonfatal CVD events and other cardiac and arrhythmic complications in people with MASLD are summarised in table 1. Collectively, these findings highlight that efforts must continue to raise awareness about MASLD and develop care pathways for identifying and treating patients at increased CVD risk, together with public health efforts to reduce the healthcare burden of MASLD and MASLD-associated cardiovascular morbidity and mortality.

**Epidemiological data on MASLD and the risk of malignant complications**

The global epidemiology of HCC is shifting away from a disease predominated by chronic viral hepatitis and alcohol abuse, with an increasing share of new cases now attributable to MASLD.1

Substantial epidemiological evidence shows that MASLD is a risk factor for HCC. As recently summarised in an elegant systematic review,27 patients with MASLD-related HCC are more likely to be older and have obesity and other metabolic comorbidities compared with patients with HCC due to other causes. In addition, MASLD-related HCC is associated with a higher proportion of patients without cirrhosis and lower surveillance rates than HCC due to other reasons. Overall survival does not differ between patients with MASLD-related HCC and those with HCC due to other causes, but disease-free survival is longer for patients with MASLD-related HCC. These data suggest that HCC surveillance strategies should be developed not only for those with MASLD who have progressed to cirrhosis but also for MASLD patients without cirrhosis who are at high risk of developing HCC.17 However, there is currently no consensus regarding HCC surveillance in non-cirrhotic MASLD patients. Future studies are needed to perform MASLD-specific cost-effectiveness analyses for HCC surveillance, principally in those with non-cirrhotic MASH.28

In a meta-analysis of 64 observational cohort studies (published until August 2020) with 1903 incident cases of HCC (50 eligible studies, n=625 984 participants) and 2288 incident cases of any extrahepatic cancer (18 studies, n=41 027 participants), Thomas et al29 showed that the HCC incidence rate was 1.25 per 1000 person-years. The HCC incidence rate was remarkably higher in patients with MASLD with advanced fibrosis or cirrhosis (14.5 per 1000 person-years) than in their counterparts without advanced fibrosis/cirrhosis. In this meta-analysis, the authors reported that the pooled extrahepatic cancer incidence rate was 10.6 per 1000 person-years. The most frequently occurring extrahepatic cancers were uterine cancer (4.27 per 1000 person-years), breast cancer (4.02 per 1000 person-years), prostate cancer (1.44 per 1000 person-years), colorectal cancer (1.43 per 1000 person-years) and lung cancer (1.35 per 1000 person-years). Extrahepatic cancer incidence rates did not appear to be significantly higher in patients with MASLD with advanced fibrosis or cirrhosis (14.5 per 1000 person-years) than in their counterparts without advanced fibrosis/cirrhosis. In this meta-analysis, the authors also showed that the pooled extrahepatic cancer incidence rate was 10.6 per 1000 person-years. The most frequently occurring extrahepatic cancers were uterine cancer (4.27 per 1000 person-years), breast cancer (4.02 per 1000 person-years), prostate cancer (1.44 per 1000 person-years), colorectal cancer (1.43 per 1000 person-years) and lung cancer (1.35 per 1000 person-years). Extrahepatic cancer incidence rates did not appear to be significantly higher in patients with MASLD with advanced fibrosis or cirrhosis.29 Interestingly, this meta-analysis also showed that extrahepatic cancers were over eightfold more frequent than HCC in people with MASLD. As the global prevalence of MASLD is around 38% and is projected to increase further within the next decade,1 these findings may support the need for early detection of extrahepatic cancers in adults with MASLD, regardless of the coexistence of advanced fibrosis or cirrhosis.

We also recently performed a meta-analysis of observational cohort studies (published until December 2020) to quantify the magnitude of the association between MASLD and the risk of
extrahepatic cancers. This meta-analysis included 10 cohort studies with 182,202 middle-aged individuals and ~8,500 incident cases of extrahepatic cancers at different sites over a median of 5.8 years. We found that MASLD was significantly associated with a ~2.5-fold increased risk of thyroid cancer and a ~1.5–2 fold increased risk of developing gastrointestinal cancers (oesophagus, stomach, pancreas or colorectal cancers). Furthermore, MASLD was significantly associated with a ~1.2–1.5 fold increased risk of developing lung, breast, gynaecological or urinary system cancers. All risks were independent of age, sex, smoking history, obesity, T2DM or other potential confounding factors (table 1). The overall heterogeneity for most of the primary pooled analyses was low. However, not enough data were available to examine whether extrahepatic cancer incidence rates increased with the severity of liver disease. Moreover, these findings have recently been confirmed in a retrospective cohort study from Germany. In this study, the investigators identified 86,777 patients with MASLD (defined by International Classification of Diseases codes) and a matched cohort of equal size without MASLD from the Disease Analyzer database (IQVIA), compiling diagnoses and demographic data from general practitioners. During a 10-year follow-up, the investigators reported significantly higher incidence rates of skin cancer, digestive organ cancer, prostate cancer, breast cancer and gynaecological cancers among MASLD patients than among those without MASLD.

The prognostic importance of extrahepatic cancers in MASLD has also been further supported by mortality data reported by Simon et al in a nationwide cohort of over 10,000 Swedish adult individuals with biopsy-confirmed MASLD and ~50,000 matched controls followed for a median of 14.2 years. In this cohort study, the authors found that all MASLD histological stages were associated with significantly increased overall mortality and that the excess mortality related to MASLD was primarily from extrahepatic cancers, followed by cirrhosis, CVD and HCC. In a subsequent analysis, the same authors examined the incidence rates of both extrahepatic cancers and HCC.32 In a subsequent analysis, the same authors examined the incidence rates of both extrahepatic cancers and HCC.32
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cancer incidence rates (13.8 vs 10.9 per 1000 person-years; adjusted HR 1.27, 95% CI 1.18 to 1.36), driven primarily by HCC. Furthermore, MASLD was associated with significantly increased pancreatic, kidney/bladder and melanoma rates.13

After the publication of the two meta-analyses mentioned above,29 30 other large cohort studies reported that MASLD might be a modifiable risk factor for extrahepatic cancer development (mainly gastrointestinal cancers). For instance, in a nationwide cohort study that included ~5.2 million individuals aged 20–39 years who underwent national health screening under the Korean National Health Insurance Service between 2009 and 2012, Park et al.31 reported that MASLD (assessed by fatty liver index ≥30) was associated with an increased risk of overall gastrointestinal cancers (adjusted HR 1.16; 95% CI 1.10 to 1.22), with adjusted HRs ranging from 1.14 to 1.53 for stomach, colorectal, pancreatic, biliary tract or gallbladder cancers, respectively. These associations remained significant even after adjustment for age, sex, smoking, obesity and alcohol consumption.44 In a cohort of 151 591 Chinese adults followed for a median of 12.6 years, the authors reported that MAFLD (assessed by ultrasonography) was associated with an increased risk of prostate (HR 1.49, 95% CI 1.07 to 2.08), thyroid (HR 1.47, 95% CI 1.01 to 2.12), kidney (HR 1.54, 95% CI 1.18 to 2.00), colorectal (HR 1.15, 95% CI 0.98 to 1.34) and breast cancers (HR 1.31, 95% CI 1.04 to 1.66), even after controlling for age, sex, education level, smoking, alcohol consumption, physical activity and family history of cancers.45 Using the Swedish National Patient Registry, Björkström et al.46 found that patients with MASLD had an increased risk of developing incident cancer over a median follow-up of 6 years compared with control subjects (9.7 vs 8.6 cases per 1000 person-years; HR 1.22, 95% CI 1.12 to 1.33). The risk for HCC was particularly high (adjusted HR 12.2, 95% CI 7.1 to 20.8). The risk for other extrapatiche cancer subtypes was also significantly increased (colorectal (adjusted HR 1.38), kidney (adjusted HR 2.12), bladder (adjusted HR 2.51) and uterine cancers (adjusted HR 1.78)).36

Finally, a meta-analysis of eight observational studies (including 56 745 MASLD individuals and 704 incident cases of gastrointestinal cancers) found that patients with lean MASLD had a greater risk of HCC (random-effects HR 1.77, 95% CI 1.15 to 2.73), pancreatic (random-effects HR 1.97, 95% CI 1.01 to 3.86) and colorectal cancers (random-effects HR 1.53, 95% CI 1.12 to 2.09) than non-lean MASLD patients. No significant differences were observed for oesophagus, biliary tract and small intestine cancers.37 These findings emphasise a possible carcinogenic role for MASLD that is independent of obesity, and further highlight the need to explore tailored cancer prevention strategies for this patient population.

Pathophysiology of MASLD and its relationship with CVD complications

Figure 1 schematically summarises the main pathophysiological aspects contributing to CVD and malignant complications in people with MASLD.

MASH is present in approximately 20% of individuals with MASLD and is characterised by chronic liver inflammation and low-grade systemic inflammation in most affected individuals.46 The aetiology of chronic liver inflammation and low-grade systemic inflammation is complex and multifactorial, and the concept behind this was discussed in 2010 and referred to as a ‘multiple parallel hits’ hypothesis.38 These ‘multiple hits’ can activate proinflammatory cascades, including various inflammatory cytokines and inflammasomes, such as the NLR family pyrin domain containing 3 (NLRP3).40 41 Chronic liver inflammation is a major driver of liver fibrosis and further complications of MASLD, both inside and outside of the liver.42 It is also well established that low-grade systemic inflammation, such as that observed in MASLD and many other associated diseases, may promote CVD outcomes43 and tumourigenesis.44 It has recently been demonstrated in a preclinical model of MASLD that small extracellular vesicles drive foam cell formation and thereby support atherogenesis and this effect was mediated by an interaction of miR-30a-3p with ABC transporter A1 (ABCA-1).45

Low-grade chronic inflammation is crucial for mediating hepatic and most extrapatiche complications of MASLD. Key pathophysiological components of MASLD include metabolic dysfunction and atherogenic dyslipidaemia.46 These two components may be considered ‘starting points’ for this disease as hepatic insulin resistance characterises most patients with MASLD and is commonly associated with an increased influx of free fatty acids into the liver, which is also aggravated by systemic insulin resistance. In addition, in MASLD there is increased hepatic de novo lipogenesis and a decrease in fatty acid oxidation and very low-density lipoprotein (VLDL) export.47 In this context, lipotoxicity reflects an important aspect of MASLD pathogenesis as specific lipids may exert proinflammatory effects and promote the release of several proinflammatory mediators and the accumulation of inflammatory leucocytes within the liver. Diverse lipid species, such as sphingolipids, ceramides, trans fatty acids or free cholesterol, can also induce liver inflammation, including upregulation of multiple proinflammatory cytokines and nuclear factor kappa B (NF-kB).48 49 Additionally, other not yet well-characterised lipids might contribute to lipotoxicity-related inflammation. Inflammatory signals cause insulin resistance or may further exacerbate existing insulin resistance,50 and NF-kB has been crucially linked to the generation of hepatic insulin resistance.51 52 Inflammation-driven insulin resistance also involves other important pathways in MASLD, such as endoplasmic reticulum stress (ER stress),53 54 Notably, obesity, present in about 80%–90% of MASLD patients, is also associated (independently of MASLD) with low-grade systemic inflammation (‘metaflammation’), ER stress dysregulation or lipotoxicity.55 A very high rate of MASLD is observed in obese individuals, further strengthening the pathophysiological link between obesity and MASLD.56 Genetic factors might also contribute to CVD outcomes as studies have observed a link between certain PNPLA3 genotypes and CVD, including carotid atherosclerosis or coronary heart disease.57–59

Another important component driving chronic inflammation in MASLD is the alteration of gut microbiota. MASLD and especially advanced stages of the disease process are commonly accompanied by substantial gut dysbiosis and the evolution of certain pathobionts.59 A profound gut dysbiosis in MASLD was demonstrated in patients with advanced liver fibrosis and dysbiosis was accompanied by the appearance of Proteobacteria and pathobionts such as Escherichia coli.60 Interestingly, the gut microbiome assessment has the potential to predict later development of MASLD.61 The instability of gut microbiota predicts the evolution of metabolic liver disease, as shown in a large prospective German study.62 Whether targeting the gut microbiome is a promising treatment option for MASLD remains unclear. Several mouse MASH models have shown protective and anti-inflammatory effects using probiotics such as Faecalibacterium prausnitzii.63 64 An altered gut virome has also been associated with the severity of MASLD, as gut virome diversity decreased in severely diseased patients.65 A gut dysbiosis might increase hepatic and systemic lipopolysaccharide (LPS) concentrations in...
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patients with MASLD. Dysbiosis, evolution of various pathogens and gut bacteria-derived metabolites might contribute to hepatic and systemic low-grade inflammation in MASLD. Besides LPS, increased circulating levels of various proinflammatory metabolites, such as gut microbiome-derived lactate, ethanol or trimethylamine oxide (TMAO), characterise MASLD. Furthermore, MASLD is accompanied by decreased total bile acid pool size, especially secondary bile acids or short-chain fatty acids.

What is frequently ignored but equally important is the relevance of diets, especially proinflammatory diets, in MASLD. This concept is important as it has been shown that dietary factors reflect key confounding factors affecting the gut microbiota composition. Research in the past decade has revealed that specific dietary components may induce and promote low-grade inflammation in various organs, including the intestine and the liver. In addition, a proinflammatory state might be promoted when anti-inflammatory diets lack or are not consumed sufficiently.

High-fat diets may typically impair the epithelial intestinal barrier and increase systemic LPS. Milk-derived fats may promote the expansion of certain pathogens, such as Bacteroides wadsworthia, and a consequent decrease of beneficial secondary bile acids, and both milk-derived fat and excessive salt consumption drive Th-1 and Th-17-driven inflammation. Other dietary proinflammatory triggers might constitute consumption of palmitic acid or trans fatty acids, and dietary components such as phosphatidylcholine may result in higher circulating levels of TMAO, which have been linked to atherosclerosis and low-grade systemic inflammation.

The importance of low-grade inflammation in CVD has been highlighted in a recent study by Ridker et al, demonstrating by analysing three large multinational trials of patients receiving statin therapy that low-grade inflammation as measured by plasma high-sensitivity C reactive protein (hsCRP) concentrations predicts more strongly the risk of CVD mortality and morbidity than when only assessing plasma LDL cholesterol (LDL-C) concentrations. This finding is important as it suggests that targeting low-grade systemic inflammation would be of major interest in the future in such patients. Patients with MASH show evidence of low-grade systemic inflammation as the circulating levels of hsCRP and IL-1 receptor antagonist (IL-1RA), another sensitive marker of systemic inflammation, are increased.

Interestingly, plasma hsCRP concentrations correlate with all-cause mortality in MASLD patients, as well as malignancy-related and CVD mortality. With respect to hepatic and extrahepatic inflammation and their driving forces, it remains unclear which ‘hits’ come first and take the lead. It seems most likely, as originally proposed in our ‘multiple parallel hits’ hypothesis that various pathophysiological factors can adversely act in parallel, such as lipotoxicity, insulin resistance, obesity, proinflammatory diets or intestinal dysbiosis, thereby causing
hepatic and extrahepatic chronic inflammation in a concerted manner. Chronic inflammation is crucially involved in MASLD progression, including liver-related complications such as HCC, but may also promote adverse CVD outcomes and extrahepatic cancers. Anti-inflammatory therapies might, therefore, play an important role in the future management of MASLD/MASH. It remains, however, unclear which components in MASLD finally cause accelerated atherosclerosis and CVD, but it can be speculated that similarly as in the liver, ‘multiple parallel hits’ may adversely affect the cardiovascular system and vasculature.

Pathophysiology of MASLD and potential associations with hepatic and extrahepatic malignancies

**Hepatocellular carcinoma**

HCC is a typical complication of MASLD-related cirrhosis but also appears at earlier non-cirrhotic stages of the disease. MASLD-related HCC might evolve in the next years as the most prevalent cause of HCC in humans. The pathophysiology of HCC is still not completely understood as it reflects a feature of many different liver diseases accompanied by chronic liver injury and inflammation. Both innate and adaptive immunity may contribute to the development of MASLD-related HCC. Preclinical studies strongly support a role for innate immunity and proinflammatory cytokines. Obesity-driven HCC development is dependent on the proinflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor (TNF), as demonstrated in dietary and genetic models of fatty liver disease in mouse models. This effect was driven by the transcription factor signal transducer and activator of transcription 3 (STAT3) and NF-kB. Interestingly, specific liver cancer progenitor cells in the liver may progress towards a malignant phenotype in an IL-6-dependent manner. Other proinflammatory cytokines, such as IL-1 alpha, may promote liver tumourigenesis. Various additional pathways drive inflammation-related HCC, such as ER stress, a pathway that is also activated in human MASLD. Many other proinflammatory ‘hits’ have the potential to drive hepatic carcinogenesis, including mammalian target of rapamycin complex 1 (mTORC1) and oxidative stress, as demonstrated in nicotinamide adenine dinucleotide phosphate oxidase (NOX) knockout mice. Whereas several previous studies have highlighted that innate immunity and its key proinflammatory players constitute major drivers of HCC development, more recent studies reported that adaptive immunity is also involved in HCC development. A landmark study from Dudek et al revealed a crucial role for T cells in liver immunopathology and MASH. These authors observed hepatic accumulation of CD8+ T cells with phenotypes that combined tissue residency with effector and exhaustion characteristics, such as programmes cell death protein (PD1) expression. IL-15 induced the forkhead box O1 (FOXO1) downregulation and C-X-C chemokine receptor 6 (CXCR6) upregulation, which together rendered liver-resident CXCR6+CD8+ T cells susceptible to metabolic stimuli and triggered autoaggression. Such autoaggressive CD8+ PD1+ T cells accumulate especially in MASH patients, and this cell type has been linked to a lack of immune surveillance in mice and human studies. Such a micromilieu might favour liver carcinogenesis, explaining why HCC evolves even in a non-cirrhotic liver. It remains unclear how metabolic signals interfere with this type of immunity. Specific T cells such as CD8+ PD1+ CXCR6+ T cells respond to metabolic stimuli even in an antigen-independent manner and thereby can kill hepatocytes, causing a highly proinflammatory milieu. The role of immunity in MASLD-related HCC has been recently reviewed. Besides chronic inflammation and immunity, some genetic polymorphisms related to a greater susceptibility to MASLD and MASH, such as the PNPLA3, TM6SF2, MBOAT7 and HSD17B13 genetic variants, have also been linked to HCC development. In support of this, a recent study reported familial clustering of liver-related complications, including HCC, in biopsy-proven MASLD patients.

**Extrahepatic cancers**

MASLD is associated with an increase in extrahepatic malignancies, as discussed in the first section of this review. An increased rate of malignancies is also seen in obesity, and it is assumed that common mechanisms can contribute to extrahepatic malignancies in obesity±MASLD. A common feature of both disorders is chronic inflammation, as chronic inflammation, including NF-kB activation, is a crucial driver of cancer development. The importance of obesity as a significant cancer driver is also supported by bariatric surgery studies where death rates from cancer were decreased with weight loss. In addition, rates of gastrointestinal cancers such as oesophageal adenocarcinoma decreased after bariatric surgery-induced weight loss. Other pathways may contribute to an increased risk of extrahepatic cancers that involve adipokine signalling. Adiponectins are key products secreted by adipose tissue, either released in excess or impaired production, as in severe metabolic disturbances. Prototypic adiponectins, such as adiponectin or leptin, have opposing effects as leptin favours a proinflammatory milieu, whereas adiponectin has substantial anti-inflammatory and insulin-sensitising effects. A common cancer associated with MASLD is colorectal carcinoma (CRC) and cancers such as CRC, oesophageal cancer, prostate cancer or breast cancer are associated with lower plasma adiponectin concentrations. Visceral adiposity, common in MASLD and associated with lower adiponectin levels, is also a risk factor for CRC. Preclinical studies highlighted the importance of adiponectin in CRC carcinogenesis as this adipokine may inhibit CRC cell growth dependent on the activation of adenosine monophosphate-activated protein kinase (AMPK) and mTOR. Several other mechanisms might promote carcinogenesis either directly or indirectly, such as increased production of reactive oxygen species, insulin-like growth factor 1 (IGF-1) or insulin resistance mainly via activation of other inflammatory pathways, such as mitogen-activated protein kinase (MAPK) p38 signalling pathways.

**CVD risk assessment, lifestyle modification and specific treatments for MASLD that may benefit CVD risk**

In this section, we consider the CVD risk assessment and recommendations for lifestyle changes and pharmacological treatments targeting CVD risk in people with MASLD. Although, as mentioned above, MASLD is an independent risk factor for CVD, and the severity of liver disease further amplifies that risk of CVD events, existing algorithms and risk calculators do not, to date, consider MASLD as a CVD risk factor in the estimation of an individual’s level of CVD risk using available risk calculators. Since liver fibrosis markedly increases the risk of adverse CVD outcomes, it might be expected that liver fibrosis would further improve CVD risk prediction in people with MASLD. However, to date, this issue remains unresolved, and CVD risk calculators do not consider any of the individual measures of liver disease in MASLD. Nevertheless, CVD risk assessment in all patients with MASLD is clinically mandatory to inform appropriate management and treatment decisions focused on attenuating CVD risk. Patients with MASLD represent a heterogeneous
group of individuals concerning their CVD risk, and with the considerable treatment options now available, clinicians need to make personalised treatment decisions since not all patients with MASLD have the same cluster of CVD risk factors nor the same absolute risk of CVD events.

CVD risk assessment in MASLD

The first consideration is how CVD risk should be assessed in patients with MASLD? Most patients with MASLD are likely to be middle-aged, and although there are exceptions, women with MASLD are most likely to be perimenopausal or postmenopausal. Because of the age demographic of patients with MASLD, this patient group should be considered for a CVD health check as most patients will be >40 years old. It is also important to consider ethnicity and the region of the globe in which the person’s risk of CVD is being assessed.

Beyond the presence of MASLD, various factors increase a person’s risk of developing CVD. These risk factors can be

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**Figure 2** Flow diagram describing a pragmatic approach to the assessment and management of CVD risk in people with MASLD. This flow diagram emphasises the need to assess individual CVD risk factors and estimate CVD risk in patients with MASLD. The flow diagram also illustrates specific treatments to attenuate CVD risk in patients at high risk of CVD, where those treatments have been shown to have proven efficacy in reducing incident CVD events. The flow diagram illustrates the importance of assessing the coexistence of T2DM, CKD, hypertension or previously diagnosed CVD causing a vascular event, such as acute myocardial infarction or ischaemic stroke. The presence of these conditions may warrant additional disease-specific treatments. For example, for patients with known CVD, it may prove necessary to focus on high-dose statin treatment with the goal of achieving a plasma LDL-C level <1.8 mmol/L. For patients with T2DM who have microvascular disease affecting the kidneys (abnormal albuminuria, ie urine ACR >30 mg/g), it may be necessary to implement treatment with SGLT-2 inhibitors. The flow diagram also illustrates the importance of estimating the 10-year risk of a first CVD event using a specific CVD risk calculator tool. Such a tool needs to have been validated in the region and population in which it will be used. For patients with ‘intermediate’ CVD risk or those who are unconvinced by the benefit of taking a statin, consideration of whether further noninvasive investigation of potential CVD is required. Where high-resolution CT is available, CACS assessment can offer a quick but relatively expensive investigation for refining CVD risk prediction. Where the CVD score is increased (eg, >90th centile adjusted for age and sex or the score is high, eg, >300 Agatston units), referral to cardiology specialists for further investigation should be considered. Such individuals may require not only treatment with a high-dose statin to achieve plasma LDL-C targets (see above) but also low-dose aspirin and ACE inhibitors (ACE-I) or angiotensin II receptor blockers. Although statins are safe in people with MASLD or MASH, some individuals will not be able to tolerate statin treatment. In these individuals, other lipid-lowering drugs, such as ezetimibe, bempedoic acid or proprotein convertase subtilisin/kexin type-9 (PCSK9) monoclonal antibody treatment, may be warranted and further specialist lipid management advice should be sought.

Antihyperglycemic drugs such as GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists have beneficial hepatic effects, mainly through weight loss. GLP-1 receptor agonists have proven efficacy to benefit type 2 diabetes mellitus, CVD and CKD. In particular, GLP-1 receptor agonists are effective in the brain and decrease appetite and induce satiety, thus reducing dietary calorie intake. These effects can facilitate weight loss, which benefits MASLD, type 2 diabetes mellitus and CVD risk factors. Angiotensin II receptor blockers or RAS inhibitors have beneficial effects on the vasculature and kidneys, reducing blood pressure, while pioglitazone that is licensed for the treatment of T2DM has been shown to have beneficial effects to treat liver disease in MASLD, decrease the risk of acute myocardial infarction and ischaemic stroke, and has durable effects to lower plasma glucose concentrations in patients with, or at risk of, type 2 diabetes mellitus. ACR, albumin-to-creatinine ratio; CACS, Coronary Artery Calcium Score; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MASLD, metabolic dysfunction-associated steatoic liver disease; RAS, renin-angiotensin system; SGLT2, sodium glucose co-transporter-2; T2DM, type 2 diabetes mellitus.
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**Figure 3** Current therapeutic approaches for MASLD or MASH with beneficial or neutral effects on the cardiovascular risk profile. There are currently no licensed treatments for MASLD or MASH. The figure summarises the evidence mainly derived from phase 2 or phase 3 randomised placebo-controlled trials of current therapeutic approaches showing promise in the treatment of this common and burdensome liver disease, in terms of improvement in liver steatosis, steatohepatitis or fibrosis. Licensed treatments for type 2 diabetes mellitus (eg, GLP-1 receptor agonists, pioglitazone or SGLT2 inhibitors) are among the most promising treatment options for MASLD or MASH and effectively also decrease the future risk of fatal and nonfatal CVD events. CVD, cardiovascular disease; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, non-alcoholic steatohepatitis.

divided into non-modifiable and modifiable risk factors. Briefly, CVD risk factors are: (a) non-modifiable, for example, older age, male sex, having a strong family history of premature CVD and being of a certain ethnicity (such as South Asian ethnicity) or having early menopause (<40 years) and (b) modifiable, for example, smoking, having an increased plasma LDL-C concentration, being sedentary, eating an unhealthy diet and having factors linked with obesity and specifically abdominal obesity, such as hypertension, insulin resistance, atherogenic dyslipidaemia and T2DM as key features of metabolic syndrome.104

With many of these modifiable CVD risk factors (eg, T2DM, hypertension and obesity), there is a further amplification of CVD risk when associated comorbidities such as CKD also occur. For example, T2DM is a strong risk factor for CKD stage ≥3 (defined by estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m² with/without coexisting abnormal albuminuria or overt proteinuria), and each of these associated renal factors, as well as chronic dialysis or renal transplantation, are strong independent risk factors for CVD.

Although increased plasma LDL-C concentration is a common risk factor in middle-aged subjects (and occurs independently of MASLD), an increased plasma LDL-C concentration will further increase the risk of CVD in people with MASLD.15 A more common dyslipidaemia frequently occurring with MASLD is the atherogenic lipoprotein phenotype, comprising increased small-dense LDL particles, low HDL-cholesterol and high triglyceride concentrations. Although subjects with MASLD with atherogenic dyslipidaemia may have normal plasma LDL-C concentrations, it is in this situation that treatment with a statin will decrease CVD risk.
While these modifiable and non-modifiable risk factors and associated comorbidities must be considered in assessing CVD risk, it is also important to recognise that some people with MASLD may have other unrelated but relatively common comorbid conditions (unrelated to MASLD) that may also increase the CVD risk. These comorbid conditions that need to be considered and recognised as important additional CVD risk factors include rheumatoid arthritis, severe mental ill health and associated treatments, and periodontal disease.

For assessing global CVD risk, some countries/regions/organisations now recommend vascular health checks or risk assessments targeted at individuals of a certain age and who do not have pre-existing CVD, T2DM or CKD as recognised easily identifiable risk factors for CVD. For example, the ACC/AHA (American College of Cardiology/American Heart Association) guidelines and in England and Wales, the National Institute for Health and Care Excellence (NICE) guidelines recommend that everyone between the ages of 40 and 75 years should be invited for a health check. This health check includes a CVD risk assessment, evaluation of alcohol consumption, physical activity levels, plasma LDL-C level, body mass index and screening for T2DM and CKD with an assessment of haemoglobin A1c and eGFR. Additionally, it is important to assess psychological stressors and health literacy and provide appropriate support where necessary. The CVD risk assessment tools should be specific to the region/country of interest, and in England and Wales, it is recommended that the QRISK CVD risk calculator is used, as this has been validated in the UK. In the USA, pooled cohort equations are recommended for CVD risk assessment. The European Society of Cardiology (ESC) recommends using sex-specific SCORE-2 calculators in European populations. For example, the ESC recommends the use of the SCORE-2 risk calculator up to the age of 70 years; for older persons (OP) above this age, the SCORE-2 OP calculator, and for people with T2DM, the SCORE-2 Diabetes calculator. The SCORE-2 Diabetes calculator was validated in people with T2DM without pre-existing CVD. Sex-specific competing risk-adjusted models were used, including both traditional CVD risk factors (age, smoking, systolic blood pressure, total cholesterol and HDL-cholesterol levels) and diabetes-related variables (age at diabetes diagnosis, haemoglobin A1c and eGFR). These models were recalibrated to CVD incidence in four European risk regions.

It is recommended that global CVD risk is assessed every 5 years, and it is important to bear in mind that ageing is the major modifiable risk factor that powerfully influences the estimate of the risk of a CVD event over the next 10 years. The 2019 ACC/AHA guideline on the primary prevention of CVD contains appropriate guidance that should be used for people with MASLD, bearing in mind all of the other CVD risk factors linked (and not linked) to MASLD considered above. In the ACC/AHA guideline, it is recommended that adults who are 40–75 years of age and are being evaluated for CVD prevention should undergo a 10-year CVD risk estimation and have a clinician–patient risk discussion before starting on pharmacological therapy, such as antihypertensive therapy, a statin or aspirin (aspirin should be used infrequently in the routine primary prevention of CVD because of lack of net benefit). For younger individuals, for example, 20–39 years of age, it is reasonable to assess common CVD risk factors every 5 years.

Statin therapy is the first-line treatment for primary prevention of CVD in people considered to be at increased risk. There is still uncertainty about the level of risk at which healthcare practitioners should advocate intervention with statin treatment. In the USA, it is considered good practice to recommend statin treatment in individuals at ‘intermediate risk’ (ie, ≥7.5% 10-year estimated CVD risk), whereas in the UK a ≥10% threshold for intervention is advocated. With the lower threshold of CVD risk, it is important to realise that virtually every 60-year-old man would be treated with a statin based on their age alone, regardless of CVD risk factors. In certain individuals with other risk-enhancing factors or in persons at intermediate CVD risk who are not keen to start statin treatment, high-resolution CT scanning of the coronary arteries to detect coronary artery calcium has a place in helping refine decision-making regarding reassurance, advice that treatment is recommended or advice that referral to Cardiology specialists is needed for consideration of further diagnostic cardiac tests. In such subjects, assessment of coronary artery calcium with high-resolution CT of the coronary arteries to assess the presence, quantity and location of coronary artery calcium is a valuable investigation to assist in refining risk prediction either upwards or downwards, as part of the process of helping shared decisions between patients and healthcare professionals. For example, if the coronary artery calcium score is ≥100 Agatston units (or ≥75 th age/sex/race percentile), a subject might be moved upward, and if the coronary artery calcium score is 0, a subject can be reassured. For younger adults, an estimation of lifetime CVD risk in the 20–59 years age group may also be considered. Additionally, non-pharmacological interventions are recommended for all adults with elevated blood pressure or hypertension, and for those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg.

Lifestyle changes and drug treatments for CVD prevention in MASLD

Healthcare professionals should advocate the cessation of smoking and the consumption of a healthy diet that encourages vegetables, fruits, nuts and minimally processed whole grains. Vegetables, lean animal or fish proteins will reduce the consumption of trans fats and red meats, processed meats, refined carbohydrates, sucrose, fructose and sweetened drinks should be limited. For most individuals with MASLD who are overweight or obese, the benefits of calorie restriction to decrease body fat, reduce liver fat and inflammation, and improve the associated metabolic syndrome features should be emphasised. There remains debate about whether small amounts of daily alcohol consumption are harmful or beneficial. That said, mild-moderate alcohol intake and metabolic syndrome are highly prevalent in the population and can frequently coexist. The few available prospective studies have indicated that mild-moderate alcohol intake is associated with an increased risk of liver-related outcomes. Systems biology analyses have suggested that alcohol intake and metabolic syndrome may potentiate the effects of each other, affecting common pathways in fatty liver disease to worsen liver-related outcomes. Consequently, regardless of any impact of modest alcohol intake on the risk of CVD in MASLD, for benefitting liver health, it would seem prudent to advocate alcohol abstinence for patients with MASLD. Patients should also be encouraged to undertake ≥150 min of moderately intense or 75 min of vigorous physical activity per week. When considering the effects of lifestyle advice to specifically treat obesity and reduce CVD risk in patients with MASLD, it is important to consider that weight loss is best achieved with calorie restriction. For example, it has been shown that marked calorie restriction induces T2DM remission in overweight or obese people recently diagnosed with T2DM. In this open-label, cluster-randomised, controlled trial (DiRECT trial), participants randomly assigned to an integrated structured,
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intense, weight-management programme (intervention) reached a significantly greater weight reduction ≥15 kg and remission of T2DM at 2 years compared with those assigned to the best-practice care in accordance with guidelines (control). Thus, a structured calorie restriction programme focused on weight loss induces T2DM remission over 2 years, although in this trial, it was uncertain how many patients also had MASLD. Losing body fat is very important for decreasing plasma glucose levels, ameliorating MASH and improving metabolic syndrome features but, to date, in MASLD it is uncertain whether these benefits can be sustained, not least if people relapse and regain body fat. It is also uncertain whether the improvement in cardiometabolic risk factors caused by calorie restriction and weight loss, translates into longer-term benefits on CVD events.

When considering potential drug treatments that may benefit MASLD and CVD, it is important to consider drug actions that are beneficial for treating cardiometabolic risk factors and that may be sustained, not least if people relapse and regain body fat. It is also uncertain whether the improvement in cardiometabolic risk factors caused by calorie restriction and weight loss, translates into longer-term benefits on CVD events.

CONCLUSION

Epidemiological evidence suggests an excellent concordance rate between NAFLD and MASLD definitions—that is, ~99% of individuals with NAFLD meet MASLD criteria and, therefore, both definitions have similar natural histories. MASLD is a “multisystem disease” where insulin resistance and related metabolic dysfunction play a pathogenic role in the development of MASLD and its most relevant liver-related morbidities and extrahepatic complications (such as CVD, T2DM, CKD and certain extrahepatic cancers). Since MASLD is an independent risk factor for CVD morbidity and mortality and most patients die from the consequences of CVD rather than from liver-related complications, it is important to try and attenuate that risk of CVD. Patients with MASLD have a heterogeneous cluster of CVD risk factors, and the absolute risk of CVD events varies considerably according to age, sex, ethnicity, region and individual risk factors. Consequently, it is essential to assess CVD risk in subjects with MASLD using region-specific CVD risk calculators. Statins are usually safe in people with MASLD and should be advocated where the 10-year estimated CVD risk of a vascular event is ≥10% (or ≥7.5% as recommended in the USA). Beyond supporting lifestyle improvements, many licensed treatments for T2DM, for example, GLP-1 receptor agonists, SGLT2 inhibitors or pioglitazone, have now been shown to reduce the risk of adverse CVD outcomes and improve coexisting risk factors. These and other well-established drug treatments that have also been shown to be beneficial for attenuating CVD risk (eg, RAS inhibitors) should be considered in individual patients with MASLD as part of a holistic approach to reducing CVD risk in this patient population.

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ORCID iDs
Giovanni Targher http://orcid.org/0000-0002-4325-3900
Christopher D Byrne http://orcid.org/0000-0001-6322-7753
Herbert Tilg http://orcid.org/0000-0002-4325-2579

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