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MAFLD: a multisystem disease

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***Abstract*:** Nonalcoholic fatty liver disease (NAFLD), affecting about 25% of general population and more than 50% of dysmetabolic patients, is an emerging cause of chronic liver disease and its complications. Recently, an international consensus of experts proposed to rename this disease as 'Metabolic dysfunction-Associated Fatty Liver Disease' (MAFLD) to focus on the bidirectional interplay between fatty liver and metabolic alterations and to stress the need of assessing fatty liver independently from alcohol consumption and other coexisting causes of liver disease. The peculiarity of NAFLD/MAFLD lies in the presence of a higher risk of not only – as expected – liver-related events but also of extrahepatic events, mostly cardiovascular and cancers. Available evidence suggests that these associations are not only the expression of sharing the same risk factors but shed light about the ability of NAFLD/MAFLD and particularly of its progressive form – nonalcoholic/metabolic dysfunction-associated steatohepatitis – to act as an independent risk factor *via* promotion of atherogenic dyslipidemia and a proinflammatory, profibrogenic, and procoagulant systemic environment. The present review summarizes available epidemiological and clinical evidence supporting the concept of NAFLD/MAFLD as a multisystemic disease, and highlights potential explanatory mechanisms underlying the association between NAFLD/MAFLD and extrahepatic disorders.

Keywords: fatty liver, MAFLD, NAFLD

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Introduction

The term nonalcoholic fatty liver disease (NAFLD) identifies a broad spectrum of liver disorders strongly related to dysmetabolic diseases and that is considered the hepatic expression of metabolic syndrome. The bidirectional epidemiological and pathophysiological link between NAFLD and metabolic disorders led to the need for an update of the nomenclature and the diagnostic criteria. For this purpose, 'Metabolic dysfunction-Associated Fatty Liver Disease' (MAFLD) has been proposed as the more appropriate term: it better reflects the pathogenetic basis of the disease and allows a more comprehensive and standardized approach to patient management. This term describes a condition characterized by the presence of hepatic steatosis (detected either by imaging techniques, blood biomarkers/scores or by liver histology) associated with type 2 diabetes mellitus (T2DM) and overweight/obesity, regardless of alcohol intake or the exclusion of other etiologies of chronic liver disease, which until now were necessary for the diagnosis of NAFLD. In non-diabetic lean/normal-weight patients, the diagnosis of MAFLD requires the presence of at least two metabolic risk abnormalities, including high waist circumference, arterial hypertension, dyslipidemia, prediabetes, high homeostasis model assessment (HOMA) score and high C-reactive protein serum levels. Thus, the rationale behind this new concept of MAFLD lies on the inclusion as diagnostic criteria of metabolic dysfunctions – well-known risk factors for disease progression that NAFLD diagnosis does not require – and on assessing fatty liver independently from alcohol consumption and other coexisting causes of liver disease.[1–3]

As the consequence of the worldwide spread of obesity and diabetes, the prevalence of NAFLD and its complications is increasing. Recent cohort

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studies reported a very high prevalence of NAFLD – from 25% in general population to 50–60% in obese and diabetic patients – with an estimated increase in 2030 ranging from +11.3% in Germany to +12% in Spain.[4–6] When considering the new definition, a recent meta-analysis showed that MAFLD affects more than a third of the global population with and estimated global MAFLD prevalence of 50.7%, specifically in overweight and obese adults, with a higher prevalence in male than female (59.0% *versus* 47.5%).[7,8]

Various studies clearly demonstrated that NAFLD and MAFLD patients have not only a higher risk of hepatic events but also of extrahepatic complications mostly cardiovascular disease (CVD) and extrahepatic cancers, suggesting that NAFLD/MAFLD is part of a multisystemic disease and identifying in the severity of liver fibrosis the most relevant prognostic factor.[9,10] In addition, different studies conducted to compare NAFLD and MAFLD highlighted that differences exist between the two entities on identifying patients at high risk of progression and of extrahepatic complications.

This review summarizes available epidemiological and clinical evidence supporting the concept of NAFLD/MAFLD as a multisystemic disease and highlights potential explanatory mechanisms underlying the association between NAFLD/MAFLD and extrahepatic disorders.

NAFLD, MAFLD, and liver-related events

Even though only a minority of NAFLD patients will progress to cirrhosis and end-stage liver disease, due to its high prevalence, NAFLD is becoming the leading cause of liver-related events worldwide. Consistent with available evidence, liver fibrosis severity has the most important prognostic role in NAFLD, being independently associated with hepatic outcomes:[11] a fibrosis stage 3 or 4 at the time of diagnosis is shown to have the worst prognosis.[10] Sanyal *et al.*[12] recently showed that the incidence of liver-related complications per 100 persons-year increased with fibrosis stage (F0–F2 *versus* F3 *versus* F4) as follows: variceal hemorrhage (0.00 *versus* 0.06 *versus* 0.7), ascites (0.04 *versus* 0.52 *versus* 1.20), encephalopathy (0.02 *versus* 0.75 *versus* 2.39), and hepatocellular carcinoma (HCC) (0.04 *versus* 0.34 *versus* 0.14).

Although liver biopsy is still considered the 'gold standard' to assess disease severity, several noninvasive tests based on blood tests or imaging have been developed. In a recent study on a general population cohort of the Mediterranean area, advanced fibrosis assessed by liver stiffness was found in 2% of NAFLD patients; this prevalence was even higher in diabetic patients where it ranged 10–20%.[4,13] In the last few years, the emerging concept of MAFLD raised the need to compare NAFLD and MAFLD. The main finding was that MAFLD criteria can discriminate more patients at risk as compared with NAFLD criteria: various observational studies reported that MAFLD better identifies patients with advanced liver fibrosis when compared to NAFLD. Lin *et al.*,[14] in one of the pioneering studies on this issue, demonstrated that noninvasive scores of liver fibrosis were significantly increased in MAFLD than in NAFLD. These findings were further confirmed: Yamamura *et al.*[15] reported that liver stiffness on elastography was higher in MAFLD than NAFLD (7.7 *versus* 6.8 kPa, respectively); Huang *et al.*[16] showed that patients diagnosed with MAFLD alone had higher degree of disease severity assessed by histological and laboratory parameters, compared to those with NAFLD alone.

In the last decades, liver decompensation occurrence has been more frequently associated with NAFLD/nonalcoholic steatohepatitis (NASH) than in the past, as other viral and non-viral etiologies are reducing their burden: Orman *et al.*[17] found that the incidence rate per 100 person-years of decompensation in NAFLD in a retrospective cohort of Indiana was increasing over time (4.0 in 2004–2006 *versus* 6.6 in 2007–2011 *versus* 11.7 in 2012–2014). Unfortunately, to date, data about trends in liver decompensation according to MAFLD diagnosis are still lacking. These changing trends in etiology are also evident in HCC occurrence and, consequently, in HCC patients who underwent liver transplantation.[18] Vitale *et al.*[19] in the retrospective analysis of the ITA.LI.CA. (Italian Liver Cancer) database showed that 'no viruses' cases increased from 2002 to 2019 and, among non-viral patients with HCC, MAFLD tumors were significantly increasing over time (3.6% in 2002–2003 *versus* 28.9% in 2018–2019), whereas the prevalence of hepatitis C virus (HCV) and hepatitis B virus (HBV) decreased. Finally, this reflects on a changing

burden of NAFLD mortality too – data on MAFLD still not available: evidence from the National Vital Statistics System (NVSS) showed that the age-standardized HCC-related mortality and cirrhosis-related mortality increased by 21.1% and 2.7%, respectively, in NAFLD.[20]

NAFLD, MAFLD, and extrahepatic manifestations

NAFLD, MAFLD, and metabolic disorder

NAFLD and metabolic disorders have a strong epidemiological and clinical interplay. The prevalence of NAFLD is higher (>50%) in obese and diabetic populations, and consequently, if we look at NAFLD patients, they have a significantly higher prevalence of metabolic disorders respect to subject without fatty liver. Indeed, as showed by Younossi *et al.*'s[21] meta-analysis on 8,515,431 patients, global prevalence of NAFLD is 25.24% (95% CI: 22.10–28.65%); metabolic comorbidities associated with NAFLD included obesity (51.34%; 95% CI: 41.38–61.20%), type 2 diabetes (22.51%; 95% CI: 17.92–27.89%), arterial hypertension (39.34%; 95% CI: 33.15–45.88%), hyperlipidemia (69.16%; 95% CI: 49.91–83.46%), and metabolic syndrome (42.54%; 95% CI: 30.06–56.05%).

Metabolic comorbidities, and especially diabetes, are risk factors for severity of liver fibrosis in NAFLD; as higher is the number of metabolic comorbidities, higher is the risk of severe liver fibrosis.[22] Moreover, diabetes and metabolic risk factors increased the risk of developing cirrhosis and its complications, including HCC and liver decompensation. In a retrospective cohort study, Kanwal and colleagues evaluated the effects of metabolic traits (diabetes, arterial hypertension, dyslipidemia, and obesity) both individually and jointly to find that each additional metabolic trait increased the risk of cirrhosis and HCC in cases with NAFLD. Although all individual traits had similar modest associations with the risk of progression to cirrhosis (and the composite endpoint of cirrhosis or HCC), their results support a stronger effect of diabetes on the risk of progression to HCC than the other metabolic traits. In fact, in individuals with obesity and arterial hypertension, concomitant diabetes was linked to a significant increase in the risk of progression to HCC (HR from 1.07 in the absence of diabetes to 8.63 with diabetes).[23] However, NAFLD *per se* can increase the risk of developing metabolic disorders. Along this line, Ma *et al.*[24] suggested the presence of a bidirectional relationship between NAFLD and cardiovascular risk factors (Figure 1), showing that NAFLD predicted the development of metabolic disorders and *vice versa*. A Korean cohort study evaluated the association between NAFLD and incidence of diabetes in a large cohort of non-diabetic young population. Baseline NAFLD was strongly associated with an increased incidence of diabetes, the risk being significantly higher in patients with NAFLD and high risk of severe fibrosis using NAFLD fibrosis score (NFS).[25] Growing available evidence about NAFLD as risk factor for diabetes was evaluated in a recent meta-analysis reporting that patients with NAFLD are exposed to a twice higher incidence of diabetes than those without. Moreover, patients with NAFLD and advanced fibrosis were particularly vulnerable to diabetes.[26] The retrospective cohort study made by Björkström *et al.*[27] on patients without diabetes at baseline and with biopsy confirmed NAFLD reported that 51% of patients with fibrosis F3–F4 developed incident diabetes compared with 31% of those with F0–F2; NASH had no effect whatsoever on it. In line with this study, Ampuero and colleagues, in a multicenter and longitudinal study of biopsy-proven NAFLD patients, identified the severity of liver fibrosis as a driver of developing metabolic outcomes such as T2DM, arterial hypertension, and dyslipidemia in metabolically healthy patients. Specifically, they observed that carrying fibrosis F3–F4 had four times higher risk of annual incidence of T2DM and arterial hypertension (AHT) *versus* fibrosis F1–F2, the risk further increasing in obese patients.[28] Considering the close link between diabetes and chronic kidney disease (CKD), a Chinese cohort study aimed to investigate the association between NAFLD and albuminuria in patients with T2DM. The prevalence of albuminuria was higher in diabetic patients with fatty liver disease and in those with advanced fibrosis than in those without (non-NAFLD *versus* liver steatosis *versus* advanced fibrosis: 41.4% *versus* 46.2% *versus* 64.2%, $p < 0.001$). After adjustment for confounding factors [Hba1c, body mass index (BMI), and hypertension], advanced fibrosis has been associated in diabetic patients with estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2, with a higher risk of albuminuria (marker of renal damage, which predicts micro and macrovascular complications related to diabetes).[29]

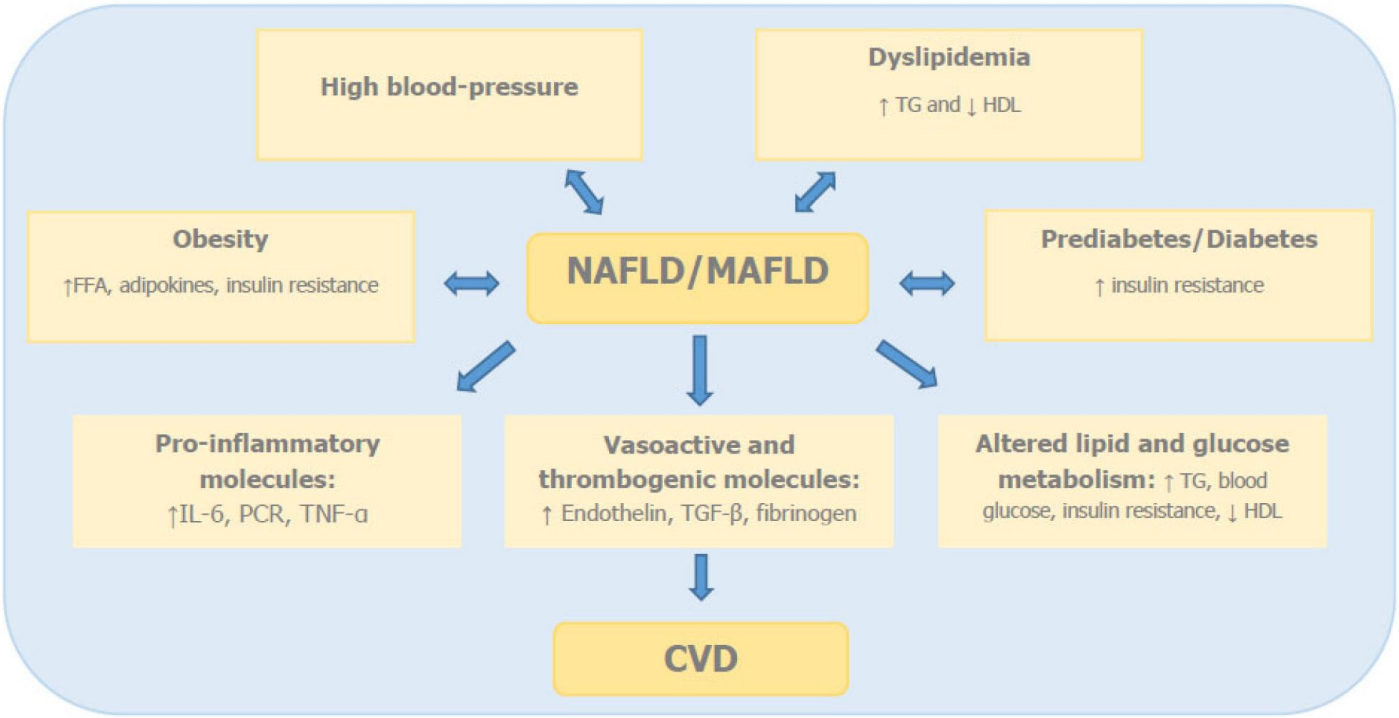

Figure 1. Bidirectional relationship between NAFLD/MAFLD and metabolic outcomes. CVD risk factors, including metabolic syndrome, hypertension, hypertriglyceridemia, IFG and type 2 diabetes at baseline are associated with increased risk of developing fatty liver. In the other direction, greater baseline liver fat is associated with a greater risk of incident arterial hypertension and type 2 diabetes. This suggests bidirectional relationship between NAFLD/MAFLD and CVD risk factors.

The new MAFLD definition emphasizes the bidirectional relationships between fatty liver disease and diabetes, CVD, or its risk factors. A recent Chinese cohort study of 6873 individuals with 4.6 years of follow-up analyzed the association of MAFLD and NAFLD with diabetes. The prevalence of NAFLD and MAFLD was 40.3% (95% CI: 39.2–41.5%) and 46.7% (95% CI: 25.5–28.4%), respectively. During the follow-up, incidence of NAFLD and MAFLD was 22.7% (95% CI: 21.3–24%), and 27% (95% CI: 25.5–28.4%), respectively. MAFLD was also associated with higher risk of incident diabetes and other comorbidities, such as CVD and CKD, with the observed rates being similar when considering NAFLD instead of MAFLD as risk factor. Notably, the risk of incident diabetes was higher when MAFLD was associated with alcohol intake or HBV infection.[30]

NAFLD, MAFLD, and CVD

NAFLD patients have a high prevalence of metabolic alterations, such as obesity, type 2 diabetes, dyslipidemia, and insulin resistance, and their natural history accounts not only for liver-related complications but also for an increased risk of CVDs. This is of great clinical relevance because natural history studies in NAFLD populations reported that CVDs are the first cause of mortality in this population.[31,32] Similarly, a population-based study, that analyzed annual age-standardized extrahepatic mortality among individuals with NAFLD in the United States between 2007 and 2017, reported that the most common and growing cause of death in NAFLD was more likely to be CVD (approximately 20%).[33]

Many studies have also focused on the association between sub-clinical cardiovascular alterations and NAFLD. Pais and colleagues, in a retrospective analysis examined the association between NAFLD and carotid atherosclerosis in a large cohort of French patients with longitudinal follow-up between 1995 and 2012. The presence and progression of carotid intima-media thickness (C-IMT), that predicts CVD events and carotid plaques, was correlated with NAFLD

defined by fatty liver index. Steatosis at baseline predicted carotid plaques occurrence [odds ratio (OR) = 1.63, 95% CI: 1.10–2.41, $p = 0.014$] independently of classical cardiovascular risk factors, such as age, sex, type-2 diabetes, tobacco use, high-sensitivity C-reactive protein (hsCRP), hypertension, and C-IMT. With this study, French colleagues wanted to demonstrate that steatosis contributes to the development of early atherosclerosis and that NAFLD is not only an observer but also a driving force of metabolic syndrome.[34]

In the setting of diabetic patients, Bonapace and colleagues focused on the correlation between NAFLD and cardiac alterations. In particular, type 2 diabetic patients had a greater prevalence of sub-clinical left ventricular diastolic dysfunction, according to steatosis presence and severity. This correlation, found in diabetic patients with normal systolic function and without a history of ischemic heart disease, was independent of hypertension and other many confounders, such as age, sex, triglycerides (TG), and HbA1c. The authors suggested that this association was the result of NAFLD as a marker of ectopic fat accumulation in myocardium.[35]

When moving from sub-clinical cardiovascular alterations to hard clinical outcomes, in an Italian cross-sectional study of 2007, Targher and colleagues analyzed the association between NAFLD and cardiovascular events in type 2 diabetic patients. In this article, NAFLD was diagnosed by ultrasound examination. NAFLD patients had remarkably higher age and sex-adjusted prevalence of coronary (26.6% *versus* 18.3%), cerebrovascular (20.0% *versus* 13.3%), and peripheral (15.4% *versus* 10.0%) vascular disease, than those without NAFLD; this association was independent of classical risk factors and remains statistically significant after adjustment for age, sex, BMI, smoking, diabetes duration, A1C, low-density lipoprotein (LDL) cholesterol, medications, and the metabolic syndrome. Consistently, this study highlights that NAFLD is a predictor of cardiovascular events in multiple sites (coronary, cerebrovascular, and peripheral vascular disease) in type 2 diabetic patients.[36]

The growing evidence about the association between NAFLD and cardiovascular alterations led to a preliminary meta-analysis in 2016 that identified NAFLD as a risk factor for incident CVD events.[37] A larger meta-analysis carried out in 2021 further investigated the correlation between NAFLD and incidence of CVD. This study analyzed data from 36 longitudinal studies with a median follow-up of 6.5 years, involving about 5.8 million people and 99,668 cases of fatal and non-fatal (angina, myocardial infarction, ischemic or hemorrhagic strokes, or coronary revascularization procedures) CVD events. NAFLD was confirmed to be associated with a moderately increased risk of fatal or non-fatal CVD events (pooled random effects HR: 1.45, 95% CI: 1.31–1.61; $I^2 = 86.18\%$). Notably, the risk remained significant also when adjusted for age, sex, smoking, adiposity measures, pre-existing diabetes, and other cardiometabolic risk factors. An important evidence from this meta-analysis is that the risk notably increased across the severity of NAFLD, defined by ultrasonographic scores, or ultrasonography plus elevated serum gamma-glutamyl transferase (GGT), or increased ^{18}F-fluorodeoxyglucose (FDG) uptake on PET, or severity of liver fibrosis assessed by histology, or by NFS. This risk increased chiefly with the stage of fibrosis (pooled random effects HR: 2.50, 95% CI: 1.68–3.72; $I^2 = 73.84\%$). However, only 5 of the 36 studies analyzed were biopsy-proven.[38]

The link between severity of liver disease and cardiovascular alterations has been also reported in cross-sectional studies assessing preclinical cardiovascular alterations in NAFLD. Sinn and colleagues, in a retrospective cohort study, assessed the association between NAFLD (diagnosed by ultrasound) and progression of coronary atherosclerosis evaluated by computed tomography (CT). Coronary atherosclerosis progression was faster in patient with NAFLD at baseline than in patients without NAFLD, the risk further increasing in patients with NAFLD and fibrosis evaluated by noninvasive scores.[39] An Italian study, instead, related morphological and functional cardiovascular alterations with biopsy-proven NAFLD. Patients with advanced fibrosis (F3–F4) had a larger amount of epicardial fat than patients with milder fibrosis (F0–F2). Furthermore, other echocardiographic indexes, such as diastolic posterior wall thickness, left ventricular mass, relative wall thickness, ejection fraction (EF), and left atrial volume, were linked to severe liver fibrosis.[40]

To compare NAFLD with MAFLD, Zhang and colleagues, in a cross-sectional study investigated the cardiovascular and renal burden of disease in adults with MAFLD and NAFLD. From nine continuous surveys more than 18 years from 1999 to 2016, they observed that the prevalence and absolute number of MAFLD cases increased significantly and were greater than those of the NAFLD cases. The MAFLD group had significantly higher odds in all components of metabolic syndrome (hypertension, dyslipidemia diabetes, obesity), especially in diabetes (OR = 5.73, 95% CI: 5.10–6.45) and central obesity (OR = 17.05, 95% CI: 15.32–18.97), compared with the non-MAFLD group. MAFLD patient had also a significantly higher 10-year CVD risk of myocardial infarction and stroke, and the Framingham cardiovascular score of the NAFLD group was lower than that of the MAFLD group (OR = 3.2, 95% CI: 2.8–3.6 *versus* OR = 3.7, 95% CI: 3.4–4.1). They also observed a non-significant increasing trend in the prevalence of any CKD in both NAFLD and MAFLD groups. So, Zhang *et al.*[41] concluded that, in this study, the absolute cardio-renal burden may be greater for MAFLD than for NAFLD.

Table 1 resumes representative studies evaluating the association between NAFLD/MAFLD and CVDs.

Consistent with all these evidence, international guidelines suggest that all NAFLD patients should be screened for CV risk independently of classical CV risk factors, and that all patients with cardiometabolic disorders should be screened for NAFLD/MAFLD and its severity.[42]

Pathophysiology of atherosclerosis and CVD development in NAFLD/MAFLD

The close correlations among NAFLD/MAFLD, visceral obesity, and insulin resistance (IR) make extremely difficult to distinguish the precise causal relationships underlying the increased risk of CVD among patients with NAFLD/MAFLD.[43]

Multiple potential mechanisms for the link between NAFLD/MAFLD and cardiovascular risk have been identified, and one model proposed two pathways: one in which cardiovascular events occur *via* traditional risk factors and the other through a more direct linkage, including systemic inflammation, altered lipid metabolism, oxidative stress, prothrombotic state, and endothelial dysfunction, which likely contribute in a complex and interrelated manner[44,45] (Figure 2).

Atherosclerosis is a chronic inflammatory disease characterized by neo-intimal plaques generation in large arteries, driving CV events, such as myocardial infarction and stroke. Atherogenic process is induced in response to endogenously modified lipids, such as oxidized low-density lipoprotein (oxLDL) that accumulate within the arterial wall, stimulating both the innate and adaptive immune responses.[46] Moreover, the excess of lipids in the cardiomyocyte results in the accumulation of toxic lipid species, which alters cellular signaling and cardiac structure.[47] Patients with NAFLD/MAFLD have a more 'atherogenic' lipid profile with decreased high-density lipoprotein (HDL) levels and increased TG and LDL levels, specifically of the small-dense LDL particles, which favor early atherosclerosis[48] which accelerates cholesterol deposition in atherosclerotic plaques.[49] Similarly, the lower particle number of HDL, observed in NAFLD/MAFLD subjects, may impair cholesterol homeostasis; indeed, the HDL is responsible, together with LDL particles, of triacylglycerols release in the plasma, derived from very low-density lipoprotein (VLDL) particles that are exchanged for cholesteryl esters. This process is mediated by cholesteryl ester transfer protein (CETP). Once these triacylglycerols have been hydrolyzed by hepatic lipase, both LDL and HDL particles become small and cholesterol-depleted.[50] Moreover, in the liver, the increase in free fatty acids (FFA) flux stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia. Oxidative stress has been also reported to play a role in increasing CVD risk in patients with NAFLD/MAFLD inducing the change in endothelial function finally leading to the formation and deposition of oxLDL in the sub-intimal space.[51]

The causal relationship between NAFLD/MAFLD, atherosclerosis, and CVD can also be the expression of the liver as the center of biomarkers of inflammation production, secreted in response to IR status, to induction of endothelial dysfunction[52] and to severity of liver damage. The necro-inflammatory stage of liver disease can lead to atherogenic dyslipidemia, to increased hepatic production of CRP, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and other acute-phase proteins, mediated by interleukin 6 (IL-6) and

Table 1. Representative studies evaluating the association between NAFLD/MAFLD and CVDs.

Authors	Study description	NAFLD/MAFLD diagnostic method(s)	Outcome	Statistical adjustments	Main results
Pais *et al.*	A retrospective single-center study between 1995 and 2012. Transversal cohort: patients with ⩾2 cardiovascular risk factors without previous cardiovascular events. Longitudinal cohort: patients with two consecutive C-IMT measurement more than 2 years apart. In the transversal cohort ($n = 5671$) In the longitudinal cohort ($n = 1872$) mean follow-up: 8 ± 4 years.	Fatty liver index (FLI)	Examine the impact of steatosis on the presence and progression of C-IMT and carotid plaques (CP) in a large cohort with longitudinal follow-up	Age, sex, type-2 diabetes, high blood pressure, tobacco use, hsCRP, and baseline C-IMT lipid, cardiovascular, and diabetes therapies	Steatosis predicted C-IMT better than diabetes or dyslipidemia. Steatosis independently predicted C-IMT ($p = 0.002$) and FRS ($p < 0.001$). Steatosis at baseline predicted CP occurrence (OR = 1.63, 95% CI: 1.10–2.41, $p = 0.014$).
Bonapace *et al.*	Cross-sectional design, studied 50 consecutive type 2 diabetic individuals without a history of ischemic heart disease, hepatic diseases.	Ultrasound	Assess whether NAFLD is associated with abnormalities in cardiac function in patients with type 2 diabetes.	Age, sex, hypertension, HbA1c, TG	In patients with type 2 diabetes and NAFLD, even if the LV morphology and systolic function are preserved, early features of LV diastolic dysfunction may be detected.
Targher *et al.* (2007)	Cross-sectional design type 2 diabetic outpatients ($n = 2839$); prevalence of NAFLD was 69.5% among participants, and NAFLD was the most common cause (81.5%) of hepatic steatosis.	Ultrasound	Determine the prevalence of NAFLD in type 2 diabetic population and to compare the prevalence of CVD and its risk factors between people with and without NAFLD	Age, sex, BMI, smoking, diabetes duration, A1C, LDL cholesterol, and medications	NAFLD patients had remarkably ($p = 0.001$) higher age and sex-adjusted prevalence of coronary (26.6 *versus* 18.3%), cerebrovascular (20.0 *versus* 13.3%), and peripheral (15.4 *versus* 10.0%) vascular disease than their counterparts without NAFLD.
Targher *et al.* (2016)	Meta-analysis of 16 observational studies There were 34,043 adult individuals, (36.3% with NAFLD). Median follow-up: 6.9 years	Ultrasound or CT or histology	Quantify the magnitude of the association between NAFLD (and NAFLD severity) and risk of CVD events	Age, sex, systolic blood pressure, smoking, LDL cholesterol, and metabolic syndrome	Patients with NAFLD had a higher risk of fatal and non-fatal CVD events than those without NAFLD (OR = 1.64, 95% CI: 1.26–2.13)

(Continued)

Table 1. (Continued)

Authors	Study description	NAFLD/MAFLD diagnostic method(s)	Outcome	Statistical adjustments	Main results
Mantovani *et al.*	Meta-analysis of 36 longitudinal studies with aggregate data on 5,802,226 middle-aged individuals and 99,668 incident cases of fatal and non-fatal CVD. Median follow-up: 6.5 years	Histology or Ultrasound or ICD codes.	Incidence of fatal or non-fatal CVD events, or both, among individuals with NAFLD compared to NAFLD-free controls	Age, sex, adiposity measures, smoking history, hypertension, dyslipidemia, and pre-existing diabetes.	NAFLD was associated with a moderately increased risk of fatal or non-fatal CVD events (pooled random effects HR: 1.45, 95% CI: 1.31–1.61, I^2 = 86.18%).
Zhang *et al.*	Cross-sectional study from nine continuous surveys more than 18 years from 1999 to 2016, 19,617 adults aged ⩾ 20 years	NAFLD: Ultrasound and the exclusion of viral hepatitis (B or C), excessive alcohol consumption or aspartate aminotransferase or alanine aminotransferase > 500 U/liter MAFLD: hepatic steatosis in addition to one of the following three: general overweight/obesity, T2DM, or evidence of metabolic dysregulation.	Investigate the cardiovascular and renal burdens in adults with MAFLD and NAFLD.	Age, sex, and race or ethnic group	MAFLD had significantly higher odds in all components of metabolic syndrome, especially in diabetes (OR = 5.73, 95% CI: 5.10–6.45) and central obesity (OR = 17.05, 95% CI: 15.32–18.97), the Framingham cardiovascular score of the NAFLD group was lower than that of the MAFLD group (OR = 3.2, 95% CI: 2.8–3.6 *versus* OR = 3.7, 95% CI: 3.4–4.1.

BMI, body mass index; CI, confidence interval; FRS, Framingham cardiovascular score; HR, hazard ratio; ICD, international classification of diseases; LDL, low-density lipoprotein; LV, left ventricular; MAFLD, Metabolic dysfunction-Associated Fatty Liver Disease; NAFLD, Nonalcoholic fatty liver disease; OR, odds ratio.

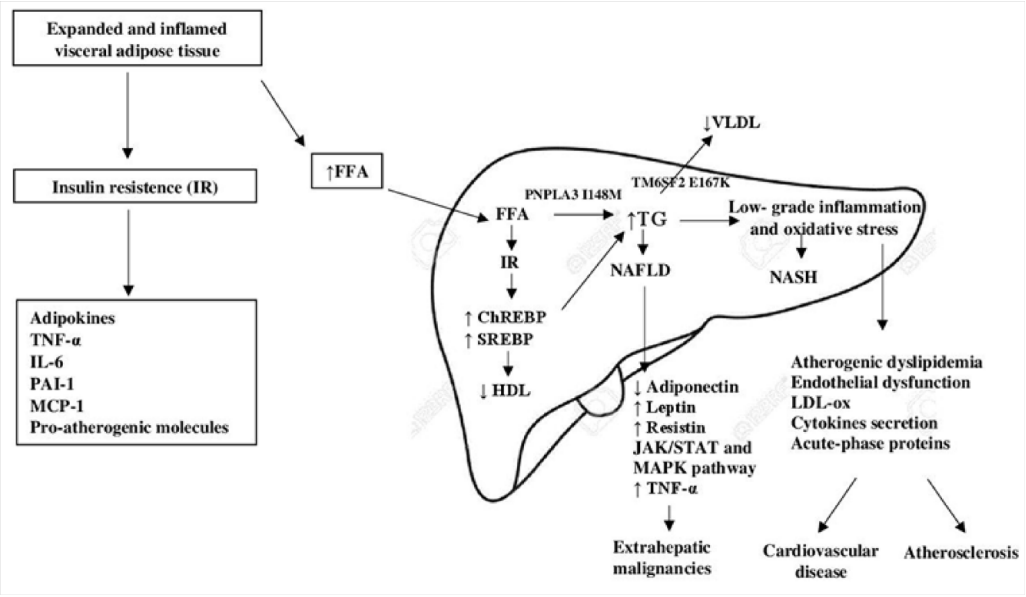

Figure 2. Liver inflammatory pathways activation and lipotoxicity induction linking NAFLD/MAFLD to extrahepatic disease. Pathogenic pathways involved in the development and progression of NAFLD are influenced by multiple, genetic, such as PNPLA3, Il148M, and TM6SF2 variants, metabolic and inflammatory factors. IR, induced by marked expansion and inflamed adipose tissue, impairs hepatic metabolic FFA utilization. Intrahepatic accumulation of toxic lipids produces inflammation and oxidative stress, driving NAFLD/MAFLD progression to NASH/MASH and contributes to cardiovascular complication. Hepatic necro-inflammation leads to endothelial dysfunction and atherogenic dyslipidemia, increasing production of acute-phase proteins and cytokines inflammatory, increasing risk of incidence of CVD and atherosclerosis. Altered adipokines production, together with IR, creates a microenvironment appropriate for cancer development, stimulating IGF-1 axis, JAK/STAT, and MAPK pathways.
PNPLA3, patatin-like phospholipase domain containing 3; TM6SF2, transmembrane 6 superfamily 2; FFA, free fatty acids; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemoattractant protein-1; ChREBP, carbohydrate response element-binding protein; SREBP, sterol regulatory-element binding protein 1c; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; NASH, nonalcoholic steatohepatitis; oxLDL, oxidized low-density lipoprotein; JAK/STAT, Janus kinase/signal transduction and activator of transcription; MAPK, mitogen-activated protein kinase.

tumor necrosis factor-α (TNF-α). These mediators might link NAFLD/MAFLD to an increased risk of CVD incidence and atherosclerosis.[53] It has been shown that increased levels of these inflammatory cytokines, which are known as risk factors for CVD, are increased in NAFLD/MAFLD patients, mainly in those with NASH/MASH, and with fibrosis suggesting that hepatic inflammation plays a key role in CVD pathogenesis.[54,55] The low-grade systemic inflammation induces endothelial dysfunction, alters endothelial tone, and promotes the atherosclerosis development, by cytokines secretion, such as IL-6, IL-1β, TNF α, and acute-phase proteins, such as CRP and Pentraxin-3 (PTX-3). In patients with NAFLD/MAFLD, elevated circulating PTX-3 levels – significantly associated with endothelial dysfunction – have been reported.[56] Higher PTX-3 levels were significantly correlated with adiponectin, asymmetric dimethylarginine (ADMA), a well-known marker of endothelial dysfunction.

Recently, it has been reported that gut microbiota is associated with NAFLD/MAFLD progression through 'microbiome signature' that could contribute to the initiation of inflammation. In this scenario, gut dysbiosis, related to NAFLD/MAFLD, is associated with increased flavin-containing monooxygenase (FMO) and trimethylamine N-oxide (TMAO) that impact cholesterol metabolism and promote foam cell formation and early atherosclerosis.[57]

NAFLD, MAFLD, and extrahepatic cancer

Emerging evidence suggests that NAFLD patients carry a higher risk of developing not only liver-related cancers but also extrahepatic cancers.

This issue is of great clinical relevance because numerous studies have shown that extrahepatic cancer is the second absolute cause of death in NAFLD patients.[31,32] Moreover, evidence also suggests that the proportions of extrahepatic cancer-related mortality have a significantly higher increase in NAFLD without cirrhosis compared with cirrhotic patients; the authors partially explained this phenomenon by the correlation of NASH and metabolic abnormalities.[33]

A Korean group described this correlation in a large cohort study with a median follow-up of 7.5 years; the cancer incidence rate was higher in NAFLD group than in their counterpart without (782.9 *versus* 592.8 per 100,000 person-years; HR 1.32, 95% CI: 1.17–1.49, $p < 0.001$). NAFLD patients showed a higher likelihood of developing HCC (HR: 16.73, 95% CI: 2.09–133.85, $p = 0.008$), colorectal cancer in males (HR: 2.01, 95% CI: 1.10–3.68, $p = 0.02$), and breast cancer in females (HR: 1.92, 95% CI: 1.15–3.20, $p = 0.01$). In this study, there was no relevant difference in the incidence rates of cancers of the esophagus, stomach, pancreas, biliary tract, lung, thyroid, kidney, bladder, non-Hodgkin's lymphoma, leukemia, or other rare tumors.[58]

Along this line, a Sweden study also reported that NAFLD patients have an increased overall cancer incidence compared with controls, (13.8 *versus* 10.9 per 1000 person-years; aHR: 1.27) driven primarily by HCC. Differently from the Korean study, this European analysis reported a small increased rate of pancreatic cancer (aHR: 2.15, 95% CI: 1.40–3.30), kidney–bladder cancer (aHR: 1.41, 95% CI: 1.07–1.86), and melanoma (aHR: 1.30, 95% CI: 1.08–1.57) in subjects with fatty liver compared with controls, while not significant differences were observed for breast, prostate, esophageal, stomach, lung, gynecological cancers, or colorectal cancer.[59]

Different studies also explored the potential link between NAFLD and risk of colorectal cancer, reporting overall conflicting results. For this reason, available evidence from observational studies was pooled in a 2018 meta-analysis that overall described a correlation between NAFLD and colorectal cancer in patients undergoing screening colonoscopy.[8] In particular, in comparison with non-NAFLD individuals, subjects with steatosis had an increase in both prevalence and incidence of adenomas and colorectal cancer, and these results being independent of age, sex, smoking, body mass index, diabetes, and other metabolic risk factors, but mainly related to Asiatic studies on patients who underwent screening colonoscopy.[60]

Mantovani and colleagues in 2021 searched to quantify the weight of the association between NAFLD and risk of extrahepatic cancer by performing a meta-analysis of observational studies. This study included 182,202 individuals (24.8% with NAFLD) and 8485 incident cases of extrahepatic cancers at different sites, over a median follow-up of 5.8 years. They have shown that NAFLD increases the risk of several extrahepatic cancers. Specifically, NAFLD was associated with a nearly 1.5- to 2-fold increased risk of developing gastrointestinal cancers, such as esophagus, stomach, pancreas, and colorectal cancers. Besides, NAFLD was associated with a 1.2- to 1.5-fold increased risk of developing non-GI cancers, such as lung, breast, gynecological, and urinary system cancers. All risks were independent of age, sex, smoking, obesity, diabetes, or other potential confounders.[61]

In spite of all the before-quoted evidence, only few studies are now available about the association between MAFLD and extrahepatic cancers.

Fukunaga and colleagues in a multicenter retrospective study compared the impact of MAFLD, respect to NAFLD, on the prevalence of colorectal adenoma. They demonstrated the superiority of MAFLD over NAFLD to identify patients with colorectal adenoma. The colleagues identified MAFLD as the only independent factor associated with colorectal adenoma (OR = 3.191; 95% CI: 1.494–7.070, $p = 0.003$), particularly non-obese MAFLD was identified as the only independent factor associated with colorectal adenoma (OR = 3.351; 95% CI: 1.589–7.262; $p < 0.001$); they also observed that NAFLD was not an independent factor associated with colorectal adenoma.[62]

In this setting, Seo and colleagues examined the relationship between NAFLD/MAFLD and colorectal adenoma in comparison with other metabolic factors in asymptomatic patients undergoing screening colonoscopy. They evaluated whether the severity of NAFLD/MAFLD [quantized by the fibrosis-4 (FIB-4) index] was associated with the risk of these neoplasms. They observed that MAFLD was statistically associated with a significant risk of colorectal

adenoma in the univariate analysis (OR = 1.31, 95% CI: 1.12–1.53, $p = 0.001$); instead, there was no significant association between MAFLD and colorectal adenoma in the multivariate analysis (OR = 1.08, 95% CI: 0.91–1.28, $p = 0.409$); anyway, NAFLD and MAFLD with an advanced fibrosis estimated by noninvasive scores were significantly associated with an increased risk of colorectal adenoma (NAFLD – OR = 1.38, 95% CI: 1.04–1.83, $p = 0.027$; MAFLD – OR = 1.45, 95% CI: 1.13–1.96, $p = 0.004$, respectively).[63]

Table 2 resumes representative studies evaluating the association between NAFLD/MAFLD and extrahepatic cancer.

All in all, these evidence raise the concern whether or not any '*ad hoc*' cancer screening will be needed for these patients.

Pathophysiology of extrahepatic cancer development in NAFLD/MAFLD

The association reported in literature between NAFLD/MAFLD and a higher risk of extrahepatic cancer, as for CVD, can not only be the expression of sharing of common metabolic risk factors but some specific NAFLD/MAFLD-related pathways, can exist (Figure 2).

Recently, it has been suggested that expanded visceral adipose tissue and NAFLD/MAFLD, as endocrine/paracrine organs, could play a role for extrahepatic cancers development.[64] Excessive adiposity is a risk factor for several, but not for all, common cancers. In this context, NAFLD/MAFLD represent an important biomarker for the malignance development risk.[65] Probable mechanisms that link adiposity and NAFLD/MAFLD with cancer involve the alteration of sex hormone metabolism, the increased insulin levels, the bioavailability of insulin-like growth factor 1 (IGF-1), the pathophysiology of adipokines, and the systemic inflammation.[66,67] In this context, IR creates a microenvironment appropriate for cancer development, stimulating IGF-1 axis;[68] indeed, elevated serum levels of IGF-1 have been associated with colorectal cancer.[69]

Several adipokines involved in liver metabolism, inflammation, and fibrogenesis can also involve in extrahepatic malignancies development, such as adiponectin, leptin, and resistin.[70]

The adiponectin is a mediator derived mainly from the adipose tissue and could be a critical link between obesity, NAFLD/MAFLD, and intra- and extrahepatic malignancies. Studies *in vitro* have been reported that the adiponectin has anticarcinogenic effects, inhibiting the growth of colon cancer cells, through the AMP-activated protein kinase (AMPK) resulting in endothelial cell apoptosis.[71] Adiponectin can also inhibit TNF-α involved in tumor cell proliferation and angiogenesis. It has been reported that, in obesity and disorders related to it, such as NAFLD/MAFLD, together with diabetes mellitus, adiponectin serum levels are significantly decreased.[72]

Leptin is another adipokine that has been found dysregulated in obesity and NAFLD/MAFLD. Leptin seems to potentiate the growth of cancers cells in the presence of low adiponectin levels. In human colon cancer cells, leptin promotes motility and invasiveness, acting by mitogen-activated protein kinase (MAPK) pathway.[73] In this way, adiponectin seems to decrease cell proliferation, by mediating an anticarcinogenic effect on the large intestine and interfering with leptin. Conversely, when the adiponectin availability is lower, leptin could exert a carcinogenic effect.[74]

Resistin is another adipokine that links cancers to NAFLD/MAFLD and obesity, *via* activation of nuclear factor-kB (NF-kB) pathway and *via* amplification of interleukin (IL)-1, IL-6, and TNF-α effects in gastrointestinal tumors.[75,76] These cytokines generate a low-grade chronic inflammation, associated with IR. The inflammatory milieu favors macrophages recruitment and release of proinflammatory cytokines into the systemic circulation. In this context, IL-6 induces the Janus kinase/signal transducer, activator of transcription (JAK/STAT) and MAPK pathways. These signalings stimulate cell proliferation and tumor progression, while TNF-α influences cancer angiogenesis, metastasis development, and cell survival and growth.[77]

Altered microbiome could also mediate the development of malignancies associated to NAFLD/MAFLD.[78,79] The mechanism is partially known and involves the alterations of gut microbiota, responsible of increase intestinal permeability and of consequent translocation of bacterial metabolites. These latter could activate the toll-like receptor (TLR) pathways *via* recognition of

Table 2. Representative studies evaluating the association between NAFLD/MAFLD and extrahepatic cancer.

Authors	Study description	NAFLD/MAFLD diagnostic method(s)	Outcome	Statistical adjustments	Main results
Kim *et al.*	Historical cohort study 25,947 subjects, 8721 (33.6%) had NAFLD. Median: 7.5 years.	Ultrasound	Cancer incidence rates in NAFLD and analyzed the association between NAFLD and cancer development.	Age, gender, smoking status, diabetes, hypertension, GGT, HDL cholesterol, LDL cholesterol, and TG	NAFLD was associated with the development of HCC, colorectal cancer in males and breast cancer in females.
Simon *et al.*	Population-based cohort study of 8892 subjects with NAFLD in Sweden. Median: 13.8 years	Histology	Cancer risk in patients with biopsy-confirmed NAFLD	Age, sex, calendar year, county of residence, CVD, diabetes, hypertension, dyslipidemia, obesity, end-stage renal disease, family history of cancer at age $<$ 50 years, education (three groups + missing category), the number of recorded hospital encounters in the year prior to the index biopsy date and alcohol abuse/misuse defined as a time-varying covariate	NAFLD patients had significantly increased overall cancer incidence driven primarily by HCC, NAFLD was associated with modestly increased rates of pancreatic cancer, kidney/bladder cancer, and melanoma but no other cancers.
Mantovani *et al.* (2018)	Meta-analysis of 11 observational studies with 1124 asymptomatic adults of predominantly Asian descent (32.1% with NAFLD). A total of 14,911 colorectal adenomas and 1684 cancers.	Histology or ultrasound or CT or magnetic resonance or spectroscopy	Presence (or the occurrence over the follow-up) of colorectal adenomas or cancer on screening colonoscopy among asymptomatic adults with NAFLD in comparison with the risk of colorectal adenomas or cancer among those without NAFLD	Age, sex, smoking, BMI, and diabetes (or metabolic syndrome)	NAFLD is independently associated with a moderately increased prevalence and incidence of colorectal adenomas and cancer.
Mantovani *et al.* (2021)	Meta-analysis of 10 cohort studies with 182,202 individuals (24.8% with NAFLD) and 8485 incident cases of extrahepatic cancers at different sites. Median follow-up: 5.8 years.	Ultrasound or CT or ICD codes	Quantify the magnitude of the association between NAFLD and risk of extrahepatic cancers.	Age, sex, smoking, diabetes, and obesity (or BMI)	NAFLD is associated with a moderately increased long-term risk of developing extrahepatic cancers (especially GI cancers, breast cancer, and gynecological cancers).

(Continued)

Table 2. (Continued)

Authors	Study description	NAFLD/MAFLD diagnostic method(s)	Outcome	Statistical adjustments	Main results
Fukunaga *et al.*	Multicenter cross-sectional retrospective study. A total of 124 subjects who underwent colonoscopy. NAFLD and MAFLD were present in 58 and 63 examinees (median age 59 years)	MAFLD: evidence of fatty liver, in addition to one of the following: obesity, T2DM, or non-obesity with evidence of metabolic dysregulation NAFLD: Ultrasound, no alcohol intake, no competing etiologies for fatty liver or coexisting causes of chronic liver disease	Investigate the impact of MAFLD on colorectal adenoma by comparing it to NAFLD in health check-up examinees	Age, sex, alcohol intake, and smoking	MAFLD is the most important factor associated with the presence of colorectal adenoma rather than NAFLD.
Seo *et al.*	Retrospective study. 3441 subjects who underwent abdominal ultrasonography and colonoscopy on the same day from January to December 2012.	NAFLD: Ultrasound MAFLD: hepatic steatosis in addition to one of the following three: general overweight/ obesity, T2DM, or evidence of metabolic dysregulation.	Investigate the relationship of colorectal adenoma and both NAFLD and MAFLD in asymptomatic individuals undergoing screening colonoscopy. Evaluated whether the severity of NAFLD/ MAFLD was associated with the risk of these neoplasms.	NAFLD adjusted for: age, sex, BMI, diabetes, hypertension, smoking, TG, HDL cholesterol, and visceral fat area. MAFLD: adjusted for age, sex, smoking, and visceral fat area.	NAFLD and MAFLD are associated with a higher risk of colorectal adenomas NAFLD and MAFLD with advanced fibrosis are associated with an increased risk of colorectal adenoma.

BMI, body mass index; GGTγ, glutamyltransferase; GI, gastrointestinal; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; ICD, international classification of diseases; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction-associated fatty liver disease.

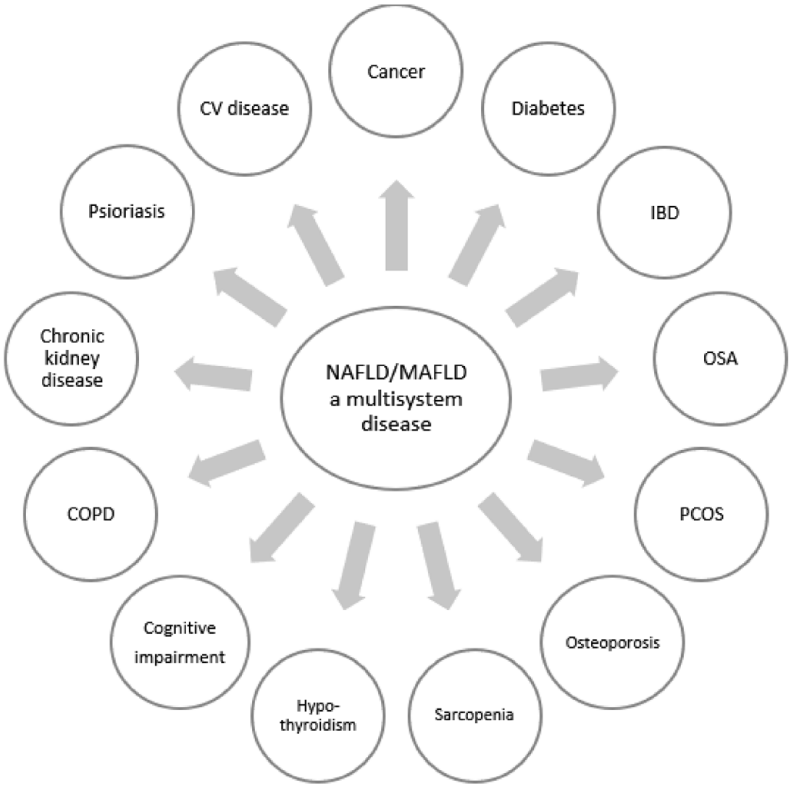

Figure 3. Summary of the major extrahepatic complications of NAFLD/MAFLD. NAFLD/MAFLD could be framed as a multisystemic disease. Sharing metabolic comorbidities, genetic background, and the severity of liver disease can modulate the risk of extrahepatic complications, even if the key question is whether NAFLD/MAFLD *per se*, *via* proinflammatory and profibrogenic pathways, is a real risk factor or it is only a surrogate of aging and of different metabolic and inflammatory risk factors. The mechanisms underlying these associations and their long-term clinical meaning need to be further investigated.

microorganism-associated patterns (MAMPs) promoting tumorigenesis through increased IL-6 signaling that protects cells from apoptosis induction.[80]

Finally, the presence of inflammation in patients with NAFLD/MAFLD or NASH/MASH might further amplify the activation of the before-quoted pathways increasing the risk of cancer development.

NAFLD and other extrahepatic complications

The presence of NAFLD/MAFLD has been also associated, even if with some conflicting results, with other extrahepatic comorbidities, such as chronic kidney disease (CKD), psoriasis, inflammatory bowel diseases (IBD), pulmonary diseases, etc. (Figure 3).

Looking at the association with CKD, Mantovani and colleagues in a 2020 meta-analysis quantified the association between NAFLD and risk of incident CKD. They analyzed 1,222,032 individuals (28.1% with NAFLD) and 33,840 cases of incident CKD stage ≥ 3 (defined by glomerular filtration rate < 60 ml/min/1.73 m^2) with a median follow-up of 9.7 years. They observed that NAFLD was significantly associated with a ~1.45-fold increased long-term risk of incident CKD stage ≥ 3.[81]

Along this line, Deng and colleagues wanted to investigate the association between MAFLD and CKD in a cross-sectional study including a total of 4869 subjects identified in the National Health and Nutrition Examination Surveys (NHANES) 2017–2018, of which 1032 (21.2%) were diagnosed with CKD. The prevalence of CKD was significantly higher in MAFLD compared with

non-MALFD patients (22.2% *versus* 19.1%, $p = 0.048$). However, after 1:1 propensity score matching by age, gender, and race, the prevalence of CKD between MAFLD and non-MAFLD group was similar. Consequently, the authors concluded that the association between MAFLD and CKD might be related to metabolic abnormalities, such as diabetes and hyperuricemia.[82]

In an updated systematic review and meta-analysis of observational studies, Bellinato and colleagues wanted to measure the risk of having NAFLD in patients with chronic plaque psoriasis and in the non-psoriatic control subjects. In a total of 249,933 patients with psoriasis (49% with NAFLD) and 1,491,402 controls (36% with NAFLD), they observed that patients with chronic plaque psoriasis had a nearly twofold higher odds of prevalent NAFLD compared to non-psoriatic healthy controls.[83] Similarly, another meta-analysis demonstrated that the risk of NAFLD in psoriatic patients compared to non-psoriatic controls was increased (six studies; $n = 267{,}761$ patients; OR = 2.15, 95% CI: 1.57–2.94), and also that the risk of NAFLD in patients with psoriatic arthritis was greater (three studies; $n = 505$ patients; OR = 2.25, 95% CI: 1.37–3.71) and increased according to the severity of the psoriasis. The pathophysiology behind these associations is still unclear but the authors believe that insulin resistance and other metabolic mechanisms may play a role.[84]

The prevalence of NAFLD in patients with inflammatory bowel disease was considered in a systematic review and meta-analysis from Lin and colleagues. The prevalence of NAFLD among IBD patients (32%) was statistically significantly higher than in the general population (25.2%; $p < 0.001$). Some factors associated with the development of NAFLD among IBD patients included older age, higher BMI, diabetes, IBD duration, and history of bowel resection. The pathophysiology of NAFLD development in IBD patients remains unclear.[85]

In the setting of pulmonary complications, Musso and colleagues showed that obstructive sleep apnoea syndrome (OSAS) is associated with a higher prevalence of NAFLD and that in patients with NAFLD, obstructive sleep apnea is associated with a higher prevalence of NASH and fibrosis. All these evidence were independent of age, gender, and BMI. They analyzed 18 cross-sectional studies (2183 participants): pooled ORs of OSAS for the presence of NAFLD, as defined by histology, radiology, and transaminases elevation, were 2.01 (95% CI: 1.36–2.97), 2.99 (1.79–4.99), 2.36 (1.46–3.82), and 2.60 (1.88–3.61), respectively. Pooled ORs of OSAS for NASH, fibrosis-any stage, or advanced fibrosis in biopsy-proven NAFLD patients were 2.37 (1.59–3.51), 2.16 (1.45–3.20), and 2.30 (1.21–4.38), respectively.[86] These data probably reflect the role of reduced oxygen levels – related to OSAS – in amplify liver damage in dysmetabolic obese patients with fatty liver. NAFLD has been also associated with reduced lung function in adults: another systematic review and meta-analysis evaluated the association between NAFLD and lung function in adults studied with spirometry for forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). There were significant differences in predicted FEV1 [pooled weighted mean difference (WMD): −2.43%, 95% CI: −3.28 to 1.58; $I^2 = 69.7\%$] and predicted FVC (pooled WMD: −2.96%, 95% CI: −4.75 to −1.17; $I^2 = 91.7\%$) between individuals with and without NAFLD in Asian and US cohorts. These correlations remained significant when adjusted for age, sex, smoking, adiposity measures, diabetes, and other metabolic risk factors.[87]

In a cross-sectional analysis from the 2005–2014 NHANES, Zhai and colleagues wanted to deepen the association between osteoporosis and NAFLD, this last being diagnosed by US Fatty Liver Index and Hepatic Steatosis Index. In participants with NAFLD aged ≥ 40 years, the authors observed a significant decreasing trend of bone mineral density throughout the decade, and also a direct association between advanced fibrosis and the occurrence of spine fractures (OR = 3.75, 95% CI: 1.04–13.53; $p = 0.044$).[88]

Similarly, when looking at sarcopenia, Wijarnpreecha and colleagues performed a meta-analysis reporting a significant increased risk of NAFLD in patients with sarcopenia, with respect to those without (pooled OR of 1.54, 95% CI: 1.05–2.26). Chronic inflammation or oxidative stress could probably underlie the pathogenetic association between NAFLD and sarcopenia.[89]

Some evidence also linked NAFLD to polycystic ovaric syndrome (PCOS). In a large Italian cohort, Petta and colleagues focused on the association between PCOS and NAFLD. They observed that PCOS is an independent risk factor

for steatosis, and that insulin resistance and hyperandrogenism are the key players of liver damage in PCOS. Steatosis was observed in 68.8% of patients with PCOS, compared to 33.3 of controls ($p < 0.001$) and this association remained significant also after adjusting for metabolic confounders (OR = 3.73, 95% CI: 1.74–8.02, $p = 0.001$).[90] Consistent with these results, Wu and colleagues in a meta-analysis of a total of 17 studies showed that PCOS women had a significantly higher risk of NAFLD (OR = 2.25, 95% CI: 1.95–2.60). This association was independent of obesity and geographic region, but related to hormone status: patients with hyperandrogenism had a significantly higher risk of NAFLD than controls (OR = 3.31; 95% CI: 2.58–4.24), while non-hyperandrogenic PCOS was not associated with the increased prevalence of NAFLD when compared to controls (OR = 1.46, 95% CI: 0.55–3.87). Consistently, the authors speculated that the association between NAFLD and PCOS may depend of androgen levels and interrelated to insulin resistance.[91]

NAFLD has been also linked to thyroid function. D'ambrosio and colleagues in a small Italian retrospective single-center study on biopsy-proven NAFLD patients observed that hypothyroid patients showed at histology a higher nonalcoholic steatohepatitis activity score ($p = 0.02$) and an increased, but not statistically significant, prevalence of NASH (89% *versus* 53%, $p = 0.06$). Notably, the association between thyroid function and the histological activity score remained significant after adjusting for age and BMI (OR = 1.7, 95% CI: 0.4–3.3, $p = 0.045$).[92]

A growing body of evidence also suggests a significant association between NAFLD and different central nervous system (CNS) disorders, such as cognitive impairment, hippocampal-dependent memory impairment, depression, and anxiety, all these being probably expression of NAFLD-related cerebrovascular alteration, neuroinflammation, and brain insulin resistance.[93] Consistent with these results, Petta and colleagues in a cohort from Southern Italy demonstrated that the presence of white matter lesions (WML) was not related with NAFLD *per se* but with its severity in terms of liver fibrosis. They tested whether NAFLD and its histological severity are associated with WML evaluated by magnetic resonance, in patients with biopsy-proven NAFLD and in non-NAFLD controls. The prevalence of WML was similar in NAFLD *versus* non-NAFLD (29.1% *versus* 24.3%; $p = 0.49$), but higher in NASH *versus* non-NASH (37.7% *versus* 21.2%, $p = 0.02$) and F2–F4 *versus* F0–F1 fibrosis (47.3% *versus* 20.3%, $p = 0.001$).[94]

All in all, this evidence shed further light about NAFLD – and sometimes about MAFLD – as a multisystemic disease even if the key question is whether NAFLD/MAFLD *per se*, *via* proinflammatory and profibrogenic pathways is a real risk factor or it is only a surrogate of aging and of different metabolic and inflammatory risk factors. Moreover, further study is needed to investigate the association between MAFLD and all the above-quoted diseases.

Can genetic drive extrahepatic prognosis?

NAFLD/MAFLD development is influenced by genetic factors, many of which were identified through genome-wide association studies (GWAS). Several single nucleotide polymorphisms (SNPs) in genes involved in metabolic homeostasis, inflammation, oxidative stress, and fibrogenesis have been identified contributing to NAFLD susceptibility and progression.[95,96]

The SNP in the PNPLA3 gene (rs738409 c.444 C > G p.I148M) is the one with the most significant association with NAFLD susceptibility,[97] NAFLD severity,[98] progression of fibrosis,[99] and risk of liver-related events.[100] This gene encodes for a lipoprotein lipase and the I148M variant, in hepatocytes, leads to fat accumulation, and, in the hepatic stellate cells, (HSC), reduces retinol release finally leading to a proinflammatory and profibrogenic phenotype.[101,102]

Looking at extrahepatic effects of this variant in NAFLD patients, some contrasting results exist. Petta *et al.*[103] observed that carrying the PNPLA3 GG genotype was associated with a higher risk of carotid atherosclerosis in patients younger than 50 years of age. In this context, PNPLA3 genotype might modulate vascular damage by regulating apoptotic activity, a process involved in the atherosclerosis pathogenesis.[104] In addition, PNPLA3 gene variants might increase lipid storage in the arterial vessels, similar to that observed in the liver, and could also induce release of ICAM-1, an endothelium-derived inflammatory marker, that has been associated with myocardial infarction and stroke.[105] Consistently, data from

NHANES 1991–1994 noted that the PNPLA3 I148M G-allele had a tendency of increased cardiovascular mortality in the total population, not in NAFLD.[106] On the other side, two recent studies on a large Chinese population and on a cohort of about 470 Japanese patients with biopsy-proven NAFLD reported a protective effect of the PNPLA3 I148M G-allele against cardiovascular events and cardiovascular-related death, respectively.[107,108] Along this line, recent evidence in obese patients suggests that PNPLA3-I148M variant confers an antiatherogenic plasma lipid profile – decreased VLDL and LDL and increased HDL and their constituents – particularly in insulin-resistant individuals.[109] When considering PNPLA3 and risk of extrahepatic mortality, a large US study did not find any association between PNPLA3 polymorphism and extrahepatic cancer-related mortality in a large US cohort,[110] while the before-quoted Japanese study reported a protective effect of the wild-type C allele against extrahepatic cancer occurrence.[107]

TM6SF2 is a gene encoding for a protein implicated in the assembly of TGs and apolipoprotein B (Apo-B) and in the VLDL secretion.[87] The SNP rs58542926 C>T in the TM6SF2 gene is a genetic variant linked with hepatic fat content, with high aminotransferases levels and with lower serum lipoprotein. The T allele has been associated with a higher susceptibility for NAFLD progression, in terms of NASH and liver fibrosis, but protects against carotid atherosclerosis and risk of cardiovascular events in obese patients[111,112] by correlating with lower levels of fasting TGs that reflect lower levels of VLDL.[113–115] The mechanism is related to reduced secretion of VLDL resulting in intrahepatic retention of TG and steatosis.

Further studies focusing on MAFLD patients and using competing risk approaches could better define the role of common genetic SNP on the risk of hepatic and extrahepatic events in NAFLD/MAFLD patients.

NAFLD/MAFLD and extrahepatic complications: the need for a competing risk approach

The concomitant increase in hepatic and extrahepatic complications, and the pivotal role of advanced fibrosis as clinical driver require considering the complex and multifaced natural history of this disease with a competing risk approach. Competing risk in fact is the risk of an event whose occurrence either precludes the happening of another event or modifies the probability that it will occur, and this is what happens in a complex clinical context like NAFLD/MAFLD.[116]

In a recent multicenter study, Pennisi and colleagues evaluated the competitive risk occurrence of liver-related events (LRE) (either ascites, variceal hemorrhage, encephalopathy, jaundice, or HCC) and extrahepatic events (EHE) [either cardiovascular events – e.g. stroke, transient ischemic attack (TIA), acute myocardic infarct (AMI), and unstable angina – or extrahepatic cancer (EHC)] in a large cohort (2135 patients) of biopsy-proven NAFLD patients stratified according to baseline severity of fibrosis. The likelihood of EHE in NAFLD was relevant and increased according to the severity of liver fibrosis, while the risk of LRE was negligible in F0–F1, low but clinically relevant in F2, and high in F3–F4. The study also evaluated the occurrence as first or second event regarding liver-related events and extrahepatic events: patients with F0–F1 and F2 fibrosis had a clinically relevant probability of EHE as first event (5.8% and 9.9%, respectively), despite a very low probability of first LRE (0.6% and 1.6%, respectively). Moreover, in this subgroup, the probability of LRE as a second event was very low (1.5% and 2.7%, respectively). However, patients with F3–F4 had a comparably high probability of both LRE and EHE as first event (12% and 9.4%, respectively), and a similarly high risk of EHE and LRE as second event (5.2% and 6.6%, respectively).[117] Similarly, Vilar-Gomez *et al.*[118] found that the risk of LRE progressively increased from NAFLD patients with F3 fibrosis to those with CTP A5 and further to those with CTP A6 cirrhosis, while a specular picture was observed regarding EHE.

Even in the prospective study of Sanyal and colleagues, when analyzing liver-related mortality using Fine-Gray model to account for competing risk of other causes of death, F3 fibrosis as compared with F0–F2 fibrosis, and F4 fibrosis *versus* F0–F2 fibrosis remained significantly associated with liver-related mortality, accounting for an HR of 5.8 and 12.7, respectively.[12,119]

Finally, using the competing risk approach, as for the study of Simon, NAFLD was no longer significantly associated with significant excess risk of cardiovascular mortality.[120] This suggests that the

relationship between NAFLD and cardiovascular mortality in some clinical settings might be less important than previously suggested.[38,121]

Further studies analyzing hepatic and extrahepatic events by a competing risk approach in MAFLD patients are needed to better explore the natural history of this new defined clinical large cohort of patients.

Conclusion

Available evidence and pathophysiological studies are enough to suggest that the observed link between NAFLD/MAFLD and extrahepatic complications/comorbidities is not only an expression of epidemiological association and of sharing common risk factors but it is also related to different mechanisms directly linking NAFLD/MAFLD to these disorders. Competing risk approaches and cluster analyses could be useful to better characterize, in different clinical setting, the role of NAFLD, and better of MAFLD, as driver of hepatic and extrahepatic complications in the individual patient.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

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Adele Tulone: Data curation; Writing – original draft.

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Stefania Grimaudo: Data curation; Writing – original draft; Writing – review & editing.

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