

CKJ REVIEW

The impact of metabolic dysfunction-associated steatotic liver disease (MASH) on the high risk of cardiovascular disease in CKD: interconnections and management

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a major contributor to systemic metabolic dysfunction and is increasingly recognized as a risk enhancer for both cardiovascular disease (CVD) and chronic kidney disease (CKD). This review explores the complex interconnections between MASLD, CVD, and CKD, with emphasis on shared pathophysiological mechanisms and the clinical implications for risk assessment and management. We describe the crosstalk among the liver, heart, and kidneys, focusing on insulin resistance, chronic inflammation, and progressive fibrosis as key mediators. The severity of liver fibrosis in MASLD is independently associated with both cardiovascular and renal outcomes. Conventional cardiovascular risk scores may underestimate risk in MASLD-CKD populations, highlighting the need for integrated approaches that include hepatic, renal, and metabolic profiling. We also review current non-invasive diagnostic tools, including fibrosis scores and cardiovascular biomarkers, as well as emerging genetic and epigenetic markers that may enhance risk stratification. The therapeutic landscape is evolving, with promising results from lifestyle interventions and pharmacological agents such as GLP-1 receptor agonists, SGLT2 inhibitors, and novel antifibrotic compounds. We also propose a practical algorithm for the screening and risk stratification of MASLD in CKD patients, incorporating non-invasive fibrosis assessment and cardiometabolic risk evaluation. This stepwise approach supports early detection and personalized management, particularly in patients with CKD or type 2 diabetes. In conclusion, MASLD significantly amplifies cardiovascular and renal risk. Early, multidisciplinary intervention is essential to improve long-term outcomes in this high-risk population.

Keywords: cardiovascular risk, chronic kidney disease, liver fibrosis, metabolic dysfunction-associated steatotic liver disease (MASLD), non-alcoholic fatty liver disease

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as the presence of excess fat accumulation in the liver (steatosis), as demonstrated by biopsy or imaging, in conjunction with at least one cardiometabolic risk factor. These risk factors include overweight, dysglycaemia or type 2 diabetes mellitus (T2DM), hypertriglyceridemia, low high-density lipoprotein cholesterol, and high blood pressure.

Non-alcoholic fatty liver disease (NAFLD) was the first defined in the 1980s and was initially characterized by exclusion of alcohol consumption, viral hepatitis, and other causes rather than addressing the pathophysiological mechanism. In 2020, the term MAFLD replaced NAFLD to reflect the central role of metabolic dysfunction in the disease. More recently, in 2023, a new international consensus proposed replacing the term ‘fatty’ with ‘steatotic’, leading to the adoption of MASLD. MASLD now forms part of the new consensus definition of steatotic liver disease (SLD), which also includes MASLD with moderate alcohol intake (MetALD), alcohol-related liver disease, specific aetiologies of SLD, and cryptogenic SLD [1, 2].

MASLD is a broad term that encompasses different stages of disease severity, ranging from simple steatosis to cirrhosis, including metabolic-associated steatohepatitis (MASH) and various stages of fibrosis (F0 to F4). MASH represents only the inflammatory phase of MASLD (steatohepatitis) characterized by hepatocellular injury and inflammation and is associated with more rapid progression of MASLD. This phase activates fibrogenic pathways that can lead to significant hepatic fibrosis at different stages, ultimately resulting in cirrhosis. The natural history of the disease is shown in Fig. 1 [1, 2].

Currently, 61 million Europeans live with diabetes, representing ~7% of the adult population [3]. Additionally, 51% of the population is overweight, with 17% classified as obese [4]. The prevalence of MASLD in the European population ranges from 23% to 33% [5]. Among individuals with diabetes, this prevalence rises to 65% [6] and reaches 75% in those with obesity [7]. Obesity and T2DM are major risk factors for development and progression of kidney disease [8]. Moreover, up to 40% of patients with T2DM develop diabetic kidney disease over time [9]. Both MASLD and CKD are strongly associated with T2DM, metabolic syndrome and insulin resistance (IR). CKD and cardiovascular disease (CVD) frequently coexist in patients with MASLD, driven by the shared risk factors. Increasing evidence suggest that MASLD may negatively impact the progression of CKD [10].

CVD remains the leading cause of death in individuals with CKD [11] and MASLD [12]. The high burden of shared risk factors and overlapping pathogenic mechanisms underlines the importance of understanding the interconnections between these conditions.

This review aims to explore the pathophysiological links between MASLD, CKD and CVD, and to evaluate current diagnostic

tools and therapeutic approaches for managing patients with these comorbidities, with a particular focus on strategies to reduce cardiovascular risk. We conducted searches in PubMed, Google Scholar, Web of Science, and the Cochrane Library, using MeSH terms such as: ‘NAFLD’, ‘fatty liver’, ‘cytokines’, ‘fibrosis’, ‘gastrointestinal microbiome’, ‘insulin resistance’, ‘chronic kidney disease’, ‘heart disease risk factors’, and ‘type 2 diabetes mellitus’. Filters were applied for human studies, English language, and a publication window covering the last 10 years (2013–2024).

Out of 238 results, we selected 68 high-quality references based on relevance, sample size, and journal impact (with a preference for Q1–Q2 indexed journals, recent meta-analyses, and clinical practice guidelines). No formal meta-analysis was performed.

PATHOPHYSIOLOGICAL INTERCONNECTIONS BETWEEN MASLD, CKD, AND CVD

The cardio-renal-hepatic axis

The interplay between the cardiovascular system and the liver is complex. A well-established bidirectional relationship exists between T2DM and MASLD: T2DM predisposes to MASLD, and MASLD increases the risk of T2DM. Disease progression tends to be more aggressive in patients with diabetes. Notably, the degree of liver fibrosis correlates with increased risk of T2DM and hypertension. Current recommendations advise systematic screening for MASLD in individuals with T2DM, and assessment of glucose metabolism in those with hepatic steatosis [1].

Several studies report a markedly increased CVD burden in patients with MASLD. These individuals often present with co-existing risk factors such as obesity, T2DM, dyslipidaemia, and hypertension. Consequently, they are prone to subclinical vascular damage—including endothelial dysfunction, atherosclerosis, and increased carotid intima-media thickness—as well as major cardiovascular events like ischaemic heart disease, arrhythmias, heart failure with preserved ejection fraction, valvular heart disease, and stroke [13–15].

This association is independent of traditional risk factors and strengthens with worsening liver damage. While MASLD is not yet classified as an independent cardiovascular risk factor, it clearly acts as a risk enhancer and should be included in cardiovascular risk assessment [16].

MASLD is also a significant risk factor for chronic kidney disease (CKD). Shared pathophysiological mechanisms and clinical features link MASLD and CKD. Eight meta-analyses have consistently shown increased CKD risk in patients with non-alcoholic or metabolic fatty liver disease, even after adjusting for obesity and T2DM, suggesting an independent role for hepatic steatosis in CKD development (Table 1) [14, 17–23].

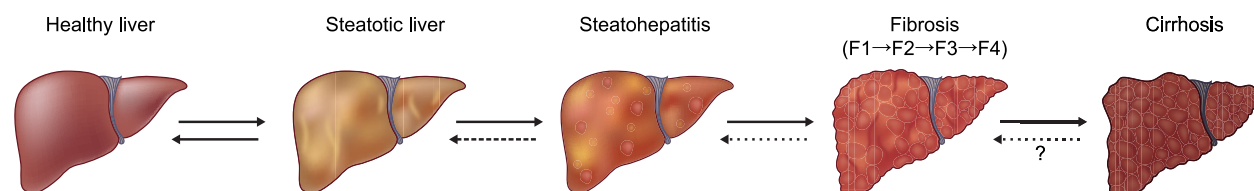


Figure 1: The natural history of MASLD. Source: images created with Freeform version 1.2.

Table 1: Meta-analyses that have examined the relationship between 'MASLD' and CKD.

Reference	Number of studies included	Definition	CKD incidence	Incidence in advanced fibrosis vs non-advanced fibrosis
Musso G et al. [17]	33	NAFLD	HR 1.79 (95% CI, 1.65–1.95)	HR 3.29, (95% CI 2.30–4.71)
Mantovani A et al. [14]	9	NAFLD	HR 1.37 (95% CI 1.20–1.53)	HR 1.59, (95% CI 1.31–1.93)
Cai X et al. [18]	14	NAFLD	RR 1.39 (95% CI 1.27–1.52)	RR 1.63 (95% CI 1.36–1.96)
Mantovani A et al. [19]	10	NAFLD	HR 1.43 (95% CI 1.33–1.54)	HR 2.75–3.25 (No CI reported)
Chen Y et al. [20]	19	NAFLD	OR: 1.95 (95% CI: 1.65–2.31)	
Ciardullo S et al. [21]	5	NAFLD		OR 2.49 (95% CI 1.89–3.29)
Agustanti N et al. [22]	4	MAFLD or NAFLD with T2D or obesity	HR: 1.35 (95% CI: 1.18–1.52)	OR 2.07 (95% CI 1.68–2.46)
Liu W et al. [23]	8	MAFLD	HR 1.38 (95% CI: 1.24–1.53)	

The risk of CKD in patients with NAFLD, MAFLD or MASLD increase with the severity of the disease [14, 17–19, 21, 22]. Notably, patients with a history of moderate to severe liver fibrosis remain at increased risk for CKD, even after apparent remission of liver disease [24]. A recent meta-analysis comparing individuals who meet the diagnostic criteria for MASLD versus those with NAFLD reported no statistically significant differences in CKD risk between groups. However, a positive trend was noted, with a slightly higher risk in the MASLD group (OR 1.06, 95% IC1.00–1.12) [25].

From a nephrological perspective, one of the few studies involving patients with biopsy-confirmed diabetic nephropathy demonstrated that the coexistence of MASLD is associated with worse renal outcomes [26]. Additionally, the coexistence of MASLD and CKD synergistically increases cardiovascular risk. Individuals with both liver fibrosis and CKD exhibit greater risks of cardiovascular morbidity and mortality compared to those with either condition alone [27, 28].

Figure 2 provides a schematic overview of the interconnections between MASLD, T2D, CVD, and CKD. Both MASLD and T2DM indeed promote cardiovascular and renal disease. When these conditions co-occur, their effects are additive and mutually reinforcing, substantially amplifying the overall risk burden [29–31].

Systemic and metabolic pathways

A key mechanism linking MASLD, CKD, and CVD is chronic low-grade inflammation coupled with peripheral IR. MASLD aggravates IR, which in turn heightens systemic inflammation, promotes hypertension, and worsens glycaemic control in T2DM. These alterations contribute to an atherogenic lipid profile and increased cardiovascular risk [32].

IR itself promotes adipose tissue dysfunction, increasing circulating free fatty acids and their hepatic uptake. This worsens hepatic IR, creating a self-perpetuating cycle. Excess lipid flux into hepatocytes may exceed mitochondrial oxidative capacity, leading to dysfunction, lipotoxic intermediates, and excessive reactive oxygen species (ROS), which activate proinflammatory pathways and hepatocyte necroinflammation [33].

Obesity-related hyperinsulinaemia and IR also promote systemic inflammation. In both liver and kidney, inflammation is a key driver of fibrosis. A strong correlation exists between IR, tumour necrosis factor- α (TNF- α), ROS, oxidized LDL (oxLDL), and the severity of hepatic inflammation and fibrosis [34].

In MASLD and CKD, systemic levels of proinflammatory cytokines—including TNF- α , IL-1, IL-6, IL-17, IL-22, IL-23, and

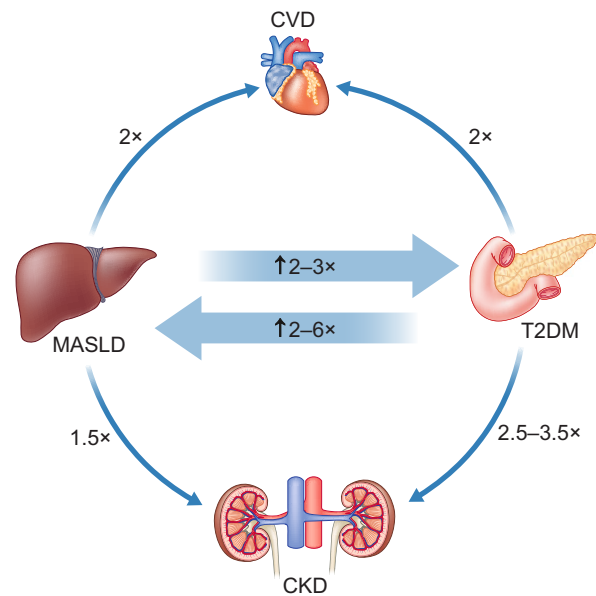


Figure 2: Schematic representation of the bidirectional interconnections between MASLD, T2DM, cardiovascular risk (CVR), and CKD. Both MASLD and T2DM independently increase the risk of cardiovascular and renal disease, and their coexistence results in a cumulative and amplified pathogenic effect. The diagram illustrates the relative risk increases reported in epidemiological studies. Source: adapted from Targher et al., *Lancet Gastroenterol Hepatol* 2021; Quek et al., *Endocr Pract* 2022. Designed with Freeform v1.2 (Apple).

CRP—are elevated, while anti-inflammatory mediators like adiponectin, TGF- β , IL-4, and IL-10 are reduced. Patients also show increased procoagulant (PAI-1, fibrinogen, factor VII) and profibrogenic factors (FGF-21, TGF- β), along with oxidative stress and endothelial dysfunction. Together, these alterations drive cardiovascular and renal disease progression [29, 35].

Figure 3 illustrates the complex interplay among heart, liver, and kidney in metabolic dysfunction [35, 36].

Gut microbiota dysbiosis and endothelial dysfunction

Alterations in gut microbiota are a shared pathogenic pathway in MASLD, CKD, and CVD. The microbiota modulates immune responses and, when dysregulated, can trigger maladaptive inflammation contributing to multisystem organ damage.

Dysbiosis—defined as changes in the composition, diversity, or function of the intestinal microbiota—combined with

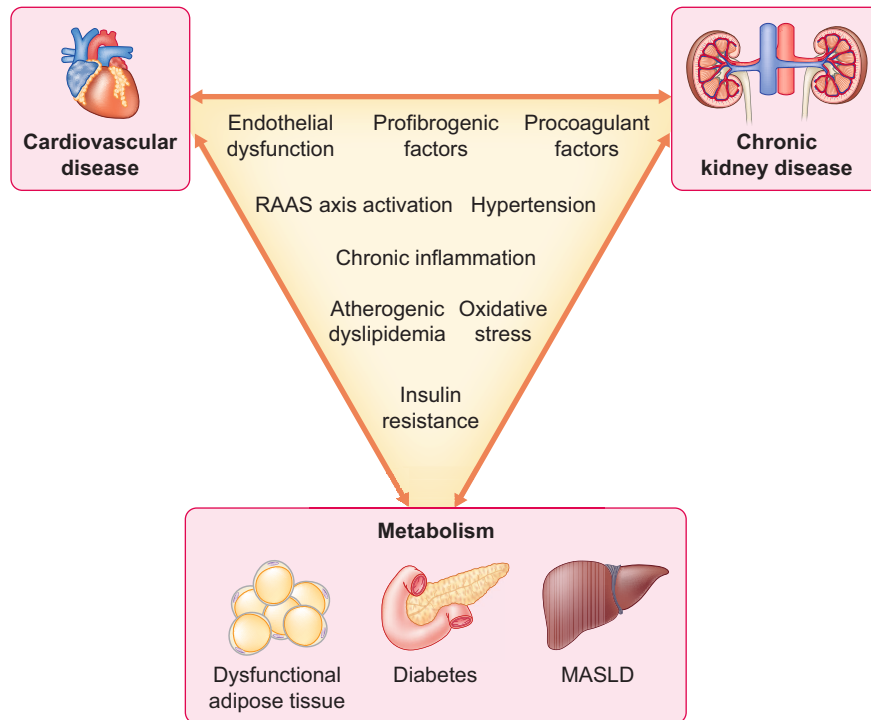


Figure 3: Molecular mechanisms involved in the cardio-reno-hepato-metabolic axis. The key pathogenic link is chronic inflammation and peripheral insulin resistance. Kidney injury in diabetic patients arises from a complex interplay of metabolic, haemodynamic, proinflammatory, and profibrotic factors. RAAS, renin-angiotensin-aldosterone system. Adapted from: Byrne CD, Targher G. *J Hepatol* 2020; Zhou XD et al. *Cardiovasc Diabetol* 2022; Mantovani A et al. *Int J Mol Sci* 2022.

increased intestinal permeability (the so-called ‘leaky gut’), promotes systemic inflammation, oxidative stress, and endothelial dysfunction. These processes facilitate the development of obesity, MASLD, hypertension, diabetes, atherosclerosis, and heart failure [37].

Environmental factors such as a Western-style diet (rich in saturated fats, trans fats, and fructose) and sedentary habits favour dysbiosis. This leads to elevated lipopolysaccharide (LPS) levels and ‘metabolic endotoxaemia’, a state of low-grade inflammation. LPS disrupts intestinal tight junctions between enterocytes, increasing permeability. Once the mucosal barrier is compromised, bacterial products reach the liver via the portal vein and eventually the systemic circulation, contributing to immune-mediated CVD, including cardiomyopathy, atherosclerosis, and heart failure [38, 39].

Patients at high cardiovascular risk often exhibit gut microbial imbalances, characterized by reduced microbial diversity and an increased Firmicutes/Bacteroidetes ratio. Despite considerable heterogeneity among studies, most have reported a depletion of anti-inflammatory bacteria (notably *Bacteroidetes*, particularly *Akkermansia muciniphila*) and an enrichment of proinflammatory taxa such as *Firmicutes*, *Actinobacteria*, and *Proteobacteria* [40, 41].

Bacterial metabolites, such as short-chain fatty acids, regulate hepatic lipogenesis. Another microbial metabolite, trimethylamine oxide (TMAO), has been associated with increased cardiovascular risk and endothelial damage by promoting atherogenesis [42].

The diagnostic role of gut microbiota as a new biomarker in CVD currently being studied. The identification of specific microbial metabolites, such as trimethylamine N-oxide (TMAO),

p-cresol, and indoxyl sulfate, could serve as diagnostic biomarkers for evaluating the risk of liver, kidney, and cardiovascular diseases. Measuring these metabolites in plasma could aid in risk stratification and disease progression monitoring [43]. Additionally, analysing the gut microbiota profile through advanced sequencing techniques may allow the identification of specific dysbiosis patterns associated with these diseases. This can be integrated into the diagnostic process to provide a more detailed view of intestinal health and its systemic impact.

Gut microbiota modulation is a promising therapeutic approach. However, it remains unclear whether symbiotic, prebiotics, probiotics, antibiotics, or conventional therapy are superior in improving outcomes in patients with CKD [44] nor with MASLD [1]. Dietary interventions that influence the microbiota, such as fibre-rich diets or specific diets to reduce TMAO, can be designed to mitigate the risk of these diseases. Adjusting the diet to promote a healthy microbiota may have positive effects on metabolic and cardiovascular health [45].

Although still in experimental stages for these conditions, faecal microbiota transplantation could be an option to restore a healthy microbiota in patients with severe dysbiosis. However, more research is needed to establish its efficacy and safety in this context [46].

Endothelial dysfunction, albuminuria, and MASLD

Multiple mechanisms contribute to endothelial dysfunction in MASLD. In the kidneys, this is often reflected by albuminuria. Both hepatic fibrosis and T2DM are recognized risk factors for albuminuria [47].

Notably, individuals with MASLD but without T2DM also show an increased risk of albuminuria. In contrast, this association is less evident in those with MASLD and coexisting T2DM. These findings suggest that IR—rather than T2DM itself—may be a key driver of albuminuria in the setting of MASLD [48].

DIAGNOSTIC STRATEGIES FOR MASLD AND CARDIOVASCULAR RISK IN CKD

Early screening for MASLD in CKD patients

In CKD, MASLD is consistently linked to worse renal outcomes, especially when liver fibrosis is present. Glomerular hyperfiltration is now recognized as an early marker of both renal and hepatic damage, and its detection should prompt proactive management. Identifying patients at risk of hepatic fibrosis has key clinical implications, particularly in intensifying cardiovascular risk reduction. The probability of advanced fibrosis in MASLD increases with the number of metabolic risk factors. While those with a single abnormality (e.g. hypertension, dyslipidaemia, or obesity) have a low risk of progression to cirrhosis, each added trait raises the risk incrementally. Current guidelines [1], recommend systematic MASLD screening in individuals with T2DM and/or abdominal obesity, especially when another metabolic risk factor is present. Conversely, in patients newly diagnosed with MASLD, clinicians should comprehensively assess cardiovascular risk and screen for comorbidities including T2DM, dyslipidaemia, hypertension, CKD, obstructive sleep apnoea, and polycystic ovary syndrome.

Non-invasive diagnostic tools

Serum biomarkers (liver enzymes and biomarkers -ALT, AST, FIB-4, NAFLD fibrosis score, ELF-)

Serum transaminases alone do not correlate reliably with the stage of fibrosis or the overall severity of liver disease. However, they remain useful when incorporated into composite indices designed to estimate fibrosis risk. Among the most widely used non-invasive tests in clinical practice is the FIB-4 score, which combines age, AST, ALT, and platelet count. This tool offers a high negative predictive value (NPV) for ruling out advanced fibrosis, is easily calculated using routinely available parameters, and is low in cost—making it the preferred first-line assessment to stratify patients by fibrosis risk [32].

A FIB-4 score <1.3 (<2.0 if >65 years) effectively rules out advanced fibrosis, while a score ≥ 2.67 is associated with a high likelihood of advanced fibrosis and requires further testing or hepatology referral. Notably, FIB-4 ≥ 2.67 has also been linked to a 40% increase in cardiovascular mortality, enhancing prediction of major adverse cardiovascular events (MACE) in this population [49]. Advanced serum biomarkers such as the enhanced liver fibrosis (ELF) test offer better diagnostic accuracy but are costlier and less accessible, limiting their use to second-line non-invasive testing (NIT) in most clinical algorithms. It is important to note that the performance of non-invasive fibrosis scores may be suboptimal in patients with advanced CKD due to factors such as altered liver enzyme levels associated with uraemia, thrombocytopenia unrelated to liver pathology, and variability in diagnostic accuracy across different ethnic populations. In this context, the use of transient elastography could improve accuracy in the assessment of liver fibrosis [50].

Non-invasive imaging: ultrasound, transient elastography (FibroScan®), MRI

Although hepatic steatosis can be readily detected using conventional ultrasound, the key clinical objective is not merely to identify fatty liver, but rather to assess the presence and extent of liver fibrosis, which remains the strongest predictor of both liver-related and cardiovascular outcomes.

Transient elastography (e.g. FibroScan) estimates liver stiffness in kilopascals (kPa), correlating with fibrosis severity. Transient elastography, most commonly performed using FibroScan, is widely recommended as a second-line assessment tool in most clinical guidelines [1].

Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) allows accurate quantification of hepatic fat and correlates well with histological features of steatohepatitis, including inflammation and fibrosis. MRI-based elastography (MRI-E) has demonstrated superior diagnostic performance compared to transient elastography for detecting advanced fibrosis. Furthermore, in prospective imaging studies, the histological presence of non-alcoholic steatohepatitis (NASH) and advanced fibrosis—confirmed via MRI—has been associated with increased cardiovascular risk [51, 52].

Despite its high accuracy, MRI-E is not a first-line tool for MASLD risk stratification due to limited availability, higher cost, and the need for specialized equipment and expertise. Recently, combined scores integrating serum biomarkers and imaging (e.g. elastography and steatosis quantification) have been proposed to enhance fibrosis assessment, though their detailed discussion lies beyond the scope of this review.

Cardiovascular risk stratification in MASLD-CKD patients

Traditional risk scores. Traditional cardiovascular scores, such as the Framingham Risk Score and ASCVD estimator, remain standard tools in the general population. However, their performance is limited in individuals with MASLD and/or CKD, as they may underestimate risk due to the underrepresentation of non-traditional factors such as inflammation, IR, and hepatic fibrosis.

In patients with both MASLD and CKD, standard risk scores should be used with caution. Additional screening using renal markers, such as estimated glomerular filtration rate and urinary albumin-to-creatinine ratio, is recommended, as in diabetes or MASLD [53]. These markers not only reflect cardiovascular risk but also indicate early renal involvement.

Patients with MASLD cirrhosis and renal dysfunction being evaluated for liver transplantation require special attention due to a high risk of cardiovascular events before, during, and after transplant. A multidisciplinary approach is essential to detect and manage metabolic and cardiac comorbidities. A stepwise, risk-adjusted cardiac work-up, ECG, echocardiography, stress cardiac MRI, or coronary CT angiography, is advised, following recent EASL and ILTS guidelines [1]. Emerging biomarkers such as high-sensitivity CRP and NT-proBNP may improve risk stratification beyond traditional scores, as both are independently associated with cardiovascular events and mortality in MASLD-CKD populations [1].

Risk stratification for progression to CKD and cardiovascular events. Early detection of CKD and CVD risk requires an integrated assessment of hepatic, renal, and cardiac biomarkers. Understanding the interaction between the hepato-adipo-cardio-renal axes is key, as MASLD, especially with advanced fibrosis, is linked to increased CKD incidence. A recent meta-analysis found a

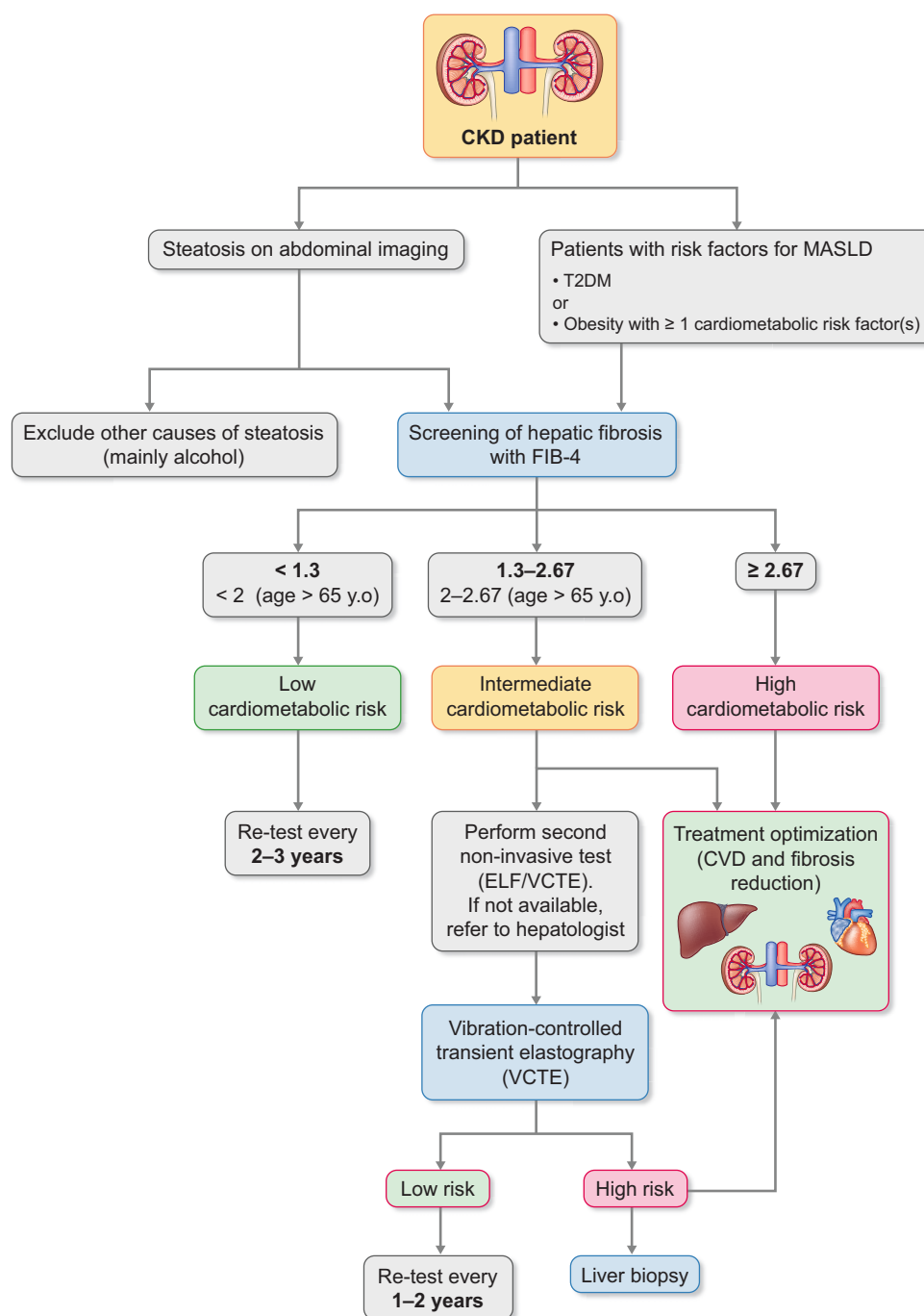


Figure 4: Proposed approach and diagnostic modalities in screening and risk stratification of MASLD-patients. Modified from: EASL-EASD-EASO CPG on MASLD. *J Hepatol.* 2024; Cusi K et al. *Endocr Pract* 2022.

1.45-fold higher risk of developing stage 3 CKD or worse in MASLD, independent of traditional risk factors [19].

Although screening for comorbidities in MASLD is widely accepted, optimal strategies for comprehensive risk assessment are not yet standardized. Among emerging biomarkers, NT-proBNP has shown independent prognostic value for cardiovascular mortality. In MASLD, both NT-proBNP and FIB-4 are associated with all-cause and cardiovascular mortality, and their combined use may improve risk stratification [1].

The proposed risk stratification strategy begins with the FIB-4 index as a first-line non-invasive test (Fig. 4). In patients with FIB-4 <1.3 (<2.0 in those aged >65 years), advanced fibrosis can be reliably excluded due to a high NPV, and significant cardiometabolic risk is unlikely. In those with intermediate FIB-4 values (≥1.3 or >2.0 if >65 years), a second non-invasive test is recommended. Patients with FIB-4 ≥2.67 are considered at high hepatic and cardiovascular risk. In both intermediate- and high-risk groups, tailored interventions targeting cardiovascular risk

and fibrosis progression should be initiated. Repeat NIT testing every 1–2 years may be appropriate, depending on the prior fibrosis stage and the burden of cardiometabolic comorbidities [1, 54].

Potential role of genetic and epigenetic markers. Polymorphisms in PNPLA3 (p.I148M) and TM6SF2 (p.E167K) are recognized risk markers for progressive MASLD and may aid in personalized risk stratification. However, current evidence does not support routine genetic testing in all patients with MASLD and/or CKD [1].

Epigenetic mechanisms are increasingly recognized as regulators of key cellular processes involved in inflammation and fibrosis. These include DNA methylation, histone modifications, and non-coding RNAs, particularly microRNAs (miRNAs). Several studies have linked miRNAs—such as miR-122, miR-34a, and miR-192—to the severity of hepatic inflammation and fibrosis in MASLD [55].

Given the association between fibrosis and cardiovascular risk, modulating specific miRNAs could become a future therapeutic strategy targeting both MASLD and cardiovascular risk.

In heart failure, altered methylation patterns in protein-coding genes and miRNAs have also been identified, suggesting a potential role as biomarkers of cardiovascular dysfunction: particularly in processes driven by inflammation and fibrosis [56].

CLINICAL MANAGEMENT OF MASLD IN CKD TO REDUCE CARDIOVASCULAR RISK

Managing MASLD in patients with CKD and CVD requires a multidisciplinary approach that targets shared metabolic pathways, chronic inflammation, and organ-specific complications.

Lifestyle modification

Lifestyle intervention remains the cornerstone of MASLD treatment. Key strategies include alcohol abstinence, smoking cessation, and sustained weight loss. A reduction of 3%–5% in body weight improves steatosis; 7%–10% can reduce steatohepatitis; and $\geq 10\%$ may significantly improve liver fibrosis [1].

Weight loss also benefits metabolic comorbidities and reduces cardiovascular risk. Notably, histological improvement in liver fibrosis through lifestyle changes has been independently linked to better renal outcomes in MASLD [57].

Physical activity, even without weight loss, is beneficial. A combination of aerobic and resistance training is recommended, with a weekly target of 150–300 minutes of moderate or 75–150 minutes of vigorous exercise [58].

Pharmacological approaches

Resmetirom, a thyroid hormone receptor- β agonist, is the first FDA-approved drug for MASLD. A phase 3 randomized controlled trial showed resolution of NASH and fibrosis improvement. Although renal and cardiovascular outcomes remain unstudied, reductions in apoB and LDL-C suggest potential cardiometabolic benefits [59].

Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as promising therapeutic agents for patients with MASLD, CKD, and CVD, targeting IR, excess adiposity, and hepatic steatosis. Through their effects on glycaemic control and appetite regulation, GLP-1 receptor agonists promote sustained weight loss and favourable changes in body fat distribution,

contributing to improvements in liver health. Evidence from clinical trials indicates that GLP-1 receptor agonists can reduce the severity of metabolic dysfunction-associated steatohepatitis (MASH), as assessed by histology, as well as decrease hepatic fat content and circulating MASH biomarkers [60]. A recent interim analysis of the phase 3 ESSENCE trial showed that semaglutide (2.4 mg) improved liver histology in patients with MASH and stage 2–3 fibrosis compared to placebo, achieving higher rates of steatohepatitis resolution and fibrosis reduction [61].

Beyond hepatic benefits, GLP-1 Semaglutide has also demonstrated cardiovascular protection, reducing major events in patients with or without T2DM [53, 54], and lowering albuminuria in CKD with obesity, suggesting renoprotective potential [62].

Tirzepatide, a dual GLP-1/ gastric inhibition polypeptide (GIP) receptor agonist, has shown efficacy in resolving MASH, though fibrosis regression has not been conclusively demonstrated. Longer treatment durations may be needed [63]. Retatrutide, a triple GIP/GLP-1/glucagon receptor agonist, has shown potent effects on hepatic fat reduction and metabolic parameters in MASLD patients [64].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown to improve cardiovascular and renal outcomes across a wide range of populations, including both diabetic and non-diabetic patients [65] [66]. In MASLD, these agents reduce hepatic fat content as assessed by imaging-based biomarkers; however, their histological benefits appear limited. While modest improvements in fibrosis scores have been reported in patients with T2DM, no significant changes have been demonstrated in histological steatosis or lobular inflammation. In individuals with T2DM, SGLT2 inhibitors have been associated with modest reductions in liver fibrosis, as measured by transient elastography (FibroScan) and the FIB-4 index [67].

Pioglitazone, a thiazolidinedione, and eraxisome proliferator-activated receptor (PPAR)- γ , an agonist approved for T2DM management, has demonstrated efficacy in MASLD. In a meta-analysis of eight randomized controlled trials found that treatment with PPAR- γ agonist significantly improved advanced fibrosis, any grade of fibrosis and promoted NASH resolution [68]. However, PPAR- γ agonist treatment remains controversial due to their side-effects, including weight gain, heart failure, and an increased risk of bone fractures. PPAR- γ agonist treatment should be used with caution in patients with history of CVD, making them less favourable for managing the cardio-renal-hepatic axis.

Statins reduce cardiovascular risk and have been linked to lower all-cause and liver-related mortality in MASLD. While they may help slow the progression of hepatic fibrosis, there is no conclusive evidence of fibrosis regression [69]. Despite historical concerns regarding hepatotoxicity, current evidence supports their safety in MASLD, including in patients with mildly elevated liver enzyme levels [49].

Bempedoic acid, an ATP citrate lyase inhibitor, reduces cholesterol and fatty acid synthesis while activating AMP-activated protein kinase, thereby suppressing gluconeogenesis and lipogenesis [70]. In animal models, it has been shown to attenuate diet-induced hepatic steatosis; however, its clinical efficacy in humans remains under investigation [71].

In recent years, several novel therapeutic agents have entered development for the treatment of MASLD, with fibroblast growth factor 21 (FGF-21) analogues and PPAR agonists emerging as particularly promising candidates. Pegzofermin, an FGF-21 analogue, has demonstrated antifibrotic effects in patients with MASH in a phase 2b clinical trial [72]. Similarly, lanifibranor, a pan-PPAR agonist, has been shown to reduce IR, improve hepatic

Table 2: Pharmacological approaches for MASLD and their effect on CKD and CVD.

Drug/class	Mechanism of action	Effect on MASLD	Effect on CKD	Effect on CVD	Potential side-effects
Pioglitazone [68] (Ppar- γ Agonist)	Activation of PPAR- γ to improve insulin sensitivity	Improves fibrosis and NASH; long-term safety concerns	Use with caution; risk of fluid retention	Risk of heart failure; use cautiously in CVD	Weight gain, fluid retention, bone fractures, bladder cancer, heart failure
Statins [69]	HMG-CoA reductase inhibitors	May reduce fibrosis progression; safe in MASLD	Safe; may lower renal risk via CVD risk reduction	Reduces CVD risk; lowers all-cause mortality	Myalgia, transaminase elevation, increased risk of T2DM
SGLT2 Inhibitors [65–67]	Inhibits renal glucose reabsorption, promotes glucosuria	Reduces liver fat; modest fibrosis benefit in T2DM	Delays CKD progression; reduces albuminuria	Reduces MACE regardless of CKD or CVD status	Genitourinary infections, volume depletion, bone loss
GLP-1 Receptor Agonists [60, 61] (Semaglutide)	Promotes insulin secretion, suppresses appetite	Reduces steatosis, MASH activity; fibrosis data preliminary	Reduces albuminuria and renal risk in T2DM & CKD	Reduces CV events in T2DM and obesity	GI (loss of appetite, nausea, constipation, diarrhoea), gallstones, pancreatitis
Tirzepatide [63] (GLP-1/GIP Agonist)	Dual GLP-1 and GIP receptor agonist, promotes weight loss	Resolves MASH; fibrosis benefit uncertain	Potential benefit; more data needed	Expected CV benefit; outcomes pending	GI, gallstones, pancreatitis
Retatrutide [64] (GIP/GLP-1/Glucagon Agonist)	Triple GLP-1 GIP receptor and glucagon agonist, promotes weight loss	Marked liver fat reduction; strong metabolic benefit	Unknown	Strong metabolic effect; CV data lacking	GI, gallstones, pancreatitis
Resmetirom [59]	Activates thyroid hormone receptor β , regulates lipid metabolism	Improves steatosis, inflammation and fibrosis (Phase 3)	Not studied	Improves lipid profile; outcomes unproven	Diarrhoea, nausea
Bempedoic Acid [70, 71]	ACLY inhibitor	Promising in animal models; human data pending	Unknown	Lipid lowering, benefits on MACE	Myalgia, gout, increase transaminase
Pegozafermin [72]	FGF-21 analogue	Antifibrotic effects in Phase 2b trial	Unknown	Unknown	Nausea, diarrhoea
Lanifibranor [73]	pan-PPAR Agonist	Improves steatosis and metabolic profile	Unknown	Improves cardiometabolic risk factors	Nausea, diarrhoea, peripheral oedema, anaemia

HMG-CoA, β -hydroxy β -methylglutaryl-CoA; ACLY: ATP citrate lyase; FGF-21: fibroblast growth factor 21.

steatosis, and favourably modulate cardiometabolic risk factors [73].

The main limitations of these pharmacological approaches are the short duration of most clinical trials and the absence of hard clinical endpoints, such as progression to cirrhosis, cardiovascular events, or renal mortality. Although the results to date are promising, the available evidence remains preliminary. There is a clear need for longer-term, high-quality clinical trials with robust endpoints to confirm the efficacy and safety of these therapies, particularly in patients with MASLD and co-existing CKD.

All of these pharmacological approaches are summarized schematically in Table 2.

Looking ahead, the therapeutic landscape for MASLD will likely evolve towards combination regimens that simultaneously target metabolic dysfunction, hepatic inflammation, and fibrogenesis through complementary mechanisms of action [74].

PROPOSED ALGORITHM

Given the well-established link between liver fibrosis and cardiovascular risk in patients with CKD and/or T2DM, early detection and a multidisciplinary approach are essential. A structured strategy for the detection and risk stratification of MASLD in this population is therefore warranted.

Figure 4 illustrates a stepwise algorithm designed specifically for patients with CKD. This approach integrates non-invasive fibrosis markers and cardiometabolic profiling to support clinical decision-making, and highlights the critical association between liver fibrosis and cardiovascular risk.

The goal of this strategy is to identify high-risk individuals early, allowing timely intervention to reduce both cardiovascular and hepatic complications. In addition, the algorithm includes periodic reassessment, which enables dynamic risk monitoring and supports personalized management tailored to the evolving clinical profile of each patient.

The target population and higher risk includes patients with T2DM, obesity, or metabolic syndrome, particularly those >50 years of age. A two-step algorithm is recommended for fibrosis assessment. First, clinicians should use non-invasive test such as FIB-4 to screen for significant fibrosis. If results are indeterminate or advanced fibrosis, a more accurate test such as liver elastography (FibroScan) should be performed. If unavailable, proprietary tests such as ELF can be considered. If results remain inconclusive or indicate advanced fibrosis, referral to a hepatologist is advised for further evaluation, follow-up, and treatment planning.

This approach supports risk-adapted intervention in CKD, integrating hepatologic and cardiovascular care. Periodic reassessment—every 1 to 2 years—is advised, particularly in those with evolving metabolic or renal profiles, to adjust the intensity of follow-up and therapy accordingly.

CONCLUSION

In conclusion, MASLD plays a significant role in amplifying both cardiovascular and renal risk, particularly in individuals with CKD and/or T2DM. Its recognition as a multisystem condition calls for a comprehensive and integrative clinical approach, moving beyond a traditionally hepatocentric perspective. In this review, we propose a practical, stepwise algorithm tailored to the nephrology setting, aimed at facilitating early detection and risk stratification of MASLD in patients with CKD. This strategy combines non-invasive fibrosis assessment with cardiometabolic profiling, supporting timely, risk-adapted interventions that can help mitigate both hepatic and cardiovascular complications.

Looking ahead, clinical strategies should aim to improve diagnostic accuracy and address shared metabolic and fibrotic pathways. Although several therapies show promise, evidence of long-term efficacy—particularly in CKD—is still limited. Integrating MASLD into routine nephrology care offers a valuable opportunity to enhance outcomes through early detection and multidisciplinary, personalized management.

CONFLICT OF INTEREST STATEMENT

None of the authors received financial support for the preparation of this article. The authors declare no conflicts of interest related to the content of this work.

AUTHORS' CONTRIBUTIONS

All three authors participated in the design of the work and in the literature search and review. All authors approved and signed the final version of the manuscript, including tables and figures.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

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