

# MAFLD: A Comprehensive Review of the Link Between Metabolic Dysfunction and Cardiovascular Risk

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**Abstract:** Metabolic dysfunction-associated fatty liver disease (MAFLD) affects over 30% of the global population. It is a multisystem condition with a strong association with cardiovascular disease (CVD), the leading cause of mortality worldwide. Key shared mechanisms, including insulin resistance, systemic inflammation, oxidative stress, and genetic predisposition, couple MAFLD with increased risks of coronary artery disease, ischemic heart disease, and heart failure. Early detection via non-invasive imaging and biomarkers is crucial for effective risk stratification. Management strategies emphasize lifestyle modifications and the development of targeted pharmacotherapies addressing metabolic and inflammatory pathways. Understanding the interconnected pathogenic mechanisms facilitates personalized interventions to reduce morbidity and improve long-term outcomes. A multidisciplinary approach remains essential to prevent and manage the cardiovascular implications of MAFLD.

**Keywords:** fatty liver, cardiometabolic risk, metabolic dysfunction, pharmacotherapy

## Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), affects over 30% of the global adult population, posing a significant health, economic, and societal challenge worldwide.<sup>1,2</sup> Over the last decade, there has been an 11.2% increase in age-standardized rates of MAFLD, which parallels the rising rates of obesity and type 2 diabetes mellitus (T2DM), reflecting a decline in overall global metabolic health.<sup>3,4</sup> Alarmingly, the prevalence of MAFLD is also rising among adolescents and children.

The core pathogenesis basis of MAFLD is linked to metabolic dysfunction. The disease spectrum ranges from simple hepatic steatosis to more advanced stages, including steatohepatitis, fibrosis, and cirrhosis.<sup>5,6</sup> MAFLD has emerged as a primary contributor to end-stage liver disease, hepatocellular carcinoma, and liver transplantation.<sup>7</sup> Moreover, it is a multisystem disease that elevates the risk of T2DM, chronic kidney disease (CKD), cardiovascular disease (CVD), and various extra-hepatic cancers.<sup>8,9</sup>

Cardiovascular disease remains the primary cause of death worldwide and is the leading cause of mortality in patients with MAFLD. The prevalence of CVD is anticipated to increase, especially in low- and middle-income nations, driven by urbanization, an aging population, and shifts in lifestyle habits.<sup>10,11</sup> A robust reciprocal correlation between MAFLD and CVD has been established through observational, cohort, and genetic studies, revealing various shared underlying pathogenic mechanisms.<sup>12</sup>

This review aims to provide an updated narrative on the relationship between MAFLD and CVD, emphasizing the key role of metabolic dysfunction in mediating this interaction. The implications for understanding pathogenesis, diagnosis, and management, particularly in relation to mitigating cardiovascular risk in MAFLD patients, will also be discussed.

## Metabolic Health and Dysfunction

There is currently no clear consensus on the variables or cut-off values used to define metabolic health. However, it is typically regarded as the lack of cardiometabolic disease or risk factors that may contribute to the potential development of such diseases. Metabolic health is characterized by normal insulin sensitivity, balanced lipid profiles, stable blood pressure, and low levels of systemic inflammation.<sup>13</sup>

Metabolic dysfunction is a complex process that reflects a failure of metabolic homeostasis, which subsequently raises the risk of cardiometabolic diseases through several interconnected mechanisms.<sup>14</sup> Key metabolic abnormalities, such as insulin resistance, elevated triglycerides, decreased HDL cholesterol, increased waist circumference, elevated fasting glucose, and a chronic low-grade inflammatory state, are frequently used to indicate metabolic dysfunction. This dysfunction is a pivotal determinant in the pathogenesis of MAFLD, with the risk of both hepatic and extra-hepatic outcomes increasing with the increase in the number of metabolic abnormalities present in a patient.<sup>15</sup>

Though MAFLD is typically associated with obesity, it is increasingly recognized in lean individuals, who constitute up to 40% of the total MAFLD population and often exhibit distinct clinical and pathological characteristics shaped by metabolic adaptation at early stages of the disease.<sup>16</sup> This adaptation is lost with the advancement of the disease, and those with lean MAFLD tend to have a worse outcome compared to their obese counterpart.<sup>17</sup> This further emphasises the fundamental role of metabolic health and dysfunction in the disease's pathogenesis, which extends beyond the definitions of overweight or obesity based on body mass index (BMI).<sup>18,19</sup>

Stemming from this, a significant paradigm shift has occurred with the redefinition of fatty liver disease as MAFLD, aligning the disease nomenclature and diagnostic criteria with the core underlying pathophysiological mechanisms of metabolic dysfunction that cause the condition.<sup>20,21</sup> MAFLD is diagnosed based on hepatic steatosis identified by histology or imaging, accompanied by evidence of metabolic dysfunction indicated by the presence of one or more of the following factors: obesity/overweight, T2DM, or two of the metabolic risk dysregulations.<sup>2,22</sup> MAFLD has been shown to more accurately identify patients with significant hepatic fibrosis and extra-hepatic manifestations, including cardiovascular disease risk, compared to other definitions of the disease.<sup>23–27</sup>

## MAFLD and Cardiovascular Disease

A robust reciprocal correlation between MAFLD and CVD has been established through observational, cohort, and genetic studies. Individuals with MAFLD face a markedly increased risk of cardiovascular events, regardless of conventional risk factors.

## Epidemiological Evidence

Studies consistently show elevated prevalence of cardiovascular morbidity and mortality in these patients, especially those with advanced fibrosis (F3–F4).<sup>28,29</sup> They are more likely to develop conditions such as coronary artery disease, stroke, atrial fibrillation, heart failure, and unfavorable ventricular remodeling, underscoring the strong link between MAFLD severity and cardiovascular outcomes.<sup>30,31</sup>

A study consisting of 9,775,066 adults revealed that MAFLD, measured by a fatty liver index (FLI) of  $\geq 30$ , was independently linked to a higher risk of new CVD events. These events were defined as a combination of myocardial infarction, ischemic stroke, heart failure, or cardiovascular death, with an adjusted hazard ratio (HR) of 1.39.<sup>32</sup> A meta-analysis involving 10 cohort studies showed that the rates of CVD and CVD-related mortality were 2.26 times and 1.57 times greater in the MAFLD group compared to the control group, respectively.<sup>33</sup> Similar results were also reported in other meta-analysis, strengthening the relationship between MAFLD and CV events.<sup>34–36</sup> Additionally, a longitudinal study of 34,865 participants found that FLI, especially moderate/severe FLI, significantly increased the risk of new-onset hypertension, which is also linked to greater cardiovascular risk.<sup>37</sup>

Research increasingly focuses on MAFLD impact in older adults, where the relationship to cardiovascular outcomes might differ from younger cohorts. Some studies indicate an increased risk of atrial fibrillation (AF),<sup>38–40</sup> but the association with major adverse cardiovascular events or mortality may be less significant after adjusting for age and comorbidities.<sup>41</sup> Notably, liver stiffness, independent of steatosis, might be relevant for cardiovascular risk.<sup>42</sup> Thus, while MAFLD is common in older adults, its impact requires careful consideration of age-related factors and liver fibrosis.<sup>43</sup> Further research is needed to clarify these nuances for targeted management.<sup>44</sup>

## Coronary Artery Disease (CAD)

Patients with MAFLD have approximately double the risk of developing coronary artery disease (CAD) compared to those without MAFLD.<sup>45</sup> Previous research has highlighted a strong association between MAFLD and increased CAD risk.<sup>46</sup> A 20-year follow-up study (1991–2009) showed that high liver fat content predicted CAD, even when adjusting for factors like age and gender, with an HR of 1.92.<sup>47</sup> Furthermore, a cross-sectional study in Iran involving 296 participants found a significantly higher prevalence of CAD in MAFLD patients, with an odds ratio (OR) of 2.01.<sup>48</sup> Meta-analysis comprising 32 studies with over 5.6 million participants also confirmed this relationship, noting a relative risk (RR) of 1.21.<sup>49</sup>

Moreover, recent studies emphasize the link between ischemic heart disease (IHD), a form of CAD, and MAFLD. Data from the NHANES survey (1999–2016) revealed that an increased FLI, indicating hepatic steatosis, correlated with higher IHD prevalence. Specifically, for every standard deviation increase in FLI, the risk of IHD rose by 27%.<sup>50</sup> Another study of 2,088 individuals demonstrated that those with mild, moderate, and severe fatty liver had increased risks of developing IHD by 1.88, 2.37, and 2.76 times, respectively.<sup>51</sup> A Danish cohort study of 94,708 individuals, including 10,897 with IHD, found that the risk of IHD increased progressively with higher liver fat content across quartiles, reaching an OR of 2.41. Additionally, the OR for IHD in individuals with versus without MAFLD was 1.65.<sup>52</sup> However, some studies may have limitations due to inadequate adjustment for potential confounders and cardiovascular risk factors and challenge to establish causal relationships.

## Heart Failure

An elevated risk of heart failure and cardiac fibrosis has been associated with MAFLD, particularly in advanced MAFLD, where essential monitoring of similar cardiac fibrosis and failure is required.<sup>53</sup> A study included about 175,000 outpatients, both with and without MAFLD, matched for sex, age, index year, and known heart failure risk factors, revealed that MAFLD was significantly linked to a 10-year increased cumulative incidence of heart failure (HR 1.34) in men and women from various age groups.<sup>54</sup> A recent meta-analysis of 11 longitudinal cohort studies, which included more than 11 million middle-aged individuals, revealed that MAFLD is linked to a 1.5-fold greater long-term risk of new-onset heart failure, a relationship that remained significant regardless of hypertension, T2DM, and other prevalent cardiometabolic risk factors.<sup>55</sup>

## Evidence from Mendelian Randomization Studies

Mendelian Randomization has emerged as a powerful tool, providing strong evidence for the causal links between metabolic traits, inflammation, MAFLD, and CVD.<sup>56</sup> Besides these epidemiological evidence, Mendelian Randomization also established a strong link between MAFLD and CVD. For instance, recent studies demonstrated that genetically predicted MAFLD increased the risk of CVD even after adjusting for established metabolic variables, supporting the notion that MAFLD actively promotes atherogenesis and vascular dysfunction rather than merely being a bystander.<sup>57,58</sup>

Another comprehensive Mendelian randomization study examining circulating blood metabolites found that specific metabolites, such as branched-chain amino acids, ketone bodies, and lipids, directly influence liver fat accumulation and may also contribute to cardiovascular risk.<sup>59</sup>

## Genetic Factors

Genetic predisposition significantly influences MAFLD and CVD, with key risk variants mainly studied in Europeans.<sup>60</sup> The most robust association was demonstrated for the single-nucleotide polymorphism (SNP) rs738409 in Patatin-like

phospholipase domain-containing protein (*PNPLA3*) that is linked to the entire spectrum of the disease including increased liver fat, cirrhosis, and cancer, independent of other factors.<sup>61,62</sup> Recent evidence suggests that *PNPLA3* variants may be protective against CVD, contrasting with the pathogenic role they play in liver disease, and is characterized by lipid accumulation with specific lipidomic features.<sup>63,64</sup>

Some other variants in Transmembrane 6 superfamily member 2 (*TM6SF2*), membrane-bound O-acyltransferases (*MBOAT7*) and 17 $\beta$ -hydroxysteroid dehydrogenase type 13 (*HSD17B13*) also has been shown consistently to impact disease progression. For example, *TM6SF2* E167K increases MASH and fibrosis risk but may protect against cardiovascular events, highlighting the complex relationship between liver and heart health.<sup>65–68</sup> The *MBOAT7* rs641738C>T variant is associated with liver fat, inflammation, and fibrosis; it alters phospholipid remodeling and immune responses, worsening liver damage.<sup>69–71</sup> *HSD17B13* is involved in lipid and retinol metabolism, mainly expressed in periportal hepatocytes, has a truncating variant (rs72613567) that offers protection against liver inflammation, fibrosis, and cirrhosis even in high-risk individuals.<sup>72–77</sup> Other loss-of-function variants, like rs62305723, also reduce liver disease risk.<sup>75</sup>

Others identified polymorphisms include in glucokinase regulatory protein (*GCKR*) and Sterol Regulatory Element-binding Protein 1 (*SREBP-1*), both of which are involved in lipid regulation, may also influence CVD risk.<sup>78</sup> Recent studies suggest that genetic changes of fibroblast growth factor 21 (*FGF21*) is a broad metabolic regulator, could be impacting both MAFLD and heart disease risks.<sup>79,80</sup> Additionally, signaling of myeloid-epithelial-reproductive tyrosine kinase (*MERTK*) are regulating core pathway of fibrosis across various organs.<sup>81,82</sup> Additionally, genetic evidence linking SNPs associated with BMI, T2D, and inflammation marked by CRP showed an association with MAFLD and cardiovascular risk.<sup>56,83</sup>

## Pathophysiology of Cardiovascular Events in MAFLD

MAFLD and CVD share numerous common risk factors, and the pathophysiological mechanisms connecting the two conditions are intricate and multifaceted, involving various pathways (Figure 1).

### Insulin Resistance

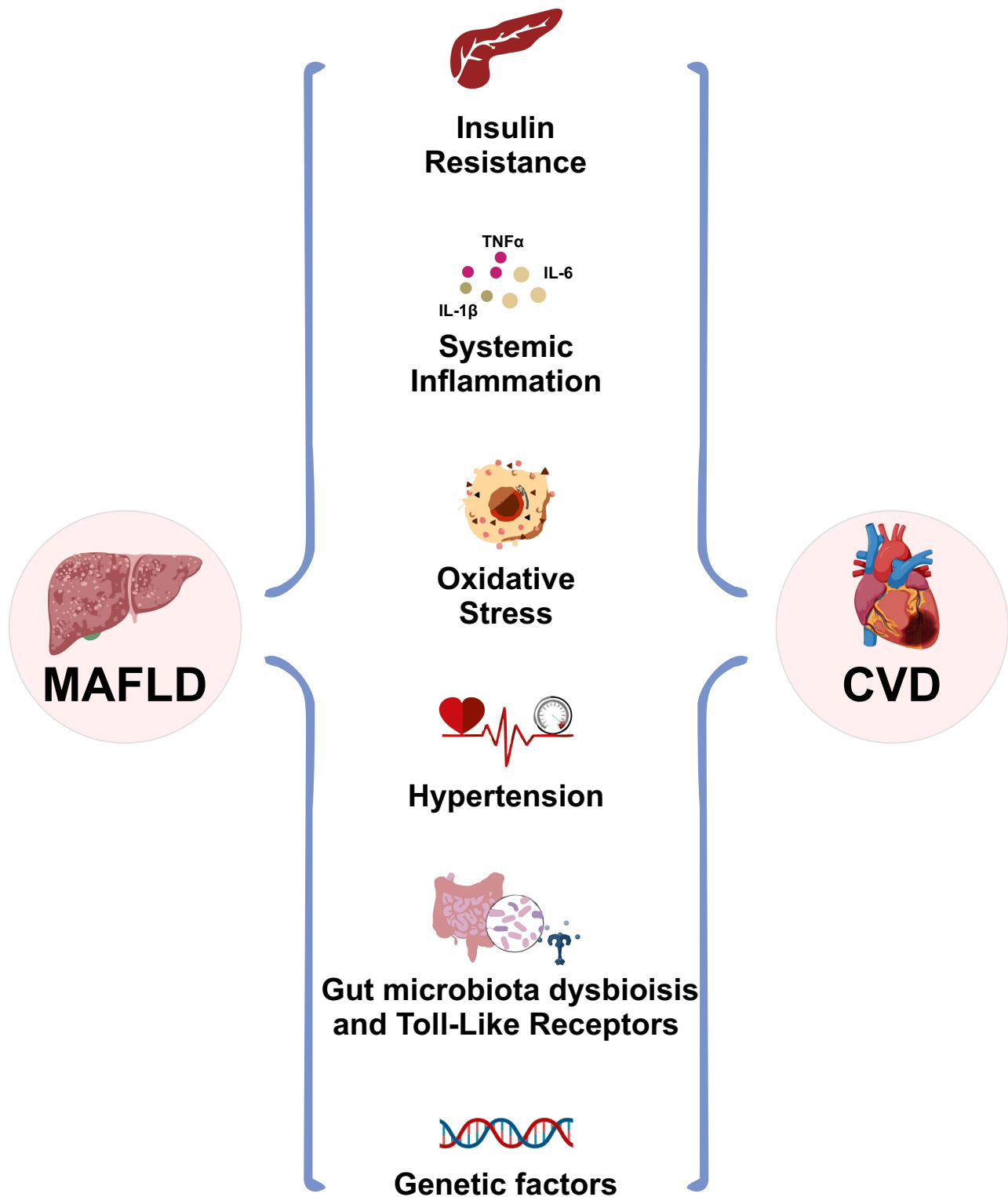
The occurrence of metabolic dysfunction that underpins the risk of MAFLD and cardiovascular events and mediates the link between the two conditions could be broadly attributed to an intertwined interaction between insulin resistance and chronic low-grade inflammation.<sup>14</sup>

Insulin resistance is a key mechanism connecting MAFLD with cardiovascular risk.<sup>84</sup> It disrupts lipid metabolism, leading to increased levels of circulating free fatty acids and the formation of atherogenic lipoprotein profiles. This is characterized by lower levels of high-density lipoprotein cholesterol (HDL-C) and higher triglyceride levels, which can lead to atherosclerosis and increase the risk of cardiovascular complications.<sup>85</sup>

As a compensatory response to insulin resistance, insulin secretion rises, resulting in hyperinsulinemia. This condition can harm the vascular endothelium by promoting hepatic gluconeogenesis and heightening systemic inflammation.<sup>84</sup> Pro-inflammatory cytokines produced due to insulin resistance exacerbate oxidative stress, further contributing to arterial stiffness and hypertension.<sup>86</sup> Furthermore, insulin resistance and the lipotoxic milieu produced by MAFLD stimulate the release of pro-coagulant factors, increasing the likelihood of thrombotic events. This significantly elevates the risk of adverse cardiovascular outcomes in patients with MAFLD.<sup>13,87</sup>

### Systemic Inflammation

Systemic inflammation is another crucial pathophysiological pathway linking CVD and MAFLD. Obesity, which occurs in about 80–90% of MAFLD patients, is linked to low-grade systemic inflammation, ER stress dysregulation, or lipotoxicity.<sup>88</sup> Excess lipids and the hypertrophy of adipocytes in adipose tissue cause local macrophages to adopt a more inflammatory phenotype, releasing cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and Interleukin-6 (IL-6).<sup>89,90</sup> These cytokines disrupt insulin receptor signaling by promoting serine phosphorylation of insulin receptor substrates, which reduces insulin sensitivity and leads to hyperinsulinemia.<sup>91</sup> Concurrently, resident Kupffer cells and recently recruited monocyte-derived macrophages in the liver produce pro-inflammatory mediators in response to metabolic stress, which worsens insulin resistance, encourages steatosis, and ultimately leads to fibrosis.<sup>91,92</sup>



**Figure 1** Overview of the shared pathophysiological mechanisms between MAFLD and CVD.

This vicious cycle, where insulin resistance fuels further inflammation and vice versa, also results in endothelial dysfunction and atherosclerotic changes, creating a pathway for cardiovascular events.<sup>91</sup>

Additionally, MAFLD can frequently exist with viral hepatitis, which may also impact the risk of CVD in these patients.<sup>93–96</sup> For instance, Chronic Hepatitis C Virus (HCV) infection can influence lipid profiles and cardiovascular

risk, with studies showing increased cholesterol and triglycerides after successful HCV eradication, particularly in genotype 3 patients.<sup>97</sup> Furthermore, recognizing that MAFLD can co-exist with other liver conditions, such as alcohol-related liver disease, highlights the potential for synergistic effects that exacerbate inflammation and disease progression, which will increase risk of CVD further.<sup>98</sup>

## Oxidative Stress

Dyslipidemia, characterized by elevated triglycerides, reduced HDL cholesterol, and increased LDL cholesterol (especially small, dense LDL particles), is a hallmark of MAFLD, which increases oxidative stress.<sup>99</sup> Oxidative stress is one of the major contributing factors to the emergence of cardiovascular events in patients with MAFLD, which occurs as a result of increased reactive oxygen species (ROS) generation, mitochondrial dysfunction, and impaired antioxidant defence.<sup>92,100</sup>

The metabolic imbalance in MAFLD causes lipid peroxidation, which damages endothelial cells and increases foam cell production, a critical step in atherosclerosis.<sup>101</sup> Furthermore, oxidative stress reduces nitric oxide (NO) bioavailability, which contributes to endothelial dysfunction and arterial stiffness, increasing cardiovascular risk.<sup>102,103</sup> Moreover, oxidative stress-induced damage to vascular cells exacerbates the progression of atherosclerotic lesions, thereby increasing the risk of cardiovascular events in this patient population.<sup>103</sup>

## Hypertension

As is well established, insulin resistance and hypertension are intricately linked to various metabolic dysfunctions, playing central roles in the pathogenesis of cardiovascular disease.<sup>104,105</sup> Hyperinsulinemia, a hallmark of insulin resistance, promotes renal salt reabsorption, which can lead to volume expansion, vasoconstriction, and consequently, elevated blood pressure.<sup>106</sup> In addition, longitudinal cohort studies have demonstrated that obesity elevates cardiovascular risk indirectly through mediating factors such as hypertension, dyslipidemia, specifically hyper-LDL cholesterol and T2D.<sup>107,108</sup>

These interrelated risk variables not only contribute significantly to the heightened incidence of cardiovascular events in obese populations but also exemplify the complex interplay between metabolic disturbances and cardiovascular health. Recognizing these interconnected pathways underscores the importance of holistic management strategies targeting both metabolic and cardiovascular risk factors to effectively mitigate disease progression and improve long-term outcomes.<sup>109</sup>

## Gut Microbiota Dysbiosis and Toll-Like Receptors

The gut-liver axis is vital in MAFLD development, with gut dysbiosis, barrier dysfunction, and endotoxemia promoting liver inflammation and fat accumulation.<sup>110</sup> Imbalances in gut microbiota can increase harmful compounds like trimethylamine N-oxide (TMAO), which is linked to atherosclerosis and cardiovascular risk, while a healthy microbiome produces beneficial metabolites such as short-chain fatty acids that support inflammation regulation and vascular health.<sup>111–113</sup>

In patients with MAFLD and CVD, notable shifts in microbiota composition—such as increased *Coprococcus* and *Veillonella* and decreased *Parabacteroides*, *Ruminococcus*, *Bacteroides*, and *Bifidobacterium*—appear to influence disease severity.<sup>114,115</sup> Furthermore, metabolomic studies suggest that MAFLD in CVD patients may worsen clinical outcomes by altering circulating metabolites and microbiota characteristics,<sup>116</sup> while changes in fungal microbiota may also impact metabolic regulation.<sup>117</sup> Collectively, these findings highlight a potential significant role for the gut–liver–heart axis in the interconnected pathophysiology of MAFLD and its related metabolic disorders and CVD risk.

Toll-Like Receptors (TLRs), a type of membrane-bound pattern recognition receptor, plays a critical role in the pathophysiology of MAFLD. TLR4 is the most widely implicated member of the TLR family, with activation by gut-derived microbial products such as lipopolysaccharides (LPS) triggering hepatic inflammatory cascades and promoting insulin resistance.<sup>118</sup> This inflammatory environment increases intestinal permeability, allowing microbial ligands to move further into the portal circulation, prolonging systemic metabolic abnormalities and aggravating liver injury.<sup>118,119</sup>

Likewise, hepatocyte damage in MAFLD and MASH triggers the release of endogenous TLR9 ligands, which maintains a pro-inflammatory environment.<sup>120</sup> Moreover, TLR1, an under-researched member of the TLR family, is

involved in MAFLD and suggested as a possible treatment target for early-stage MAFLD.<sup>120</sup> TLR1 expression is associated with the degree of hepatic steatosis and inflammation, and its pharmacologic suppression reduced pro-inflammatory cytokine expression.<sup>121</sup>

## Assessment of Cardiovascular Risk in Patients with MAFLD

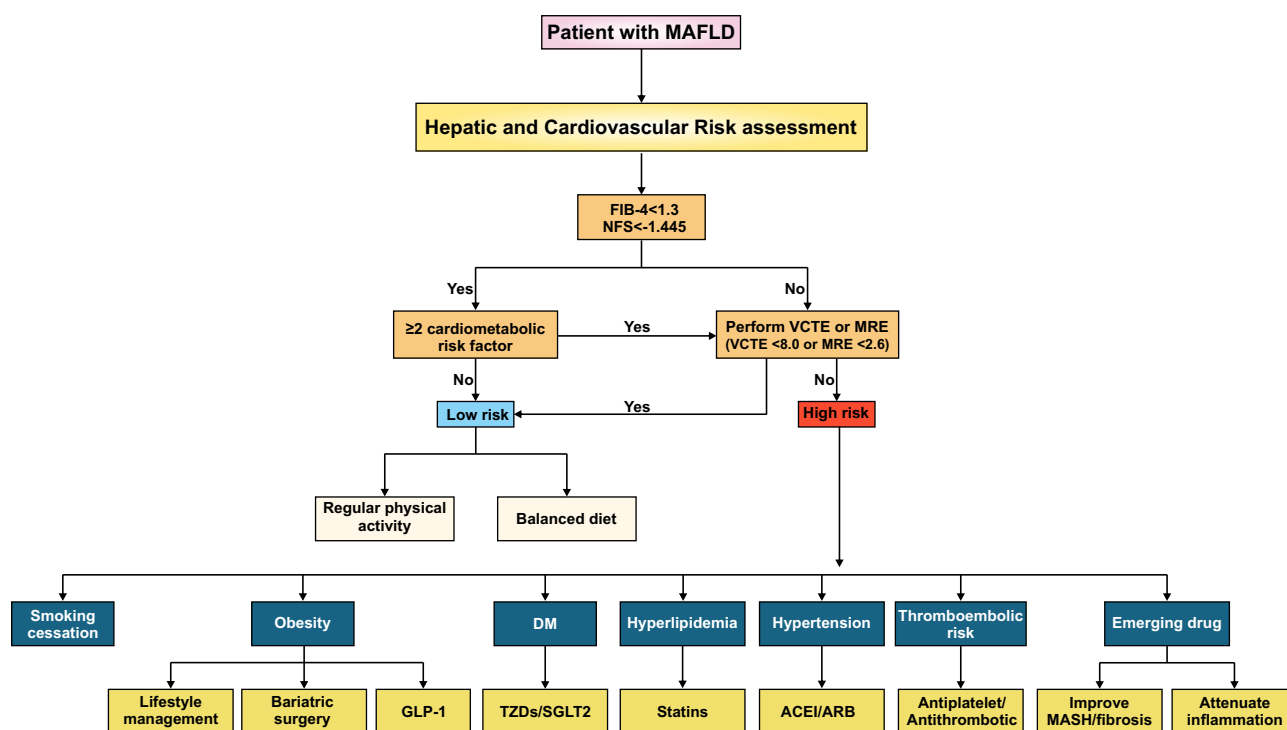
Given that the primary cause of death for patients with MAFLD is CVD, therefore, accurate risk assessment is crucial for timely interventions.<sup>33,122</sup> A multidisciplinary approach that includes non-invasive hepatic and cardiovascular evaluations is essential, as liver and heart dysfunction are closely intertwined.<sup>123</sup>

Non-invasive screening methods, including Coronary Artery Calcium (CAC) scoring and the Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator, have gained prominence for routine cardiovascular health assessments.<sup>33,124</sup> Advanced imaging techniques, such as Two-Dimensional Speckle Tracking Echocardiography (2D-STE) and Three-Dimensional Speckle Tracking Echocardiography (3D-STE), provide valuable insights into cardiac function.<sup>124,125</sup>

Similar to liver biopsy, which is the gold standard for diagnosing MAFLD, Coronary Computed Tomography Angiography (CCTA) is the preferred method for diagnosing coronary artery disease (CAD). CCTA allows the measurement of epicardial fat volume (EFV) and the assessment of coronary stenosis. Studies have linked increased EFV to a higher risk of major adverse cardiac events (MACE) among MAFLD patients.<sup>126–128</sup> Assessing cardiovascular risk in MAFLD requires a comprehensive approach integrating advanced imaging and risk prediction tools to facilitate early intervention and improve patient outcomes.

## Clinical Management and Pharmacotherapy

The management of MAFLD patients relies on a multidisciplinary prevention and management approach that aims not only to resolve hepatic inflammation and fibrosis but also to attenuate the cardiovascular risk (Figure 2). The holy grail of management of both conditions remains the lifestyle changes.



**Figure 2** Proposed algorithm for the assessment and management of cardiovascular disease risk in patients with MAFLD.

## Lifestyle Modifications

Losing weight by 7–10% has been linked with regression of liver fibrosis and reducing cardiovascular risk in these patients. This can be achieved via calorie restriction, improving the quality of diet and regular exercise, with a role for pharmacotherapy and bariatric surgery in selected indications.<sup>129</sup>

A Mediterranean diet prioritising fruits, vegetables, whole grains, lean meats, and healthy fats, while minimising processed foods and carbohydrates, has shown strong associations with decreased hepatic steatosis and cardiovascular risk.<sup>130</sup>

Aerobic exercises with moderate to strenuous activity for 2.5–5 h/ week can reduce liver fat, enhance insulin action, and lower hepatic inflammation. While Resistance Training for a minimum of 2 sessions/ week is reported to augment muscle mass, glucose uptake, and enhance metabolic health. Exercise recommendations should be tailored according to individual fitness levels, comorbidities, and patient preferences.<sup>2</sup> Moreover, a combination of aerobic and weight exercise provides a synergistic effect with more recorded exercise maintenance over time.

Mechanistically, frequent exercise enhances free fatty acid flow and substrate metabolism in the liver, muscle, and adipose tissues.<sup>129,131,132</sup> This helps to minimize steatosis and improve metabolic balance. It had been shown that exercise could be beneficial, even in the absence of weight loss.<sup>2</sup>

## Pharmacotherapy

Although the Food and Drug Administration (FDA) does not explicitly require all MAFLD drugs to have a positive impact on cardiovascular disease, they do consider cardiovascular risk in the approval process and encourage the development of drugs with potential benefits for both MAFLD and cardiovascular health or at least have no negative effect. Pharmacological interventions can target different pathways related to the pathophysiology of MAFLD and its metabolic comorbidities to enhance liver health and lower the risk of cardiovascular complications.<sup>133</sup>

## Medications

### Resmetirom (THR- $\beta$ Agonist)

Resmetirom (MGL-3196), a selective THR- $\beta$  agonist, is currently the only approved treatment for MAFLD that was approved in 2024. Its efficacy and safety were confirmed in a Phase 3 trial involving patients with biopsy-confirmed steatohepatitis and fibrosis stages F1-F3, showing significant reductions in liver fat, improvements in non-invasive fibrosis markers, and NASH resolution without increasing fibrosis, more effectively than placebo. Additionally, it lowered LDL-C and triglyceride levels, which are linked to cardiovascular risk.<sup>134</sup> Resmetirom was well tolerated, with mild to moderate gastrointestinal symptoms and transient liver enzyme increases being the most common adverse effects.<sup>135</sup>

It improves hepatic lipid oxidation, promotes mitochondrial biogenesis, and reduces de novo lipogenesis by targeting THR- $\beta$  in hepatocytes. It also offers broader cardiometabolic benefits by addressing key metabolic issues at the liver level.<sup>134</sup>

### Pioglitazone (PPAR- $\gamma$ Agonist)

Pioglitazone, a thiazolidinedione, activates PPAR- $\gamma$  mainly in fat, liver, and muscle, improving insulin sensitivity and promoting fat cell development. PPAR- $\alpha$ , found in liver and muscle, enhances fatty acid breakdown, lowers triglycerides, and has anti-inflammatory effects.<sup>136,137</sup> PPAR- $\delta$ , expressed throughout the body, regulates fatty acid use and energy expenditure, aiding in glucose absorption and reducing inflammation.<sup>136,137</sup> Beyond glucose control, pioglitazone exhibits anti-inflammatory, antifibrotic, and lipid-modulating properties, which help treat liver fat buildup and prevent disease progression, and it has been linked to fewer cardiovascular events.<sup>138–140</sup>

Studies show pioglitazone improves liver enzymes and metabolic health, especially in prediabetic patients, with histological benefits like reduced liver fat and inflammation.<sup>141</sup> However, pioglitazone use is limited by potential side effects such as weight gain and fluid retention, as well as concerns regarding heart failure exacerbation.

New PPAR drugs, such as Lanifibranor and Saroglitazar, show promise in fibrosis reduction and MASH resolution.<sup>142,143</sup> Dual PPAR- $\alpha/\gamma$  agonists promote liver fat breakdown and enhance blood sugar metabolism, addressing key factors in MAFLD development.<sup>137,144</sup>

## Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 RAs have shown promise in treating hepatic necroinflammation, diabetes, and CVD.<sup>145</sup> By mimicking GLP-1, these agents increase insulin secretion, reduce glucagon, slow gastric emptying, and promote satiety. They are effective in reducing hepatic steatosis, inflammation, and improving glycaemic control and weight loss in MAFLD.<sup>145,146</sup>

Studies showed that GLP-1 RAs induce histological improvements in inflammation and fibrosis, along with decreased liver fat and normalized enzymes.<sup>145</sup> Semaglutide, used for T2DM and obesity, boosts insulin secretion and reduces appetite, with promising hepatic and cardiovascular benefits.<sup>147,148</sup> Liraglutide, initially used for T2DM, reduces hepatic steatosis, inflammation, hepatocyte ballooning, and liver stiffness, showing potential in MAFLD management.<sup>149,150</sup>

## Metformin

Metformin reduces hepatic steatosis and liver enzymes in MAFLD with T2DM by inhibiting hepatic gluconeogenesis through activation of AMP-activated protein kinase (AMPK), a key energy regulator. AMPK activation improves insulin sensitivity, promotes fatty acid oxidation, and decreases liver fat synthesis, while also enhancing mitochondrial function, reducing oxidative stress, and modulating inflammation—key factors in MAFLD progression.<sup>151,152</sup> Recent research suggests it may also protect liver cells by decreasing ferroptosis and apoptosis via oxidative stress pathways, potentially halting disease progression at the cellular level.<sup>153,154</sup> Additionally, metformin improves endothelial function, reducing cardiovascular risks associated with diabetes.<sup>155</sup>

## Empagliflozin

Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor originally used for managing hyperglycemia in T2DM, has gained attention for its significant cardiometabolic benefits beyond glycemic control.<sup>156</sup>

Empagliflozin has been used as a targeted therapy for MAFLD for its role in the reduction of hepatic steatosis, fibrosis, and aminotransferase levels via de novo lipogenesis, enhancing fatty acid oxidation, decreasing hepatic inflammation, and oxidative stress.<sup>153</sup> Moreover, Empagliflozin has been favored in patients with cardiovascular events for its role in reducing visceral adiposity, improving endothelial function, and its anti-inflammatory effect.<sup>157</sup>

## Statins and Other Lipid-Lowering Drugs

Lipid-lowering medications, especially statins, are well-established treatments due to their cardiovascular benefits and emerging liver-protective effects.<sup>158</sup> They effectively treat dyslipidemia in MAFLD patients, with meta-analyses showing improvements in lipid profiles and liver enzymes, particularly in patients without advanced liver disease.<sup>159</sup>

Besides statins, drugs like ezetimibe, fibrates, and omega-3 fatty acids have also been studied, especially for mixed dyslipidemia.<sup>160</sup> Fibrates, such as fenofibrate and pemafibrate, activate PPAR- $\alpha$ , reducing triglycerides, improving hepatic steatosis, and decreasing endoplasmic reticulum stress, which also enhances insulin sensitivity, lowers liver fat, and may reduce fibrosis by altering gene expression, including downregulating Transforming growth factor beta (TGF- $\beta$ ).<sup>161,162</sup>

Omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are crucial for various health benefits and have been shown to lower liver fat and improve liver enzyme levels in MAFLD patients.<sup>163,164</sup>

## Obeticholic Acid

Obeticholic acid (OCA) is a semi-synthetic derivative of chenodeoxycholic acid that acts as a selective farnesoid X receptor (FXR) agonist, a nuclear receptor highly expressed in the liver and intestines, playing key roles in bile acid, glucose, and fat metabolism. Activation of FXR by OCA reduces hepatic lipogenesis and enhances insulin sensitivity.<sup>165</sup> It has shown promise in improving the histological features of MASH and fibrosis, with studies reporting

significant improvements in liver fibrosis scores compared to placebo.<sup>166</sup> However, potential off-target effects, particularly dyslipidemia, necessitate cardiovascular risk monitoring, especially during long-term therapy.<sup>167,168</sup>

Additionally, the pipeline for MAFLD treatment comprises various other promising drugs offer additional strategies for fatty liver disease and related metabolic disorders. For instance, Efruxifermin, a long-acting fibroblast growth factor 21 (FGF21) analog showed limited fibrosis reduction in MASH cirrhosis patients in a Phase 2b trial, although some benefits were observed at 96 weeks.<sup>169</sup> Dapagliflozin, a SGLT2 inhibitor improved MASH and fibrosis.<sup>170</sup>

Some drugs combinations or multi-targets ones have also demonstrated promising results. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist significantly reduced weight in obese, type 2 diabetic adults.<sup>171</sup> Cotadutide, a dual GLP-1 and glucagon receptor agonist, reduced UACR, suggesting kidney benefits in type 2 diabetes and CKD in a phase 2 study.<sup>172</sup> Pemvidutide, a GLP-1/glucagon dual receptor agonist, may address obesity comorbidities.<sup>173</sup> These emerging therapies highlight the evolving landscape and potential for more targeted approaches in managing MAFLD and associated cardiovascular risks.

## Conclusion

MAFLD is a multisystem disease closely linked to increased cardiovascular risk, driven by metabolic abnormalities such as insulin resistance, inflammation, and dyslipidemia. With it rising prevalence worldwide, early assessment and a multidisciplinary approach that combines risk stratification, non-invasive screening, individualized treatment strategies, comprehensive management, including lifestyle modifications and targeted therapies, is vital to improve patient outcomes and address the interconnected pathways of liver and cardiovascular health.

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