Review

The Interplay Between Metabolic Dysfunction-Associated Steatotic Liver Disease and Heart Failure: Mechanisms, Associations, and Clinical Implications

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The Interplay Between Metabolic Dysfunction-Associated Steatotic Liver Disease and Heart Failure: Mechanisms, Associations, and Clinical Implications

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Abstract: The interplay between metabolic dysfunction-associated steatotic liver disease (MASLD) and heart failure (HF) reveals a significant and complex relationship marked by shared metabolic, inflammatory, and fibrotic pathways. This review explores their combined epidemiology, pathophysiology, and clinical implications, emphasizing the need for integrative management approaches. MASLD, which encompasses a range of liver conditions from benign steatosis to advanced fibrosis and hepatocellular carcinoma, is tightly linked with metabolic syndrome, while HF represents the culmination of systemic and cardiovascular stresses often exacerbated by comorbid conditions like diabetes and hypertension. Their mutual pathophysiology involves disruptions in lipid metabolism, systemic inflammation, insulin resistance, and fibrosis, with MASLD-associated inflammatory markers accelerating HF progression and vice versa. Epidemiological studies underscore MASLD's association with elevated cardiovascular risk, particularly HF, which persists even after adjusting for traditional risk factors. This narrative review underscores the urgent need for early diagnosis, risk factor management, and novel therapeutic targets to mitigate the escalating burden of MASLD and HF on global health, especially within aging populations increasingly affected by metabolic disorders.

Keywords: NAFLD; fluid retention; ejection fraction; inflammation

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a global public health concern, characterized by the accumulation of excess fat in the liver[1]. MASLD includes a range of conditions, from simple steatosis to more severe metabolic dysfunction-associated steatohepatitis (MASH), which can lead to fibrosis, cirrhosis, and hepatocellular carcinoma[2,3]. The disease is strongly associated with metabolic risk factors, such as obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension, and is considered a hepatic manifestation of metabolic syndrome[4].

Heart failure (HF) is a prevalent, multifaceted syndrome whose epidemiology and pathophysiology reflect a broad interplay of cardiovascular, metabolic, and systemic factors[5,6]. As HF rates rise globally, especially within aging and metabolically challenged populations[5,7], understanding these underlying mechanisms is essential for developing effective, targeted therapies that can mitigate disease progression and reduce the substantial healthcare burden of HF.

This manuscript briefly reviews the MASLD and HF interplay, their combined pathophysiology, and their clinical aspects.

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Metabolic Dysfunction-Associated Steatotic Liver Disease

The prevalence of MASLD has increased dramatically over recent decades. Currently, MASLD affects about 38% of the global adult population[8], with particularly high rates in North America, South America, the Middle East, and parts of Asia[8–10]. This rise reflects the increasing prevalence of obesity and metabolic syndrome in these regions[10]. For instance, the United States is projected to see over 100 million cases of MASLD by 2030, driven largely by lifestyle factors such as high-calorie diets and sedentary behavior[11].

Epidemiological studies highlight a particularly concerning trend. MASLD and MASH are no longer diseases primarily affecting middle-aged and older adults [8,12,13]. Increasing rates are now reported in adolescents and young adults, likely due to early onset of obesity and metabolic syndrome, which can lead to liver disease progression at a younger age[14]. With a global prevalence of 7-14% in epidemiological studies in adolescents and young adults, in the U.S., it is estimated that about 5.8% of children and adolescents have MASLD[8,14], underscoring the urgent need for preventive measures across all age groups.

Risk factors such as obesity and diabetes mellitus not only increase MASLD risk but also drive its progression to MASH[15]. MASH has been found in 63% of patients with MASLD undergoing liver biopsy in an Asian multi-center study, which is more likely to lead to advanced fibrosis and other severe liver complications[4]. The presence of MASH was not associated with a higher incidence of atherosclerotic cardiovascular events, although a trend was apparent[16]. However, another study showed that among those with MASH, the prevalence of cardiovascular diseases, including heart failure, coronary artery disease, and stroke, is markedly higher compared to those without liver disease or with less severe forms of MASLD[17]. This interrelationship complicates disease management, as patients with both MASLD/MASH and cardiovascular disease (CVD) require a more intensive and nuanced approach to managing metabolic and liver health.

Ethnic and racial disparities further complicate the MASLD epidemiology[18]. Hispanic individuals, for example, have disproportionately higher MASLD rates, partly due to genetic predispositions that affect fat metabolism in the liver[19]. Meanwhile, African American populations show relatively lower MASLD prevalence but may present with more advanced fibrosis at diagnosis[20,21]. This variability underscores the need for tailored diagnostic and treatment approaches based on demographic factors.

Screening and diagnosing MASLD, particularly MASH, present challenges due to the disease's asymptomatic nature in early stages. Imaging techniques, like ultrasound and elastography, are frequently used, yet liver biopsy remains the gold standard for MASH diagnosis, especially to assess fibrosis stages [22–24]. However, biopsy is invasive and costly, limiting its feasibility for large-scale screening. As a result, MASLD often remains undiagnosed until complications arise, highlighting a need for accessible and non-invasive diagnostic alternatives[24].

MASLD's epidemiology reflects complex interactions among metabolic, genetic, and lifestyle factors, resulting in a high prevalence and substantial health burden. With MASLD projected to rise further due to global trends in obesity and metabolic syndrome, a comprehensive approach—including public health initiatives targeting lifestyle factors and improved screening methods—is essential to manage and mitigate this growing epidemic[8,25,26].

Heart Failure

HF is a complex clinical syndrome marked by the heart's inability to pump blood effectively to meet the body's needs, either due to weakened heart muscles (systolic dysfunction) or stiffened ventricles (diastolic dysfunction)[27,28]. HF represents the final stage of numerous cardiovascular diseases and is often categorized by the ejection fraction (EF) metric, which assesses the percentage of blood the left ventricle pumps out with each contraction[29]. Based on EF, HF can be classified as heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), or mildly reduced ejection fraction (HFmrEF)[29,30].

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The global prevalence of HF is significant, affecting over 64 million people worldwide, with rates steadily increasing due to aging populations, better survival from other cardiovascular conditions, and rising levels of risk factors like hypertension, diabetes mellitus, and obesity[31,32]. In the United States alone, over 6 million adults are affected, and this number is projected to increase substantially over the coming decades[33,34]. Epidemiologically, HF is most common in individuals over 65 years of age[35,36], with men generally experiencing a higher incidence of HFrEF[37], and women more commonly affected by HFpEF, especially among those with diabetes mellitus or hypertension[35,38,39].

The incidence of HF varies widely by geography, socioeconomic factors, and ethnicity, with higher prevalence noted in African American and Hispanic populations. This discrepancy is likely due to a combination of genetic predispositions and greater prevalence of risk factors, including hypertension and metabolic syndrome[5,40]. Racial and ethnic disparities in healthcare access and quality further contribute to the increased HF burden within these populations[5]. Similarly, HF is a leading cause of hospitalization and readmission in older adults, posing a significant burden on healthcare systems worldwide[41,42]. In the U.S., HF accounts for over 1 million hospitalizations annually, with costs estimated to reach $70 billion by 2030, underscoring the pressing need for effective prevention and management strategies[33].

The pathophysiology of HF involves complex interactions among myocardial injury, neurohormonal activation, and systemic inflammation[27,43]. These processes vary depending on HF subtype but commonly result in a progressive decline in cardiac function. In HFrEF, myocardial infarction, chronic ischemic damage, or dilated cardiomyopathy often causes weakening of the heart muscle, impairing its ability to contract forcefully. This leads to reduced cardiac output, which activates compensatory mechanisms like the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Although initially beneficial, chronic neurohormonal activation promotes fluid retention, vasoconstriction, and further cardiac remodeling, ultimately exacerbating HF[44,45].

HFpEF, on the other hand, is primarily associated with impaired ventricular relaxation rather than contractile function, often resulting from stiffening of the myocardium due to conditions like hypertension, left ventricular hypertrophy, or metabolic comorbidities such as obesity and diabetes mellitus. This leads to increased diastolic pressures and difficulty in filling the left ventricle during diastole, causing symptoms despite a preserved EF. Chronic systemic inflammation is a key feature in HFpEF pathophysiology, often driven by comorbidities, which in turn contribute to vascular stiffness, microvascular dysfunction, and myocardial fibrosis[46–48].

Emerging research highlights metabolic and inflammatory pathways as significant contributors to HF, especially HFpEF[49]. These mechanisms are increasingly relevant given the high prevalence of metabolic conditions such as MASLD among HF patients. The relationship between HF and comorbidities like MASLD points to the importance of a comprehensive, multi-system approach to HF management, addressing not only cardiovascular health but also metabolic and inflammatory conditions that influence HF progression[16,50,51].

Metabolic Dysfunction-Associated Steatotic Liver Disease and Heart Failure Pathophysiology

The pathophysiological link between HF and MASLD centers on shared metabolic, inflammatory, and fibrotic pathways that intensify both conditions[51]. Central to this link is the role of metabolic syndrome and chronic low-grade inflammation, both of which foster cardiovascular and hepatic complications through cellular and molecular mechanisms that reinforce disease progression[52,53]. As MASLD often coexists with metabolic risk factors such as insulin resistance, dyslipidemia, and hypertension, it predisposes patients to increased cardiovascular strain, contributing directly to HF development and worsening its prognosis [50,54,55].

At the cellular level, HF and MASLD share disruptions in lipid metabolism that lead to toxic lipid accumulation and lipotoxicity in both cardiac and hepatic tissues[51,56]. Shin et al. [57], Svobodová et al. [58], and Zhao et al. [59] emphasize that in MASLD, hepatic steatosis results in the buildup of free fatty acids (FFAs) and toxic lipid intermediates, which impair mitochondrial function

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and induce oxidative stress. These alterations stimulate reactive oxygen species (ROS) production and subsequent inflammatory cytokine release, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), creating a chronic inflammatory state[60]. Similarly, in HF, lipotoxicity impairs cardiomyocyte function, leading to mitochondrial dysfunction and oxidative stress that weaken cardiac output[61,62]. This shared pathway of lipotoxicity exacerbates both hepatic and myocardial injury, establishing a cyclical progression where HF promotes MASLD and vice versa.

Molecular signaling pathways involved in insulin resistance also play a significant role in linking MASLD to HF[16,56]. Insulin resistance, frequently observed in MASLD, reduces glucose uptake and promotes FFA mobilization, contributing to lipid overload in the liver and heart[63]. It had been reported that impaired insulin signaling enhances the activation of the RAAS and sympathetic nervous system, further elevating blood pressure and cardiac workload, which are deleterious in HF[64,65]. This continuous RAAS activation contributes to vasoconstriction, sodium retention, and cardiac remodeling, worsening HF while simultaneously promoting MASLD progression through vascular and systemic inflammatory pathways (**Figure 1**) [66–68].

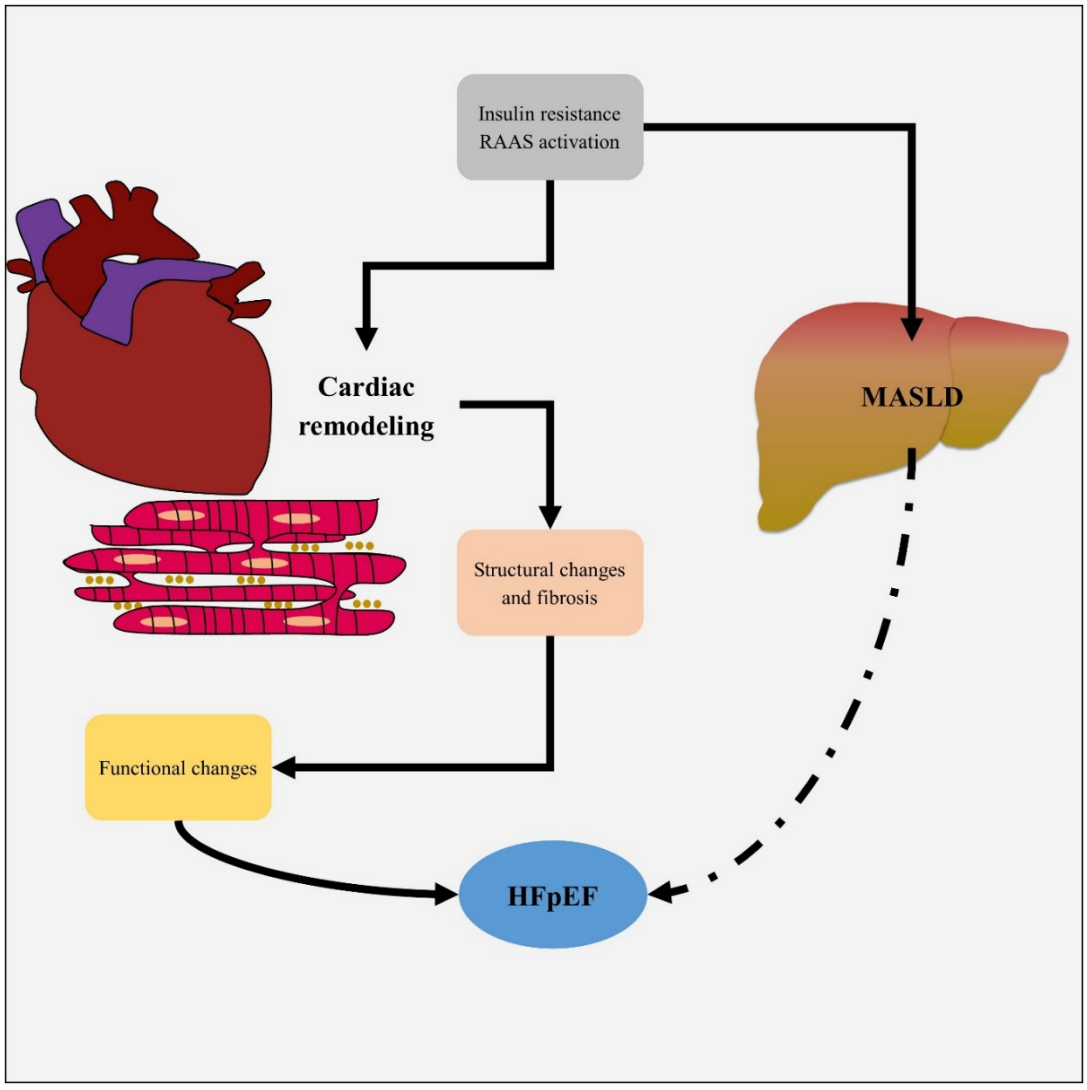

Figure 1. Cardiac remodeling and MASLD share pathophysiological drivers leading to HFpEF. Structural changes cause functional alterations in the heart, while hepatic flow obstruction impacts preload reserve.

Fibrosis is a critical aspect of both MASLD and HF pathophysiology, with the progression of fibrosis in one organ often influencing the other. In the liver, Kupffer cells and hepatic stellate cells

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respond to inflammatory signals by producing collagen and extracellular matrix proteins, leading to liver fibrosis[69]. This fibrotic process is paralleled in HF, where inflammatory cell infiltration and fibroblast activation lead to cardiac fibrosis[70,71]. Over time, this fibrosis impairs the structural integrity and function of both organs, with liver stiffness often correlating with reduced cardiac output in HF patients[72,73]. Notably, patients with advanced MASLD and fibrosis show a 1.5-fold increase in HF risk, underscoring the impact of fibrosis in linking these two conditions[74,75].

Chronic systemic inflammation bridges MASLD and HF[76,77], as myocardial injury accelerates the progression of MASH by triggering immunoinflammatory response [78]. Van Wagner et al. demonstrate that cytokines such as IL-1β and TNF-α, released from the liver in MASLD, contribute to endothelial dysfunction and increased vascular permeability, worsening cardiac hemodynamics[79,80]. The persistence of this inflammatory state exacerbates HF pathogenesis, driving adverse cardiac remodeling and fibrosis. This mutual inflammatory feedback between MASLD and HF presents a major challenge, as it perpetuates a cycle of systemic inflammation and tissue damage across both organs.

Therefore, the shared pathophysiology of HF and MASLD involves overlapping mechanisms of lipotoxicity, insulin resistance, fibrosis, systemic inflammation, and mitochondrial dysfunction. The interdependent cellular and molecular interactions between these pathways foster disease progression in both organs, highlighting the need for a comprehensive approach to manage HF in patients with MASLD. Addressing these common mechanisms offers potential for novel therapeutic targets that could mitigate the progression of both HF and MASLD, improving outcomes for this high-risk population.

Metabolic Dysfunction-Associated Steatotic Liver Disease and Heart Failure Association

The connection between liver diseases and heart failure is widely recognized. Heart failure can result in congestive hepatopathy, while severe liver disease can lead to cirrhotic cardiomyopathy. Recent studies, however, suggest a link between heart failure and early-stage liver conditions, such as noncirrhotic MASLD. Additionally, growing evidence indicates a possible association between MASLD and heart failure with preserved ejection fraction[16].

The association between MASLD and cardiovascular diseases, particularly heart failure, reveals a complex interplay that suggests a risk amplified by shared risk factors such as type 2 diabetes mellitus, hypertension, and obesity[16,50,51]. Studies demonstrate that MASLD, especially in its severe form known as MASH, increases CVD prevalence and mortality compared to other liver diseases and general populations, although some findings vary based on sample characteristics, cardiovascular endpoints, and confounding factors[17,81].

It is likely that cardiometabolic risk factors play a greater role in the development of CVD than MASH, which could explain the similar risks of CV events found in many of these studies, especially those comparing populations with MASH vs. MASLD[81] while other study showed that MASH was associated with a higher prevalence of coronary artery disease (CAD)[81]. However, one analysis showed a heightened prevalence of CAD in MASH patients undergoing liver transplantation compared to those with hepatitis C or alcoholic cirrhosis, with CAD present in 52.8% of MASH cases versus 20.0% in alcoholic cirrhosis patients[82]. The risk for three-vessel disease in MASH patients was also significantly greater, suggesting an advanced atherosclerotic burden within this population. Odds ratios for significant CAD in MASH patients undergoing transplant evaluations reached 3.12 (95% CI: 1.33–5.32), underscoring an elevated cardiovascular risk that may necessitate more aggressive intervention strategies[81].

In a robust study, Simon et al. [83] used liver biopsy as a gold standard, matching 10,422 MASLD patients with 46,517 controls. They found MASLD significantly linked to heart failure, with a hazard ratio (HR) of 1.75 (95% CI: 1.63, 1.87). This risk rose with liver disease severity, independent of common cardiometabolic factors.

Several studies underscore a disproportionately high incidence of CVD-related comorbidities in MASLD and MASH populations. In one study, the baseline prevalence of CVD among liver transplant patients with MASH reached 37.7%, significantly exceeding the 17.0% observed in non-

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MASH cases ($p < 0.001$). Similarly, hypertension and diabetes mellitus were markedly higher in MASH cohorts, with nearly two-thirds of patients meeting obesity criteria, emphasizing the metabolic overlap that likely fuels cardiovascular risk escalation. In contrast, non-MASH liver transplant patients demonstrated only a 30% prevalence of diabetes mellitus and a 15.6% rate of hypertension, underscoring the metabolic syndrome's intensification in MASH cases[81,84].

Heart failure emerges as a particularly concerning outcome among patients with MASLD, as this cohort consistently experiences an elevated risk for heart failure independent of traditional cardiovascular risks. MASLD patients are estimated to face a 1.5-fold greater likelihood of developing heart failure compared to non-MASLD populations, and this association persists even after adjusting for diabetes mellitus, hypertension, and obesity, suggesting an intrinsic risk element within MASLD pathology[17,74,75]. Importantly, data also reveal that liver disease severity correlates with heart failure risks, with individuals experiencing advanced fibrosis or cirrhosis exhibiting higher incidences of HFpEF, a common and challenging heart failure subtype associated with MASLD[51].

A retrospective cohort study on 98,685 participants showed that participants with MASLD had an increased risk of HF compared with non-MASLD individuals (HR: 1.40, 95% CI: 1.30–1.50)[85].

Nonetheless, conflicting results exist concerning cardiovascular outcomes in MASLD patients post-transplant. For instance, in one cohort study of liver transplant recipients, cardiovascular event rates did not significantly differ between patients with MASH versus those with alcoholic cirrhosis within one year post-transplant. Despite MASH patients' higher comorbidity rates, the cardiovascular event incidence remained relatively balanced, possibly due to the pre-transplant cardiovascular evaluation processes that select only patients with manageable cardiac conditions. These findings suggest that MASLD's cardiovascular impact may be moderated in clinical settings where risk is carefully managed, though it does not eliminate MASLD's intrinsic association with cardiovascular deterioration[81].

Examining mortality outcomes also yields nuanced insights into MASLD's cardiovascular impacts. In studies comparing MASH to other etiologies, one-year mortality due to cardiovascular complications was higher in MASH than in hepatitis C virus (HCV) and alcohol-related cirrhosis cases, with hazard ratios of 1.30 and 1.34, respectively. Cardiovascular deaths were significantly more common within the MASH group, often concentrated within the first months post-transplant, possibly reflecting MASH's pronounced cardiovascular burden even amid other high-risk liver conditions[81,86].

Interestingly, despite MASLD's established cardiovascular associations, some studies suggest a protective element in specific contexts. In a cohort comparing MASLD versus HCV-positive and HCV-negative groups, MASLD patients had a lower cardiovascular mortality rate (HR 0.65) than HCV-positive individuals. This inverse association's etiology is unclear, although it may involve differences in systemic inflammatory profiles or complications unique to HCV. Additionally, MASLD patients' cardiovascular event prevalence varies by demographic factors, such as age and sex, further complicating an overarching assessment of MASLD's cardiac outcomes[81].

Conclusion

In conclusion, MASLD, especially in its MASH form, poses a substantial cardiovascular risk, accentuating the prevalence of heart failure and ischemic conditions. However, the presence of comorbidities like diabetes mellitus and obesity often obscures whether MASLD itself directly escalates cardiovascular risks or serves as a proxy marker for metabolic dysfunction. The disproportionate occurrence of heart failure among MASLD patients suggests an independent risk element, though clinical outcomes often depend on broader metabolic health and disease severity. For patients with advanced liver involvement, aggressive management of cardiometabolic factors may mitigate MASLD's cardiovascular impacts, supporting preventive strategies to reduce mortality.

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