



HFpEF and MASLD: converging mechanisms and clinical implications

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Abstract

Heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD) are increasingly prevalent, interrelated conditions driven by the global rise in obesity and metabolic syndrome. Once viewed in isolation, HFpEF and MASLD are now recognized as organ-specific manifestations of shared systemic metabolic dysfunction. Evidence from the past decade highlights not only overlapping risk factors but also a dynamic, bidirectional inter-organ crosstalk between the liver and the heart that shapes their natural history. In this Review, we explore the epidemiological and mechanistic basis of the MASLD–HFpEF connection, focusing on shared metabolic drivers such as lipotoxicity, meta-inflammation and oxidative stress. We also discuss emerging liver-derived mediators, including hepatokines, metabolites and extracellular vesicles, that influence cardiac structure and function. Finally, we highlight diagnostic and therapeutic strategies relevant to both conditions and propose a multiorgan framework to improve their clinical recognition and management. Understanding the liver–heart axis is key to rethinking cardiometabolic disease beyond organ silos and towards more integrated, mechanism-based approaches.

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- Cardiometabolic heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD) are manifestations, with unique features, of a shared systemic metabolic disorder, namely the metabolic syndrome, affecting the heart and liver, respectively.
- Both cardiometabolic HFpEF and MASLD have been recognized as multiorgan metabolic diseases, aligning with growing evidence linking their epidemiological and pathogenic features.
- Beyond a shared metabolic framework, cardiometabolic HFpEF and MASLD influence each other through direct liver–heart crosstalk, but our understanding of this relationship is still in its early stages.
- Recognizing the overlap between the clinical presentation of HFpEF and MASLD offers an opportunity for a unified diagnostic approach, improving clinical assessment and aiding in the stratification of patients at risk of these conditions.
- A shared therapeutic approach for HFpEF and MASLD, targeting common features of metabolic disease, is extremely relevant given the limited disease-specific treatments and lack of substantial outcome improvements so far.

Introduction

Metabolic disorders encompass a complex network of systemic and organ-specific diseases, with obesity and impaired glucose and lipid homeostasis at its core. Clinical evidence suggests that the cumulative risk of individual metabolic conditions exceeds their additive effect, emphasizing the need to understand their interconnections. The most prevalent subtype of heart failure (HF), HF with preserved ejection fraction (HFpEF), is linked to a cardiometabolic profile that stems from metabolic syndrome, particularly obesity and insulin resistance. Similarly, the reclassification of non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) reflects the crucial role of systemic cardiometabolic factors in the development of this condition. Although often viewed separately, HFpEF and MASLD are closely interconnected, sharing overlapping metabolic pathways and drivers, along with direct liver–heart crosstalk.

In this Review, we provide insights into liver-related and heart-related metabolic disease, covering preclinical mechanisms and clinical implications for patient care. We focus on shared pathological drivers, such as toxic lipid accumulation and maladaptive inflammation, which contribute to structural and functional decline in both the liver and the heart. By examining the latest advances in the classification of these conditions and the examination of their shared pathophysiology and inter-organ interactions, we highlight opportunities for integrated preventive, diagnostic and therapeutic approaches, especially given that treatment options for both conditions are emerging.

Cardiometabolic diseases: HFpEF and MASLD

HF is a clinical syndrome in which structural or functional alterations of the heart lead to heterogeneous signs and symptoms, including pulmonary and/or systemic congestion. On the basis of left ventricular (LV) ejection fraction (LVEF), HF is classified into three major types:

HFpEF (LVEF $\geq 50\%$), HF with mildly reduced ejection fraction (LVEF 41–49%) and HF with reduced ejection fraction (HFrEF; LVEF $\leq 40\%$), each marked by distinct aetiologies^{1,2}. In HFpEF, several mechanisms, including impaired LV diastolic relaxation, defective cardiac energetics, pulmonary hypertension and peripheral muscle dysfunction, elevate LV filling pressures, impair cardiac output during exertion, and affect oxygen utilization in peripheral tissues³. These alterations result in reduced exercise capacity, diminished quality of life, high risk of hospitalization and increased mortality. Importantly, HFpEF is not a precursor of HFrEF⁴ but is itself a deadly syndrome with a rising prevalence⁵. Moreover, HFpEF is not a single disease but a constellation of heterogeneous phenotypes^{6,7}. A prevalent HFpEF phenotype in individuals with obesity, termed cardiometabolic HFpEF, is closely associated with the inflammatory–metabolic traits of metabolic syndrome⁸.

MASLD represents a spectrum of progressive liver diseases characterized by steatotic liver disease (SLD) and at least one feature related to metabolic syndrome^{9,10}. Mechanistically, the ‘two-hit’ hypothesis posited that metabolic syndrome-related lipid accumulation sensitizes the liver to inflammatory damage and tissue remodelling, driving disease progression¹¹. This theory has since evolved into a ‘multiple-hit’ model incorporating genetic susceptibility and lifestyle, environmental, and epigenetic factors^{12,13}.

Patients diagnosed with NAFLD (that is, SLD in patients not reporting high alcohol intake¹⁴) almost perfectly overlap with those now classified as having MASLD, with >99.5% of patients with NAFLD having at least one cardiometabolic risk factor¹⁵. Furthermore, patients with NAFLD and those with MASLD have similar clinical outcomes, suggesting that MASLD is a refined definition of NAFLD rather than a distinct disease^{16–19}. Accordingly, in this Review, we adopt the MASLD nomenclature also when the cited literature includes patients with NAFLD.

MASLD begins with isolated SLD, characterized as lipid accumulation in hepatocytes without inflammation or fibrosis in the liver. In about one-third of these patients, the disease progresses to metabolic dysfunction-associated steatohepatitis (MASH), a pivotal stage defined by lobular inflammation, hepatocyte ballooning and variable liver fibrosis²⁰ (Fig. 1). This transition is driven by toxic lipid species and oxidative stress, which promote hepatocyte injury, release of damage-associated molecular patterns and Kupffer cell activation. The process is amplified by cytokine-mediated inflammation, starting in the liver but progressing to systemic relevance²¹. Clinically, MASH correlates with a higher prevalence of obesity, type 2 diabetes mellitus (T2DM) and dyslipidaemia²², which synergistically accelerate hepatic injury. Histological evidence of liver inflammation or fibrosis strongly correlates with increased risk of liver-related events and all-cause death²³. Approximately 40% of patients with MASH develop progressive fibrosis²⁴, a key prognostic marker. A subset of patients eventually develops cirrhosis and MASH-related hepatocellular carcinoma, the latter even in the absence of advanced liver fibrosis⁹.

In summary, although current definitions regard cardiometabolic HFpEF and MASLD as distinct diseases, their shared metabolic risk factors are well recognized. Unlike HFpEF, MASLD follows a clearly delineated progression from mild steatosis to end-stage liver disease. Epidemiological data suggest that beyond shared risk factors, a deeper, more direct link exists between these two conditions.

Joint epidemiological and clinical significance

With the rise in the prevalence of metabolic diseases, HFpEF and MASLD have emerged as the dominant form of HF and the most common chronic liver disease, respectively. Since the late twentieth

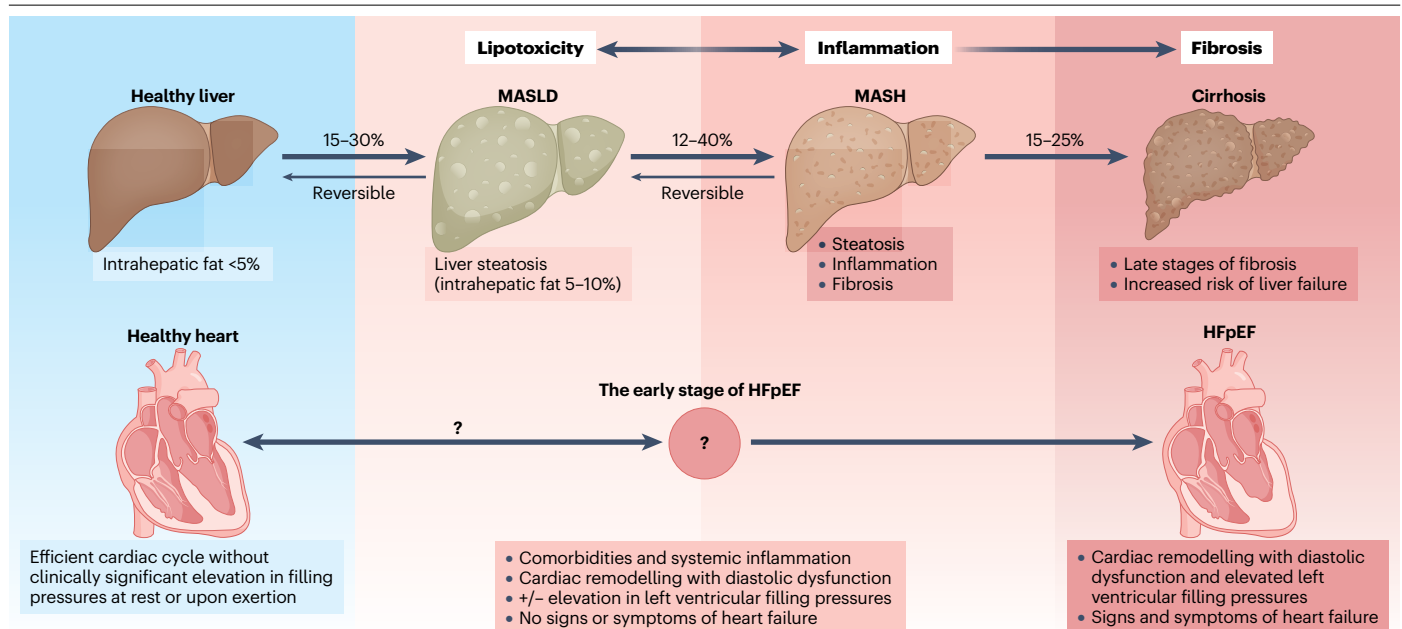


Fig. 1 | Parallels in the disease progression of cardiometabolic HFpEF and MASLD. Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a spectrum of progressive fatty liver diseases linked to systemic metabolic disruption. Approximately 15–30% of individuals with MASLD develop simple steatotic liver disease, marked by macrovesicular fat accumulation in $\geq 5\%$ of hepatocytes. In 12–40% of these patients, the disease progresses to metabolic dysfunction-associated steatohepatitis (MASH), characterized by inflammatory damage and hepatocyte ballooning. Although MASLD and MASH are reversible, disease progression often leads to liver fibrosis, with 15–25% of patients advancing to irreversible cirrhosis and risk of liver failure and hepatocellular carcinoma. In cardiometabolic heart failure with preserved ejection fraction

(HFpEF), a clear progression model is less established. Early HFpEF stages might be marked by mild diastolic dysfunction, comorbid metabolic syndrome, increasing left ventricular filling pressure, and exercise intolerance, but diagnosing these stages is challenging. Many patients are first identified with advanced cardiac HFpEF manifestations, including marked left ventricular hypertrophy and high chamber pressures, although left ventricular ejection fraction is preserved. Future research comparing the trajectories in metabolic liver and heart disease might help to identify reversible HFpEF stages, given that the two conditions share central pathogenic features, including inflammation, toxic lipid accumulation (lipotoxicity) and fibrosis in both the heart and liver.

century, HFpEF has been the main driver of the increasing burden of HF globally²⁵, while the prevalence of HFrEF has remained persistently high²⁶. Together, HFpEF and HFrEF now affect 1–3% of individuals in Western countries, with HFpEF accounting for $>50\%$ of new HF diagnoses, a percentage that is steadily increasing²⁶. Among patients with HFpEF, up to 80% have overweight or obesity²⁷ and 40–50% have T2DM²⁸. Similarly, 30% of adults globally have MASLD²⁹, and the prevalence of MASLD is 55–70% in individuals with T2DM^{30,31} and 70–75% in individuals with overweight or obesity³². Metabolic syndrome is a strong predictor of both HFpEF⁸ and MASLD³³.

MASLD both results from and contributes to metabolic syndrome, complicating the evaluation of its individual effects on overall disease risk. However, patients with MASLD have an elevated risk of cardiovascular diseases (CVD), including HF, with cardiometabolic mortality being up to five times higher than liver-related mortality in these patients^{34,35}. Large community-based cohort studies have identified MASLD as an independent risk factor for incident HF and HF-related deaths^{36–38}, even after adjusting for traditional cardiometabolic risk factors commonly associated with metabolic syndrome³⁹. The severity of MASLD independently correlates with an increased risk of new-onset HF, worse clinical outcomes and higher HF risk scores^{40,41}. Although MASLD has been linked to both HFrEF and HFpEF, emerging evidence points to a particularly strong association with the HFpEF phenotype. In a retrospective cohort study involving 870,535 individuals without

previous HF, those with MASLD had a significantly higher risk of incident HF – especially HFpEF (adjusted HR 1.24, 95% CI 1.14–1.34), compared with HFrEF (adjusted HR 1.09, 95% CI 0.98–1.2) – over an average follow-up of 14.3 months⁴². In a different cohort, MASLD was also independently associated with a higher risk of hospitalization for HFpEF (subdistribution HR 1.91, 95% CI 1.27–2.86)⁴³. Meta-analyses further support a robust link between MASLD and LV diastolic dysfunction⁴⁴, showing that MASLD is associated with echocardiographic hallmarks of HFpEF such as decreased E/A ratios, increased E/e' ratios, and elevated left atrial volume and LV mass indices^{45,46}. In smaller observational studies, MASLD was present in 27–53% of patients with HFpEF, with advanced liver fibrosis found in up to 38% and cirrhosis in up to 12% of patients^{47–49}. More advanced stages of heart and liver disease were observed in patients with both HFpEF and MASLD, suggesting a synergistic interaction between the two conditions⁴⁷. MASLD-associated liver fibrosis is a negative predictor of physical capacity⁵⁰ and all-cause mortality in patients with HFpEF^{48,51}.

Overall, a dual-layer relationship between cardiometabolic HFpEF and MASLD emerges. First, both conditions share risk factors in the framework of metabolic syndrome, making their co-occurrence highly probable. Second, in patients with MASLD, the risk of developing HFpEF is high even after adjusting for standard cardiometabolic risk factors, suggesting a direct link between MASLD and cardiometabolic HFpEF^{52,53}. This connection is further supported by findings showing

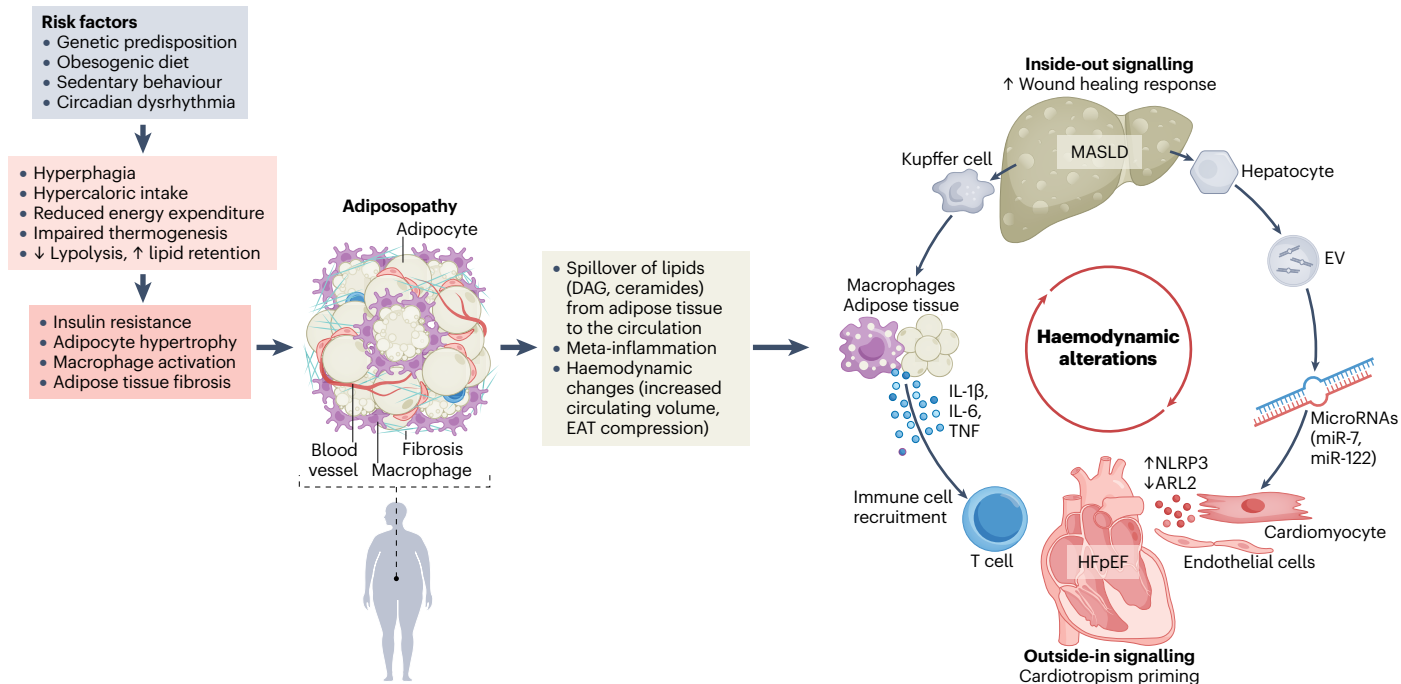


Fig. 2 | Shared pathogenic framework in the development of HFpEF and MASLD. Cardiometabolic heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD) share several comorbidities and predisposing factors. Alongside features of metabolic syndrome (hypertension, type 2 diabetes mellitus, central obesity and dyslipidaemia), both HFpEF and MASLD are also frequently associated with haemodynamic dysregulation, intestinal dysbiosis, adipose tissue dysfunction and circadian rhythm disruption. Together, these factors predispose individuals to metabolic dysfunction in both the heart and the liver. The mechanisms leading to overt disease remain uncertain, but seem to involve cycles of tissue damage and inflammation in both organs. In MASLD, hepatic lipid accumulation leads to

an overactivation of immune cells through ‘inside-out’ mechanisms; the immune cells in turn induce tissue damage and an excessive wound healing response. By contrast, HFpEF manifests through ‘outside-in’ systemic inflammation (meta-inflammation) that primes immune cells for cardiac infiltration, independent of myocardium-derived mediators. Nevertheless, both conditions share a unified framework in which meta-inflammation affects heart and liver function early in disease development and perpetuates inflammatory insults as the diseases progress. ARL2, ADP-ribosylation factor-like protein 2; EAT, epicardial adipose tissue; EV, extracellular vesicle; DAG, diacylglycerol; NLRP3, NOD-like receptor family, pyrin domain containing 3; TNF, tumour necrosis factor.

that lean adults with MASLD, despite having a normal body mass index (BMI) and more favourable metabolic profiles than patients with MASLD who have overweight or obesity, still have an increased risk of cardiometabolic disease and death⁵⁴. In these patients, the elevated risk is at least partially mediated by cardiac remodelling and LV diastolic dysfunction^{55,56}. The growing body of epidemiological evidence linking MASLD to cardiometabolic HFpEF poses the question of whether a shared pathophysiology underlying metabolic heart and liver disease exists beyond simple coexistence.

Common pathogenic frameworks

Although complex, a natural history of metabolic disease can be outlined (Fig. 2). Excessive caloric intake together with a sedentary lifestyle result in lipid accumulation in adipose tissue, with visceral adipose tissue having a crucial role in the development of both MASLD⁵⁷ and cardiometabolic HFpEF⁵⁸. Adverse adipose tissue remodelling, or adiposopathy⁵⁹, is a condition marked by adipocyte hypertrophy, a pro-inflammatory shift in adipose-tissue-resident immune cells^{60–62}, formation of crown-like structures around dead adipocytes⁶³, capillary rarefaction⁶⁴, adipose tissue fibrosis⁶⁵, mitochondrial dysfunction^{66,67} and the release of pro-inflammatory adipokines⁶⁸. Adiposopathy is key for metabolic syndrome progression and related organ damages.

As lipid storage exceeds the visceral adipose tissue capacity, these alterations activate inflammatory cascades, resulting in the spillover of lipids and immunomodulatory factors into the circulation as evidenced by increased plasma levels of IL-6, IL-1 β , and tumour necrosis factor (TNF) and reduced plasma levels of adiponectin. This inflammatory milieu promotes insulin resistance, impairing the capacity of insulin to suppress de novo lipogenesis in the liver and lipolysis in adipose tissue. Consequently, an excessive release of free fatty acids (FFAs) redistributes lipid stores to ectopic locations, perpetuating a vicious cycle of insulin insensitivity and low-grade metabolic inflammation, referred to as meta-inflammation⁶⁹.

Due to its proximity to the myocardium, epicardial adipose tissue (EAT) contributes to cardiac metabolic disease, especially in obesity⁷⁰. EAT thickness is strongly associated with LV diastolic dysfunction^{71,72} and heightened HF risk⁷³ but also correlates with MASLD severity, particularly liver steatosis and fibrosis⁷⁴. However, EAT is absent in rodents⁷⁵, which limits the data available from animal models. Whether EAT has a mechanistic role in cardiac and liver disease or simply reflects systemic adiposopathy remains unclear.

Despite the roles of the heart as a ‘catabolic’ engine and of the liver as an ‘anabolic’ regulator of systemic energy homeostasis, metabolic disease affects both organs in striking similarity. This convergence

suggests a shared pathogenic substrate underlying metabolic dysfunction in both the heart and the liver⁷⁶. Shared pathogenic mechanisms are largely driven by excess lipid-mediated toxicity (lipotoxicity) and local immune alterations, despite several additional pathogenetic pathways having been proposed (Box 1).

Lipotoxicity

In metabolic syndrome, high circulating levels of FFAs promote excessive lipid uptake and deposition in both the heart and the liver^{77,78}. Hepatic lipid overload was first recognized in the 1980s but its role in HFpEF has only begun to receive attention over the past decade⁷⁹. Cardiac steatosis, similar to hepatic steatosis in MASLD, is well documented in animal models^{80–82} and human studies^{83,84}. Cardiac steatosis independently predicts LV diastolic dysfunction, with its severity aligning with the degree of lipid deposition^{85,86}. Likewise, increased hepatic triglyceride content fuels progression to liver inflammation, fibrosis and cancer^{87,88} (Fig. 1).

The lipotoxicity theory suggests that lipid droplets temporarily buffer lipid content in cells when the supply of fatty acids exceeds the oxidative capacity of the cell. However, once lipid storage becomes excessive, reactive lipids (such as acylcarnitines, diacylglycerols and ceramides) accumulate, disrupting cellular processes⁸⁹. Data from Mendelian randomization studies indicate that triglycerides trapped within lipid droplets are involved in steatosis-related inflammation and fibrosis, irrespective of other metabolic changes⁹⁰. Although cardiac lipid toxicity is less studied than in the liver, lipotoxicity mechanisms are largely conserved across organs, suggesting shared pathways. In the liver, surplus FFAs initially stimulate mitochondrial activity but chronic FFA overload damages mitochondria, resulting in impaired fatty acid oxidation (FAO) and accumulation of acylcarnitines^{91,92}. This imbalance drives lipid metabolism towards harmful intermediates, such as diacylglycerols and ceramides, which activate lipid-sensing protein kinase C (PKC) isoforms that hinder insulin signalling and promote MASLD^{93,94}. In cardiomyocytes, PKC activation triggers NADPH oxidase activity and increases reactive oxygen species (ROS) production^{95,96}.

In the heart and liver, lipid overload perturbs endoplasmic reticulum homeostasis, activating the unfolded protein response that is crucial for lipid and protein balance⁹⁷. For example, chronic activation of the serine/threonine-protein kinase/endoribonuclease IRE1–X-box-binding protein 1 (XBPI) axis exacerbates hepatic steatosis by redirecting lipids to already overwhelmed storage systems⁹⁸. Failure of the adaptive unfolded protein response triggers deleterious stress responses, as demonstrated in mice with HFpEF with impaired IRE1–XBPI signalling^{80,81}. Vicious cycles of mitochondrial dysfunction, ROS generation and endoplasmic reticulum stress are well documented in both cardiac and hepatic lipotoxicity^{99,100}. Ultimately, lipotoxicity and ROS promote microvascular dysfunction^{101,102} and stimulate fibrotic pathways in hepatic stellate cells and cardiac fibroblasts^{99,103}, driving tissue remodelling. Lipotoxicity not only drives fibrosis but is also involved in inflammation and immune system activation, with distinct pathways characterizing MASLD and HFpEF progression.

Meta-inflammation

Immune alterations in MASLD are complex, showing nonlinear progression and marked variability among individuals. Inflammation has a pivotal role, even in early MASLD, driving disease progression towards MASH and advanced stages^{104,105}. By contrast, although inflammation is widely accepted as a key feature of cardiometabolic HFpEF,

supported by the presence of circulating inflammatory markers^{106,107} and myocardial immune responses^{108,109}, the precise mechanisms remain elusive. Of note, a biopsy-based study did not confirm a definitive role for inflammation in HFpEF despite the presence of metabolic syndrome¹¹⁰. Nonetheless, parallels with MASLD might offer insights into the inflammatory nature of HFpEF by using knowledge from the better-characterized hepatic disease (Fig. 1).

In HFpEF, meta-inflammation seems to prime immune cells towards cardiac tropism in an ‘outside-in’ manner, independent of direct recruitment to the myocardium (Fig. 2). In mice with HFpEF, an impaired unfolded protein response in T cells (equal to the mechanism described above for cardiomyocyte dysfunction) results in T cell infiltration into the heart and inflammation and diastolic dysfunction driven by adaptive immunity¹¹¹. Additionally, a two-way interaction between energy metabolism and the immune system shapes the immune response in cardiometabolic HFpEF^{112,113}. MASLD more typically follows an ‘inside-out’ pattern: lipid-induced hepatocyte injury triggers the release of pro-inflammatory mediators, which activate an exaggerated immune response and fuel cycles of injury and fibrosis¹⁰⁵

Box 1 | Additional pathogenic frameworks

Genetic predisposition

Genetic polymorphisms, such as rs738409 in *PNPLA3* or rs58542926 in *TM6SF2*, are linked to the progression of metabolic dysfunction-associated steatotic liver disease⁴⁴⁶. Intriguingly, although both polymorphisms impair hepatic lipid secretion, thereby promoting lipid accumulation in the liver, they are associated with lower plasma triglyceride levels and reduced risk of cardiovascular disease^{149,447,448}. Whether these variants can promote cardiometabolic heart failure with preserved ejection fraction (HFpEF) remains unknown. So far, genome-wide association studies (GWAS) in HFpEF cohorts have yielded limited results, probably reflecting the heterogeneity of HFpEF phenotypes and underscoring the need for phenotype-specific GWAS³¹⁹. A landmark GWAS identified novel loci affecting liver triglyceride content, revealing two steatotic liver disease types: one liver-specific with cardiovascular protection, and one systemic, linked to heightened risks of liver disease, hypertension, cardiovascular disease and heart failure⁴⁴⁹. Mendelian randomization studies are warranted to confirm causality between steatotic liver disease and cardiometabolic HFpEF.

Circadian dysfunction

Circadian rhythm disruption is a known metabolic risk factor⁴⁵⁰, and circadian dysfunction might be an overlooked contributor to both cardiometabolic HFpEF and metabolic dysfunction-associated steatotic liver disease. In a mouse model of jetlag, chronic circadian misalignment induced HFpEF-like cardiac features through suppression of the CLOCK–soluble guanylyl cyclase–cGMP–cGMP-dependent protein kinase 1 pathway⁴⁵¹, and also led to glucose intolerance, steatotic liver disease-related hepatocellular carcinoma, and hepatocellular carcinoma metastasis in mice with humanized livers, independently of diet⁴⁵². The role of circadian dysfunction in concurrent liver–heart metabolic disease and its mechanisms remain largely unexplored.

(Fig. 2). Early endothelial dysfunction, with reduced nitric oxide (NO) bioavailability, sets the stage for hepatocyte lipid accumulation and sustained inflammation¹¹⁴.

Oxidative stress and lipid peroxidation

Oxidative stress, defined by an imbalance between pro-oxidant and antioxidant forces, has a central role in the pathogenesis of both MASLD and HFpEF. In the liver, increased mitochondrial ROS generation and NADPH oxidase activity are well-established drivers of oxidative stress, exacerbated by dysfunctional lipid metabolism and chronic inflammation¹¹⁵. This oxidative environment, together with the catalysing effect of ferroptosis, promotes lipid peroxidation, resulting in the formation of reactive lipid aldehydes such as malondialdehyde and 4-hydroxynonenal, which further damage hepatocyte membranes and cellular proteins, accelerating the progression from steatosis to inflammation and fibrosis¹¹⁶.

Similarly, in HFpEF, excess FFAs and diacylglycerol species within cardiomyocytes trigger an increase in oxidative stress indicators and pro-fibrotic and apoptotic factors¹¹⁷. These alterations are paralleled by upregulated lipid peroxidation and accumulation of malondialdehyde, which impair diastolic function and perpetuate myocardial remodelling¹¹⁸. ROS also activate redox-sensitive signalling pathways, such as nuclear factor- κ B (NF- κ B) signalling and the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, linking oxidative stress directly to inflammation and fibrosis in both organs¹¹⁹.

Gut permeability and microbiota-derived metabolites

Gut permeability and microbiota alterations are increasingly recognized as crucial modulators in MASLD and HFpEF. In MASLD, a compromised intestinal barrier permits the translocation of lipopolysaccharides and other microbial products to the blood, which promote hepatic inflammation via Toll-like receptor 4 (TLR4)-mediated signalling and foster the progression to MASH¹²⁰. Similarly, in HFpEF, increased gut permeability driven by venous congestion and low-grade systemic inflammation enables the spillover of gut-derived endotoxins into the bloodstream, which then activate pro-inflammatory and pro-fibrotic cascades in the myocardium¹²¹.

Gut microbiota dysbiosis also skews microbial metabolite production, including via elevating the levels of trimethylamine N-oxide (TMAO). TMAO, which is generated from dietary choline and carnitine by gut microbes, is associated with endothelial dysfunction, increased vascular stiffness and myocardial fibrosis, all hallmarks of HFpEF. TMAO also exacerbates hepatic lipid accumulation and inflammation by increasing oxidative stress and mitochondrial dysfunction^{122,123}. These gut–liver–heart interactions highlight the pivotal role of the gut in amplifying the metabolic–inflammatory axis and underscore the therapeutic potential of interventions targeting the gut barrier and gut microbiota in both MASLD and HFpEF.

Haemodynamic changes in later stages of MASLD

Together with shared molecular pathways, which reflects the systemic effects of meta-inflammation, haemodynamic changes might contribute to liver–heart disease progression, especially when MASLD progresses to advanced stages with the development of liver fibrosis. Hepatic blood flow dynamics are unique: the liver receives 25% of cardiac output, predominantly via the portal vein, which drains the splanchnic vasculature (the principal blood reservoir of the body)¹²⁴. In physiological states, this venous reservoir serves as a preload reserve, augmenting cardiac output during increased demand.

However, as intrahepatic vascular resistance rises – often early in the course of MASLD owing to sinusoidal compression by lipid-laden hepatocytes¹²⁵ – hepatic outflow to the inferior vena cava becomes impaired, compromising preload. This preload failure can limit cardiac output augmentation during exertion and might directly contribute to the exercise intolerance observed in patients with HFpEF and MASLD^{126,127}.

MASH and cirrhosis can further disrupt this equilibrium. Advanced liver disease induces portal hypertension caused by both architectural distortion and dynamic vasoconstriction driven by sinusoidal endothelial dysfunction, reduced NO bioavailability, and increased vasoconstrictor tone. Portal hypertension, in turn, leads to splanchnic arterial vasodilatation and systemic hypotension, exacerbated by increased production of vasodilators, such as NO and carbon monoxide, and circulating inflammatory mediators¹²⁸. The net result is a hyperdynamic circulatory state with reduced systemic vascular resistance and elevated cardiac output¹²⁹, placing chronic stress on the heart.

Elevated cardiac output is not synonymous with cardiac health. Cirrhotic cardiomyopathy affects up to 50% of patients with liver cirrhosis¹³⁰, which commonly presents as diastolic dysfunction (approximately 60% in early stages¹³¹) driven by myocardial hypertrophy and interstitial fibrosis that reduce ventricular compliance¹³². These changes closely resemble the phenotype seen in HFpEF.

The structural remodelling of the liver also contributes to neurohumoral activation. In MASH, the compression of sinusoids triggers sympathetic nervous system activation, correlating positively with elevated heart rate and cardiac remodelling¹³³. This finding is supported by evidence showing a direct association between hepatic triglyceride content and increased heart rate¹³³.

Elevated central venous pressures in right-sided HFpEF, frequently owing to pulmonary hypertension, can propagate retrograde pressure into the hepatic veins, causing hepatic congestion. Congestive hepatopathy, characterized by centrilobular congestion and necrosis, is found in 15–65% of patients with severe HF and can accelerate the progression of MASLD to fibrosis or cirrhosis¹³⁴.

In summary, the structural and vascular remodelling associated with MASH and cirrhosis exerts substantial haemodynamic perturbations that contribute to impaired preload reserve, systemic vasodilatation, neurohumoral dysregulation and myocardial dysfunction. These alterations are not merely coincidental but constitute a pathological axis that contributes to the high prevalence and clinical overlap of MASLD and cardiometabolic HFpEF.

Inter-organ crosstalk

In clinical settings and observational studies, it is challenging to separate the changes in the heart and liver that are mediated by shared pathognomonic mechanisms (namely, the common cardiometabolic risk factors of metabolic syndrome) from the effects of a direct inter-organ crosstalk, necessitating insights from preclinical studies. In mice, proof-of-concept, preliminary data indicate that the combination of MASLD and hypertension leads to progression to cardiometabolic HFpEF¹³⁵ but the exact mechanisms have not been explored. Importantly, the new diagnostic criteria and updated definitions of these entities indicate that they are manifestations of the same spectrum of metabolic disease. Consequently, systemic risk factors seen in metabolic syndrome and its associated comorbidities cannot be considered confounders because they are integral to the diagnoses. Simply put, without systemic metabolic deregulatory changes, there is no cardiometabolic HFpEF or MASLD (with notable exceptions), and

thus no potential for liver–heart crosstalk in cardiometabolic disease. Nevertheless, novel insights from preclinical and clinical studies provide exciting evidence of direct inter-organ crosstalk of the two conditions, with the potential to fundamentally change our understanding of these interrelated diseases.

Liver–heart axis

The mechanisms linking MASLD to cardiometabolic HFpEF remain incompletely understood but several key factors can be outlined. Given the central role of the liver in global metabolic homeostasis, MASLD indirectly heightens the susceptibility to CVD. MASLD is associated with elevated plasma levels of pro-inflammatory factors (IL-1 β , IL-6, TNF and C-reactive protein), pro-oxidative factors (ROS and homocysteine), and vasoactive or pro-thrombotic factors (factors VIII, IX, XI and XII¹³⁶ and endothelin 1 (ref. 137)), and thus contributes to meta-inflammation and endothelial dysfunction. MASLD leads to atherogenic dyslipidaemia and is linked to insulin resistance, which fuels dysglycaemia and systemic insulin insensitivity¹³⁸. A bidirectional relationship also exists between MASLD and systemic arterial hypertension^{139,140}, with MASLD driving hypertension by activating the sympathetic nervous system and renin–angiotensin–aldosterone system as well as by impairing the vasodilatory effects of insulin and the vasoconstrictive action of elevated FFAs¹⁴¹. Collectively, these alterations mediate the progression of (coronary) atherosclerotic disease and contribute to the development of atrial and ventricular cardiomyopathies^{142,143}. Clinically, these factors manifest as ischaemic heart disease, cardiac arrhythmias and HF, especially cardiometabolic HFpEF^{39,144–149}.

Although systemic cardiometabolic risk factors are integral to HFpEF pathogenesis, emerging evidence suggests that MASLD might independently drive metabolic heart disease, extending beyond the detrimental effects of MASLD on overall metabolic health¹⁴⁹. In a study including young men with newly diagnosed liver fat accumulation who were otherwise healthy and matched healthy control individuals, hepatic steatosis was associated with increased EAT volume and intramyocardial fat content and impaired myocardial energetics, as evidenced by reduced phosphocreatine-to-ATP ratios measured by cardiac magnetic resonance (CMR)¹⁵⁰. This finding led to a series of clinical investigations that collectively reinforced the correlation between hepatic and myocardial steatosis, and identified LV diastolic dysfunction as a consistent denominator¹⁵¹. Most importantly, abnormal myocardial energetics were largely independent of metabolic risk factors and often preceded clinical signs of cardiac dysfunction such as impaired LV relaxation^{150,151}. Further evidence supporting the independent effect of hepatic steatosis on myocardial metabolism comes from a mouse model of MASLD with knockout of *Ppara* (which encodes peroxisome proliferator-activated receptor- α (PPAR α)) in hepatocytes¹⁵². These mice, which were fed a normal chow diet and had no systemic metabolic changes such as obesity, systemic insulin resistance or altered plasma lipids, developed HFpEF characteristics driven by myocardial steatosis, lipotoxicity and fibrosis, secondary to hepatic lipid accumulation^{152,153}.

To further dissect the complex metabolic changes occurring in MASLD and HFpEF, several studies have used preclinical models of MASH that develop HFpEF-like phenotypes even in the absence of obesity^{154,155}. These models provide valuable insights into direct liver–heart interactions independent of systemic metabolic changes and reinforce the emerging concept of a liver-driven cardiomyopathy.

Although the exact sequence of events remains unclear, a direct liver–heart axis in cardiometabolic disease is emerging. This notion

raises the compelling question of which factors cross the inter-organ barrier. The following section summarizes known and potential liver-derived mediators that drive the development of metabolic heart disease, as observed in cardiometabolic HFpEF.

Liver metabolites

Hepatic insulin resistance in MASLD results in elevated gluconeogenesis and de novo lipogenesis despite systemic energy surplus. Consequently, MASLD contributes to both hyperglycaemia and dyslipidaemia¹⁵⁶. The excess circulating lipids reach the coronary capillaries, leading to a lipid oversupply in the myocardium during metabolic disease. This lipid oversupply fuels cardiac steatosis, lipotoxicity and FAO at the expense of glucose metabolism^{157,158}. A clinical study using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) imaging showed lower myocardial glucose uptake in patients with MASLD than in healthy controls, which was inversely proportional to diastolic function, measured by LV filling pressure and E/e' ratio¹⁵⁹. SLD is associated with myocardial insulin resistance¹⁶⁰, a characteristic of metabolic cardiomyopathy¹⁶¹, and also observed in cardiometabolic HFpEF¹⁵⁷. In MASLD mice, cardiac insulin resistance is driven by lipotoxicity via the diacylglycerol-mediated activation of the PKC ϵ pathway¹⁶², leading to impaired insulin–AKT signalling and disrupted glucose transporter type 4 translocation¹⁶³. Myocardial insulin resistance exacerbates a shift in substrate utilization towards excessive FAO, which is associated with impaired signalling of key metabolic regulators, including PPAR α , PPAR γ co-activator 1 α (PGC1 α) and AMP-activated protein kinase (AMPK) activity¹⁶⁴. Overall, MASLD reduces cardiac metabolic flexibility, contributing to metabolic inefficiency in HFpEF, which ultimately results in energy deprivation¹⁵⁷.

However, the extent of the contribution of MASLD to metabolic remodelling of major energy substrate pathways (FAO and glucose metabolism) in cardiometabolic HFpEF remains uncertain, warranting further investigation. Future research will shed more light on the precise role of MASLD in reshaping cardiac substrate usage, influencing not only their catabolic but also their anabolic fate, which probably has an important, but under-investigated, role in HFpEF pathology¹⁶⁵.

Of note, the contribution of SLD to alterations in circulating lipid levels varies across different stages of MASLD. The secretion of VLDL plateaus once hepatic steatosis exceeds 6–10% of liver weight, probably constrained by factors such as phospholipid availability and apolipoprotein B production^{166,167}. After progression to overt fibrosis or cirrhosis, VLDL levels decrease with functional tissue loss¹⁵⁶. Dynamics in metabolic crosstalk across the disease stages remain largely unexplored.

Ketone bodies, mainly β -hydroxybutyrate, are produced by the liver during low glucose availability, providing energy for tissues, including the heart¹⁶⁸. While usually low in non-fasted states, β -hydroxybutyrate becomes a crucial fuel in HFpEF hearts via β -hydroxybutyrate dehydrogenase 1 (BDH1) upregulation to support ATP production^{169–171}. Clinical studies have linked low plasma β -hydroxybutyrate levels in patients with MASLD to disease severity and impaired FAO^{172–174}. By contrast, ketone oxidation seems to be unaltered or even impaired in HFpEF, with BDH1 downregulation observed in mice with HFpEF¹⁷⁵. Given that ketone bodies support metabolic health beyond simple ATP production, such as by suppressing NLRP3 inflammasome-mediated inflammation¹⁷⁶, a role for ketone bodies in cardiometabolic disease originating from the liver is highly likely.

The interplay between the liver, which is central to energy homeostasis but is impaired in MASLD, and the heart, an 'engine out of fuel'

in HFpEF¹⁷⁷, illustrates a key dynamic in metabolic disease. MASLD might directly disrupt substrate utilization in HFpEF, but the extent of its effects and role across the MASLD spectrum remain unknown. The relevance of other energy substrates, such as branched-chain amino acids, which are disrupted in MASLD¹⁷⁸ and were shown to regulate cardiac energy substrate selection in rodents¹⁷⁹, is largely unexplored. Additionally, metabolite functions beyond energy production, including nutrient signalling and gene expression regulation, add further complexity to these under-investigated processes.

Hepatokines

Liver lipid accumulation affects protein synthesis and secretion, potentially establishing metabolic crosstalk with the heart¹⁸⁰. Studies in mice revealed that hepatic steatosis alters around 20% of liver-secreted proteins^{181,182}. Remarkably, secreted proteins from the hepatocytes of mice fed a high-fat diet induced metabolic remodelling in mouse cultured myotubes and macrophages, activating pathways linked to insulin resistance, disrupted fatty acid metabolism and inflammation^{181,182}. Many hepatokines that are upregulated in patients with MASLD are associated with metabolic syndrome and cardiometabolic risk by impairing glycaemic control and promoting inflammation¹⁸³, which further supports the idea of hepatokines as metabolic disruptors. For instance, fetuin A (also known as α 2-HS-glycoprotein, an endogenous inhibitor of insulin receptor tyrosine kinases) mediates the binding of circulating FFAs to TLR4, which promotes pro-inflammatory signalling^{184,185}. High circulating levels of fetuin A are an independent risk factor for metabolic syndrome and adverse cardiometabolic outcomes^{186,187}, although its role in HFpEF is unknown.

The fibroblast growth factor (FGF) family includes 22 members, with FGF21 emerging as a key metabolic regulator in liver–heart crosstalk^{188,189}. Mainly produced by the regulation of PPAR α in the liver in response to FFAs¹⁹⁰, FGF21 levels in plasma rise in the setting of metabolic syndrome and MASLD, correlating with disease progression^{191,192}. Despite its upregulation in MASLD, FGF21 has been shown to promote the reversal of hepatic steatosis, inflammation and fibrosis by increasing FAO, reducing lipid uptake and improving hepatic insulin sensitivity in animal models^{193–197}. As such, FGF21 agonists hold promise as therapies for cardiometabolic diseases.

FGF21 requires β -klotho and FGF receptor 1 (FGFR1) for signalling^{198,199}, both of which are expressed in the heart. FGF21 provides cardioprotection by increasing antioxidant capacity and fatty acid metabolism, and promoting mitochondrial health through cAMP-responsive element-binding protein (CREB) and PGC1 α ²⁰⁰. In several mouse models of diabetes and/or obesity, loss of FGF21 aggravates cardiac steatosis and lipotoxic damage, and elevations of FGF21 are metabolically protective^{201–203}. After myocardial infarction, FGF21 reduces mineralocorticoid receptor activity, promoting heart–liver protective crosstalk²⁰⁴. However, chronic FGF21 elevation might drive cardiac pathological remodelling and diabetes-associated HFpEF²⁰⁵. The metabolically stressed heart itself can upregulate FGF21 expression, potentially serving as an autocrine loop that supports cardiac health, although the contribution of myocardium-derived FGF21 to the circulating levels of FGF21 remains uncertain²⁰⁶. In a cohort of patients with ischaemic heart disease, circulating levels of FGF21 were elevated in those who also had HFpEF versus those without HF²⁰⁷. However, the prognostic value of FGF21 levels in HF is unclear²⁰⁸ because elevated circulating levels of FGF21 might reflect a compensatory attempt to preserve cardiometabolic homeostasis in conditions of impaired tissue responsiveness, rather than an effective biological activity. In this

proposed ‘FGF21-resistant’ state, reduced expression or functionality of the β -klotho–FGFR1 receptor complex and attenuation of downstream signalling pathways, including ERK1/ERK2-dependent transcriptional programmes, blunt FGF21-mediated regulation of lipid metabolism, mitochondrial function and redox balance^{209–211}. Consequently, high FGF21 concentrations in HF and metabolic syndrome might serve as a biomarker of disrupted endocrine signalling and maladaptive cardiometabolic stress, helping to reconcile the elevation of FGF21 levels with limited prognostic and therapeutic efficacy.

Other hepatokines are dysregulated in MASLD and with systemic energy imbalances^{183,212,213}; however, their roles in cardiometabolic disease, particularly in the liver–heart crosstalk, remain poorly understood. For example, liver-secreted adropin regulates body weight as well as glucose and lipid homeostasis, and is downregulated in metabolic diseases²¹⁴, including MASLD²¹⁵. In experimental models of diabetic cardiomyopathy, adropin improves cardiomyocyte energetics by increasing glucose oxidation^{216–218}, resulting in improved metabolic efficiency and diastolic function^{216,219}.

The liver-derived factors coagulation factor XI and serum amyloid A proteins (SAA1 and SAA4) have been identified as novel mediators linking metabolic liver and heart disease. Distinct from its role in coagulation, factor XI activates the bone morphogen protein (BMP)–SMAD1/SMAD5 pathway in cardiomyocytes, resulting in protection against inflammation, fibrosis and HFpEF development in mice²²⁰. Notably, patients with HFpEF had reduced plasma levels of factor XI, suggesting the involvement of this protein in human HFpEF²²⁰. SAA1 and SAA4, which are acute-phase proteins, were found to uniquely overlap in the plasma proteomes of patients with MASLD or HFpEF, and correlate with increased transcription in the heart of genes involved in extracellular matrix remodelling²²¹. Future research is needed to uncover the roles of lesser-known hepatokines as mediators in MASLD and HFpEF liver–heart crosstalk.

Extracellular vesicles

Extracellular vesicles are cell-derived particles carrying proteins, metabolites, lipids and nucleic acids, reflecting their parent cell's constitution. Their formation and release are highly regulated processes, enabling targeted effects on local and distant organs through receptor–ligand interactions or molecule delivery^{222,223}. Extracellular vesicles have important roles in intercellular communication and are implicated in various diseases, including metabolic syndrome, because they transfer metabolic information and are intricately connected to cellular lipid metabolism²²⁴.

Accumulating evidence suggests a role for extracellular vesicles in the cardiometabolic liver–heart axis. In the liver, extracellular vesicles are central to MASLD pathology by recruiting immune cells and amplifying inflammation, injury and fibrosis in lipotoxic environments^{225,226}. An elevation of hepatic extracellular vesicle concentrations in the blood of patients with MASLD suggests systemic effects of these extracellular vesicles^{227,228}, an observation that is further supported by preclinical studies showing that extracellular vesicles from steatotic hepatocytes triggered distant inflammatory responses^{229–231}. In mice with MASLD, liver-derived extracellular vesicles disrupted the coronary endothelium via microRNA miR-7-induced NLRP3 inflammasome activation²³¹, although myocardial consequences were not reported. Similarly to hepatocytes, direct extracellular vesicle uptake is well established in cardiomyocytes²³². MASLD-associated extracellular vesicles contain inflammation-associated proteins, mitochondrial stress molecules^{233,234}, distinct microRNA profiles (particularly rich in miR-122)^{235,236}, and even intact mitochondria²³⁷, suggesting direct effects on myocardial metabolism.

The liver microRNA miR-122 regulates carbohydrate and lipid metabolism to favour lipogenesis^{238,239}. miR-122 levels in plasma are elevated in patients with MASLD compared with healthy individuals and correlate with disease progression and serum lipid profiles²⁴⁰. High miR-122 levels in plasma have been linked to adverse outcomes in cardiac diseases, including acute and chronic HF^{241–243}. In the heart, miR-122 drives maladaptive hypertrophy, inflammation and apoptosis, ultimately resulting in myocardial fibrosis and organ failure²⁴⁴. Extracellular vesicle-associated miR-122 isolated from individuals with obesity was shown to disrupt cardiomyocyte mitochondrial function in vitro by blocking ADP-ribosylation factor-like protein 2 (ref. 245). In obese mice, cardiac structural and metabolic remodelling was mitigated by liver-specific suppression of miR-122 (ref. 245).

Considering the dynamic nature of extracellular vesicles and their ability to transfer receptor ligands, cargo, and enzymatic activity and act as metabolic modulators far from their cell of origin²⁴⁶, the extent of extracellular vesicle-mediated inter-organ crosstalk remains vastly unexplored. Extracellular vesicles not only mirror the status of their parent cell, which could be used for biomarker development, but have a pathophysiological role in cardiometabolic disease. More comprehensive studies to unravel extracellular vesicle function in metabolic health and disease are needed.

Diagnostic implications

Recognizing the substantial epidemiological overlap and mechanistic connection between MASLD and cardiometabolic HFpEF supports the use of unified diagnostic pathways and integrated multiorgan assessment tools from the first presentation in the clinic of patients with cardiometabolic disease (Fig. 3). Diagnostic algorithms for isolated MASLD or cardiometabolic HFpEF are included in dedicated guidelines^{1,9,247–249}. MASLD is defined by the combination of SLD with metabolic risk factors and no other causes of SLD⁹ (Box 2). Guidelines from the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) recommend screening for MASLD and fibrosis only in individuals with T2DM or abdominal obesity plus one or more additional metabolic risk factors or persistently elevated aminotransferase levels in plasma²⁴⁷. The guidelines recommend a stepwise approach using blood-based fibrosis scores, such as Fibrosis-4 (FIB-4), followed by imaging techniques such as vibration-controlled transient elastography (VCTE)²⁴⁷ (Fig. 3). Of note, current HF guidelines do not recommend screening for MASLD^{248,249}. However, considering the high prevalence of MASLD in patients with HFpEF⁴⁷, with a large proportion of these patients already at a late stage of the disease^{47,48}, screening for MASLD should be considered in all patients with cardiometabolic HFpEF.

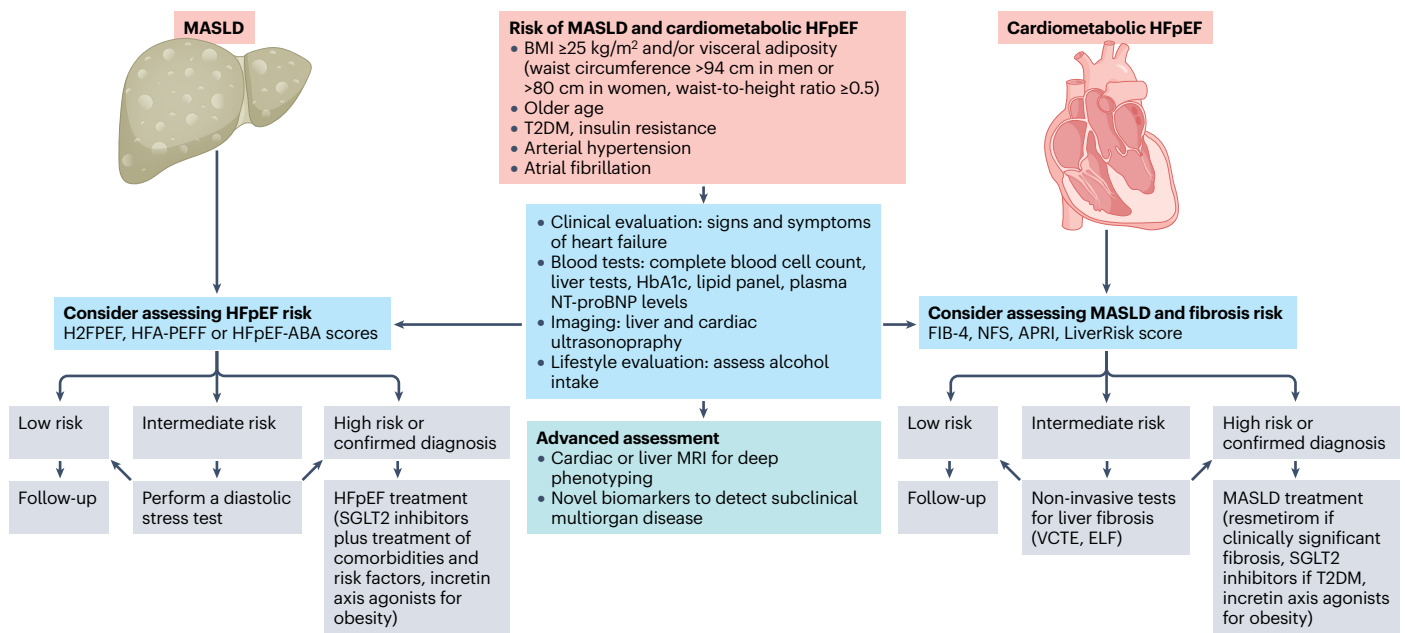


Fig. 3 | Integrated diagnostic algorithm to stratify patients at risk of cardiometabolic liver–heart diseases. An integrated approach for the diagnosis of cardiometabolic heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatotic liver disease (MASLD) is valuable for three patient groups: individuals at risk of HFpEF or MASLD without confirmed disease, patients with HFpEF who have not undergone liver evaluation, and patients with MASLD without cardiac assessment. Patients with a high risk of HFpEF or MASLD – those with elevated body mass index (BMI), visceral adiposity, older age (≥ 65 years), insulin resistance, type 2 diabetes mellitus (T2DM), hypertension or atrial fibrillation – should undergo a comprehensive evaluation, including clinical exams, relevant blood tests, liver and cardiac ultrasonography, and alcohol intake history. Clinical scoring tools, such as H2FPEF, HFA-PEFF and HFpEF-ABA for HFpEF, and Fibrosis-4 (FIB-4), NAFLD Fibrosis Score (NFS), aspartate

aminotransferase-to-platelet ratio index (APRI) and LiverRisk for MASLD, support patient risk stratification and integrated diagnosis. Patients with a low risk of MASLD or HFpEF can be monitored with regular follow-ups, whereas those with a confirmed diagnosis of these conditions should start guideline-based treatments. Individuals with an intermediate risk of HFpEF might benefit from diastolic stress testing, and patients with MASLD with increased risk of fibrosis should undergo vibration-controlled transient elastography (VCTE) or biomarker-based testing (such as the enhanced liver fibrosis (ELF)). Advanced magnetic resonance imaging (MRI) and biomarker panels provide further insights into subclinical multiorgan disease and can improve prognostic accuracy. HbA1c, glycated haemoglobin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium–glucose cotransporter 2.

The diagnosis of HF is based on symptoms and/or signs of HF caused by structural and/or functional cardiac abnormalities and elevated plasma natriuretic peptide levels or objectively evident congestion¹ (Box 2). In the presence of LVEF $\geq 50\%$, other cardiac abnormalities are required to diagnose HFpEF¹. Given the frequent coexistence of MASLD and HFpEF, along with the substantially elevated risk of HF in patients with MASLD⁴⁰, screening for HFpEF might be warranted in all patients with MASLD.

In summary, guidelines for HF or MASLD lack recommendations on reciprocal assessment. Raising clinician awareness on the coexistence of MASLD and HFpEF is key to prompting a multiorgan diagnostic and therapeutic approach in patients with cardiometabolic disease. Expanding practical diagnostic pathways for integrated multiorgan assessment is also essential for improved patient care (Fig. 3).

Multiorgan imaging

First-line clinical approach: ultrasonography. Echocardiography is a cornerstone in HFpEF diagnosis²⁴⁸ and, similarly, B-mode liver ultrasonography is the first-line test to detect liver steatosis²⁵⁰ (Table 1). However, conventional ultrasonography can miss a diagnosis of SLD when liver fat content is low²⁵¹, and interoperator variability limits the consistency of results. VCTE is widely used to detect and stratify liver fibrosis in patients with MASLD²⁵². However, this method is associated with high rates of false negative diagnoses in patients with obesity²⁵³.

Box 2 | Diagnostic criteria for MASLD and cardiometabolic heart failure with preserved ejection fraction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by the presence of hepatic lipid accumulation (on the basis of imaging findings or liver biopsy) in combination with at least one of five cardiometabolic risk factors (overweight or obesity, dysglycaemia or type 2 diabetes mellitus, high plasma triglyceride levels, low plasma HDL cholesterol levels, and arterial hypertension) and no other discernible cause for steatotic liver disease⁹. MASLD in patients who report mild or moderate alcohol intake and have metabolic risk factors is classified as metabolic and alcohol-related liver disease (MetALD), whereas MASLD in patients with heavy alcohol intake is diagnosed as alcohol-associated liver disease (ALD).

A heart failure diagnosis is based on typical symptoms and/or signs of heart failure (for example, dyspnoea, reduced exercise capacity and peripheral oedema) caused by structural and/or functional cardiac abnormalities and at least one of the following: elevated plasma natriuretic peptide levels and/or cardiogenic pulmonary or systemic congestion assessed by imaging or invasive haemodynamic measurement of intracardiac pressures at rest or with provocative testing¹. In patients with left ventricular ejection fraction $\geq 50\%$, other cardiac structural or functional abnormalities (such as abnormal enlargement of cardiac chambers, moderate or severe left ventricular hypertrophy, signs of diastolic dysfunction, or increased left ventricular filling pressures) are required to diagnose heart failure with preserved ejection fraction¹. If the diagnostic criteria are not met at rest but the pre-test probability is high, a diastolic stress test is recommended in the diagnostic work-up²⁵⁴.

Considering that patients with MASLD have a high risk of cardiometabolic HFpEF and vice versa, ultrasonography assessment of both the liver and the heart might help in a systemic diagnostic work-up. Cardiac diastolic stress imaging is the recommended second-level assessment when suspicion of HFpEF is high and echocardiography at rest is inconclusive²⁵⁴ (Table 1).

Second-line and research strategies: magnetic resonance. Multiparametric CMR enables accurate assessment of cardiac structure and function in patients with cardiometabolic HFpEF^{255–258}, even in those with obesity with suboptimal echocardiographic windows. For research purposes, proton (¹H) magnetic resonance spectroscopy (MRS) can be used to quantify myocardial triglyceride content^{84,259}, and native and post-gadolinium T1 mapping in magnetic resonance imaging (MRI) can be used to estimate myocardial fibrosis^{260,261}. Additionally, CMR can be used to evaluate cardiac energy metabolism using ³¹P-MRS to measure phosphocreatine-to-ATP ratios¹⁷⁷ and ¹³C-MRS to assess pyruvate metabolism²⁶² (Table 1). Despite high costs and limited availability, CMR provides the highest quality data on cardiac morphology and function. Advances in acquisition strategies and post-processing techniques have substantially mitigated previous limitations in the setting of atrial fibrillation, enabling robust image reconstruction despite irregular RR intervals and motion-related artefacts²⁶³. Whether CMR indices could be feasible soft end points in clinical trials of cardiometabolic HFpEF is unknown.

MRI is also extremely useful for liver assessment. Liver MRI is the most informative imaging technique for screening and stratification of patients with MASLD^{247,264} (Table 1). Liver proton density fat fraction (PDFF) MRI is the gold-standard non-invasive modality for hepatic lipid quantification in clinical and research settings and uses the same ¹H-MRS principles applied to quantify myocardial steatosis in CMR. Iron-corrected T1 (cT1) mapping reliably assesses liver disease activity, even in patients with obesity²⁶⁵.

Intriguingly, abnormal liver features (high PDFF and cT1 values) on MRI correlated with reduced stroke volume and increased LV concentric remodelling in a study population from the UK Biobank, highlighting the close interplay between liver and cardiac function²⁶⁶. Moreover, in another study of UK Biobank participants, early changes in cT1 independently correlated with major CVD events and all-cause mortality, regardless of metabolic syndrome status²⁶⁷. In addition, the same MRI features accurately tracked the effects of glucagon-like peptide 1 (GLP1) receptor (GLP1R) agonists on resolution of MASH without worsening of fibrosis in clinical trials that included patients with MASLD²⁶⁸.

In summary, steatosis and fibrosis are key features of both cardiometabolic HFpEF and MASLD. MRI provides extremely accurate evaluations of lipid content and fibrosis in the heart and liver, potentially representing the ultimate diagnostic tool when both cardiometabolic HFpEF and MASLD are suspected.

Biomarkers and diagnostic scores

Ultrasonography and MRI are key for HFpEF and MASLD diagnosis but are unsuitable for population screening. Candidate selection for multiorgan imaging should be guided by pre-test probability, estimated using validated diagnostic scores that integrate medical history, clinical findings and laboratory data (Fig. 3).

HFpEF. In the absence of overt congestion, elevated natriuretic peptide plasma levels are essential for HF diagnosis and is the most commonly used clinical biomarker for HFpEF¹. Although recommended in HF

Table 1 | Diagnostic strategies in cardiometabolic HFpEF and MASLD

Condition	Diagnostic approach	Description	Refs.
Imaging			
Cardiometabolic HFpEF	Echocardiography	Cardiac morphology and function (first-line approach)	1
	Lung ultrasonography	Detection of lung congestion (accuracy increases after exercise)	427–429
	Diastolic stress test	Second-level evaluation in patients with a high pre-test probability with non-diagnostic echocardiography at rest	254
	Cardiac MRI	Gold standard for window-independent assessment of cardiac morphology, systolic and diastolic function (cardiac MRI strain and phase contrast), fibrosis (cT1 mapping), fat content (¹ H-MRS), epicardial adipose tissue thickness, metabolism (³¹ P-MRS, ¹³ P-MRS), CAD and microvascular dysfunction	84,177, 255–262, 430,431
MASLD	Liver B-mode ultrasonography	Qualitative detection of steatotic liver disease (first-line approach)	250,251
	Attenuation imaging	Quantitative detection of steatotic liver disease	432,433
	VCTE, CAP	Second-level evaluation of fibrosis (VCTE) and steatosis (CAP), high failure rates in patients with obesity	252,253, 434,435
	Liver MRI	Gold standard for hepatic lipid quantification (liver PDFF), fibrosis (cT1 mapping, MRE) and inflammation	247, 264–268
Invasive assessment			
Cardiometabolic HFpEF	Invasive haemodynamic assessment	Gold standard for HFpEF diagnosis (restricted to research settings in most cases)	436,437
MASLD	Liver biopsy	Gold standard for MASLD diagnosis (in research settings) and differential diagnosis with other chronic liver diseases	247, 438–440
Biomarkers			
Cardiometabolic HFpEF	Natriuretic peptide levels in plasma	Currently required to diagnose HFpEF (in the absence of obvious congestion or invasive haemodynamic assessment), lower values in patients with obesity	1,269, 270,272
	Inflammation, renal function and adiposopathy	Blood levels of TNF, IL-1β, IL-6, CRP, myeloperoxidase, cystatin C, NGAL, KIM1, FABP4, adiponectin, leptin and resistin (in research settings)	441–443
	Fibrosis	Blood levels of galectin 3, soluble ST2, PIIINP, ICTP, MMP2, MMP7, MMP9, TIMP1, IGFBP1, IGFBP7 and endotrophin (in research settings)	273–279
	Complex pathways	GDF15, FGF21, FGF23, adrenomedullin and endothelin 1 (in research settings)	274,280–284
MASLD	Liver function, lipid profile and glucose metabolism	AST, ALT, bilirubin, γGT, albumin, prothrombin time, aPTT, platelet counts, blood levels of total cholesterol, LDL-C, HDL-C, triglycerides, fasting glucose and HbA1c	247
	Inflammation	Blood levels of cytokeratin 18, IL-6, IL-8, TNF, adiponectin (in research settings)	290–292
	Fibrosis	Enhanced liver fibrosis test (PIIINP, hyaluronic acid, TIMP1), PRO-C3 blood levels	300,444
	–	FGF21 blood levels (in research settings)	293
Integrated scores			
Cardiometabolic HFpEF	H2FPEF	BMI, use of hypertensive medications, atrial fibrillation, age, PASP, E/e'	285
	HFA-PEFF	Plasma natriuretic peptide levels, echocardiographic features (left atrial size, diastolic parameters, LV mass and relative wall thickness, tricuspid regurgitation velocity and LV global longitudinal strain)	254
	HFpEF-ABA	Age, BMI, atrial fibrillation	286
MASLD	Screen for liver steatosis	FLI (BMI, plasma triglyceride levels, waist circumference, γGT blood levels); HSI (BMI, T2DM, ALT-to-AST ratio); NAFLD LFS (metabolic syndrome, T2DM, fasting serum insulin levels, AST, ALT-to-AST ratio)	287–289
	Screen for liver fibrosis	FIB-4 (age, platelet count, AST, ALT); APRI; NFS (age, BMI, impaired fasting blood glucose levels, ALT-to-AST ratio, platelet count and albumin); FNI (ALT, plasma HDL-C levels, HbA1c); LiverRisk score (sex, age, total plasma cholesterol levels, fasting blood glucose levels, ALT, AST, γGT blood levels, platelet count); ADAPT algorithm (age, T2DM, PRO-C3 blood levels, platelet count); machine learning-derived algorithm (BMI, blood levels of PRO-C3, collagen type IV, AST, albumin and globulin)	247,294–299, 445
	Imaging and biomarkers scores	MAST (MRE, PDFF and AST); FAST (VCTE, AST); MEFIB (MRE, FIB-4)	301–303

γGT, γ-glutamyltransferase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CAP, controlled attenuation parameter; cT1, iron-corrected T1; CRP, C-reactive protein; FABP4, fatty acid-binding protein 4; FAST, FibroScan-AST score; FGF, fibroblast growth factor; FIB-4, Fibrosis-4; FLI, fatty liver index; FNI, fibrotic non-alcoholic steatohepatitis index; GDF15, growth differentiation factor 15; HbA1c, glycated haemoglobin; HDL-C, HDL cholesterol; HFpEF, heart failure with preserved ejection fraction; HSI, hepatic steatosis index; ICTP, collagen type I carboxy-terminal telopeptide; IGFBP, insulin-like growth factor-binding protein; KIM1, kidney injury molecule 1; LDL-C, LDL cholesterol; LV, left ventricular; MASLD, metabolic dysfunction-associated steatotic liver disease; MAST, MRI-AST score; MEFIB, magnetic resonance elastography and fibrosis-4 score; MMP, matrix metalloproteinase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD LFS, non-alcoholic fatty liver disease liver fat score; NGAL, neutrophil gelatinase associated lipocalin; NFS, NAFLD fibrosis score; PASP, pulmonary artery systolic pressure; PDFF, proton density fat fraction; PIIINP, procollagen type III N-terminal peptide; PRO-C3, N-terminal propeptide of type 3 collagen; ST2, IL-1 receptor-like 1; TIMP1, tissue inhibitor of metalloproteinase 1; TNF, tumour necrosis factor; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

evaluation, guideline cut-offs might miss cardiometabolic HFpEF because patients with obesity often have normal or low plasma natriuretic peptide levels despite elevated cardiac filling pressures^{269–271} and similar risks of death or HF hospital readmissions²⁷². Therefore, patients with obesity and MASLD with low natriuretic peptide levels might still have a substantial risk of HF.

Other biomarkers are under investigation to improve diagnostic accuracy in patients with HFpEF, targeting different areas of HFpEF pathophysiology, including fibrosis^{273–279}, inflammation and other pathways^{274,280–284}, but their role is still limited to research purposes (Table 1).

Clinical scores, such as H2FPEF²⁸⁵ and HFA-PEFF²⁵⁴, have been developed to help clinicians in the diagnosis of HFpEF. A score of 0 on H2FPEF and <2 on HFA-PEFF excludes HFpEF, whereas scores ≥ 5 on H2FPEF and ≥ 6 on HFA-PEFF confirm a diagnosis of HFpEF (Table 1). A simplified algorithm that considers only BMI, age and presence of atrial fibrillation (HFpEF-ABA score) has been proposed to select patients at higher risk of HFpEF²⁸⁶. These scores are not the gold standard for HFpEF diagnosis (which should be based on the universal definition of HF¹) but can aid in risk stratification in patients with MASLD for clinical or research use within a multiorgan assessment approach.

MASLD. Several clinical scores^{287–289} have been developed to detect liver steatosis at different stages (Table 1), whereas different biomarkers are needed to stratify the risk of MASH^{290–292} (Table 1). Interestingly, liver-secreted FGF21, a potential mediator of metabolic liver–heart crosstalk, has been proposed as a blood biomarker for MASH, especially in combination with cytokeratin 18 blood levels²⁹³. Given that screening for MASLD or MASH in individuals without fibrosis is not recommended by clinical guidelines²⁴⁷, these tools should be considered mainly in research settings.

Screening for liver fibrosis, which is essential for identifying patients at a high risk of liver-related events and, therefore, recommended for the diagnosis of patients with MASLD²⁴⁷, requires different scores from those used to identify liver steatosis (Table 1). The most widely used fibrosis scores, endorsed by international guidelines, are FIB-4 (ref. 294), aspartate aminotransferase (AST)-to-Platelet Ratio Index (APRI)²⁹⁵ and NAFLD Fibrosis Score (NFS)²⁹⁶. Of note, only NFS was specifically developed for MASLD; the other scores do not distinguish between liver fibrosis aetiologies. Subsequently developed scores offer improved accuracy for large-scale fibrosis screening^{297–299}. These tools use routine clinical parameters, making them suitable for both population-level screening and daily clinical practice. However, age-inclusive scores (such as FIB-4, NFS and LiverRisk) might introduce bias in longitudinal assessments as patients age. In research or specialized centres, biomarkers such as the enhanced liver fibrosis (ELF) test³⁰⁰ might improve patient stratification. ELF, which measures procollagen type III N-terminal peptide and tissue inhibitors of metalloproteinase 1 (TIMP1) levels in the blood, might also be altered in the setting of HFpEF, although the role of this test in cardiometabolic HFpEF remains unclear. A combinational approach of biomarkers and imaging results has also been proposed and tested to improve diagnostic accuracy^{301–303} (Table 1).

Integrated diagnostic algorithms

An integrated diagnostic approach can be pursued for cardiometabolic HFpEF and MASLD, particularly in three clinical contexts: individuals at risk of either condition without a formal diagnosis, patients

with established cardiometabolic HFpEF but no liver assessment, and those with MASLD who have not undergone cardiac evaluation (Fig. 3).

Several risk factors, such as elevated BMI (≥ 25 kg/m²), visceral adiposity (waist circumference >94 cm in men, >80 cm in women), older age, T2DM or insulin resistance, hypertension, and atrial fibrillation, are shared between MASLD and HFpEF. These variables are commonly incorporated into the respective diagnostic scores. Accordingly, when such factors are present, it might be appropriate to estimate the pre-test probability of both conditions using validated tools.

Widely used screening instruments include H2FPEF, HFA-PEFF or HFpEF-ABA for HFpEF and Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI) or NAFLD Liver Fat Score (NAFLD LFS) for MASLD, as well as fibrosis-specific scores such as FIB-4, NFS or LiverRisk²⁴⁷. Importantly, scores estimating the risk of MASLD (such as FLI, HSI or NAFLD LFS) are not recommended by the EASL–EASD–EASO guidelines, given that only the presence of fibrosis predicts liver-related events, and only therapeutic strategies targeting fibrosis have been shown to significantly reduce liver disease progression. Screening for MASLD, in those with or without fibrosis, should therefore be limited to research settings or used to refine cardiovascular risk stratification.

An initial multiorgan assessment can include a clinical evaluation (for example, exertional dyspnoea, oedema or blood pressure), laboratory tests (complete blood count, liver tests such as blood levels of AST, alanine aminotransferase, γ -glutamyltransferase and albumin, HbA1c, and plasma HDL cholesterol, LDL cholesterol, triglyceride and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels), and liver and cardiac ultrasonography. Alcohol intake should also be reviewed. Patients with a low estimated risk of both MASLD and HFpEF should be monitored, whereas those with established disease might warrant a specialist referral to start a guideline-based treatment.

Patients with an intermediate risk of HFpEF might benefit from diastolic stress testing²⁵⁴. In patients with MASLD, those with elevated risk of liver fibrosis might warrant non-invasive evaluation such as VCTE or ELF testing²⁴⁷. All patients with an established HFpEF diagnosis might benefit from a liver assessment with fibrosis scores²⁴⁷, whereas patients with MASLD might be evaluated for HF using NT-proBNP levels and echocardiography, aided by HFpEF scores (Fig. 3). For research purposes, MRI and extended biomarker panels might support early detection and prognosis, or serve as end points in multiorgan studies.

Shared therapeutic strategies

In both patients with cardiometabolic HFpEF or MASLD, only limited therapeutic strategies are available to substantially improve outcomes. Interestingly, considering the shared pathophysiological background, some of these interventions are not disease specific but have been shown benefits in both conditions (Table 1).

Non-pharmacological interventions

Given that excessive visceral adiposity is pivotal to the progression of both cardiometabolic HFpEF and MASLD, weight loss is recommended for both settings. In MASLD, weight loss has been consistently linked to a significant reduction in organ damage and, therefore, EASL–EASD–EASO guidelines recommend a sustained reduction of body weight of $\geq 5\%$ to reduce liver fat content, 7–10% to reduce liver inflammation and $\geq 10\%$ to reduce liver fibrosis²⁴⁷. Although data correlating weight loss and improved cardiometabolic HFpEF outcomes are scarce, in patients

with HF with a BMI ≥ 35 kg/m², the Heart Failure Society of America recommends a reduction of at least 5–10% of body weight³⁰⁴. Of note, a reduction of $>30\%$ of liver triglyceride content is also predictive of a reduction in fibrosis irrespective of weight loss³⁰⁵. Several strategies might be adopted to lose body weight and reduce liver triglyceride content (Table 2).

Dietary approaches. Hypocaloric low-carbohydrate diets and low-fat diets seem to be effective in reducing liver lipid content and related biomarkers^{306,307}. Similarly, improvements in diastolic function, walking distance and NT-proBNP levels have been observed in patients with cardiometabolic HFpEF after calorie restriction, especially if combined with exercise training³⁰⁸. Compared with a simple calorie restriction, Mediterranean diets have an added value for liver lipid content reduction, might be easier to maintain long-term and has been shown to improve global cardiovascular health^{309–312}. In patients with HF, and those with HFpEF in particular, a Mediterranean diet has been shown to significantly reduce inflammation and plasma NT-proBNP levels compared with low-fat diets^{313,314}. Of note, however, randomized controlled trials (RCTs) with hard clinical end points are yet to be performed.

Ketogenic diets or intermittent fasting are widely adopted for weight loss³¹⁵, but available data are conflicting as for the efficacy and safety of very low-carbohydrate ketogenic diets or intermittent fasting in the setting of MASLD^{316–318} or HFpEF, where clinical evidence do not support a clear benefit and clinical trials³¹⁹ are ongoing. Concerns about potential cardiovascular, renal and metabolic adverse effects have also been raised³²⁰, so caution is warranted when proposing these dietary interventions.

Collectively, a Mediterranean diet is the recommended dietary approach for patients with MASLD²⁴⁷ and is also promising in those with cardiometabolic HFpEF as well, even if more robust RCT data are lacking. The efficacy and safety of other dietary strategies, especially in the long term, are unknown.

Physical activity. Sedentary behaviour is independently associated with an increased risk of MASLD diagnosis and progression^{321,322}. In addition, lower physical activity independently correlates with higher incidence of HFpEF but not HFrEF³²³. Physical inactivity promotes MASLD mainly via altered metabolism and increased insulin resistance, whereas in HFpEF, considering the pivotal role of skeletal muscle dysfunction, the effects of a sedentary lifestyle might be even more deleterious than in patients with MASLD³²⁴. Accordingly, exercise training is a class I recommendation for HF treatment^{249,325–327}. Several exercise training protocols have been shown to significantly improve exercise capacity (on cardiopulmonary exercise testing) and quality of life, but high-intensity interval training has emerged as the most effective lifestyle intervention in HFpEF³²⁸. In MASLD, several RCTs and meta-analyses showed that exercise alone reduces liver steatosis, independently of weight loss^{329,330}. Therefore, physical activity is recommended in all patients with MASLD, but only the total amount of exercise per week is considered relevant, given that different protocols are similarly effective (for example, a minimum of 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity physical activity)²⁴⁷. Given the large body of evidence that supports the prescription of exercise training in both patients with MASLD or HFpEF, this intervention should be strongly recommended and exercise protocols should be tailored to patient preferences.

Bariatric surgery. Bariatric surgery is a weight-lowering intervention recommended in patients with BMI ≥ 40 kg/m², BMI 35–40 kg/m² in the presence of associated comorbidities, or BMI 30–35 kg/m² if the individuals have T2DM and/or hypertension that is poorly controlled despite optimal medical therapy³³¹. Bariatric surgery induces stable weight loss, remission of T2DM³³² and overall cardiometabolic benefits. In patients with MASLD, bariatric surgery improves steatohepatitis (histological findings) and liver-related outcomes and reduces the incidence of major adverse cardiovascular events (MACE)^{333–335}, with a greater benefit when Roux-en-Y gastric bypass is the chosen procedure^{336,337}.

Similar beneficial effects have been observed in cardiometabolic HFpEF, in which bariatric surgery has been shown to improve symptoms and NYHA class, reduce HF readmissions and reverse LV remodelling, and improve LV compliance^{338–340}. In a nationwide analysis, mortality was lower among patients with obesity and HFpEF treated with bariatric surgery than in patients with obesity and HFpEF without bariatric surgery³⁴¹. A lower risk of atrial fibrillation was also observed³⁴¹. These data suggest that bariatric surgery in cardiometabolic HFpEF might reduce mortality and improve resource utilization with low safety concerns³⁴¹. However, the evidence only comes from case series, retrospective studies or registries, with no RCTs performed thus far. More interventional studies to support the use of this treatment in patients with cardiometabolic HFpEF are needed.

Altogether, in patients with obesity who have an approved indication, bariatric surgery should be considered if MASLD is present²⁴⁷. The concomitant diagnosis of cardiometabolic HFpEF might further strengthen the indication for bariatric surgery, even if supporting data from RCTs are lacking.

Pharmacological interventions

SGLT2 inhibitors. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are oral antidiabetic drugs that inhibit glucose reabsorption in the proximal tubule of the kidney, thereby increasing glucose excretion and lowering blood glucose levels. However, the mechanisms of action of these drugs are complex, and include improving insulin resistance, reducing fatty acid synthesis and blocking de novo lipogenesis³⁴². SGLT2 inhibitors induce modest but stable weight loss, blood pressure reduction and protection from MACE, including HF³⁴². The weight loss is due to renal energy loss and reduction in fat mass, with reductions in both visceral and abdominal subcutaneous adipose tissue³⁴³.

In preclinical models, SGLT2 inhibitors such as empagliflozin and dapagliflozin have shown profound benefits on cardiac remodelling. In mouse models of HF, treatment with empagliflozin preserved systolic function and improved myocardial energetics, even in *in vitro* and *ex vivo* experiments, ruling out confounding systemic effects^{344,345}. Mechanistically, empagliflozin reduced cardiac fibrosis and hypertrophy by downregulating the transforming growth factor- β –SMAD signalling pathway and oxidative stress via activation of the NRF2–ARE pathway³⁴⁶. These pathways mitigate extracellular matrix deposition and preserve myocardial architecture. Additionally, in hypertensive rat models, treatment with SGLT2 inhibitors led to upregulation of PPAR α and mitochondrial medium-chain specific acyl-CoA dehydrogenase, which are key regulators of FAO, as well as *NPPA* and *NPPB* (encoding atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), respectively), suggesting improved energy metabolism and cardio-renal signalling³⁴⁷. Another novel mechanism involves modulation of the gut microbiota. In mice, SGLT2 inhibitors reduced the abundance of bacterial taxa responsible for producing uraemic toxins

Table 2 | Shared therapeutic strategies in cardiometabolic HFpEF and MASLD

Therapeutic strategy	SWOT (strengths, weaknesses, opportunities and threats) analysis				Refs.
	Strength	Weakness	Opportunity	Threat	
Non-pharmacological interventions					
Weight loss	<p>≥5% weight loss reduces liver fat content, and ≥10% weight loss improves fibrosis in patients with MASLD</p> <p>In patients with HFpEF with BMI ≥35 kg/m², 5–10% weight loss improves symptoms and functional capacity</p>	Difficult long-term maintenance; risk of sarcopenia and frailty in patients with HFpEF if poorly supervised	Early intervention in obesity-driven MASLD and HFpEF; combination with physical activity and pharmacological weight-loss therapies	Weight regain; excessive restriction might worsen exercise tolerance or precipitate HF decompensation	247,304
Dietary approaches	<p>Mediterranean diet (consumption of unrefined cereals, nuts and seeds, olive oil as main source of lipids, moderate intake of fish and poultry with low intake of red meat, exclusion of sugar-sweetened beverages and ultraprocessed foods with high sugar and saturated fat content) improves liver steatosis, metabolic profile and cardiometabolic risk</p> <p>Low-carbohydrate and low-fat diets improve liver and HFpEF markers.</p>	Variable adherence; mixed evidence for ketogenic diets, particularly in HFpEF	Personalized dietary strategies targeting insulin resistance and inflammation	Extreme diets might adversely affect volume status or renal function in HFpEF	33, 307–315
Physical activity	Recommended by HF and MASLD guidelines; improves exercise capacity, diastolic function, cardio-respiratory fitness and quality of life in HFpEF and reduces HF hospitalizations; reduces liver fat content independently of weight loss	Limited tolerance in advanced HFpEF; requires structured and supervised programmes in patients with frailty	Moderate-intensity and high-intensity exercise are equally effective for liver fat reduction; guideline targets of ≥150 min per week of moderate activity or ≥75 min per week of vigorous activity applicable to both MASLD and HFpEF; high-intensity interval training improves liver steatosis and HFpEF symptoms	Poor long-term adherence; risk of musculoskeletal injury in older patient populations with comorbidities	249, 325–330
Bariatric surgery	Indicated for BMI ≥40 kg/m ² , ≥35–40 kg/m ² with comorbidities or ≥30–35 kg/m ² with uncontrolled T2DM or hypertension; reduces liver steatosis and fibrosis and improves HFpEF outcomes	Invasive; perioperative risk; limited to selected patients	Disease-modifying option in severe obesity-related MASLD and HFpEF	Perioperative HF decompensation; long-term nutritional deficiencies	247, 331–341
Pharmacological interventions					
SGLT2 inhibitors	Class I recommendation in HFpEF; reduce HF hospitalizations, improve glycaemia and reduce body weight Reduce liver fat and fibrosis in MASLD; recommended in patients with MASLD and T2DM	Limited liver histology data; risk of genitourinary infections	Synergistic use with GLP1R agonists; management of early-stage fibrosis	Uncertain safety in patients with advanced liver disease	342,343, 361–363
Incretins (GLP1R agonists): semaglutide and tirzepatide	<p>Improve quality of life and exercise capacity and reduce cardiovascular death or worsening HF in patients with cardiometabolic HFpEF</p> <p>Reduce liver fat, fibrosis and cardiovascular events in patients with MASLD</p> <p>Effective weight loss</p>	Gastrointestinal adverse effects; cost	Early use in obesity-related MASLD–HFpEF phenotypes to modify disease trajectory	<p>Long-term safety; weight regain and unclear cardiovascular effects at drug discontinuation</p> <p>Sarcopenia if not paired with physical activity</p> <p>Adherence in older or frail patients with HFpEF</p>	247, 365–402
Mineralocorticoid receptor antagonists (for example, finerenone)	<p>Improve outcomes in HFpEF</p> <p>Antifibrotic effects suggested in animal models of MASLD</p>	Limited clinical data on MASLD; risk of hyperkalaemia and renal dysfunction	Target shared in cardiac and hepatic fibrotic pathways	Safety limitations in advanced HF or liver disease	403–409
Thyroid hormone receptor agonists (resmetirom)	<p>Approved for patients with MASLD with fibrosis; reduce liver fat and improves liver function</p> <p>Potential benefit in HFpEF</p> <p>Oral therapy</p>	Early clinical use; limited long-term and HFpEF-specific data; cost	Combination with cardiometabolic therapies to target the liver–heart pathogenetic axis	Unknown cardiovascular effects	410,411

Table 2 (continued) | Shared therapeutic strategies in cardiometabolic HFpEF and MASLD

Therapeutic strategy	SWOT (strengths, weaknesses, opportunities and threats) analysis				Refs.
	Strength	Weakness	Opportunity	Threat	
Pharmacological interventions (continued)					
Statins	Reduce plasma LDL-C levels, proven cardiovascular protection, safe in patients with HFpEF and patients with compensated MASLD	No reversal of liver fibrosis; HFpEF-specific benefit not established	Prevention of cardiovascular events; potential anti-inflammatory effects on liver and myocardium	Rare hepatotoxicity; under-prescription due to liver safety concerns	421,422
Vitamin E	In MASLD, improves liver histological features and reduces plasma aminotransferase levels Lower incidence of HFpEF reported in one randomized controlled trial	Limited evidence for functional or vascular benefit in HFpEF	Adjunctive therapy in selected patients with MASLD–HFpEF without diabetes	Potential long-term safety concerns with high-dose supplementation	10, 412–416
PPAR agonists (pioglitazone and lanifibranor)	Reduce steatohepatitis and fibrosis in MASLD	Fluid retention and weight gain; safety concerns in HFpEF	Development of safer agents with improved cardio-hepatic balance	Worsening HF symptoms limit clinical use in HFpEF	417–420

AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; GLP1R, glucagon-like peptide 1 receptor; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LDL-C, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium–glucose cotransporter protein 2; T2DM, type 2 diabetes mellitus.

such as p-cresol sulfate, which can impair cardiac contractility and rhythm³⁴⁸. These effects were validated in human engineered heart tissues, where p-cresol exposure worsened cardiac tissue function, further implicating the gut microbiota–heart axis as a therapeutic target that can be modulated by SGLT2 inhibition³⁴⁸.

SGLT2 inhibitors also exert direct beneficial effects on the liver. In mouse models, dapagliflozin and canagliflozin attenuate hepatic steatosis and fibrosis through downregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, which suppresses glycolysis and promotes macrophage polarization from a pro-inflammatory M1-like to an anti-inflammatory M2-like phenotype³⁴⁹. This shift reduces hepatic inflammation and lipogenesis³⁴⁹. Although SGLT2 inhibitor-induced weight loss contributes to reductions in visceral and hepatic fat, which are key drivers of MASLD progression³⁵⁰, certain effects seem to be independent of body weight change. In obese mice, ipragliflozin significantly decreased hepatic lipid accumulation without altering body weight, concurrently increasing hepatic sirtuin 1 (SIRT1) signalling, accompanied by increased expression of PGC1 α , PPAR α and FGF21, suggesting upregulation of lipid oxidation and energy metabolism pathways³⁵¹. Empagliflozin further improved liver inflammation and fibrosis in mice with MASH by inhibiting CD8⁺ T cell activation via enhanced ketogenesis³⁵². This effect involved the upregulation of BDH1 in CD8⁺ T cells, elevation of β -hydroxybutyrate levels and suppression of interferon regulatory factor 4, a transcription factor crucial for T cell effector function³⁵². Integrated multiomics analyses also revealed that SGLT2 inhibitors reshape inter-organ metabolic communication. In mice treated with dapagliflozin, combined proteomic, phosphoproteomic and metabolomic profiling showed modulation of liver and cardiac signalling in addition to renal effects³⁴⁸. Hepatic changes included suppression of apical nutrient transporters, reduction in glucotoxicity and decreased expression of inflammation-related proteins, whereas cardiac tissue showed remodelling in mitochondrial energy metabolism and cytoskeletal organization, consistent with improved cardiac function³⁴⁸.

Notably, SGLT2 inhibitor treatment has been associated with modulation of circulating cytokines, reinforcing the concept of hepatic–cardiac signalling. Clinical and preclinical studies have demonstrated that SGLT2 inhibitors, including empagliflozin

and dapagliflozin, reduce circulating levels of pro-inflammatory cytokines such as IL-6 (refs. 353,354), TNF³⁵⁴, CC-motif chemokine 2 (ref. 354), and IL-1 β and IL-8 (ref. 355). Additionally, SGLT2 inhibitors influence adipokine profiles, which are crucial mediators in cardiometabolic health. Compared with placebo, treatment with SGLT2 inhibitors decreased circulating leptin levels and increased adiponectin concentrations in patients and mice with diabetes^{356,357}. Elevated circulating leptin levels are associated with pro-inflammatory and pro-fibrotic effects in both the liver³⁵⁸ and the heart³⁵⁹, contributing to insulin resistance and adverse remodelling. By contrast, adiponectin has anti-inflammatory and anti-fibrotic properties, increasing insulin sensitivity and exerting protective effects on the myocardium and liver^{292,360}. The modulation of these adipokines by SGLT2 inhibitors might underlie some of the beneficial effects of these drugs on metabolic homeostasis and organ function. These alterations in cytokines and adipokines might contribute to the observed improvements in hepatic inflammation and fibrosis in MASLD as well as to improved cardiac function in HFpEF with SGLT2 inhibitor treatment, highlighting the role of these agents in modulating the liver–heart axis.

Because of their beneficial effect on cardiovascular and renal outcomes, some SGLT2 inhibitors (empagliflozin and dapagliflozin) have been approved for the treatment of chronic kidney disease and HF, irrespective of concomitant T2DM. In HFpEF, SGLT2 inhibitors are currently the only pharmacological class with a class I recommendation to reduce HF hospitalizations or cardiovascular mortality³⁶¹. In patients with MASLD, empagliflozin and dapagliflozin reduced liver fat and histology-assessed fibrosis, regardless of the presence or absence of T2DM^{362,363}, whereas licogliflozin was effective in reducing alanine aminotransferase levels in plasma³⁶⁴. SGLT2 inhibitors are not recommended in MASLD guidelines in individuals without T2DM because RCTs with liver histological end points have not yet been conducted in this patient population^{10,247}. However, two considerations apply: SGLT2 inhibitors are recommended for the treatment of T2DM in patients with MASLD²⁴⁷, but the potential reduction of MACE in patients with MASLD without diabetes has never been investigated.

Collectively, SGLT2 inhibitors must be prescribed for all patients with HFpEF, with or without MASLD. SGLT2 inhibitors should be

considered a first-line treatment for T2DM in patients with MASLD²⁴⁷ and in patients with MASLD with HFpEF (for compelling indications)³⁶¹.

Incretins. Incretin axis analogues, such as GLP1R agonists (including semaglutide)³⁶⁵, double GLP1–gastric inhibitory polypeptide receptor agonists (tirzepatide)³⁶⁶ and triple GLP1–gastric inhibitory polypeptide receptor–glucagon receptor agonists (retatrutide)³⁶⁷, increase insulin secretion, suppress glucagon release and slow gastric emptying. Their pleotropic effects include reduction in blood glucose levels and appetite, with remarkable weight loss³⁶⁸, thus offering multiple beneficial cardiometabolic effects, including favourable outcomes in both patients with cardiometabolic HFpEF or MASLD.

GLP1R expression has been reported in the heart³⁶⁹, including in cardiomyocytes, as well as in endothelial cells³⁷⁰. Therefore, GLP1R agonists are known to exert both direct and indirect cardioprotective effects. Activation of GLP1R in endothelial cells stimulates the AMP-activated protein kinase (AMPK)–AKT–eNOS signalling cascade, increasing NO availability and promoting vascular relaxation^{371,372}. GLP1R agonists lower blood pressure by improving endothelial function, promoting vasodilatation³⁷³ and stimulating ANP secretion³⁷⁴. In animal models, these antihypertensive effects are dependent on intact endothelial GLP1R signalling, with liraglutide inducing consistent blood pressure reductions³⁷⁵. These mechanisms collectively support improved vascular function and haemodynamics. Additionally, GLP1R agonists exert anti-atherosclerotic effects by inhibiting matrix metalloproteinases, thereby stabilizing the plaques and slowing disease progression³⁷⁶. These drugs also reduce systemic inflammation by suppressing NF- κ B signalling and decreasing the levels of pro-inflammatory cytokines and adhesion molecules implicated in vascular injury and LV remodelling³⁷⁷. Increasing evidence suggests that, in HFpEF, the benefits of GLP1R agonists extend beyond weight loss³⁷⁸. In a preclinical model of cardiometabolic HFpEF, comparing the weight loss achieved with semaglutide versus the reduction in caloric intake, GLP1R agonists provided additive improvements, including better glycaemic control, improved exercise capacity and cardiac function, and reduced inflammation, fibrosis and hypertrophy³⁷⁹. These effects were associated with endothelial GLP1R signalling and modulation of mitochondrial, cytoskeletal and metabolic pathways³⁷⁹.

Incretin analogues have also been shown to modulate systemic inflammation, reducing circulating inflammatory cytokine levels³⁸⁰ as well as other pathways, potentially linking hepatic and cardiac pathways. For instance, GLP1R agonists have been associated with increases in circulating levels of FGF21 in both humans and animal models³⁸¹. In mice, GLP1 analogues stimulate hepatic FGF21 production, which contributes to the inhibition of hepatic glucose output and improvement of lipid metabolism³⁸¹. This mechanism suggests a direct hepatic action of GLP1 analogues, reinforcing the interplay between hepatic and cardiac tissues.

Positive effects of semaglutide in HF have been observed in large RCTs, including the subgroup of patients with HF in the cohort of patients with obesity without diabetes included in the SELECT trial³⁸², as well as in dedicated RCTs recruiting patients with obesity and HFpEF (STEP-HFpEF programme³⁸³). In a pooled data analysis of the STEP-HFpEF, STEP-HFpEF DM, SELECT and FLOW trials, semaglutide reduced the risk of cardiovascular death or worsening HF events by 31% and worsening HF events by 41% compared with placebo³⁸³. In patients with obesity without diabetes, tirzepatide led to greater weight loss than semaglutide^{366,384}, improved exercise capacity and quality of life in patients with HFpEF compared with placebo³⁸⁵, and lowered the risk

of a composite of death from cardiovascular causes or worsening HF in patients with HFpEF and obesity³⁸⁶. In addition, significant improvements in cardiac function, volume overload and NT-proBNP levels have been observed in patients with HFpEF treated with GLP1R agonists compared with placebo^{384,387,388}. However, these trials were not fully blinded because of visible weight loss, and the effect on HF-related events might be influenced by improvements in overall cardiometabolic health rather than direct effects on the HFpEF syndrome itself. Therefore, although treating obesity seems to improve outcomes in this patient population, whether these benefits extend to a direct therapeutic effect on HFpEF remains debated.

Preclinical studies provide strong evidence that GLP1R agonists exert direct beneficial effects on MASLD, independent of weight loss and glycaemic control. In mice with diet-induced obesity, semaglutide significantly reduced hepatic lipid accumulation and improved liver enzyme profiles, either compared with vehicle treatment or control mice, in which weight loss was achieved with caloric restriction, suggesting effects beyond weight reduction³⁸⁹. Similarly, exenatide ameliorated hepatic steatosis via activation of the SIRT1 pathway in mice fed a high-fat diet, an effect that was abolished in SIRT1-deficient models, supporting a direct hepatic mechanism³⁹⁰. Additionally, exenatide attenuated fructose-induced steatosis in rats through modulation of the β -catenin signalling pathway, highlighting another direct route by which GLP1R agonists influence hepatic lipid metabolism³⁹¹. Together, these findings support a role for GLP1R agonists in directly targeting hepatic pathways involved in MASLD beyond their systemic metabolic effects.

Several RCTs have shown that incretin axis analogues reduce liver fat content and liver enzyme levels in blood. Semaglutide treatment promoted the resolution of steatohepatitis, with the latest findings indicating a reduction in fibrosis compared with placebo^{392,393}. Tirzepatide reduced liver and visceral fat content in patients with T2DM compared with insulin degludec³⁹⁴ and outperformed placebo in resolving MASH without worsening fibrosis, as assessed by histology, in patients with MASH and obesity, with or without T2DM²⁶⁸. Similarly, in a phase II trial involving patients with MASH, the dual GLP1R–glucagon receptor agonist survodutide showed benefits in histological parameters³⁹⁵. Other dual GLP1R–glucagon receptor agonists (cotadutide, efinopeg-tudide and pemvidutide) improved markers of steatosis, inflammation and/or fibrosis in patients with MASLD and overweight or obesity, when compared with placebo (for pemvidutide and cotadutide) or with other GLP1R agonists (for cotadutide and efinopeg-tudide)^{396–398}. Similarly to SGLT2 inhibitors, no significant reduction in liver-related outcomes has been seen in patients with MASLD treated with incretin analogues in RCTs³⁹⁹. However, several retrospective studies have reported reductions in liver-related events in patients with MASLD treated with incretin axis analogues compared with those taking non-incretin axis analogues, especially in those with T2DM^{400–402}, and a signal for lower risk of HF in these patients has been reported⁴⁰². Given the limited RCT data, these drugs are currently recommended in patients with MASLD plus T2DM and/or obesity²⁴⁷. However, considering the benefits observed in cardiometabolic HFpEF, incretin analogues should be considered in all patients with obesity with liver–heart metabolic dysfunction.

Other drugs. In HFpEF, the FINEARTS-HF trial⁴⁰³ demonstrated the efficacy of finerenone, a non-steroidal mineralocorticoid receptor antagonist, in reducing worsening HF events or cardiovascular mortality in patients with LVEF >40% compared with placebo, leading to FDA approval for its use in adults with HF with mildly reduced ejection

fraction or HFpEF. Mineralocorticoid receptor antagonists might be particularly effective in obesity-related HFpEF, where adipocyte aldosterone production activates mineralocorticoid receptors^{404–406}. Pre-clinical studies indicate that mineralocorticoid receptor antagonists might mitigate insulin resistance in mice fed a high-fat diet⁴⁰⁷ and improve liver histology parameters in animal models of MASH by reducing steatosis and fibrosis⁴⁰⁸. In clinical settings, in a subgroup analysis of the FIDELITY pooled analysis, finerenone had a neutral effect on liver function but the effect on MACE reduction compared with placebo was greater in patients with higher FIB-4 scores⁴⁰⁹. The specific effects of finerenone on liver fat content or histology-assessed steatohepatitis have not yet been explored in clinical trials.

Resmetirom, a liver-specific thyroid hormone receptor- β 1 agonist, has received FDA provisional approval for patients with MASLD with active steatohepatitis (NAS \geq 4) and clinically significant fibrosis (stage 2–3)²⁴⁷. Resmetirom promoted steatohepatitis resolution and reduced fibrosis compared with placebo in the MAESTRO-NASH trial⁴¹⁰, and improved MRI-PDFF scores and reduced liver stiffness without affecting heart rate or causing arrhythmias in the MAESTRO-NAFLD trial⁴¹¹. However, the effects of resmetirom in patients with MASLD with HF have not been investigated.

Vitamin E supplementation has established cardiometabolic benefits, including reduced oxidative stress and inflammation, improved endothelial function and lipid profiles, and reduced insulin resistance⁴¹². Meta-analyses of RCTs in MASLD show improvements in histological parameters and reductions in aminotransferase levels with vitamin E supplementation compared with placebo or untreated controls^{413,414}. Vitamin E is therefore recommended in the American Association for the Study of Liver Diseases MASLD guidelines¹⁰ but not in EASL–EASD–EASO guidelines²⁴⁷. A large RCT involving >39,000 healthy women found a lower incidence of HFpEF over 10.2 years with vitamin E supplementation⁴¹⁵, with mechanistic data from a small study suggesting improved vascular function in patients with HFpEF⁴¹⁶. Nevertheless, large RCTs specifically evaluating the effects of vitamin E supplementation in HFpEF are lacking.

PPAR agonists, particularly pioglitazone, improved steatohepatitis and liver fibrosis in RCTs^{417–419}, with similar findings for the pan-PPAR agonist lanifibranor in a phase IIb trial⁴²⁰. However, adverse effects, such as peripheral oedema and weight gain, have raised concerns about their use in patients with HF⁴²⁰. Until the safety of PPAR agonists in HFpEF is confirmed, detection of cardiometabolic HFpEF should be part of the diagnostic work-up before initiating treatment with these agents.

Statins and fibrates are lipid-lowering agents that have been explored in MASLD. Statins primarily reduce plasma LDL cholesterol levels and are widely recommended for cardiovascular risk reduction in patients with MASLD, even in those with compensated cirrhosis, because of their safety and the lack of evidence of hepatotoxicity. Conversely, fibrates target triglyceride levels and might be beneficial in MASLD-related dyslipidaemia, although robust data on liver-specific outcomes are lacking. Data suggest that treatment with pemafibrate, a selective PPAR α modulator, was associated with lower rates of MASLD diagnoses compared with placebo⁴²¹, whereas statins were linked to lower prevalence of MASH and MASLD in pooled analyses⁴²². Despite these promising associations, statins and fibrates are not recommended specifically for treating hepatic disease activity in MASLD owing to limited direct evidence of benefit for liver histology parameters^{10,247}.

Anti-inflammatory drugs have also been investigated in liver–heart metabolic diseases. Preclinical data from rodent models suggest a

potential benefit of colchicine in HFpEF⁴²³, and ongoing clinical trials are exploring its efficacy in patients with HFpEF⁴²⁴. However, the potential benefits of colchicine in MASLD remain unexplored. Similarly, IL-1 receptor blockade has been shown to be ineffective in HFpEF⁴²⁵, and available data do not support its use in MASLD¹⁵⁵. Further data on IL-6 blockade with ziltivekimab in patients with HFpEF are anticipated⁴²⁶, but its hepatic effects have not yet been investigated.

Outstanding questions and knowledge gaps

Despite the growing recognition of the interplay between MASLD and cardiometabolic HFpEF, several key uncertainties remain. Foremost is the issue of causality: does hepatic dysfunction actively contribute to myocardial remodelling? Or do both conditions reflect parallel consequences of systemic metabolic stress? Longitudinal studies with serial multiorgan imaging and biomarker tracking are essential to clarify directionality.

A second gap concerns the organ-specific contributions to systemic metabolic dysfunction. While the liver's role in glucose and lipid homeostasis is well established, its contribution to energy imbalance in HFpEF – via impaired ketogenesis or altered hepatokines signalling – is poorly quantified. Conversely, the potential for cardiac tissues to influence systemic metabolism through endocrine pathways, such as natriuretic peptides or cardiac-derived FGF21, remains underexplored.

Diagnostic standardization is another challenge. Whereas MASLD now has unified metabolic criteria, HFpEF remains heterogeneous and often underdiagnosed, particularly in individuals with obesity with low plasma natriuretic peptide levels. Integrated diagnostic scores capturing both hepatic and cardiac dysfunction are lacking but could substantially improve risk stratification.

Despite emerging evidence supporting the existence of a direct liver–heart communication in MASLD and HFpEF, our mechanistic understanding of this inter-organ crosstalk remains incomplete. Key mediators, such as hepatokines, lipids and bile acid metabolites, and liver-derived extracellular vesicles, are only beginning to be characterized. In particular, the molecular composition, target cell specificity and functional consequences of extracellular vesicles released from steatotic hepatocytes remain poorly defined, especially in the context of myocardial remodelling and dysfunction. Much of the current knowledge stems from preclinical models, which, while informative, might not fully recapitulate the complexity of human pathophysiology. Human studies validating these mechanisms are scarce, and large-scale, tissue-specific translational research is lacking. As a result, proposed pathways remain to be confirmed, and the extent to which liver-derived signals causally contribute to HFpEF phenotypes is yet to be established. Future work integrating omics-based profiling, spatial transcriptomics and functional validation in human tissues will be crucial to unravelling these inter-organ dynamics and their therapeutic relevance.

Therapeutically, although GLP1R agonists and SGLT2 inhibitors offer dual-organ benefits, mechanistic clarity and clinical stratification are lacking. Whether improvements in liver parameters translate into better cardiac outcomes, and which MASLD phenotypes respond best, are important unanswered questions.

Lastly, the roles of sex, age and ethnicity in shaping the liver–heart axis are understudied. Differences in fat distribution, metabolic responses and HF phenotypes across populations might influence disease expression and treatment efficacy. Addressing these gaps will be crucial to advancing precision diagnostics and therapies for patients with overlapping MASLD and cardiometabolic HFpEF.

Conclusions

Over the past decade, it has become increasingly clear that HFpEF and MASLD are not isolated disease entities but manifestations of a shared cardiometabolic disorder characterized by systemic metabolic stress and maladaptive inter-organ communication. Rather than the two conditions representing coincidental comorbidities, accumulating epidemiological and experimental evidence supports the existence of a bidirectional liver–heart axis in which hepatic metabolic dysfunction, inflammation and endocrine signalling actively shape myocardial structure, energetics and diastolic function while cardiac congestion and altered haemodynamics further aggravate hepatic stress. This reciprocal crosstalk provides a pathophysiological framework that helps to explain the higher burden of cardiometabolic HFpEF in patients with MASLD observed in clinical practice, which cannot be explained by the simple coexistence of shared metabolic risk factors. Importantly, this intertwined pathogenesis highlights why strategies focused on a single organ or risk factor have had limited success and underscores the need for a systems-level approach that integrates liver and cardiac biology to improve risk stratification, early detection and therapeutic targeting. Viewing HFpEF and MASLD through the lens of shared metabolic and inflammatory mechanisms shifts the clinical focus from the management of late-stage disease towards earlier interception of cardiometabolic stress across organs. In this context, coordinated liver–heart phenotyping and integrated clinical algorithms have the potential to inform co-management strategies for HFpEF and MASLD that are more closely aligned with disease biology, providing a practical opportunity to redefine prevention, diagnosis and treatment in two syndromes that increasingly coexist and co-evolve.

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F.C., S.P.H., S.S. and G.G.S. researched data for article. F.C., S.P.H. and G.G.S. wrote the manuscript. F.C., S.P.H., L.L., S.R. and G.G.S. provided substantial contribution to discussion of content. F.C., C.L., A.J.L., M.P., D.M.M., O.J.R., B.R., M.F., S.R., Y.W., M.V., S.H.S. and G.G.S. reviewed and/or edited the manuscript before submission.

Competing interests

G.G.S. reports consultancy service and/or has interest in Boehringer Ingelheim, Pfizer, NovoNordisk, e-Therapeutics and Sanofi. M.F. is a consultant and/or has ownership interest in Abbott, Acorai, Ajax, Alio Health, Alleivant, Artha, Astellas, Audicor, AxonTherapies, Bodyguide, Bodyport, Boston Scientific, Broadview, Cadence, Cardiosense, Cardioflow, Clinical Accelerator, CVRx, Daxor, Edwards LifeSciences, Echosens, EKO, Endotronix, Feldschuh Foundation, Fire1, FutureCardia, Gradient, Hatteras, HemodynamiQ, Impulse Dynamics, ISHI, Lumina Health, Medtronic, NovoNordisk, NucleusRx, Omega, Orchestra, Parasymp, Pharmacosmos, Presidio, Procyreon, Proton Intelligence, Puzzle, ReCor, SciRent, SCPharma, Shifamed, Splendo, Summacor, SyMap, Terumo, Vascular Dynamics, Vironix, Viscardia and Zoll.

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