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Review Article

Cardiac Syndromes in Liver Disease: A Clinical Conundrum

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Abstract

Understanding the interaction between the heart and liver is pivotal for managing patients in whom both organs are affected. Studies have shown that cardio-hepatic interactions are bidirectional and that their identification, assessment, and treatment remain challenging. Congestive hepatopathy is a condition that develops in the setting of long-standing systemic venous congestion. If left untreated, congestive hepatopathy may lead to hepatic fibrosis. Acute cardiogenic liver injury develops as a combination of venous stasis and sudden arterial hypoperfusion due to cardiac, circulatory, or pulmonary failure. The treatment of both conditions should be directed toward optimizing the cardiac substrate. Hyperdynamic syndrome may develop in patients with advanced liver disease and lead to multiorgan failure. Cirrhotic cardiomyopathy or abnormalities in pulmonary vasculature, such as hepatopulmonary syndrome and portopulmonary hypertension may also develop. Each complication has unique treatment challenges and implications for liver transplantation. The presence of atrial fibrillation and atherosclerosis in liver disease brings another layer of complexity, particularly in terms of anticoagulation and statin use. This article provides an overview of cardiac syndromes in liver disease, focusing on current treatment options and future perspectives.

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Introduction

Understanding the interaction between the heart and liver is pivotal for managing patients in whom both organs are affected. From a heart perspective, cardiac dysfunction can lead to acute and chronic liver injury, adversely affecting patient outcomes. Moreover, patients with heart and liver disease share risk factors or present with overlapping clinical syndromes (e.g., fatigue, pedal edema, and reduced exercise capacity) that make it challenging to distinguish them.[1] Also, patients with liver disease have often been excluded from cardiovascular trials, leading to scarce evidence for the efficacy and safety of many cardiovascular therapies.

From a liver perspective, the course of liver disease includes a clinically silent phase that is often referred to as compensated cirrhosis. The development and persistence of portal hypertension will cause portosystemic shunting, and decline in the metabolic and immunological functions of the liver. The resulting, increase of circulating levels of vasodilators that escape from the splanchnic into the systemic circulation causes a drop in systemic vascular resistance.[2] The lack of an immunological barrier leads to translocation of bacterial products from the gut, further augmenting splanchnic and systemic vasodilatation.[3] Autonomic dysfunction develops with progression of liver disease causing hyporeactivity of the cardiovascular system to adapt to splanchnic and systemic vasodilatation.[4] Hyporeactivity of the cardiovascular system coupled with systemic vasodilatation reduces the effective blood volume, which triggers the renin-angiotensin-aldosterone system and leads to sodium-fluid retention.[5] Abnormal neurohumoral regulation further alters renovascular autoregulation, aggravating renal vasoconstriction and worsening renal function.[6] These changes activate compensatory mechanisms of the cardiovascular system, such as increased heart rate, cardiac output, and plasma volume, to maintain adequate organ perfusion leading to hyperdynamic syndrome (HDS).[7,8] From that point, the liver disease evolves into a multiorgan syndrome affecting the heart, lungs, kidneys, and brain. However, HDS often becomes clinically evident only after the triggering event, for example bleeding esophageal varices, ascites, hepatic encephalopathy, or infection, known as decompensated cirrhosis.

Thus far, studies have shown that cardio-hepatic interactions are bidirectional and that their identification, assessment, and treatment are challenging. This article provides an overview of the cardiac syndromes in liver disease, focusing on congestive hepatopathy (CH), cardiogenic liver injury (CLI), cirrhotic cardiomyopathy (CCM), hepatopulmonary syndrome (HPS), and portopulmonary hypertension (PoPH). We also discuss the implications of atrial fibrillation (AF) and

Keywords: Liver disease; Congestive hepatopathy; Cardiogenic liver injury; Cirrhotic cardiomyopathy; Hepatopulmonary syndrome; Portopulmonary hypertension.

Abbreviations: AF, Atrial fibrillation; CLI, Cardiogenic liver injury; CVD, Cardiovascular disease; CCM, Cirrhotic cardiomyopathy; CH, Congestive hepatopathy; HCV, Hepatitis C virus; HPS, Hepatopulmonary syndrome; HDS, Hyperdynamic syndrome; LT, Liver transplantation; MCS, Mechanical circulatory support; NOACs, Non-Vitamin K antagonists; PAH, Pulmonary arterial hypertension; PH, Pulmonary hypertension; PoPH, Portopulmonary hypertension; VKA, Vitamin K antagonist.

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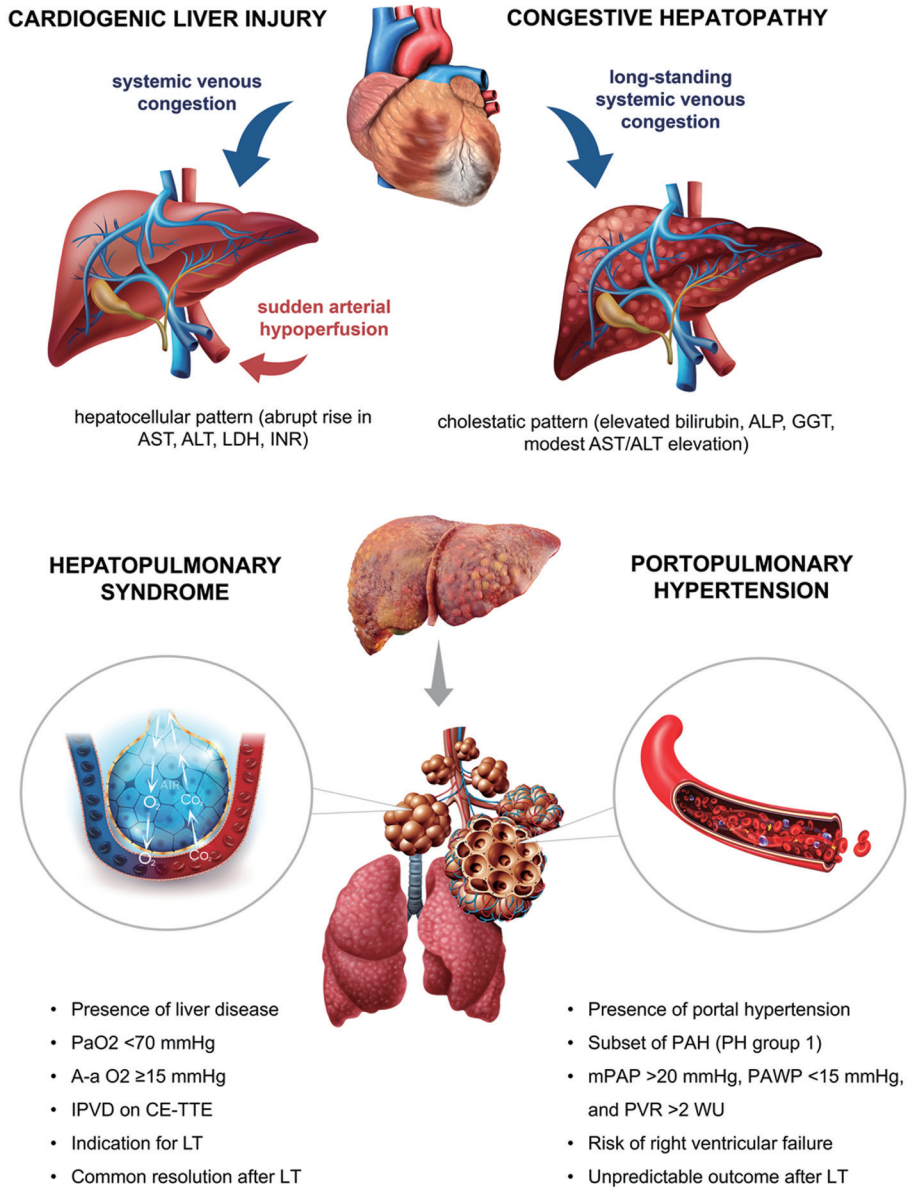

Fig. 1. Clinical features of cardiac syndromes in liver disease. Upper part of the figure depicts how a cardiac dysfunction can cause liver dysfunction including cardiogenic liver injury and congestive hepatopathy. As shown in the figure, cardiogenic liver injury is an acute event that occurs due to sudden arterial hypoperfusion superimposed on chronic venous congestion. In contrast, congestive hepatopathy is a chronic condition that develops in the setting of long-standing systemic venous congestion. The lower part of the figure depicts a cardiopulmonary complication of liver dysfunction such as hepatopulmonary syndrome. The hepatopulmonary syndrome is defined by the triad of liver disease, IPVD, and arterial deoxygenation with increased alveolar-arterial oxygen pressure gradient (A-a O_2). To illustrate dissimilarities with hepatopulmonary syndrome, the PoPH was presented in the lower part of the figure. The PoPH is defined as diagnostic triad of portal hypertension, mean pulmonary artery pressure (mPAP) >20 mmHg with PAWP≤15 mmHg, and pulmonary vascular resistance (PVR) >2 WU. Of note, PoPH can develop in patients with portal hypertension with or without liver disease. CE-TTE, contrast-enhanced transthoracic echocardiography; LT, liver transplantation; O2, oxygen; PaO2, arterial partial pressure of oxygen.

atherosclerosis in liver disease regarding anticoagulation and statin use. Finally, we provide recommendations on current treatment options and future research perspectives.

How the heart affects the liver

CH

Prevalence and etiopathogenesis: CH is a chronic condition that develops in the setting of long-standing systemic venous congestion (Fig. 1). The prevalence of CH is estimated to range from 15% to 65% in patients with chronic heart failure.[9,10] The primary cause of systemic venous congestion is right-side heart failure alone or, more commonly, with left-side heart failure. Systemic venous congestion leading to CH also prevails in cor pulmonale,[1] tricuspid regurgitation,[11] constrictive pericarditis,[12] restrictive cardiomyopathy,[1] and congenital heart disease.[13]

Patients with congenital heart disease are prone to hepatic complications because of the primary cardiac defect, concomitant pulmonary disease, or as a complication of palliative procedures like the Fontan procedure,[13] The Fontan pro-

cedure separates the systemic and pulmonary circulation in patients with single-ventricle physiology by creating a bypass between systemic venous return and pulmonary arteries. Hepatic dysfunction after the Fontan procedure results from an interplay between hypoxia and systemic venous congestion because of narrowing of the Fontan conduit over time, development of pulmonary hypertension (PH), and dysfunction of the systemic ventricle.[13]

The pathophysiological mechanisms involved in CH. First, the lack of valves in hepatic veins allows a backward transfer of elevated pressure directly from the right atrium and inferior vena cava to hepatic veins.[14] Consequently, intrahepatic cholestasis results from increased sinusoidal pressure and disruption of the tight intercellular junctions in the biliary canaliculi.[15] Injury to the biliary system causes reactive inflammation leading to hepatic fibrosis. Second, stagnant blood flow and elevated sinusoidal pressure increase fluid loss into the third space and the formation of sinusoidal microthrombi, which also facilitates fibrogenesis.[16] Finally, patients with heart failure often have hepatic steatosis secondary to obesity, diabetes, and hyperlipidemia or have anemia, all of which predispose the liver to hypoxic injury leading to further cell necrosis.[17] A histological hallmark of CH is centrilobular cell necrosis that may eventually lead to hepatic fibrosis.[18]

Clinical manifestations and diagnosis

Most patients with CH are asymptomatic, so CH is usually discovered as abnormal hepatic biochemistry in patients with cardiac diseases. It is characterized by modest aminotransferase elevation of up to three-times normal, decreased albumin levels, and a predominant cholestatic pattern of elevated bilirubin, gamma-glutamyl transferase, and alkaline phosphatase.[19,20] If symptomatic, patients may experience dull right upper quadrant pain because of stretching of the liver capsule. Approximately one in four patients presents with ascites, usually without splenomegaly.[21] In patients with ascites, a serum-to-ascites albumin gradient ≥1.1 g/dL and total ascites protein of >2.5 g/dL have 63% sensitivity and 93% specificity for a cardiac cause of ascites. The diagnostic accuracy improves when incorporating serum or ascites B-type natriuretic peptide (BNP) level.[22]

No imaging study is pathognomonic for CH. However, different imaging modalities have been investigated to assess CH in patients with heart failure. Spectral Doppler studies have shown an increased portal vein pulsatility and hepatic arterial resistance in patients with right-sided heart failure.[23] Studies on shear wave elastography have demonstrated a good correlation between liver elasticity and advanced heart failure[24] and right-sided filling pressures.[25] Interestingly, authors reported a dose-dependent relationship between dispersion slope and heart failure severity even preceding abnormal hepatic biochemistry.[24] However, the prognostic and therapeutic utility of Doppler ultrasonography and elastography remains to be proven in patients with heart failure.

Management and prognosis

The primary goal of the treatment of CH is to optimize the underlying substrate that has led to hepatic dysfunction. Diuretic therapy is the primary therapy for right-sided-volume overload to improve CH. Furthermore, a post hoc analysis of the PARDIGM-HF trial demonstrated that sacubitril/valsartan, not only reduced the risk of death and rehospitalization, but also improved all measures of liver function compared with enalapril in patients with reduced ejection fraction.[26] The current American guidelines on valvular heart disease recommend valve surgery in patients with symptomatic severe tricuspid regurgitation to alleviate systemic venous and hepatic congestion and decrease reliance on diuretics.[27] In patients refractory to medical therapy, mechanical circulatory support (MCS) and heart transplantation improve liver dysfunction.[28] However, the level of CH severity that determines the indication for MCS or heart transplantation is unclear.

The primary use of the model for end-stage liver disease (MELD) score has been to prioritize patients on the waiting list for liver transplantation (LT). However, studies have shown that MELD and MELD-XI, excluding the international normalized ratio (INR) for patients on anticoagulation, scores also indicates a poor prognosis in patients undergoing heart transplantation or left ventricular assist device implantation.[29,30] Farr *et al*.[31] reported improved risk stratification of MELD-XI score when combined with liver biopsy in heart transplant candidates. Recently, a novel histological congestive hepatic fibrosis scoring system was validated to assess the severity and progression of CH.[32] This 4-point grading system was developed using liver biopsies of patients with various cardiac etiologies, including congenital, ischemic, and valvular heart disease.[33] The score was reproducible and correlated well with right atrial and ventricular dilatation, and right atrial pressure measured during right heart catheterization and estimated by echocardiography.[32,33]

Takent together, the clinical importance of CH is threefold: as a marker of advanced cardiac disease, as a condition that can progress to liver cirrhosis, and as a risk factor predisposing the liver to cardiogenic injury as discussed below. Finally, Table 1 summarizes our recommendations for treatment of CH based on currently available evidence.

CLI

Prevalence and etiopathogenesis

CLI (e.g., shock liver, ischemic, or hypoxic hepatitis) is an acute condition that occurs as a combination of venous stasis and sudden hepatic hypoperfusion in the setting of acute cardiac, circulatory, or pulmonary failure (Fig. 1).[34,35] The prevalence of CLI is estimated at 20 to 30% in patients with acute heart failure.[36] However, that may be less than the true prevalence because CLI remains unrecognized if unsuspected. A meta-analysis by Tapper *et al*.[37] found that an acute cardiac event preceded ischemic hepatitis in 78% of patients and septic shock in 24%, with an overall in-hospital survival rate of 51%. Importantly, even a mild hemodynamic disturbance can lead to liver injury in patients with prior venous congestion because of exhausted compensatory mechanisms of sinusoidal endothelial cells and hepatocytes to increase oxygen extraction from the blood.[38] This is why patients with chronic venous stasis are at a high risk of experiencing CLI.

Clinical manifestations and diagnosis

CLI is clinically characterized by abrupt increases of lactate dehydrogenase (LDH) and hepatic aminotransferases of more than 20-fold, and prolongation of prothrombin time within the first 3 days from the index event.[39] CLI can also present with a clinical picture like acute viral hepatitis or acute liver failure. An increase of LDH and aminotransferase levels with an ALT/LDH ratio of <1.5 and a rapid decline to normal values once the underlying substrate has been optimized are highly suggestive of hypoxic injury.[40] In acute HF, studies have shown that the cholestatic liver enzyme pattern correlates strongly with signs of congestion, whereas the hepatocellular pattern correlates more with systemic hypoperfusion.[39]

Table 1. Summary of recommendations for treatment of cardiac syndromes in liver disease based on current evidence

Congestive hepatopathy
Treat underlying cardiopulmonary disease.
Diuretic therapy should be used to optimize right-sided filling pressures.
Consider starting or switching from ACEi/ARBs to sacubitril/valsartan in patients with heart failure regardless of ejection fraction.
Patients with congestive hepatopathy due to severe tricuspid regurgitation should be evaluated for transcatheter or surgical valve therapy.
Patients with congestive hepatopathy and heart failure with ascites should be treated with combination of loop diuretics and aldosterone antagonist at natriuretic dose.
Cardiogenic liver injury
Initial therapy is correction of an underlying cardiac, circulatory, or pulmonary failure.
Acute heart failure with volume overload should be treated with diuretics to reduce backward venous pressure while maintaining adequate systemic perfusion
Norepinephrine should be the first-line vasopressor for patients in circulatory shock.
Dobutamine should be the first-line inotropic agent for patients in circulatory shock unless specific scenarios (e.g., milrinone might be a better option in patients with pulmonary hypertension).
MCS should not be delayed for patients in circulatory shock refractory to medical therapy.
In refractory cases, patients should be evaluated for liver transplantation.
Cirrhotic cardiomyopathy
Volume overload should be treated with restriction of sodium intake and diuretic therapy in patients with hyperdynamic syndrome or cirrhotic cardiomyopathy.
Patients with cirrhotic cardiomyopathy and ascites should be treated with combination of loop diuretics and aldosterone antagonist at natriuretic dose.
Patients with cirrhotic cardiomyopathy and grade 3 ascites should be treated with large volume paracentesis.
Consider using beta blockers with proven clinical benefit in patients with heart failure with reduced ejection fraction for treatment of cirrhotic cardiomyopathy. Consider carvedilol as the first-line beta blocker in patients with cirrhotic cardiomyopathy at risk of variceal bleeding.
Reduce dose or hold beta-blockers in patients with ascites if hypotension or worsening renal function.
ACEi/ARBs should be withheld in patients with decompensated cirrhosis.
Hepatopulmonary syndrome
Supportive management including oxygen therapy when arterial PaO_2<60 mmHg.
Liver transplantation is the effective treatment for hepatopulmonary syndrome to improve survival.
Portopulmonary hypertension
Patients with confirmed diagnosis of portopulmonary hypertension should be evaluated for drugs with shown benefit in treatment of pulmonary artery hypertension. Type of agent should be chosen on an individual basis after considering adverse drug effects.
Treatment goal should be keeping PVR normal or near normal and mPAP<35mmHg.
All patients with portopulmonary hypertension should be monitored closely and periodically evaluated for liver transplantation.
Atrial fibrillation and liver disease
NOACs are preferred over the Vitamin K antagonists for prevention of thromboembolism in patients with liver disease and non-valvular atrial fibrillation.
NOACs are not recommended in Child-Pugh class C and should be used with caution in Child-Pugh class B.
Periodical assessment of the patient's severity of liver disease and thromboembolic risk including a shared decision making with the patient when discussing risks and benefits of anticoagulation.
Cardiovascular risk and metabolic dysfunction-associated fatty liver disease
Patients with MAFLD should be followed closely and periodically evaluated for modifiable cardiovascular risk factors such as obesity, diabetes, dyslipidemia, and hypertension.
When indicated, statins should be given at their conventional doses in patients with compensated cirrhosis.
Statins should be avoided in patients with acute liver injury (including cardiogenic liver injury) and decompensated cirrhosis or Child-Pugh class C.

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MAFLD, metabolic dysfunction-associated fatty liver disease; mPAP, mean pulmonary artery pressure; NOAC, non-vitamin K antagonist; PaO_2, partial pressure of oxygen; PVR, pulmonary vascular resistance.

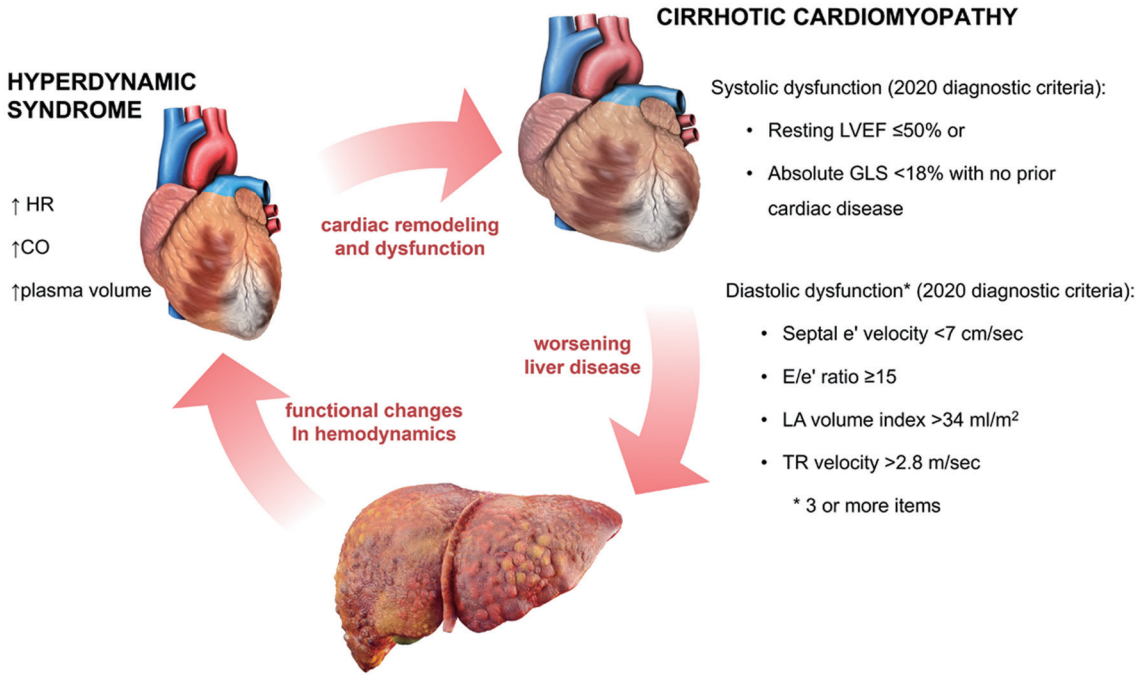

Fig. 2. Evolution of cardiac dysfunction from hyperdynamic syndrome to cirrhotic cardiomyopathy. In advance stage, the liver disease leads to splanchnic and systemic vasodilatation, disruption of immunological barrier, gut bacteria translocation, and autonomic dysfunction, evolving into a multiorgan syndrome affecting the heart, lungs, kidneys, and brain. These changes activate the compensatory mechanisms of the cardiovascular system (increase heart rate, cardiac output, and plasma volume) to maintain adequate organ perfusion leading to hyperdynamic syndrome (HDS). In subgroup of patients, liver disease can further affect the heart muscle leading to cirrhotic cardiomyopathy in the absence of known cardiovascular disease that would explain myocardial abnormalities. The 2020 cirrhotic cardiomyopathy diagnostic criteria for systolic dysfunction include either resting left ventricular ejection fraction ≤50% or absolute global longitudinal strain (GLS) <18% in the absence of known cardiac disease. The diagnostic criteria for advanced diastolic dysfunction include three or more echocardiographic changes such as septal e' velocity <7 cm/sec, E/e' ratio≥15, left atrial volume index >34 mL/m^2, and TR velocity >2.8 m/sec (in the absence of pulmonary hypertension). CO, cardiac output; LVEF, left ventricular ejection fraction.

Management and prognosis

Given that a meta-analysis of 1,782 patients with ischemic hepatitis did not reveal systemic hypotension in 43% of cases, proper management of CLI should start with suspicion of this condition.[37] Of note, elevated serum phosphate levels and the development of advanced hepatic encephalopathy in patients with CLI have a poor prognosis.[41] The mortality risk in patients with CLI persists even if hepatic biochemistry returns to normal values after an acute adverse event.[42]

The cornerstone of the management of CLI is an aggressive correction of an underlying condition. Treatment varies depending on the type of cardiac, circulatory, or pulmonary failure. For example, acute HF patients with predominant volume overload should be aggressively treated with diuretics to reduce backward venous pressure while maintaining adequate systemic perfusion. Aggressive correction of hypoxia while keeping organ perfusion intact in patients with respiratory failure is warranted. It should be noted that the splanchnic circulation is the weakest link of tissue hypoperfusion because of compensatory vasoconstriction to maintain the perfusion of vital organs such as the heart and brain. If it persists, ischemic injury to the endothelial barrier of the gut will develop, causing bacterial translocation and activation of systematic inflammatory response and multiorgan failure.[43] Therefore, patients with CLI because of sudden hepatic hypoperfusion should be aggressively treated with vasoactive and/or inotropic agents. However, the choice of specific agents in CLI is controversial. In cardiogenic shock, epinephrine has been linked with an increased rate of arrythmia, refractory shock, and decreased splanchnic perfusion compared with norepinephrine.[44,45] Similarly, dopamine treatment was found to induce more arrhythmia than norepinephrine[46] and increased 28-day mortality in patients with cardiogenic shock.[47] Norepinephrine is the vasopressor of choice for treating septic shock.[48] Dobutamine is an inotropic agent of choice[49] because it increases cardiac output and improves splanchnic circulation in circulatory shock.[50] However, a recent trial comparing dobutamine to milrinone for treating cardiogenic shock found no difference in in-hospital death.[51] Milrinone is often preferred for treating patients with severe PH because of its positive effects on pulmonary artery pressure and right ventricular function. However, milrinone has a less desirable pharmacological profile for minute-to-minute titration than dobutamine because of its longer half-life. Finally, MCS to correct tissue oxygenation and the metabolic needs of patients in circulatory shock and refractory to medical therapy should not be delayed. In refractory cases, patients should be evaluated for LT. Table 1 summarizes our recommendations for the treatment of CLI based on currently available evidence.

How the Liver Affects the Heart

CCM

Prevalence and etiopathogenesis: CCM describes a diseased heart muscle in the setting of cirrhosis and in the apparent absence of cardiovascular disease (CVD) that could explain myocardial abnormalities (Fig. 2).[52] The estimated prevalence of CCM in patients with liver disease varies from 26% to 81% because of differences in the descriptive cri-

teria.[53,54] The current understanding is that CCM develops independently of the etiology of cirrhosis, but its severity is relative to the degree of liver damage.[54] Several pathophysiological mechanisms have been implicated in the development and progression of CCM.[55] However, the HDS has a key role (see the Introduction).[56] There may be a link between reduced baroreceptor response and remodeling of left ventricular hypertrophy in patients with liver disease.[57] In addition, the cirrhotic proinflammatory state leading to increased cardiomyocyte apoptosis and contractile dysfunction represents another critical component in the pathogenesis of CCM.[56] Additional research is needed to further clarify the mechanism for the development and progression of CCM.

Clinical manifestations and diagnosis: Diagnostic criteria for CCM were first proposed in 2005 and redefined in 2020 with the addition of new recommendations on myocardial strain.[55] The 2020 diagnostic criteria for systolic dysfunction include either a resting left ventricular ejection fraction ≤50% or an absolute global longitudinal strain (GLS) absolute value of <18% in the absence of known cardiac disease.[58] The diagnostic criteria for advanced diastolic dysfunction include three or more echocardiographic changes, such as a septal e' velocity of <7 cm/sec, E/e' ratio≥15, left atrial volume index >34 mL/m^2, or a tricuspid regurgitation (TR) velocity >2.8 m/sec in the absence of PH.[58] The 2005 diagnostic criteria for CCM included supportive criteria such as chronotropic incompetence (inability to increase heart rate adequately during exercise to match cardiac output to metabolic demands), QT interval prolongation, electromechanical uncoupling (systolic time intervals or aortic pressure-ECG trace desynchrony), elevated brain natriuretic peptide or troponin I, and an enlarged left atrium.[55] However, those criteria are not supported by the latest CCM definition. Elevated high sensitivity troponin T and NT-proBNP levels have been associated with the severity of liver disease, portal hypertension, and survival,[59,60] but no prognostic scoring has incorporated these two biomarkers regarding liver cirrhosis and CCM, which may be worth investigating in the future.

Management and prognosis: CCM has an unfavorable prognosis, and management with established HF therapies is challenging because data from high-quality CCM trials are lacking.[61] Volume overload in HDS patients is treated by restriction of sodium intake and judicious use of diuretics. Patients with cirrhosis and ascites should be treated with a combination of loop diuretics and aldosterone antagonists at natriuretic doses (spironolactone 100–400 mg/day) to counteract secondary hyperaldosteronism in HDS.[62] That is important because the indicated cardiac doses of spironolactone (25–50 mg/day) do not have natriuretic effect. Studies of aldosterone antagonists have also shown improvement of left ventricular remodeling and hepatic hemodynamics by lowering the hepatic venous pressure gradient,[63] and are included in both the American and British guidelines for managing ascites in cirrhosis along with large volume paracentesis in patients with grade 3 ascites.[64,65]

The QT interval is prolonged in CCM. It is often seen in patients with cirrhosis without CCM, and is associated with a lower survival rate.[66] Patients with cirrhosis are also at risk of acute gastrointestinal (GI) bleeding, which may further prolong the QT interval.[67] Small observational studies have reported that nonselective beta-blockers like propranolol and nadolol shortened the QT interval in some patients with cirrhosis, but they did not investigate the effect on survival.[68,69] A recent trial of metoprolol succinate in 78 patients with CCM did not find either a beneficial effect on cardiac remodeling or adverse effects during 6 months of follow-up. Half of the patients in the placebo and treatment arms were already on propranolol at inclusion. Given the limitations of this study, a beneficial effect of metoprolol succinate on CCM could not be excluded. Additional studies with more participants and longer follow-up are needed to investigate the effectiveness of beta-blockers in CCM. A recent meta-analysis reported that carvedilol was effective and as safe as a nonselective beta blocker for the primary and secondary prevention of variceal bleeding in cirrhotic patients.[70] No trials have investigated the use of carvedilol to treat CCM. Current American and British guidelines recommend beta-blockers to prevent variceal bleeding in patients with ascites, with dose reduction or discontinuation in patients with hypotension or worsening renal function because of increased risk of exacerbation of systemic vasodilatation and organ hypoperfusion.[65]

Agents like terlipressin, which is used to treat hepatorenal syndrome, depress cardiac function and may unmask latent cardiac dysfunction.[71] A recent randomized clinical trial (RCT) reported that dobutamine reversed the cardiosuppressive activity of terlipressin in patients with hepatorenal syndrome, but did not improve renal function.[72] The study included only 25 patients without an established diagnosis of CCM, and no invasive hemodynamic parameters were recorded. Furthermore, the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) is limited in patients with decompensated cirrhosis as they may worsen the systemic vasodilatory state.[65] A recent nationwide propensity-matched cohort of patients with cirrhosis did not find an association between ACEi/ARBs and renal failure in cirrhotic patients without ascites.[73] However, the authors reported an increased risk of renal failure in cirrhotic patients with ascites regardless of ACEi/ARB use. The use of sacubitril/valsartan in CCM has not been investigated. Despite their known clinical benefits in patients with heart failure, there is limited data on using sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with cirrhosis.[74] Studies of the use of SGLT2 inhibitors for treating ascites are currently underway.

CCM may worsen the outcome of invasive procedures such as transjugular intrahepatic portosystemic shunt (TIPS) and LT.[75] Although controversial, there is evidence that LT can lead to a reversal of CCM and shortening of the QT interval.[76] However, the resolution of CCM after LT took up to 6 months, which required close postoperative monitoring.[77] It would be reasonable to repeat echocardiography 3 to 6 months after LT or TIPS in stable patients with CCM. Table 1 summarizes our recommendations for the treatment of HDS and CCM based on currently available evidence.

HPS

Liver disease and portal hypertension may affect pulmonary circulation in two distinct ways. A patient with liver disease can develop HPS characterized by intrapulmonary shunt with hypoxemia, or PoPH characterized by pulmonary arterial hypertension (PAH). Nevertheless, overlap between HPS and PoPH may also occur.[78] Despite both conditions often presenting similarly with dyspnea, treatment strategy and clinical prognosis differ significantly. It should be noted that both conditions have specific perioperative implications for LT which are discussed elsewhere.[79,80]

Prevalence and etiopathogenesis: HPS develops as a result of alterations in the pulmonary microcirculation that impair gas exchange in the setting of liver disease and in the absence of cardiopulmonary disease (Fig. 1).[81,82] The estimated prevalence of HPS is around 25%, with a wide range depending on the diagnostic methodology used.[83,84] HPS usually develops in patients with chronic liver disease with portal hypertension, but it has also been reported after

Table 2. Hemodynamic patterns in patients with liver disease and elevated mean pulmonary artery pressure

Cardiac syndrome	mPAP[b]	PAWP[b]	PVR[b]	CO[b]
Hyperdynamic syndrome	↑	WNL	↓	↑↑
Cirrhotic cardiomyopathy[a]	↑↑	↑	↑	↓
Portopulmonary hypertension	↑↑	WNL	↑	↓

[a]Cirrhotic cardiomyopathy with left ventricular dysfunction; [b]Parameters recorded during the right/left heart catheterization. CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WNL, within normal limits.

CLI.[85,86] The pathophysiology of HPS includes an increase in the number and size of capillary and precapillary vessels that causes a ventilation-perfusion mismatch leading to hypoxemia.[87] Experimental data have demonstrated increased levels of nitric oxide synthase, endothelin-1, and TNF-alfa in the pulmonary vasculature of patients with HPS.[88,89] Angiogenesis also appears to play a role in HPS pathogenesis, shown by an increase in pulmonary vessels along with activation of VEGF-A angiogenic pathways.[90] Nevertheless, additional study is needed to characterize the mechanism underlying HPS.

Clinical manifestations and diagnosis: HPS is defined by a triad of liver disease, intrapulmonary vascular dilatation (IPVD), and arterial deoxygenation with increased alveolar-arterial oxygen pressure gradient.[82] Patients need to meet all three criteria to establish a diagnosis. The diagnostic criteria of the International Liver Transplant Society Practice Guidelines include the presence of IPVD demonstrated by a positive contrast-enhanced transthoracic echocardiography (CE-TTE) showing a delayed appearance of intravenously injected microbubbles in the left heart three or more cardiac cycles after visualization of microbubbles in the right heart.[82,91] Arterial deoxygenation is defined as arterial hypoxemia (PaO_2<70 mmHg) with an alveolar-arterial oxygen gradient (AaO_2) ≥15 mmHg, or >20 mmHg if >64 years of age.[82] Patients with HPS often complain of dyspnea on exertion or at rest, and may present with digital clubbing, cyanosis, and diffuse telangiectasias at advance stages.[82] HPS-specific findings are worsening dyspnea and oxygen desaturation, a decrease of PaO_2 of >4 mmHg or SpO_2 of >5%, when moving to an upright position and relief by recumbency. These findings are also known as platypnea-orthodeoxia syndrome.[84] Regardless of symptoms, all liver disease patients should undergo pulse oximetry screening.[82] If SpO_2 is below 96%, arterial blood gas analysis is needed to confirm arterial deoxygenation, and CE-TTE is needed to confirm the presence of IPVD.

Management and prognosis: Once the diagnosis is made, the HPS should be graded according to arterial PaO2 as this would dictate further management and indications for LT.[80,92] There are no currently effective medical therapies for HPS except supportive management, including oxygen therapy when arterial PaO2 drops below 60 mmHg.[82,93] LT is the most widely studied and only effective treatment for HPS that has been proven to improve survival.[83,94] Finally, resolution of HPS after LT may take several months and requires continued supplemental oxygen therapy. Table 1 summarizes our recommendations for the treatment of HPS based on currently available evidence.

PoPH

Prevalence and etiopathogenesis: PoPH is defined as the presence of PH in the setting of portal hypertension with or without liver disease (Fig. 1),[82] and is classified as a subgroup of PAH by the World Health Organization (WHO).[95] The development of PoPH is not associated with the etiology or the severity of the liver disease.[80] Approximately 2 to 6% of patients with portal hypertension develop PoPH, which requires right heart catheterization to establish a diagnosis and support treatment decisions.[95] The pathophysiology of PoPH is unclear, but autoimmune factors and smooth muscle proliferation in the pulmonary vasculature may be involved.[96] Inflammatory and vasoconstrictive mediators in the splanchnic circulation and endothelial dysfunction caused by shear stress in HDS may also be involved in PoPH.[82] Additional experimental data are needed to add to our understanding of pathogenesis of PoPH and to test the relevance of newer vasoactive medications.

Clinical manifestations and diagnosis: Three clinical conditions should be considered in patients with liver disease who present with dyspnea and elevated mean pulmonary artery pressure (mPAP) including PoPH, HDS, and CCM (Table 2). It is critical to differentiate these clinical entities as their prognosis and treatment defer tremendously. In the most recent European Society of Cardiology and European Respiratory Society guidelines on PH, the diagnostic triad of PoPH includes the presence of portal hypertension, an mPAP of >20 mmHg with a pulmonary artery wedge pressure (PAWP) of ≤15 mmHg, and a pulmonary vascular resistance (PVR) >2 Woods units (WU) in the absence of other causes of precapillary PH including lung disease or chronic thromboembolic disease.[95] However, it should be noted that patient selection in existing studies of PoPH was based on old diagnostic criteria, with mPAP≥25 mmHg, PAWP≤15 mmHg, and PVR >3 WU. Besides right heart catheterization, echocardiography is an important follow-up tool to monitor right ventricle function which is an important determinant of exercise capacity and outcome in patients with PoPH.[95]

Management and prognosis: Although PoPH is categorized under broader group of PAH, several management points should be appraised. First, patients with PoPH have a low response rate to pulmonary vasoreactivity testing intended to identify candidates suitable for high-dose calcium channel blockers.[97] Second, patients with PoPH have been excluded from almost all RCTs investigating PAH therapies, including nitric oxide, prostacyclin analogs, endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitors (PDE-5i), and guanylate cyclase stimulators.[95,98] So far, the PORTICO study has been the only RCT specifically designed for patients with PoPH, which enrolled 85 PoPH patients with mean MELD score of 8.5 (44% Child-Pugh class A, and 13% class B).[99] Investigators have demonstrated that macitentan significantly improved PVR compared with placebo during 12 week of follow-up, but no changes in secondary outcomes such as NT-proBNP level, 6-minute walking distance, or WHO Functional Class were observed.

Another prospective registry of 637 patients with PoPH and median MELD score of 11 (57% Child-Pugh class A and 33% class B) investigated the efficacy of ERA and PDE-5i for treatment of PoPH.[100] After a median treatment of 4.5 months, both ERA and PDE-5i in combination or as monotherapy improved 6 minute walk distance, WHO-FC, cardiac output, and PVR, with overall survival of 51% at 5 years. The

5-year survival of PoPH patients who eventually underwent LT was 81%. The most recent European guidelines recommend initial monotherapy with drugs approved for PAH for PoPH patients (class IIa), but discourage their use in patients with portal hypertension and unclassified PH (i.e., mPAP>20 mmHg, elevated CO, PAWP≤15, and PVR≤2.0 WU).[95] European guidelines do not recommend anticoagulation in PoPH because of increased bleeding risk and unproven survival benefits. Finally, studies have suggested that as beta-blockers worsen pulmonary hemodynamics and cardiopulmonary reserve in patients with PoPH they should not be used to lower portal pressure.[101] Unlike HPS, which often improves after LT, the postoperative prognosis of PoPH is highly unpredictable and varies with the severity of the disease. Therefore, the International Liver Transplant Society has proposed a preoperative goal of pulmonary vasodilators as reduction of mPAP to <35 mmHg and PVR to <5 WU, or an mPAP of ≥35 mmHg and a PVR of <3 WU, to minimize the risk of graft failure and improve survival.[82] However, the proposed goals require further validation in prospective studies. The European guidelines recommend that LT to be considered in PoPH patients as long as the PVR is normal or near normal with pulmonary vasodilators (class IIa).[95] Finally, PoPH patients should be referred to centers with expertise in managing both conditions. Table 1 summarizes our recommendations for the treatment of PoPH based on currently available evidence.

AF and Liver Disease

AF is the most common arrhythmia and the primary cause of cardioembolic events,[102] and chronic liver disease is associated with an increased risk of new-onset AF.[103] Published data has shown patients with AF with liver disease have significantly higher rates of stroke, major bleeding, and all-cause death than patients with AF without liver disease. A significant contributor to the differences in rate may be undertreatment of patients with AF and liver disease because of fear of bleeding.[104] Despite its use as a standard therapy for stroke prevention in patients with AF, its use is challenging in liver disease because decreases of both anticoagulation and clotting factors make the true coagulative state variable and unpredictable.[105] Vitamin K antagonists (VKAs) are used to reduce the risk of thromboembolic events in AF[106] and were also shown to be effective for anticoagulation compared with no treatment in patients with liver disease.[107] As VKAs increase the risk of major and non-major bleeding events in patients with liver disease,[107] non-vitamin K antagonists (NOACs) are the standard anticoagulation treatment for patients with AF.[106] Patients with AF and liver disease are underrepresented in RCTs of the efficacy and safety of NOACs, but cohort studies have consistently shown reported the non-inferiority of NOACs to for stroke prevention in liver disease, and a safer bleeding profiles compared with VKA.[108,109]

A recent meta-analysis of 4,011 patients with AF and liver cirrhosis and a pooled analysis of 20,042 patients with AF and liver disease (mean Child-Pugh score of 7.3±2.4, and MELD score of 10±6.4) found that the efficacy of NOACs for reducing the risk of stroke or thromboembolism was similar to that of VKAs, with a significantly lower risk of major and intracranial bleeding.[107,110] A subgroup analysis by Chen *et al*.,[107] found that patients treated with apixaban or dabigatran had significantly decreased rates of GI bleeding. The results are promising but were obtained in observational studies. RCTs are needed to provide the final answer. NOACs are not currently recommended in Child-Pugh class C, and should be used with caution in Child-Pugh class B.[110,111] We recommend periodical assessment of the severity of liver disease and thromboembolic risk when discussing the risks and benefits of anticoagulation with the patient. Table 1 summarizes our recommendations on the use of anticoagulation in patients with AF with liver disease based on currently available evidence.

Atherosclerosis and Liver Disease

Cardiovascular risk and metabolic dysfunction-associated fatty liver disease (MAFLD)

MAFLD, formerly known as nonalcoholic fatty liver disease (NAFLD), has an estimated global prevalence of 51% in overweight or obese individuals.[112] The recent name change is a shift from a diagnosis of exclusion to one that emphasizes the metabolic dysfunction leading to fatty liver disease.[113] Moreover, previous reports suggested that the MAFLD criteria are better than the NAFLD criteria for identifying patients with worsening atherosclerotic CVD risk. The MAFLD criteria are evidence of hepatic steatosis and one of the following, overweight or obesity, diabetes, or evidence of metabolic dysregulation.[114] NAFLD is strongly associated with coronary heart disease even after adjusting for risk of coronary heart disease and presence of features of metabolic syndrome.[115] Likewise, coronary events are the leading cause of death in NAFLD patients.[116] Therefore, patients with MAFLD should be followed closely and periodically evaluated for modifiable cardiovascular risk factors such as obesity, diabetes, dyslipidemia, and hypertension.[117] To that end, lifestyle modifications and exercise should be emphasized to improve insulin sensitivity even without weight reduction, and statins should be prescribed for those with increased CVD risk, following the current guidelines.[118]

Statins and liver disease

Statins are used to treat hypercholesterolemia and have proven benefits in reducing cardiovascular morbidity and mortality.[119] However, fear of hepatotoxicity has led to under prescription in liver disease patients[120] despite the demonstrated safety of statins in patients with nonalcoholic steatohepatitis (NASH).[121–123] Liver disease is not considered to increase the risk of statin side effects, and the benefits outweigh the low risk of serious liver injury.[124] Several small RCTs and cohort studies showed that statins use were safe in patients with chronic liver disease,[125–127] and the trial results are supported by a meta-analysis of 121,058 patients with chronic liver disease showing that statins were not only safe but were also associated with a decreased risk of hepatic decompensation and mortality.[128] Statins care thus considered safe when administered at the indicated doses to patients with chronic liver disease, including those with compensated cirrhosis.[129] However, trials of the safety of statins in decompensated disease are limited. A recent trial of pravastatin in 160 Child-Pugh class B patients found no safety issues during the follow-up period,[130] but larger RCTs are needed to confirm the safety and efficacy of different classes of statins in Child-Pugh class B. According to the Statin Liver Safety Task Force updated document, statins should be avoided in patients with acute liver injury and decompensated cirrhosis or Child-Pugh class C.[131] Table 1 summarizes our recommendations for the management of cardiovascular risk in MAFLD based on currently available evidence.

Cardiovascular Risk and Chronic Hepatitis C Virus (HCV) Infection

Chronic HCV patients have a higher prevalence of prema-

ture atherosclerosis than the general population, with HCV RNA and HCV-related steatosis being independent risk factors associated with atherosclerosis.[132] At least one study found that HCV patients had a significantly lower prevalence of hypertension, diabetes, and hyperlipemia than controls, but had a higher risk of coronary artery disease, even after adjustment for the risk factors of coronary artery disease.[133] Another study reported a decreased risk of stroke in chronic HCV patients taking interferon-based therapy, suggesting that HCV itself is actively involved in the pathogenesis of ischemic events.[134] Attention to CVD should not be neglected when caring for HCV patients. Finally, one should be aware of the drug interaction of statins with direct-acting antivirals for HCV, which is described elsewhere.[135]

Conclusion

This review highlights the complexity of cardiac syndromes in liver disease, particularly in patients with advanced age and multiple comorbid conditions. Such patients require multidisciplinary care involving both hepatologists and cardiologists beginning in the early stages of disease. Implementing a clinical pathway to ensure timely clinical decision making and appropriate management is the key to improving short- and long-term outcomes in patients with liver disease. Studies of cardio-hepatic interactions as a multiorgan syndrome rather than as only a liver-specific condition are recommended, including consideration of epigenetic data for targeted molecular treatments and the development of suitable animal models. Well-designed RCTs are needed to provide answers to the current questions regarding management of decompensated liver disease and preventive strategies for compensated liver disease.

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Conflict of interest

NP has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Drafting of the manuscript (MB, PL), critical revision of the manuscript for important intellectual content (NP, MK). All authors have made a significant contribution to this study and have approved the final manuscript.

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