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REVIEW

# Cardiac dysfunction in patients with cirrhosis and acute decompensation

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## Abstract

The prevalence of cirrhotic cardiomyopathy (CCM) has been reported as high as 60%–70% in patients with liver cirrhosis and is associated with various negative outcomes. There has been a growing understanding of CCM over recent years. Indeed, the development of imaging techniques has enabled new diagnostic criteria to be proposed by the Cirrhotic Cardiomyopathy Consortium. However, important unanswered questions remain over pathophysiological mechanisms, optimal diagnostic modalities and potential treatment options. While there has been an increasing volume of literature evaluating CCM, there is a lack of clarity on its implications in acute decompensation, acute-on-chronic liver failure and following interventions such as transjugular intrahepatic portosystemic shunt insertion and liver transplantation. This review aims to summarise the literature in these challenging domains and suggest where future research should focus. We conclude that systemic inflammation and structural myocardial changes are likely to be crucial in the pathophysiology of the disease, but the relative contribution of different components remains elusive. Furthermore, future studies need to use standardised diagnostic criteria for CCM as well as incorporate newer imaging techniques assessing both myocardial structure and function. Finally, while specific treatments are currently lacking, therapeutics targeting systemic inflammation, microbial dysbiosis and bacterial translocation are promising targets and warrant further research.

**KEYWORDS**
cirrhotic cardiomyopathy, decompensated cirrhosis

**Abbreviations:** ACLF, acute-on-chronic failure; AD, acute decompensation; BNP, brain natriuretic peptide; CCM, cirrhotic cardiomyopathy; CI, cardiac index; CO, cardiac output; DD, diastolic dysfunction; DRA, diuretic responsive ascites; E/A ratio, ratio of early-to-late (atrial) phases of ventricular filling; E/e' ratio, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; ECV, extracellular volume fraction; EF, left ventricular ejection fraction; EIVPD, ejection intraventricular pressure difference; FXR, farnesoid X receptor; GI, gastrointestinal; GLS, global longitudinal strain; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome–acute kidney injury; iNOS, inducible nitric oxide; LAVI, left atrium volume index; LBP, lipopolysaccharide-binding protein; LT, liver transplantation; LVSWI, left ventricular stroke work index; MACE, major adverse cardiac events; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; NF-kB, nuclear factor-kB; NO, nitric oxide; RA, refractory ascites; SBP, spontaneous bacterial peritonitis; TDI, tissue Doppler imaging; TIPS, transjugular intrahepatic portosystemic shunt; TLR4, toll-like receptor 4; TNFα, tumour necrosis factor-alpha; TR, tricuspid regurgitation; UDC, unstable decompensated cirrhosis.

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## 1 | INTRODUCTION

Cardiac dysfunction is an established complication of cirrhosis and includes both structural and functional cardiac changes, collectively referred to as 'Cirrhotic cardiomyopathy'. It is the focus of active research since cirrhotic cardiomyopathy appears to be associated with complications related to cirrhosis decompensation such as hepatorenal syndrome, and poor outcomes in such patients, especially in the context of infection, and in those undergoing liver transplantation. However, there remain issues of ongoing debate including the underlying pathogenesis and thereby targets for therapy; the optimal diagnostic modalities; the impact of a diagnosis of cirrhotic cardiomyopathy on survival; and thereby, consideration for interventions such as liver transplantation.

The aim of this review is to critique the literature on cirrhotic cardiomyopathy in the setting of cirrhosis acute decompensation and address the unresolved issues highlighted above.

**Key points**

- The Cirrhotic Cardiomyopathy Consortium diagnostic criteria have progressed the field by standardising criteria and including components of subclinical cardiovascular dysfunction.
- Portal hypertension, systemic inflammation and structural myocardial changes are likely to be key pathophysiological drivers, with multiple pathways implicated.
- There is currently conflicting data on cardiac parameters in acute decompensation with further prospective studies using novel imaging techniques required.
- Current therapies provide symptomatic benefits, whereas future therapeutics should target both the gut–liver axis and systemic inflammation to prevent/reverse disease progression.

## 2 | ACUTE DECOMPENSATION IN CIRRHOSIS

The course of cirrhosis from a compensated to a decompensated state has long been assumed to be a gradual development occurring over a period of months to years, defined by the development of ascites, hepatic encephalopathy or portal hypertensive gastrointestinal bleeding.[1] However, it has become clear that this is not always the case as some patients may progress very rapidly over days to weeks, with the development of extra-hepatic organ failure and associated high mortality, a syndrome called acute-on-chronic liver failure (ACLF).[2] In recent years, specific diagnostic scores have been developed to standardise the diagnosis and prognosis of both ACLF and acute decompensation, and the prevalence of ACLF has been noted to be high.[3] In the main, the development of acute decompensation (AD) and ACLF occurs in the setting of pronounced systemic inflammation as recently described by the systemic inflammation hypothesis, whereby in the context of chronic injury, a new inflammatory trigger further aggravates existing inflammation. This then serves as the driver of organ impairment and progression of portal hypertension, including more pronounced circulatory dysfunction. This may manifest as organ hypoperfusion which together with a direct deleterious effect of inflammatory mediators results in the development of organ failure and the syndrome of ACLF.[4] The severity of systemic inflammation has been associated with the onset and severity of ACLF, and the strength of the association was higher than that noted with markers of circulatory dysfunction.[5]

## 3 | CIRRHOTIC CARDIOMYOPATHY

Profound circulatory dysfunction has been an acknowledged hallmark of decompensated cirrhosis and the evolution of portal hypertension since the 1950s.[6] The pronounced arterial vasodilatation and rising pressure within the portal system are accompanied by low systemic vascular resistance and low effective central blood volume, with a resultant compensatory activation of potent neurohumoral systems, leading to increased cardiac output and hyperdynamic circulation. These circulatory changes encouraged further studies of cardiac 'responsiveness' in advanced cirrhosis, and the finding of chronic cardiac dysfunction in cirrhosis, irrespective of aetiology. This has led to the description of the entity termed 'Cirrhotic cardiomyopathy'. According to the 2005 working definition, cirrhotic cardiomyopathy (CCM) encompasses systolic and/or diastolic dysfunction, the presence of electromechanical disturbances and changes in levels of serological markers of cardiomyocyte injury (Table 1) in the absence of concurrent cardiac disease.[7] These criteria have been applied in clinical studies over the last decade and our knowledge of CCM has expanded progressively. However, there has been a lack of consensus regarding how many of these criteria are required to obtain the diagnosis of CCM which has led to inconsistencies regarding both CCM prevalence and association with disease severity. Advances in cardiovascular imaging in recent years have enabled the Cirrhotic Cardiomyopathy Consortium to propose a revised set of CCM criteria, which can be seen in Table 2.[8] These updated guidelines have taken into account new imaging modalities that can identify subclinical cardiovascular dysfunction.

Another area of controversy relates to the underlying pathogenesis of CCM, with a summary of important processes highlighted in Figure 1. Different hypotheses have been proposed including mechanical shear stress due to a hyperdynamic circulation and portal hypertension, where the cardiac work is increased to maintain the circulation resulting in strain upon myocardial fibres, gradually promoting contractile dysfunction. In favour of this hypothesis is the study of De Binay et al. where they found cardiac dysfunction in non-cirrhotic portal fibrosis, indicating that portal hypertension is an important factor in the development of cardiac dysfunction.[9]

**TABLE 1** The 2005 World Congress of Gastroenterology diagnostic and supportive criteria for cirrhotic cardiomyopathy.

| **The World Congress of Gastroenterology criteria for cirrhotic cardiomyopathy** |
|---|
| **A working definition of cirrhotic cardiomyopathy** |
| Cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease |
| **Diagnostic criteria** |
| Systolic dysfunction |
| • Blunted increase in CO with exercise, volume challenge or pharmacological stimuli<br>• Resting EF < 55% |
| Diastolic dysfunction |
| • E/A ratio <1<br>• Prolonged deceleration time (>200 msec)<br>• Prolonged isovolumetric relaxation time (>80 msec) |
| **Supportive criteria** |
| • Electrophysiological abnormalities<br>• Abnormal chronotropic response<br>• Electromechanical uncoupling<br>• Prolonged QTc interval<br>• Enlarged left atrium<br>• Increased myocardial mass<br>• Increased BNP and proBNP<br>• Increased troponin I |

Abbreviations: BNP, brain natriuretic peptide; CO, cardiac output; EF, left ventricular ejection fraction; E/A ratio, ratio of early-to-late (atrial) phases of ventricular filling.

**TABLE 2** The 2019 Cirrhotic Cardiomyopathy Consortium criteria for cirrhotic cardiomyopathy.

| **The Cirrhotic Cardiomyopathy Consortium criteria for cirrhotic cardiomyopathy** |
|---|
| Systolic dysfunction (any of the following) |
| • LV ejection fraction ≤50%<br>• Absolute GLS <18% |
| Advanced diastolic dysfunction (≥3 of the following) |
| • Septal e' velocity <7 cm/s<br>• E/e' ratio ≥15<br>• LAVI >34 mL/m$^2$<br>• TR velocity >2.8 m/s |

Abbreviations: E/e' ratio, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity; GLS, global longitudinal strain; LAVI, left atrium volume index; Septal e' velocity, septal mitral annular early diastolic velocity; TR, tricuspid regurgitation.

Chronic systemic inflammation is believed to play a key role too in the development of CCM. Patients with advanced cirrhosis have chronic low-grade systemic inflammation and this has been suggested to be important in the evolution of AD and ACLF.[10,11] Furthermore, the activation of cytokines and vasoactive hormones and alterations in circulatory function in cirrhotic patients with ascites resemble that seen in patients with sepsis and septic shock. Patients with septic shock commonly exhibit sepsis-induced myocardial dysfunction with decreased contractility and impaired diastolic relaxation, therefore, it could be speculated that CCM may also share this common underlying pathophysiological pathway.[12]

The clinical manifestations of CCM as it develops are few, as the condition is often subclinical. However, CCM may be unmasked during circulatory stressful episodes such as infections, and invasive procedures (transjugular intrahepatic portosystemic shunt insertion and liver transplantation), where the cardiac demands are increased, or during pharmacological or exercise testing.[13–15]

## 4 | EXPERIMENTAL CIRRHOTIC CARDIOMYOPATHY IN RELATION TO SYSTEMIC INFLAMMATION

Several inflammatory mediators have been shown to be involved in the development of cardiac dysfunction. In an experimental study investigating cardiac dysfunction in association with non-alcoholic steatohepatitis (NASH), the authors reported the development of several cardiac abnormalities including myocardial fibrosis in mice progressing from non-alcoholic fatty liver disease to NASH with bridging fibrosis. In mice with myocardial fibrosis, they also found increased levels of various markers of inflammation, oxidative stress and fibrosis.[16] In experimental models of septic cardiomyopathy, increased levels of cytokines including interleukins, TNFα and inducible nitric oxide have all been shown to play important roles in relation to the development of cardiac dysfunction.[17–19] This increase in systemic inflammation is thought to be in part due to decreased intestinal motility, increased gut permeability and alterations in the gut microbiome, leading to increased bacterial translocation and endotoxaemia.[20]

Tumour necrosis factor-alpha (TNFα) signalling is complex, stimulating many intracellular pathways including endocannabinoid synthesis in macrophages and nuclear factor-kB (NF-kB) activation, a crucial transcription factor for the regulation of inflammatory processes. NF-kB activity is integral in the pathogenesis of cirrhotic cardiomyopathy with inhibition leading to improved cardiac contractility in cirrhotic hearts.[21,22] NF-kB activation also results in nitric oxide (NO) synthesis through the transcription of inducible nitric oxide synthetase (iNOS) and subsequent cGMP production. NO has been shown to be overproduced in cirrhotic cardiomyopathy with subsequent reduction in cardiac contractility.[23,24] Indeed, increased iNOS levels have been demonstrated in cirrhotic rat hearts with non-selective inhibition restoring blunted contractile function.[24,25]

Macrophage activation and endocannabinoid signalling are also implicated in cardiac dysfunction in cirrhosis. In a cirrhotic rat model, Gaskari et al. found increased monocyte recruitment in the cirrhotic hearts together with increased myocardial endocannabinoid levels in response to haemorrhage. These changes were related to reduced cardiomyocyte contractility.[26] Similar results were obtained by Batkai et al. who also reported that the reduced cardiac contractility was partially explained by endocannabinoid activation of cardiac

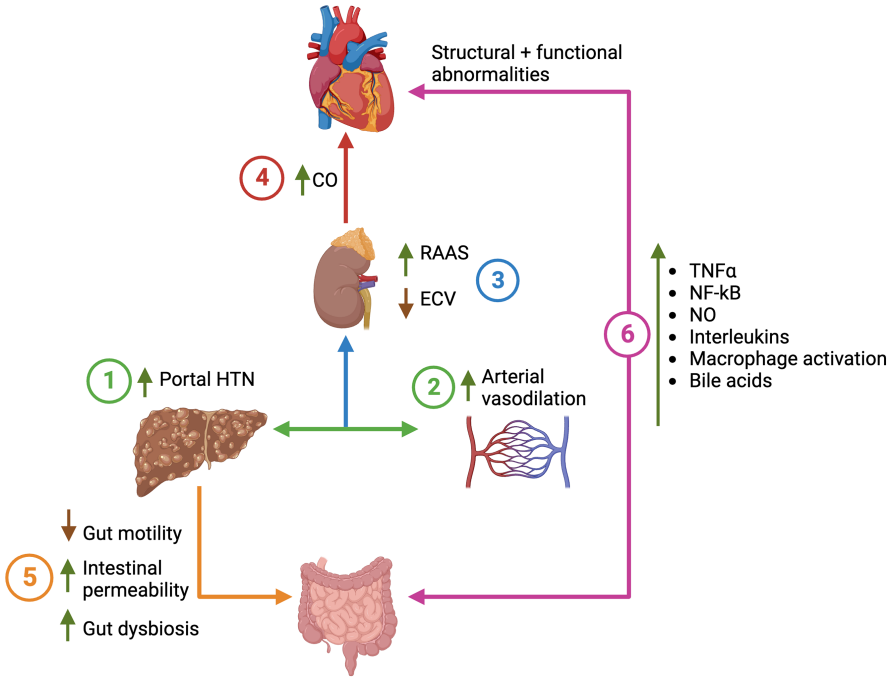


**FIGURE 1** Summary of the pathophysiology underlying cirrhotic cardiomyopathy. ECV, Effective circulating volume; RAAS, renin–angiotensin–aldosterone system.

CB[1] receptors. These receptors have previously been implicated in the decreased cardiac beta-adrenergic signalling in cirrhosis.[27]

Elevated bile acids have also long been speculated to have a role in cirrhotic cardiomyopathy with increased bile acids demonstrating an association with reduced heart rate and contractility.[27,28] More specifically, lipophilic bile acids have been implicated in the development and severity of cardiac mitochondrial dysfunction.[29,30] Indeed Baruch et al. demonstrated that reduction in lipophilic bile acid content by administration of a hydrophilic bile acid, ursodeoxycholic acid, could help prevent the development of the hyperdynamic circulation seen in cirrhosis.[31] Furthermore, Wiese et al. recently demonstrated a relationship between increased serum-conjugated bile acids and parameters of both myocardial fibrosis and cardiac dysfunction.[32] Farnesoid X receptor (FXR) is a nuclear transcription factor involved in bile acid metabolism and has been found to be expressed in various cells of the cardiovascular system; therefore, there has been a growing interest in its potential therapeutic role. Furthermore, FXR agonists have demonstrated anti-inflammatory properties through down-regulation of TNFα and NF-kB, and their potential in cirrhotic cardiomyopathy remains to be explored further.[33]

All together these studies indicate an important link between inflammation and cardiac dysfunction in cirrhosis and highlight potential novel therapeutic targets that should be studied in future research.

## 5 | CARDIAC DYSFUNCTION IN RELATION TO CIRRHOSIS ACUTE DECOMPENSATION AND ACUTE-ON-CHRONIC LIVER FAILURE

Only a few studies have investigated cardiac dysfunction in the setting of cirrhosis acute decompensation. This is most likely because these unstable patients are a very challenging research population to study, given they often are admitted during the night, require significant intensive supportive management and it may be difficult to get robust cardiac functional data, as they may not be able to undergo the required cardiovascular investigations. The association between acute gastrointestinal (GI) bleeding and cardiac dysfunction has been investigated by assessment of QTc prolongation. Trevisani et al. investigated QTc prolongation in 70 cirrhotic patients and 40 non-cirrhotic patients with acute GI bleeding and found that QTc increased in cirrhotic patients during the bleeding episode, was associated with a higher MELD score and independently predicted survival.[34] However, Zhao et al. were unable to establish the relationship between QTc prolongation and poor survival in another study.[35] Furthermore, none of the studies included cardiac imaging. A challenge in the setting of GI bleeding is that both the acute treatment with potent vasoactive agents, such as terlipressin, and the use of non-selective beta-blocker prophylaxis influence cardiac function, thereby making it difficult to accurately assess CCM.

The relationship among cardiac dysfunction, spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS) was first reported by Ruiz-del-arbol et al. They did a prospective study in 23 patients with SBP investigating haemodynamic and renal function upon admittance to the hospital and after the resolution of the infection. Their main finding was that the eight patients who went on to develop HRS had a lower cardiac output (CO) at admission (5.7 vs. 7.4 L/min) which further decreased despite resolution of the infection, without any changes in systemic vascular resistance, heart rate or cardiopulmonary pressures. These patients also had higher white blood cell counts, higher TNFα and higher levels of neurohumoral markers. Additionally, they found a negative correlation between TNFα and CO.[36] These findings indicated a strong link among cardiac function, inflammation and renal failure

and led to other studies investigating this relationship. The same research group investigated systemic haemodynamics before and after the development of HRS and found that 27 patients who developed HRS had a lower initial CO than the 39 without HRS (6.0 vs. 7.2 L/min), and that CO was further reduced at follow-up. Additionally, they found markedly increased levels of renin activity and norepinephrine in patients who develop HRS. CO and renin activity independently predicted the development of HRS.[37] Similar results were obtained by Krag et al., who demonstrated a reduced glomerular filtration rate and renal blood flow together with a higher creatinine in patients with advanced cirrhosis and a cardiac index <1.5 L/min/$m^2$. Moreover, a low cardiac index was associated with the development of HRS and poor survival during a follow-up of 12 months.[38]

However, the role of pathophysiological mechanisms behind hepatorenal syndrome–acute kidney injury (HRS-AKI) is controversial and a recent study using echocardiography suggested that patients with HRS-AKI actually experience higher CO than those without HRS-AKI.[39] These findings are supported by Danielsen et al. who did a prospective study aiming to characterise cardiac and blood flow alterations in multiple regions, in a population including advanced decompensated cirrhosis and ACLF. The authors demonstrated that individuals with HRS-AKI had significantly higher CO and Cardiac Index (CI) than the rest of the decompensated cirrhosis cohort, which consisted of those with responsive and refractory ascites. In addition, those with HRS-AKI and ACLF were characterised by an additional increase in CO and CI, although the sample size was only five patients.[40] A possible explanation for the contrasting results is that this study used phase-contact magnetic resonance imaging (MRI) to quantify macrovascular flow which has been found to be comparable to right heart catheterisations, whereas previous imaging techniques may have underestimated CO.[41] The caveat for interpretation of this data is that the numbers with advanced ACLF and decompensation in this study were very small, and thereby the results may not be reflective of a larger, similar population.

A study by Turco et al. investigated the prognostic relevance of inflammation and the cardiodynamic state in 238 patients with cirrhosis (151 compensated and 87 decompensated). They found a progressive increase in CI in relation to progression in portal hypertension with development of varices and ascites, but a decrease in patients with refractory ascites. Moreover, C-reactive protein and a cardiac index >4.2 L/min/$m^2$ or <3.2 L/min/$m^2$ were predictive of decompensation and death.[42] Diastolic dysfunction (DD) has also been investigated in relation to SBP, systemic inflammation and development of HRS, however, with conflicting results. Ruiz-del Arbol et al. reported DD to be an independent predictor of HRS type 1 and mortality.[43] Whereas Nazar et al. were unable to confirm this relation.[44,45]

The impact of systemic inflammation, a key component of acute decompensation, on cardiac function has been investigated by Karagiannakis et al. They evaluated cardiac function with dobutamine stress echocardiography and markers of bacterial translocation and inflammation (lipopolysaccharide binding protein (LBP) and cytokines) in 45 patients with 22 having ascites. They found patients with grade 2 DD had higher LBP levels, higher brain natriuretic peptide (BNP) levels and more pronounced left atrial enlargement compared to patients without DD. In multivariate analysis, LBP levels and non-alcoholic aetiology were independently associated with DD. Furthermore, E/e' ratio was correlated with LBP. After dobutamine-induced stress, DD patients had a smaller increase in cardiac index than those without, however, it was not statistically significant.[46] In a study by Yotti et al., they investigated left ventricular systolic function and the relationship to activation of the sympathetic nervous system and inflammation in 59 patients with cirrhosis and 59 age-matched controls. They found the resting LV systolic function to be enhanced in patients with mild-to-moderate cirrhosis. However, in response to vasoconstrictor stress, systolic function decreased mainly in those patients exhibiting higher baseline systolic function, systemic vasodilation and inflammation. The change in systolic function was strongly related to circulating levels of interleukin 1B and NO.[45] A link among systemic inflammation, macrophage activation and myocardial structural changes was also reported in a study by Wiese et al. They found associations between myocardial structural changes and several inflammatory biomarkers. In a multivariate analysis, IL-6 and soluble macrophage mannose receptors remained the strongest independent predictors of myocardial structural changes.[47]

The relationship between cardiac function and refractory ascites has also been assessed by Téllez et al.[48] This was a prospective study of patients with diuretic-responsive ascites (DRA, $n = 18$) versus those with refractory ascites (RA, $n = 20$) treated with propranolol for 4 weeks. Cardiac systolic function was assessed by ejection intraventricular pressure difference (EIVPD) as a load-independent marker. Propranolol caused a significant reduction in EIVPD in the RA compared to DRA cohorts (−20% vs. −2%, $p < .01$). Furthermore, renal perfusion pressure (RPP) dropped below 65 mmHg, the threshold for autoregulation, in 55% in the RA group versus 12% in the DRA group ($p = .01$), which was reflected by a significant increase in creatinine in the RA group. This study highlights that patients with refractory ascites are at particular risk of cardiac and renal dysfunction. However, while the study and haemodynamic measurements involved were robust, the numbers recruited were small.

Finally, while the PREDICT study did not formally assess cardiac dynamics, the subclassification of the unstable decompensated cirrhosis cohort (UDC) who had severe portal hypertension did highlight a potentially at-risk group following AD. These individuals were defined by the absence of ACLF, but either died or required at least one hospital readmission within the 3-month follow-up period. Circulatory dysfunction and hypovolemic shock as the main cause of death were significantly more prominent in this group compared to the other two cohorts, suggesting significant cardiac dysfunction.[49] In addition, a study by Fernández et al. reported that ACLF patients with a concomitant bacterial infection more frequently developed circulatory failure (34% vs. 18%).[50] Hence bacterial translocation and the following inflammatory cascade may contribute to the development of cardiac dysfunction.

To summarise, there is increasing evidence of a relationship among cardiac dysfunction, systemic inflammation, AD and ACLF; however, more studies are needed to clarify the specific mechanisms at play.

## 6 | CARDIAC DYSFUNCTION IN RELATION TO TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT INSERTION AND LIVER TRANSPLANTATION

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) is used to treat refractory variceal bleeding and refractory ascites.[1] In relation to this procedure, cases of unexplained cardiac complications have been reported despite the careful exclusion of patients with clinical cardiac risk. Therefore, it has been hypothesised that CCM predisposes patients to develop haemodynamic instability after TIPS insertion because the heart is not able to handle the significantly increased preload due to the redirection of blood from the splanchnic circulation to the systemic circulation.[51] The presence of DD has been related to poor survival following TIPS.[52,53] Conversely, Wannhoff et al. found no differences in survival rates between patients with pre-TIPS DD and those without, over a follow-up of 5 years, even though the prevalence of DD was 40.7%. However, they did find indications of an ongoing cardiac volume overload,[54] whereas Filì et al. report a trend towards a lower CI following TIPS in patients with DD.[55] A study by Busk et al. also investigated the effect of TIPS on haemodynamics including cardiac function. They assessed cardiac function in 25 patients pre-TIPS, 1 week post and then 4 months after TIPS, with the finding of a transient increase in CO and proatrial natriuretic peptide at 1-week post-TIPS, which returned to baseline at 4 months. They only found subtle changes in echo-parameters of DD.[56] More recently, Radunski et al. performed cardiac MRI in 17 patients prior to TIPS insertion and 207 (170–245) days post. Increased preload resulted in significantly increased volumes of all cardiac chambers with significant LV hypertrophy but with no change in NT-proBNP or evidence of cardiac decompensation.[57] Hamilton et al. retrospectively investigated prognostic variables in 234 patients undergoing TIPS. They found INR, bilirubin, sodium, model for end-stage liver disease (MELD), MELD-Na and right ventricle systolic dysfunction to be associated with 90-day mortality. However, only MELD-Na remained significant in a multivariate model.[58]

Liver transplantation (LT) is also known to induce cardiovascular stress and has been associated with an unexpectedly high rate of cardiac complications. At the same time, LT has also been reported to result in improved systolic and diastolic function, as well as reversal of QT prolongation within 3–12 months of surgery.[59–61] Hence, the relationship between LT and cardiac dysfunction continues to be debated. In a study of 157 LT recipients, DD post-LT was associated with higher MELD, higher levels of BNP, a higher frequency of dialysis and higher in-hospital mortality.[62] The presence of DD prior to LT has also recently been shown to be an independent predictor of systolic heart failure, immediately following LT.[63] Cardiac dysfunction was noted in half of the 72 children with biliary atresia awaiting LT by Gorgis et al. They showed that cardiac dysfunction was associated with prolonged time in the intensive care unit, increased risk of dialysis and longer hospital stays post-LT. Left ventricular mass index, in particular, correlated with markers of disease severity, vasopressor use, mechanical ventilation and dialysis.[64]

Advanced echocardiographic techniques including evaluation of myocardial contractility by Speckle tracking or assessment of microvascular perfusion by dobutamine stress perfusion imaging have also been applied in this setting. Jansen et al. investigated the role of left ventricular myocardial contractility in 168 patients with cirrhosis awaiting LT. They found that increased myocardial contractility in decompensated patients was an independent predictor of reduced transplant-free survival.[65] Biabhav et al. evaluated 296 LT patients with stress perfusion imaging and found abnormal microvascular perfusion in 18 patients and DD in 109 patients. However, abnormal microvascular perfusion was the only independent predictor of a cardiovascular event following LT ($p = .004$; hazard ratio 7.7).[66]

Indeed, the advancement in echocardiography has highlighted crucial differences in this cohort when comparing the original diagnostic criteria in 2005 with the modified guidelines of 2019. Spann et al. studied 210 LT patients and demonstrated that 77% of patients met the original criteria for CCM, but only 30% met the revised criteria pre-transplant. The original definition of CCM was not associated with major adverse cardiac events (MACE) post-transplantation, but the revised criteria were.[67] However, in contrast, Ali et al. demonstrated the opposite findings with only the original criteria independently predicting MACE at 1-year post LT.[68] As such, the relationship between cardiac dysfunction and identifying optimal candidates for LT remains a challenge but the application of new imaging techniques may well help clarify our understanding of the underlying pathophysiology. Indeed, a recent meta-analysis of patients with cirrhosis compared to healthy controls suggested that global longitudinal strain (GLS), which is a marker of early systolic and diastolic dysfunction, detecting subclinical myocardial changes, could play a crucial role in liver transplant screening.[69]

## 7 | CARDIAC DYSFUNCTION IN RELATION TO SURVIVAL

The impact of cardiac dysfunction on survival has been investigated in several studies and there seems to be good evidence of a relationship between systolic dysfunction and poor survival.[36,38,42,62] Alvarado-Tapias et al. performed a retrospective study of cirrhosis patients on primary prophylaxis with non-selective beta-blockers and demonstrated that in patients with decompensated cirrhosis, CO can predict mortality, suggesting a significant cut-off value of 5 L/min, below which mortality significantly increased.[70] This threshold corresponded to significantly lower values in parameters of systolic function, such as left ventricular strain. Conversely, the

relationship between diastolic dysfunction and poor prognosis is less clear as studies have shown contradictory results.[43,44,71–74] These differences may partly reflect the lack of consensus regarding the grading of diastolic dysfunction in cirrhosis and the heterogeneity in the study populations. In a study by Cesari et al., 115 patients with cirrhosis were followed up for more than 6 years, and E/e' and increased left atrial dimension were among the predictors of death, indicating that DD may influence prognosis. However, MELD, age and body surface area were the main predictors of death.[75] Another study by Giannelli et al. used right heart catheterisation to determine left ventricular stroke work index (LVSWI), which considers not only CO but also arterial pressure, providing a global assessment of cardiac function. In a multivariate analysis, the authors observed that patients receiving beta-blockers with an LVSWI cut-off <64.1 g-m/$m^2$ led to a higher risk of transplant waiting-list mortality, than those not on beta-blockers.[76] While the results are interesting, LVSWI is a new concept in cirrhosis and requires further validation.

## 8 | FUTURE PERSPECTIVES ON DIAGNOSTICS AND TREATMENT

As previously outlined, the diagnosis of CCM is very challenging. The 2005 World Congress of Gastroenterology guidelines required conventional 2D echocardiography to detect systolic and diastolic dysfunction, as well as electrocardiography to diagnose electrophysiological abnormalities.[7] The development of ECHO tissue Doppler imaging (TDI), which can measure the velocity of myocardial motion, enabled more accurate measurement of systolic and diastolic dysfunction and led to the development of the 2019 Cirrhotic Cardiomyopathy Consortium diagnostic criteria.[8] However, concerns remain that TDI does not take into account the full spectrum of abnormalities that can occur in the development and progression of CCM. While this article has highlighted other techniques in the form of stress imaging, MRI and dynamic studies involving cardiac catheterisation, these are not routinely used in clinical practice due to limited availability, cost, lack of validity and in the case of invasive procedures, risk of complications.

While TDI is currently used to diagnose CCM, the underlying pathophysiology is complex and structural cardiac changes including myocardial fibrosis have been suggested to be involved in the process.[62,77] This is likely to be an emerging area of research and possibly highlight new targets for diagnosis and treatment. Indeed, it is now possible to use non-invasive MRI techniques to assess the presence of fibrosis. Cardiac MRI can non-invasively assess myocardial tissue characteristics such as infiltration, oedema and fibrosis, by quantification of the myocardial extracellular volume fraction (ECV) based on pre- and post-contrast, longitudinal relaxation (T1) times. This technique has been validated histologically demonstrating a strong correlation with diffuse myocardial fibrosis.[78,79] Myocardial ECV has also been shown to be a strong predictor of poor outcomes in several cardiac diseases including cardiomyopathies, heart failure and diabetes.[80–82]

Few clinical studies have investigated structural cardiac changes in patients with cirrhosis. Lossnitzer et al. performed cardiac MRI with late gadolinium enhancement in 20 patients with end-stage liver disease and described a pattern of focal fibrosis resembling the appearance of myocarditis.[83] Sampaio et al. also performed a cardiac MRI including late gadolinium enhancement imaging and dobutamine stress in 36 patients with mild-to-moderate cirrhosis. They found no focal myocardial fibrosis; instead, they reported abnormal myocardial contractility in response to pharmacological stress, indicating intrinsic myocardial abnormalities.[84] Cardiac MRI with T1 imaging has been applied in patients with viral hepatitis C and moderate liver disease with the finding of abnormal T1 values, indicating diffuse myocardial fibrosis.[85] Wiese et al. applied cardiac MRI with myocardial ECV quantification in 52 patients with cirrhosis and 10 healthy controls and reported an increased myocardial ECV in patients with cirrhosis, with the highest ECV in patients with advanced cirrhosis. Interestingly, they also showed a relationship between a high myocardial ECV and reduced transplant-free survival.[86] The finding of a relationship between myocardial structural changes and the severity of cirrhosis was confirmed by Isaak et al.[87] Similarly, Kim et al. assessed myocardial ECV and cardiac function pre-LT and 1 year after LT. They found evidence of myocardial fibrosis and a hypercontractile left ventricle pre-LT, which then normalised 1 year after LT.[88] Therefore, the assessment of structural myocardial changes using cardiac MRI is a promising area that requires further research and validation.

While there has been a growing interest in research into antifibrotic drugs as potential therapies, and with some demonstration of pre-clinical experimental success, this has not yet successfully translated into clinical studies.[89]

There is currently no specific treatment for cirrhotic cardiomyopathy with treatment focusing on diuretic therapy for symptomatic relief. Angiotensin receptor antagonists are known to provide prognostic benefits in heart failure but are not recommended in advanced cirrhosis due to concerns over reducing renal perfusion and exacerbating hepatorenal syndrome. Aldosterone antagonists can lead to improvements in haemodynamics through antagonism of the renin–angiotensin–aldosterone system. Furthermore, beta-blockers have been shown to reduce QT prolongation as well as their known portal hypertensive-reducing effects.[90,91] However, their use in advanced cirrhosis, where there is further beta-receptor downregulation, impaired vagal activity and greater arterial under-filling, is at present not advised, given concerns of further aggravating impaired systolic function.[92,93] Novel therapeutics should target components of systemic inflammation as detailed earlier, such as FXR agonists. In a similar vein, targeting microbial dysbiosis and bacterial translocation as key pathogenic drivers are promising targets. The Gut Heart trial is exploring the role of rifaximin in heart failure with potential implications for cirrhotic cardiomyopathy, if efficacy is demonstrated.[94] Finally, with emerging treatment options for ACLF with therapies such as TAK-242 (a Toll-like receptor 4 (TLR4) antagonist), there may well be benefits given the elevated TLR4 levels demonstrated in the cirrhotic myocardium.[95,96] While there are many potential targets to

explore, the optimal strategy remains elusive and an unmet clinical therapeutic need.

## 9 | CONCLUSION

Cirrhotic cardiomyopathy is important to consider in patients with cirrhosis, as cardiac dysfunction is related to the development of acute decompensation and has prognostic implications in patients undergoing liver transplantation. Systemic inflammation and structural myocardial changes are likely to play important roles in the underlying pathophysiology, but more studies are warranted to elucidate their specific contributions further. In order to gain further insights into the implications of CCM on prognosis and the development of complications, it is necessary to standardise the algorithms used for the diagnosis of CCM and to consider the inclusion of newer imaging techniques, focusing on myocardial structure and function, and further, to investigate these features in large cohort studies.

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