Review

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Cardiomyopathy in cirrhosis: From pathophysiology to clinical care

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Summary

Cirrhotic cardiomyopathy (CCM) is defined as systolic or diastolic dysfunction in the absence of prior heart disease or another identifiable cause in patients with cirrhosis, in whom it is an important determinant of outcome. Its underlying pathogenic/pathophysiological mechanisms are rooted in two distinct pathways: 1) factors associated with portal hypertension, hyperdynamic circulation, gut bacterial/endotoxin translocation and the resultant inflammatory phenotype; 2) hepatocellular insufficiency with altered synthesis or metabolism of substances such as proteins, lipids, carbohydrates, bile acids and hormones. Different criteria have been proposed to diagnose CCM; the first in 2005 by the World Congress of Gastroenterology, and more recently in 2019 by the Cirrhotic Cardiomyopathy Consortium. These criteria mainly utilised echocardiographic evaluation, with the latter refining the evaluation of diastolic function and integrating global longitudinal strain into the evaluation of systolic function, an important addition since the haemodynamic changes that occur in advanced cirrhosis may lead to overestimation of systolic function by left ventricular ejection fraction. Advances in cardiac imaging, such as cardiac magnetic resonance imaging and the incorporation of an exercise challenge, may help further refine the diagnosis of CCM. Over recent years, CCM has been shown to contribute to increased mortality and morbidity after major interventions, such as liver transplantation and transjugular intrahepatic portosystemic shunt insertion, and to play a pathophysiologic role in the genesis of hepatorenal syndrome. In this review, we discuss the pathogenesis/pathophysiology of CCM, its clinical implications, and the role of cardiac imaging modalities including MRI. We also compare diagnostic criteria and review the potential diagnostic role of electrocardiographic QT prolongation. At present, no definitive medical therapy exists, but some promising potential treatment strategies for CCM are reviewed.

Keywords: cardiac; cirrhosis; hemodynamics; MRI; echocardiography; prolonged QT Interval; therapy

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Introduction

Cirrhotic cardiomyopathy (CCM) is defined as cardiac dysfunction in patients with cirrhosis in the absence of prior heart disease.[1,2] The vasodilatation that occurs in patients with cirrhosis may mask early systolic cardiac dysfunction and the early decrease in contractility by decreasing afterload and increasing preload (and thus cardiac output). Resting diastolic evaluation is insensitive in patients with symptoms limited to exertional dyspnoea since the increase in left ventricular filling pressures and pulmonary congestion in these patients may only occur during exercise. Therefore, the diagnosis of CCM may be difficult. Recent advances in diagnostic imaging have advanced detection of CCM in patients with cirrhosis. The present review aims to summarise the pathogenesis and pathophysiology of CCM, discuss advances in diagnostic imaging, compare the 2005 World Congress of Gastroenterology (WCG) criteria and the 2019 Cirrhotic Cardiomyopathy Consortium (CCC) criteria, review electrophysiological changes in CCM, and discuss its clinical relevance and potential treatment strategies.

Pathophysiology/pathogenesis

The features of cirrhosis include hepatic structural and functional disturbances that lead to hepatocellular insufficiency and portal hypertension, which causes mesenteric congestion. The congested gut is more permeable, allowing for bacteria/endotoxin translocation. These features impact the heart via two major pathways: inflammation and protein/lipid synthetic/metabolic defects (Fig. 1)[3]).

Inflammation

First, pro-inflammatory cells are increased in hypertrophic hearts.[4] Monocyte/macrophage infiltration is associated with systolic dysfunction. Our lab studied the role of monocyte/macrophage

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infiltration in the cirrhotic rat heart.[5] We found that monocytes/macrophages were increased in these hearts and myocardial contractility was decreased. Using gadolinium chloride to block the recruitment of monocytes/macrophages significantly improved cardiac contractility.

Second, proinflammatory cytokines are increased. The inflammatory phenotype arises from intestinal congestion because of portal hypertension; lipopolysaccharide enters the systemic circulation stimulating production of pro-inflammatory cytokines such as tumour necrosis factor-α (TNFα), interleukin (IL)-1β and IL-6. There is a close correlation between inflammation and disturbance of calcium transients in cirrhotic hearts. Adding TNFα directly to atrial myocytes, Zuo and colleagues[6] observed that it directly increases spontaneous calcium release, decreases the amplitude of calcium transients, and reduces the calcium content in the sarcomere reticulum. Furthermore, TNFα has regulatory effects on calcium transient proteins. Kao *et al.*[7] reported that 24-hour incubation of cardiomyocytes with TNFα enhances methylation in the promoter region of *SERCA2a* and decreases its protein expression. They speculated that inhibition of TNFα-induced hypermethylation may be a novel treatment strategy for heart failure. Rao *et al.*[8] demonstrated that T-type calcium channels on atrial myocytes were reduced in a TNFα concentration-dependent manner during a 24-hour incubation. The peak calcium current was also decreased in a TNFα concentration-dependent manner. Gregolin and coworkers[9] showed that inflammation significantly reduced the phosphorylation of cardiac phospholamban, contributing to systolic and diastolic dysfunction in a rat model of thioacetamide (TAA)-induced cirrhosis.

Proinflammatory cytokines also depress cardiac function via two evanescent gases, nitric oxide and carbon monoxide, which inhibit cardiac contraction via the second messenger cGMP. Another inflammatory pathway, the endocannabinoid CB-1 system, also inhibits ventricular contractility in CCM.[5] We previously demonstrated that endocannabinoids are increased locally in cirrhotic rat hearts, and administration of the CB-1 antagonist

Key points

- Cirrhotic cardiomyopathy (CCM) is a syndrome of depressed cardiac function in the absence of primary heart disease in patients with cirrhosis.
- Its pathogenesis/pathophysiology is related to an inflammatory phenotype and protein/lipid/carbohydrate synthetic/metabolic defects.
- Modern echocardiographic techniques assessing systolic and diastolic function are used to diagnose CCM.
- CCM contributes to the pathogenesis of renal dysfunction and worse outcomes after interventions such as transjugular intrahepatic portosystemic shunt insertion and liver transplantation.
- There is currently no definitive medical therapy, but animal studies provide support for several possible treatment strategies.

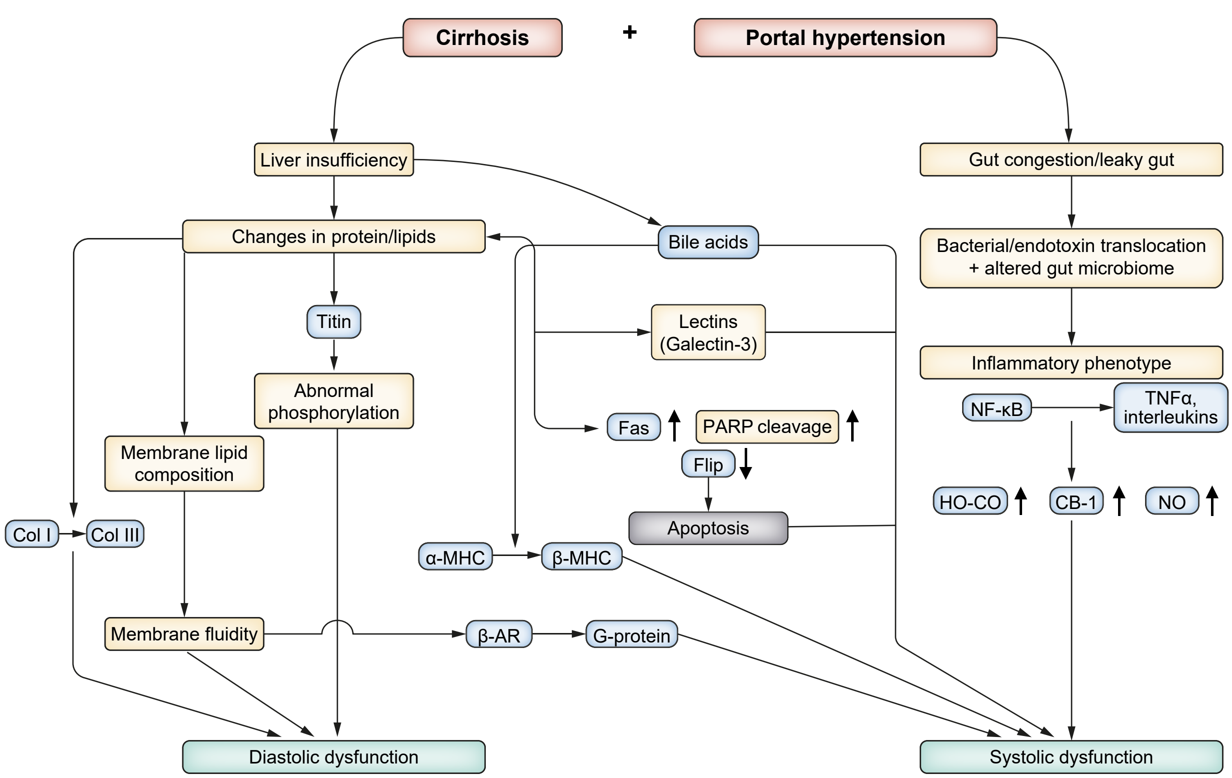

Fig. 1. Mechanistic pathways of cirrhotic cardiomyopathy. β-AR, β-adrenergic receptor; CB, cannabinoid; CO, carbon monoxide; Col, collagen; FLIP, Fas-associated death domain-like interleukin 1β-converting enzyme-inhibitory protein; HO, heme oxygenase; MHC, myosin heavy chain; NO, nitric oxide; PARP, poly(ADP-ribose) polymerase; TNF, tumour necrosis factor. (Reproduced from ref. 3).

AM251 completely restored the inhibited contractility of ventricular papillary muscles.[5]

Protein/lipid/carbohydrate synthetic/metabolic defects

Hepatocellular insufficiency causes synthetic/metabolic defects of cardiac proteins, lipids and carbohydrates, such as the β-adrenergic receptor,[10,11] titin, collagens, myosin heavy chain (MHC), cholesterol, and lectins. The β-adrenergic receptor plays an essential role in cardiac contraction.[12] It was observed more than six decades ago that catecholamine infusion in patients with cirrhosis results in weaker cardiac responsiveness compared to controls.[13] We measured the myocardial binding characteristics of the β-adrenergic receptor and heart rate responsiveness to isoprenaline in a rat model of cirrhosis.[10] Compared to sham-operated controls, myocardial β-adrenergic receptor density was significantly lower and a significantly higher dose of isoprenaline was required to raise basal heart rate by 50 beats/min.[10] Thus, β-adrenergic receptor downregulation is associated with myocardial hyporesponsiveness to catecholamines in the cirrhotic heart.

The giant protein titin is largely responsible for the passive elastic recoil of early diastole. Titin abnormalities are associated with dilated cardiomyopathy.[14] It has three isoforms, N2A, N2B and N2BA. N2B is a relatively shorter protein isoform with less elasticity and more passive stiffness compared to the N2BA isoform.[15] Nagueh *et al.*[16] suggested that the increased ratio of N2BA:N2B plays an important role in patients with dilated cardiomyopathy. Although we did not observe a change in the ratio of N2BA:N2B in cirrhotic rats in our study, its regulator (protein kinase A) was significantly decreased in cirrhotic hearts,[17] which would impact the phosphorylation of titin and consequently, diastolic function.

Another myofilament that plays a critical role in cardiac contraction is MHC. There are two isoforms of MHC, α-MHC and β-MHC. α-MHC is a faster-contracting, more powerful phenotype and β-MHC is a slower, weaker phenotype. We confirmed a switch from α-MHC to β-MHC in the cirrhotic rat ventricle.[18] In normal rats, α-MHC is the predominant isoform (90%), whereas the predominant phenotype is β-MHC in the bile duct ligation (BDL)-cirrhotic ventricle. This suggests that the shift from α-MHC to β-MHC in the cirrhotic heart plays an important role in suppressed cardiac contractility.[19]

Lipid changes, mainly increased cholesterol in the cardiac sarcolemmal plasma membrane, result in reduced membrane fluidity. As all cardiac function-related receptors and ion channels including adrenergic receptors, cannabinoid receptors, L-type calcium channels, and Na^+/K^+-ATPase are embedded in the plasma membrane of cardiomyocytes, any biochemical and fluidity changes can affect their function and that of their downstream signalling pathways.[20,21]

Lectins are carbohydrates with ubiquitous distribution and functions. We recently demonstrated a role of galectin-3 as a proinflammatory, pro-apoptotic and pro-oxidant influence on cardiac function in a BDL-cirrhotic rat model. Treatment of these rats with a galectin-3 inhibitor improved ventricular function.[22]

Cardiac imaging modalities in CCM

Cardiac imaging is key to the diagnosis of CCM. In the following section, we describe and contrast cardiac imaging techniques used to diagnose CCM.

Echocardiography

Transthoracic echocardiography is the primary imaging modality recommended in the 2019 CCM diagnostic criteria due to its widespread availability and the wealth of structural and hemodynamic information obtained.[1] A comprehensive approach is required (Fig. 2).

Systolic dysfunction

Standard 2-dimensional echocardiography

Left ventricular (LV) systolic function is usually determined by LV ejection fraction (LVEF), with LVEF <50% considered abnormal.[1] However, since vascular resistance is often reduced in cirrhosis, resulting in hyperdynamic systolic function with increased cardiac output, LVEF is rarely <50% even when systolic dysfunction is present.[23–25] Therefore, a higher LVEF threshold in cirrhosis has been proposed.[26,27] However, other measures are needed to better define LV systolic function in CCM.

Speckle-tracking echocardiography

Myocardial strain by speckle-tracking echocardiography has emerged as a method to identify early systolic dysfunction amongst patients with preserved LVEF. It is defined as the change in length of the contracting myocardium in one spatial orientation relative to the baseline length. While strain can be measured in several dimensions (circumferential, longitudinal, and radial), longitudinal strain is often affected early in cardiomyopathies.[28,29] Therefore, global longitudinal strain (GLS) is recommended for the evaluation of early systolic dysfunction in patients with cirrhosis.[1] Because the myocardium shortens in the longitudinal dimension during systole, GLS is recorded as a negative number by convention, with normal values being ≤-18%, borderline between -16% and -18%, and abnormal >-16%.[30] For simplicity, we refer to the absolute GLS value in this review (*i.e.*, decreased GLS means lower absolute value <16% and normal GLS means >18%).

While several studies have shown decreased GLS in cirrhosis compared to controls,[31–33] others observed increased or unchanged GLS in these patients.[34,35] The conflicting results likely reflect the different effects of haemodynamic changes of cirrhosis in patients with a healthy myocardium *vs.* those with CCM, where GLS is expected to be decreased. Since GLS is affected by both contractility and preload,[36] in the healthy myocardium, the high output state of advanced cirrhosis could lead to increased GLS.[36] Mechelinck *et al.* observed that both low (<17-18) and high GLS (>24-26) were associated with increased mortality.[37] GLS was high in patients with more advanced cirrhosis (*i.e.*, portal hypertension, decompensated stage) although increased GLS did not necessarily correlate with higher Child-Pugh grades.[37] Even modestly impaired GLS (<20.5%) confers a 6-fold increase in post-transplant congestive heart failure (CHF) and coronary artery disease.[23] Similar conflicting results are observed post-liver transplant, where some observed decreased GLS (from 24.9% to 20.6%) in a subset of patients 1 year after liver transplantation,[38] while others found increased GLS (from 18.5% to 20.8%) at 18.2 months post-transplant.[39] However, in both studies, GLS generally tended to normalise after liver transplant.

Diastolic dysfunction

Four echocardiographic parameters are required for diastolic dysfunction (DD) assessment: septal and lateral mitral annular

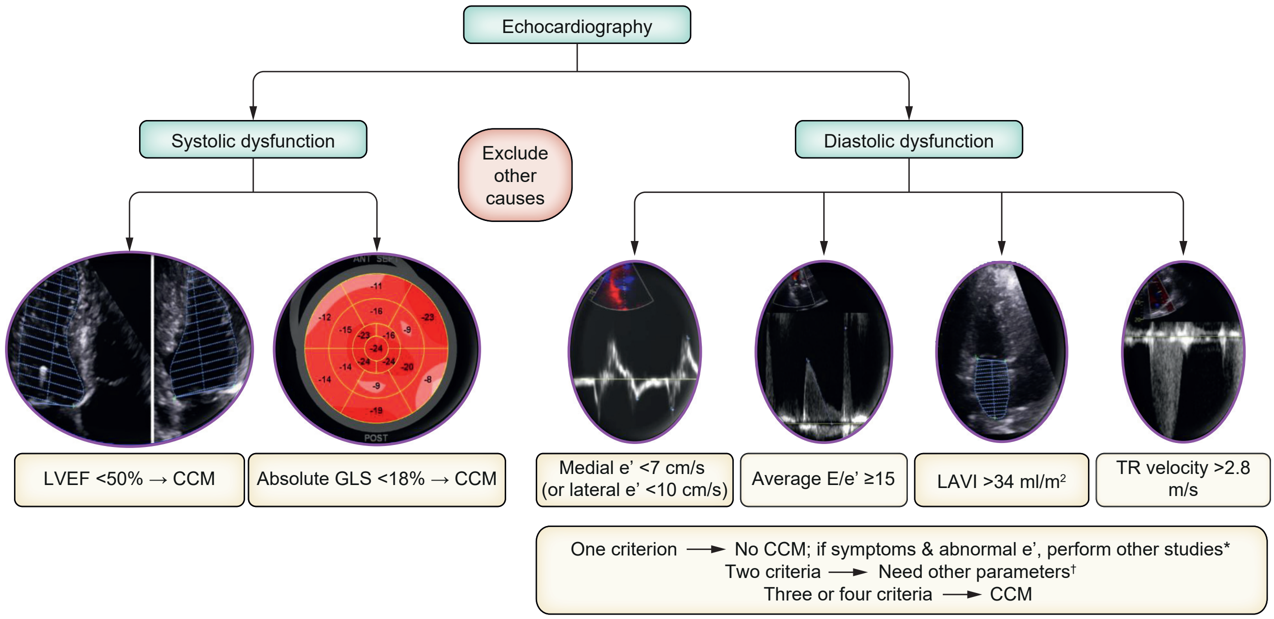

Fig. 2. Diagnosis of cirrhotic cardiomyopathy using echocardiography. *Diastolic stress echocardiography or right heart catheterisation. †This includes the ratio of pulmonary vein peak systolic velocity to peak diastolic velocity or systolic time velocity integral to diastolic time-velocity integral, isovolemic relaxation time, left atrial strain, or left ventricular mass index and relative wall thickness. CCM, cirrhotic cardiomyopathy; GLS, global longitudinal strain; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

peak early diastolic velocity (e'), the ratio of the peak velocity of mitral inflow during early diastole (E) to the average of septal and lateral e' (E/e'), left atrial volume indexed to body surface area, and tricuspid regurgitation (TR) velocity.[40]

Doppler echocardiography

Tissue Doppler imaging is a variant of pulsed wave Doppler that measures the myocardial (tissue) rather than blood (flow) velocity.[40] The septal and lateral e' reflect the velocities of the septal and lateral mitral annuli during myocardial relaxation in early diastole. Low values (septal e' <7 cm/s; lateral e' <10 cm/s) indicate impaired LV relaxation in DD. In a retrospective study, low septal e' was the most predictive variable for the composite outcome of arrhythmia, CHF, cardiac arrest, and/or cardiac death after liver transplant, although GLS was not assessed.[41] Importantly, e' has limited accuracy in patients with regional wall motion abnormalities, mitral annular calcification, prosthetic mitral valves, or pericardial disease.[40]

Pulsed wave doppler can also be applied to early diastolic blood flow through the mitral valve from the left atrium (LA) into the LV; the peak velocity of this flow is the mitral E velocity and is a reflection of the pressure gradient between the LA and the LV.[40] The E/e' ratio correlates to pulmonary capillary wedge pressure and is a widely accepted non-invasive surrogate of LV filling pressure,[42] where E/e' ≥15 is elevated, 9-14 is borderline, and ≤8 is normal. An E/e' >9.2 correlates with post-transplant incident arrythmias and atrial fibrillation in patients with decompensated cirrhosis.[23] Importantly, E/e' may be less accurate in normal individuals without heart disease, moderate/severe mitral regurgitation, and in conditions when the e' is not reliable.[40]

The peak TR velocity measured via continuous wave Doppler reflects right ventricular systolic pressure.[43] Since increased left-sided pressures lead to pulmonary venous hypertension, peak TR velocity >2.80 m/s could indicate DD in the absence of pulmonary arterial hypertension. However, in liver disease, increased right ventricular systolic pressure can reflect multiple disease processes (*e.g.*, portopulmonary hypertension). Therefore, peak TR velocity alone is non-specific and should be considered in combination with other diastolic function variables and clinical criteria.

Standard 2-dimensional echocardiography

Increased LV filling pressure is transmitted to the LA, which subsequently dilates and remodels over time. Therefore, LA enlargement, defined as left atrial volume indexed to body surface area >34 ml/m^2 in sinus rhythm and >40 in atrial fibrillation, is an indicator of chronic DD[40,43] and is associated with risk of CHF after liver transplant.[44]

Diagnosing diastolic dysfunction

In patients with normal LVEF, DD is diagnosed when ≥3 of 4 abnormal diastolic function parameters exist (Fig. 2). If ≤1 criterion is met, diastolic function is considered normal. When ≤2 criteria are present, diastolic function is indeterminate.[1,40,43] A diastolic stress test during exercise and/or invasive measurement with right heart catheterisation may be needed for further evaluation. As with systolic dysfunction, other causes of DD should be excluded before diagnosing CCM.

When to perform echocardiography in patients with cirrhosis

Echocardiographic imaging has been suggested at 6-month intervals pre-transplant for all patients with cirrhosis, especially those with clinical evidence of CHF.[1] Patients with pre-transplant CCM should undergo echocardiography at 6, 12, and 24 months after transplant to assess for worsening or persistent cardiac dysfunction.[1] Whether asymptomatic patients with cirrhosis with less severe liver disease but potential markers of higher risk, such as prolonged QTc or elevated cardiac biomarkers, should undergo routine echocardiographic screening for CCM is unknown[26–29] and future studies are needed to address these questions.

Stress echocardiography

Patients with cirrhosis, especially in advanced stages, often have hypercontractile LV at rest, leading to less contractile reserve.[45] In the WCG criteria for CCM, an increase of LVEF on stress testing of <5% indicates decreased contractile reserve and probable subclinical LV systolic dysfunction.[46] However, given the lack of standardised criteria to define impaired contractile reserve on stress testing, the use of stress echocardiography to identify subclinical systolic dysfunction was not part of the 2019 diagnostic criteria for CCM.[1]

However, stress echocardiography plays a well-established role in identifying DD and may be useful in CCM. Patients with early DD may have similar haemodynamics to normal individuals at rest, which only become abnormal upon exercise (*i.e.*, increased cardiac output occurs at the expense of increased filling pressures during stress). Diastolic stress tests can be performed when patients are symptomatic but only have abnormal e' at rest.[40]

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) can provide complementary information to echocardiography and has an emerging role in the evaluation of CCM.[47,48] Compared to echocardiography, CMR has higher accuracy, reproducibility, and sensitivity and is not affected by poor acoustic windows, but processing of certain parameters, such as myocardial strain, can be time-consuming.[48] Furthermore, dobutamine stress testing can be performed using CMR to determine the presence of myocardial ischaemia and/or decreased contractile reserve.[49]

Late gadolinium enhancement (LGE) is a widely used CMR technique for myocardial tissue characterisation, including fibrosis, which is not readily assessed by echocardiography.[50] Focal fibrosis is less common in CCM than diffuse myocardial fibrosis, although the pattern and association of myocardial LGE with outcomes in patients with cirrhosis has not been well-studied.[38] This may be due to the limitations of LGE, which demonstrates relative differences in myocardial recovery times between areas of fibrosis or scar (LGE) and normal myocardium. Without normal reference myocardium for comparison, diffuse myocardial fibrosis can be missed by LGE imaging.[51]

Myocardial extracellular matrix volume fraction (ECV) using T1 mapping is a relatively new technique that measures the fraction of the myocardial space occupied by extracellular matrix and may be a more effective CMR method to assess diffuse fibrosis.[52,53] Myocardial ECV fraction is increased in patients with cirrhosis compared to healthy individuals and correlates with increasing Child-Pugh class.[38,54] High ECV is associated with worse transplant-free mortality,[54] but ECV may normalise 1 year after liver transplant, indicating that early-stage interstitial fibrosis can be reversible.[38]

CMR T2* imaging sequences, which quantify the relaxation parameter R2* in the ventricular septum, have been validated as a non-invasive measurement of cardiac iron overload, with lower T2* values indicating progressive iron overload.[55] Cardiac iron overload can occur in advanced cirrhosis, even in the absence of haemochromatosis.[56–58] A T2* <15 ms in liver transplant candidates is associated with increased post-transplant mortality and CHF.[57,59] It was also found that patients with an MELD (model for end-stage liver disease) score ≥25, Child-Pugh class C, and LVEF <65% were at a 5-fold increased risk of T2* <20 ms.[59] Despite the advantages of CMR and the additional information it can provide in patients with cirrhosis, at present, transthoracic echocardiography remains the initial test of choice to evaluate CCM given its wide availability, efficiency, and low cost. Further studies are needed to evaluate the additional role that CMR may play in the diagnosis of CCM; the current clinical use of CMR in CCM is mainly for the evaluation and exclusion of other potential causes of systolic or diastolic dysfunction.

Table 1. Diagnostic criteria systems for cirrhotic cardiomyopathy.

Criteria	Systolic dysfunction	Diastolic dysfunction
WCG criteria (2005)	LVEF <55% or Blunted increase in contractility on stress testing	E/A ratio <1.0 or DT >200 ms or IVRT >80 ms
CCC criteria (2019)	LVEF ≤50% or GLS <18	≥3 of the following E/e' ratio ≥15 e' septal <7 cm/s TR velocity >2.8 m/s LAVI >34 ml/m^2

CCC, Cirrhotic Cardiomyopathy Consortium; DT, mitral deceleration time; E/A, E-wave to A-wave ratio; GLS, global longitudinal strain (absolute value); IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; WCG, World Congress of Gastroenterology.

Diagnostic criteria: old *vs.* new?

The initial diagnostic criteria for CCM resulted from a consensus conference at the 2005 World Congress of Gastroenterology,[60] and are called the WCG criteria. In 2019, a group of multidisciplinary experts in the field (the Cirrhotic Cardiomyopathy Consortium, CCC), generated a new set of diagnostic criteria based on updated echocardiographic imaging parameters, called the CCC criteria.[1] The comparisons are shown in Table 1.

The use of the transmitral early (E) to late filling velocity (A) ratio (E/A, a parameter of diastolic function) in the WCG criteria has several limitations. First, E/A ratio is preload-dependent and its value decreases with interventions such as diuresis, dialysis, and paracentesis and increases with volume overload. Second, the left ventricular wall becomes stiffer with aging resulting in slower early filling velocity (E) and decreased E/A ratio.

Whether the CCC criteria are superior to the WCG criteria remains incompletely clarified. However, we believe that for several reasons, at present, the new criteria are superior.

There are currently six studies that have compared the WCG and CCC criteria or examined only the CCC criteria,[23–25,41,61] as listed in Table 2.[62]

Spann *et al.*[41] analysed 1,165 patients with echocardiography before liver transplantation. They further analysed 210 who met the WCG or CCC inclusion criteria. According to the WCG criteria, 77% (162/210) of patients had CCM, while this percentage was 30% (64/210) if they applied the CCC criteria. A limitation of this study is the retrospective nature and the unavailability of GLS because it was not a standard of measurement during the study period. Furthermore, none of their patients demonstrated an LVEF of <50%. Thus, the systolic criteria were not applicable. All the cases of CCM diagnosed according to the CCC criteria were based on DD. They found that the occurrence of major adverse cardiac events (MACEs; 44 patients) and deaths (31 cases) after liver transplantation were associated with the CCC criteria but not the WCG criteria. Based on these findings, the authors concluded that the CCC criteria are superior to the WCG criteria in predicting MACEs and post-transplant mortality.

Table 2. Prevalence of CCM according to the different diagnostic criteria.

Authors (Patients)	2005 WGC	2019 CCC	*p* value
Razpotnik *et al.*[61] (consecutive patients with cirrhosis)	66.2%	55.7% with GLS>22% 19.7% with GLS<18% only	*p* = n.s. *p* <0.05
Singh *et al.*[25] (LT candidates)	74.8%	85.6% with GLS<18% only	*p* = n.s.
Spann *et al.*[41] (LT candidates)	77%	30% without GLS	*p* <0.05
Arman *et al.*[62] (LT recipients)	78.6%	17.6%	*p* <0.01
Cesari *et al.*[24] (consecutive patients with cirrhosis)		29% including GLS>22%	
Izzy *et al.*[23] (LT recipients)		38.8%	

CCC, Cirrhotic Cardiomyopathy Consortium; GLS, global longitudinal strain; LT, liver transplant; WCG, World Congress of Gastroenterology.

Singh and coworkers[25] retrospectively reported data on 278 patients. According to the CCC criteria, 238 (85.6%) had CCM. This percentage was 74.8% (208/238) based on the WCG criteria. The mortality rates before liver transplantation were 19.3% in patients who met CCC criteria, 20.2% in those who met the WCG criteria and 25.0% in the patients with no CCM; none of these differences were statistically significant. The LVEF was >50% in all included patients. The patients with advanced DD based on the CCC criteria had a higher mortality rate than the other groups. However, the rates of acute kidney injury and hepatic encephalopathy before liver transplantation and the mortality after liver transplantation were similar in the CCC and WCG groups.

Razpotnik and coworkers[61] compared the CCC, WCG and 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines in 122 patients with cirrhosis. This prospective study found that 67.2% met WCG-CCM criteria and 55.7% met CCC-CCM criteria. Unfortunately, this study was conducted when the first publication of the CCC criteria contained a crucial error in listing GLS >22% as a criterion of CCM, and the relevant corrigendum[63] was only published several months later.[64] Therefore, the comparisons were based on the incorrect CCC criteria and were thus not accurate. When the correct CCC criteria were applied to these data, the prevalence of CCM dropped dramatically to only 19.7%.

A preliminary retrospective study by Arman *et al.*[62] analysed 131 patients with cirrhosis who underwent liver transplantation. They found that 103 (78.6%) met WCG criteria and 23 (17.6%) met the new CCC criteria. The patients who met the WCG criteria were older (58 *vs.* 55, $p = 0.034$), had lower mean heart rate (78 *vs.* 95, $p = 0.025$), and lower Fick cardiac index (3.8 *vs.* 4.6, $p = 0.022$). Meeting WCG criteria but not CCC criteria before liver transplantation was associated with MACEs after liver transplantation. They also found that patients with MACEs after liver transplantation had a higher prevalence of hepatorenal syndrome (HRS), ascites, and lower diastolic blood pressure.

Izzy *et al.*[23] evaluated 141 patients using CCC criteria and found that 34.8% had CCM. The risk of cardiovascular disease after liver transplantation was significantly higher in patients with CCM than in those without CCM ($p = 0.016$). This study did not compare the WCG and CCC criteria.

It seems that CCC criteria have some advantages in predicting adverse cardiovascular events after liver transplantation. However, WCG criteria also have predictive value for patients with cirrhosis undergoing major procedures. Cesari and coworkers[24] analysed 83 consecutive patients with cirrhosis and reported that after a 6-year follow-up period, the mortality rate was similar in those with or without altered GLS or advanced DD at baseline. These data suggested that the CCC diagnostic criteria were not valuable in predicting prognosis in patients with cirrhosis. These authors concluded that the CCC criteria are mainly descriptive, predominantly based on contemporary cardiovascular imaging parameters, and may lack prognostic value. Główczyńska *et al.*[65] contended that the exercise stress test is a reliable, safe and useful tool for the diagnosis of CCM in liver transplant candidates and should be included in cardiovascular assessment before liver transplantation.

It is clear that further comparative studies, preferably prospective, are needed. However, at present, the consensus seems to be that the WCG criteria are less useful because the criteria are not stringent or discriminatory enough, *i.e.* approximately 60-80% of patients with cirrhosis have CCM based on these criteria. On the other hand, only about 20-40% have CCM based on the CCC criteria. The only outlier to this trend, for reasons that remain unclear, is the study of Singh and colleagues who reported a surprising 85.6% prevalence with the CCC criteria.

Should prolonged QT interval be a diagnostic criterion?

Although there are several methods to correct QT interval for heart rate, Zambruni *et al.* confirmed that the Fridericia method is the most appropriate for patients with cirrhosis (Table 3).[66]

Factors associated with QTc prolongation have been studied. Bernardi *et al.*[67] showed that QTc prolongation is not related to aetiology of cirrhosis but to severity of liver dysfunction. There was a significant correlation between QTc length and Child-Pugh score; moreover, worsening of Child-Pugh score was associated with increasing QTc (ΔQTc). Henriksen *et al.*[68] also reported a positive correlation between QTc length and Child-Pugh score. However, Tsiompanidis and coworkers[69] did not find a correlation.

A study from the Lee lab confirmed that the cellular mechanism behind a prolonged QT interval in a rat model of biliary cirrhosis involved the abnormal function of two types of cardiomyocyte potassium channels: a transient outward and a delayed-rectifier current.[70]

Should a prolonged QT interval be part of the diagnostic criteria? There is no evidence of a connection between QTc prolongation and diastolic or systolic dysfunction. However, CCM is different from conventional cardiomyopathy; thus, if QTc prolongation has predictive value for cardiac-related mortality, it should be considered a criterion in CCM diagnosis. Bernardi *et al.*[67] verified that patients with a QTc longer than 440 ms had significantly lower survival rates than those with a normal QTc. Most, but not all other studies also reported a correlation between QTc prolongation and mortality.[71,72] Given these considerations, QTc prolongation might be considered in the diagnostic criteria for CCM.

Clinical relevance of CCM

CCM is associated with HRS. Ruiz del Arbol and colleagues showed that ventricular dysfunction precedes development of

Table 3. Normal values for QTc intervals by Fridericia correction[115,116].

QTc interval	Males	Females
Normal	<430 ms	<450 ms
Borderline	430-450 ms	450-470 ms
Prolonged	>450 ms	>470 ms

HRS triggered by bacterial infections.[73] The same Spanish group[74] followed 66 patients with cirrhosis, with tense ascites and normal serum creatinine levels; 27 patients who had lower mean arterial pressure and cardiac output developed HRS. Krag *et al.*[75] reported that lower cardiac index (<1.5 L/min/m) is associated with lower glomerular filtration rate and renal blood flow.

Ventricular dysfunction may also be associated with mortality risk. Rabie *et al.*[76] found that patients with an E/A ≤1.0 had significantly lower survival rates after transjugular intrahepatic portosystemic shunt (TIPS) insertion compared to those with an E/A >1.0. Cazzaniga *et al.*[77] reported that an E/A ≤1 at day 28 after TIPS is an independent predictor of death (relative risk 8.9; 95% CI 1.9 to 41.5; p = 0.005). Six of 10 patients with an E/A ≤1 died, whereas all 22 patients with E/A ratio >1 survived. Giannelli[78] demonstrated that reduced LV stroke work index was associated with mortality in patients with cirrhosis waitlisted for liver transplantation.

Finally, increasing evidence indicates a critical role of CCM in the setting of liver transplantation. Although an extensive review of this topic is beyond the scope of this manuscript, this subject has recently been reviewed in detail.[60,79,80] In particular, several studies have focused on whether CCM increases the morbidity and mortality of the transplantation procedure or predisposes to increasing risk of MACEs such as arrhythmias and heart failure, in the peri- and post-operative periods after liver transplantation.

Therapeutic strategies

Generally speaking, there is no specific treatment for CCM. Because of the marked peripheral vasodilatation and resultant hypotension associated with cirrhosis, vasodilators that are used in non-cirrhotic heart failure are unsuitable for the treatment of CCM. For example, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are contraindicated in patients with decompensated cirrhosis because of the risk of hypotension and HRS.[2] However, animal studies have revealed some potential treatment options (Table 4).[81–85]

Animal studies

Statins

Statins are pleiotropic molecules and can reduce liver fibrosis, inflammation, and portal pressure.[82] Mura *et al.*[86] demonstrated that simvastatin mitigates lipopolysaccharide-induced sinusoidal endothelial dysfunction by increasing nitric oxide availability. Marrone *et al.*[87] found that simvastatin decreases the expression of α-smooth muscle actin and procollagen I, alleviates oxidative stress in hepatic stellate cells and improves liver fibrosis.

Animal and human studies have shown that statins have anti-inflammatory and antifibrotic effects, reduce liver decompensation, disease progression, hepatocellular carcinoma development, and death.[88] Statins decrease levels of TNFα,[89] a proinflammatory cytokine, and thereby have an inhibitory effect on cirrhosis.[90] Niaz *et al.*[82] recently performed a study on the effect of atorvastatin on chronotropic dysfunction in cirrhotic rats, and showed that isoproterenol-stimulated atrial responses were significantly decreased in cirrhotic rats; this decreased contractility was reversed by atorvastatin. Moreover, the QTc interval, serum brain natriuretic peptide, TNFα, and malondialdehyde (MDA) levels were increased in cirrhotic rats, and atorvastatin significantly decreased these parameters.[35] All these data suggest that atorvastatin may have therapeutic potential in CCM.

Spermidine

Spermidine has multiple functions as an antioxidant and anti-inflammatory agent.[81] In cirrhotic rats, the level of heart oxidative stress is increased as evidenced by an increase of MDA, and decreased superoxide dismutase (SOD, a key antioxidant), and glutathione. Sheibani *et al.*.[81] tested the therapeutic effect of spermidine on CCM in rats following BDL. In comparison with the sham-control group, proinflammatory cytokines such as serum TNFα, IL-1β, and cardiac pNF-kB/NF-kB ratio were significantly increased in BDL rats. MDA, an index of oxidative stress, was significantly increased, while SOD levels were significantly decreased. Contractility of papillary muscles from BDL rats was significantly decreased. When spermidine (10 mg/kg) was

Table 4. Potential therapies in cirrhotic cardiomyopathy.

First author(s)	Substance	Mechanism of action	Species/model	Comments
Mookerjee *et al.*[114]	β-blocker (propranolol)	decrease portal pressure, intestinal permeability, and systemic inflammation	Patients with cirrhosis	Authors suggest to use during ‘therapeutic window’[117]
Silvestre *et al.*[108]	β-blocker (metoprolol)	decrease portal pressure, intestinal permeability, and systemic inflammation	RCT in patients with cirrhosis	No effect on contractile response to stress or cardiac remodelling
De Souza *et al.*[85]	Exercise	Alleviate liver injury, cardiac remodelling	Thioacetamide-cirrhotic rats	Improved cardiac function
Bortoluzzi *et al.*[83]	Albumin	Decrease inflammatory and oxidative stress	CCl_4-cirrhotic rats	Enhanced systolic function
Mousavi *et al.*[84]	Taurine	reduce lipid peroxidation, reactive oxygen species, protein carbonylation	Bile duct-ligated cirrhotic rats	Improved mitochondrial function and increased ATP levels
Sheibani *et al.*[81]	Spermidine	Decrease inflammatory and oxidative stress	Bile duct-ligated cirrhotic rats	Enhanced systolic function
Yoon *et al.*[22]	Galectin-3 inhibitor (N-acetyllactos-amine)	Decrease inflammation by inhibiting TNFα	Bile duct-ligated cirrhotic rats	Increased blood pressure; enhanced systolic and diastolic function
Niaz *et al.*[82]	Statin (atorvastatin)	Decrease inflammation and cardiac fibrosis	Bile duct-ligated cirrhotic rats	Increased chronotropic responses to isoproterenol, decrease QTc interval

CCl_4, carbon tetrachloride; RCT, randomised-controlled trial.

administered to BDL rats, it significantly reduced the levels of proinflammatory cytokines, such as serum TNFα, interleukin 1β, the pNF-kB/NF-kB ratio in the BDL heart. Furthermore, spermidine significantly reduced MDA and increased SOD levels. Moreover, the QTc interval was significantly decreased in the BDL + spermidine group compared with that in BDL controls (204 ± 4 *vs.* 170 ± 5 ms, p <0.001). Spermidine also significantly increased the contractility of papillary muscles (p <0.001). To summarise, spermidine significantly improved the cardiac condition and thus may be a candidate for the treatment of CCM.

Albumin

It is well known that albumin has anti-inflammatory and antioxidative effects.[91] Bortoluzzi and colleagues[83] performed a study to test the therapeutic effect of albumin on CCM induced by carbon tetrachloride (CCl_4) in rats. They found that in cirrhotic animals, the protein expression of Gαi2 (an inhibitory protein), TNFα, and iNOS (inducible nitric oxide synthase) was significantly increased (all p <0.05), as was NAD(P)H-oxidase activity (p <0.05) and nuclear translocation of NF-κB (p <0.05). Adcy3 (adenylate cyclase 3), a membrane-associated enzyme that catalyses the formation of the secondary messenger cAMP which plays an essential role in stimulating cardiac contractility, was significantly decreased in the cirrhotic heart (p <0.05). These changes resulted in a significant reduction in cardiac contractility in cirrhotic rats compared to controls (p <0.01). Albumin infusion reversed these changes in the cardiac tissue of cirrhotic rats to control levels (all p <0.05) and significantly increased cardiac contractility.

Bile acids

Bile acids suppress cardiac function and play an important pathogenic role in CCM.[92] There are many ways to manipulate the serum content of bile acids and improve cardiac function. For example, cholestyramine, a bile acid-binding resin, significantly decreases serum bile acids and improves cardiac function.[92] Taurine although not a bile acid is abundant in bile. It protects the murine heart in transverse aortic constriction-induced heart failure[93] by mitigating apoptosis, reducing myocyte hypertrophy, fibrosis and oxidative stress. As apoptosis,[94] myocyte hypertrophy,[95] fibrosis[96] and oxidative stress[91] are all features of CCM, taurine may be a useful treatment. Mousavi and coworkers[84] evaluated the protective effect of taurine in a rat model of BDL-induced CCM. They reported that taurine significantly reduced lipid peroxidation, reactive oxygen species and protein carbonylation in the cirrhotic heart. Cardiac total antioxidant capacity, the ratio of reduced to oxidised glutathione and mitochondrial ATP content were also increased by taurine. Overall, taurine alleviated oxidative stress and improved mitochondrial function in the BDL cirrhotic heart.[84] Furthermore, taurine led to a reduction in markers of liver and heart injury.

Galectin-3 inhibitor

Galectin-3 is significantly increased in patients with cirrhosis[97] and animal models.[22] Various studies implicate a pathogenic role of galectin-3 in non-cirrhotic types of cardiac dysfunction. Increased galectin-3 is associated with both systolic[98] and diastolic dysfunction.[99] van Kimmenade and colleagues[100] revealed a correlation between galectin-3 and heart failure. The infusion of recombinant galectin-3 into the pericardial space in rats depresses LVEF, reduces the amplitude of the negative slope of dP/dt_{max} and leads to fractional shortening.[101] *N*-acetyllactosamine, a galectin-3 inhibitor, significantly reduces cardiac fibrosis and inflammation,[102] and improves left ventricular function, consequently reducing the risk of heart failure.[103] We previously demonstrated that *N*-acetyllactosamine downregulates galectin-3, decreases the cardiac level of TNFα and improves cardiac function in cirrhotic rats.[22] Therefore, our results imply that galectin-3 inhibition may be a potential therapeutic strategy.

Exercise

Exercise benefits many patients with different conditions. For example, exercise improves cardiopulmonary function in patients with coronary artery diseases.[104] de Souza *et al.* used[85] TAA to induce cirrhosis in rats and reported that the TAA + exercise group had significantly milder liver injury compared with TAA control rats. Furthermore, exercise alleviated cirrhosis-associated cardiac remodelling, such as the diastolic and systolic left ventricular diameters, and improved systolic and diastolic dysfunction. These data indicated that exercise training alleviates the CCM phenotype in TAA-cirrhotic rats.

Human studies

As there is no proven specific treatment for CCM, management of patients with CCM should concentrate on symptomatic treatment of CHF, *e.g.* with oxygen therapy, sodium restriction, and diuretics.[105] Besides reducing the risk of bleeding from oesophageal varices,[106] β-blockers alleviate systemic inflammation by reducing portal pressure, mesenteric venous congestion and intestinal permeability, thereby reducing the entry of inflammatory cytokines into the circulation. The alleviation of systemic inflammation may benefit the heart.[107] Moreover, β-blockers shorten the QTc interval in cirrhosis[106] and thus decrease the risk of ventricular arrhythmias. However, a six-month randomised-controlled trial demonstrated that β-blockers do not improve cardiac morphology and function in patients with CCM.[108] Moreover, Alvarado-tapias *et al.*[109] found that β-blockers may reduce survival in patients with decompensated cirrhosis. Giannelli *et al.*[78] investigated the therapeutic role of non-selective β-blockers (NSBBs) in patients with refractory ascites and found that NSBBs increase mortality in patients with compromised cardiac performance on the liver transplantation waiting list; patients with refractory ascites are at higher risk of compromised cardiac performance.

There is a "window theory" on the use of NSBBs in patients with cirrhosis.[110] Sympathetic nervous system activity is near normal in early stage cirrhosis, thus NSBBs may not be effective; in advanced stages of cirrhosis, NSBBs may not be appropriate because they reduce cardiac contractility and arterial pressure. The window phase is thus between "too early and too late". However, the time points at which the window "opens and closes" remain unclear.

Fukuta *et al.* performed a meta-analysis and found that exercise training improves exercise capacity, quality of life,[111] and clinical outcomes[112] in patients with heart failure. This may also apply to patients with CCM. Yuan *et al.*[113] evaluated cardiac health in patients with hepatitis B virus-related cirrhosis and suggested that physical exercise should be emphasised in the daily routine of patients with cirrhosis to improve exercise tolerance and general well-being. Clinicians should highlight the beneficial effect of exercise on improving quality of life in patients with CCM.

Because CCM is based on cirrhosis, the substitution of a diseased liver for a healthy one may reverse CCM, and liver transplantation is currently the only effective treatment option. There is relatively little literature on transplantation correcting CCM but current evidence suggests that this is indeed the case.[105] However, a detailed discussion of transplantation is beyond the scope of this review.[79]

Future perspectives: 5-year timeline

We believe the most pressing needs over the next 5 years are three important areas. First, long-term prospective studies, preferably multicentric, that examine outcomes such as mortality and relevant complications including renal dysfunction, bleeding and decompensation risk, and other complications potentially related to CCM are needed. These studies should address whether the old or the new diagnostic criteria are superior predictors of clinically relevant outcomes.

Second, refinement of diagnostic imaging methods, in particular whether echocardiography is sufficient or if MRI cardiography provides useful additional information, should be tested prospectively. In this regard, the ILTS (International Liver Transplant Society) Cardiovascular Special Interest Group is currently considering the possibility of a multicentre prospective study comparing echocardiography and MRI cardiac scanning.

Finally, clinical studies should be performed to assess the safety and efficacy of treatment modalities that have shown promise in animal studies.

Conclusions

We have reviewed the latest advances in cardiac imaging including echocardiography and MRI methods. The new 2019 diagnostic criteria seem to be superior to the 2005 criteria, but further studies are needed. Although prolonged QT is found in a significant subset of patients with cirrhosis, whether it should be one of the diagnostic criteria for CCM remains unresolved to date. Finally, animal studies suggest a number of potential treatment avenues to explore in the future. However, at present, liver transplantation appears to be the only therapeutic strategy that is effective in treating CCM.

Abbreviations

BDL, bile duct ligation; CCC, Cirrhotic Cardiomyopathy Consortium; CCM, cirrhotic cardiomyopathy; CHF, congestive heart failure; CMR, cardiac magnetic resonance; DD, diastolic dysfunction; E/A, E-wave to A-wave ratio; ECV, extracellular matrix volume fraction; GLS, global longitudinal strain; IL-, interleukin-; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; LVEF, LV ejection fraction; MHC, myosin heavy chain; NSBBs, non-selective β-blockers; TAA, thioacetamide; TIPS, transjugular intrahepatic portosystemic shunt; TNFα, tumour necrosis factor-α; TR, tricuspid regurgitation; WCG, World Congress of Gastroenterology.

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept: SSL and GL. Writing first draft: all authors. Revision of manuscript for content: all authors. Final revision and approval of R1 resubmission: all authors.

Supplementary data

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