REVIEW

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Cirrhotic Cardiomyopathy: Mechanisms, Diagnostic Tools and Therapeutic Options

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ABSTRACT

End-stage liver disease is linked to cardiovascular complications that can manifest as hyperdynamic circulation and may progress to overt heart failure in the context of cirrhotic cardiomyopathy (CCM). The incidence of CCM is significantly elevated among individuals with cirrhosis. However, due to the absence of overt symptoms at rest and the preservation of left ventricular systolic function, the diagnosis is frequently overlooked. The severity of CCM correlates directly with the degree of liver disease and is associated with poorer prognostic outcomes in both pre- and post-transplantation. Diagnosis is important because CCM is a major contributor to perioperative cardiovascular complications (including pulmonary edema and death) after liver transplant. These complications arise from the rapid escalation of systemic vascular resistance, which unmasks the subclinical left ventricular systolic dysfunction. Another clinical context in which CCM becomes evident is following transjugular intrahepatic portosystemic shunt placement. The abrupt increase in preload from blood redistribution can precipitate cardiac decompensation. The purpose of this review is to increase clinical recognition of this specific phenotype of heart failure with preserved ejection fraction. It aims to synthetize the pathophysiological mechanisms, definition, and diagnostic of CCM, also to highlight its clinical significance in the cirrhotic population and explore the possible therapeutic options. A literature review was performed using Pubmed and focused on the relevant and recent articles and trials concerning CCM. Based on literature data and on institutional experience, we propose an algorithm for cardiac assessment in cirrhosis to improve CCM diagnosis and ensure better outcomes.

Key words: cirrhotic cardiomyopathy – diastolic dysfunction – end stage liver disease – liver transplant – transjugular intrahepatic portosystemic shunt.

Abbreviations: ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor neprilisine inhibitor; BB: beta blocker; BNP: brain natriuretic peptide; CCM: cirrhotic cardiomyopathy; CMR: extracellular volume fraction calculation; cardiac magnetic resonance; CO: carbon monoxide; DD: diastolic dysfunction; ECV: ESLD: end-stage liver disease; GLS: global longitudinal strain; HC: hyperdynamic circulation; HD: hyperdynamic circulation; HF: heart failure; HRS: hepato-renal syndrome; LA: left atrium; LGE: late gadolinium enhancement; LT: liver transplant; LV: left ventricle; LVEF: left ventricule ejection fraction; MRA: mineralocorticoid antagonist; NO: nitric oxide; NT-proBNP: N-terminal pro BNP; RAAS: renin-angiotensin-aldosterone system; SBS: spontaneous bacterial peritonitis; SGLT2i: sodium glucose cotransporter 2 inhibitors; SNS: sympathetic nervous system; sPAP: pulmonary artery systolic pressure; SVR: systemic vascular resistance; TDI: tissue Doppler imaging; TIPS: transjugular intrahepatic portosystemic shunt; TR: tricuspid regurgitation; TTE: transthoracic echocardiography.

INTRODUCTION

Cirrhotic cardiomyopathy (CCM) is a relatively new clinical entity. It was defined for the first time in 2005 at the World Congress of Gastroenterology at Montreal. Its main characteristic is a subclinical cardiac contractility impairment during stress or exercise, and, more common, left ventricle (LV) diastolic dysfunction (DD). Exclusion of other previous cardiovascular disease is essential for diagnosis.

Cirrhotic cardiomyopathy can occur in all types of cirrhosis. Its pathogenesis involves multiple cellular and systemic mechanisms, with hyperdynamic circulation (HC) representing the central driver in end-stage liver disease (ESLD).

Clinically it manifests as the inability of the heart muscle to react to external stress factors, resulting in an inadequate cardiac output increase and hypoperfusion. Systemic vasodilation and reduced systemic vascular resistance (SVR) mask the LV impaired systolic function in normal conditions. Clinical significance of CCM results from the high incidence of heart failure (HF) events and deaths that occur early after liver transplant (LT) and transjugular intrahepatic portosystemic shunt (TIPS). Assessing cardiac function is important in cirrhotic patients with signs or symptoms of HF, but also in asymptomatic patients when candidacy for TIPS or LT is considered.

No single diagnostic tool can definitively confirm the existence of CCM. Clinicians must integrate non-specific clinical findings, multimodality imaging (echocardiography, cardiac magnetic resonance), pharmacological stress tests and biomarkers [N-terminal pro brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP)].

The introduction of novel diagnostic criteria in 2019, which incorporated subclinical systolic dysfunction parameters such as global longitudinal strain and a comprehensive evaluation of diastolic function, seeks to enhance the recognition of this condition.

PATHOPHYSIOLOGY: CIRRHOSIS AND HYPERDINAMIC CIRCULATION

The pressure difference between the portal vein and the inferior vena cava in cirrhosis leads to shear stress and bacterial translocation, inflammation, and angiogenesis, favouring the development of collateral vessels (portosystemic shunts). The compromised liver experiences a decline in its metabolic and immune functions, resulting in elevated levels of splanchnic vasodilators and inflammatory cytokines redirected towards the systemic circulation.

Hyperdynamic circulation is defined by reduced SVR and low blood pressure, which are detected by arterial baroreceptors. This triggers activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), determining tachycardia, renal vasoconstriction and retention of sodium and water resulting in excess of total body fluid (Fig. 1). This is accompanied by a paradoxical systemic circulation hypovolemia, as the blood volume within the splanchnic circulation is increased [1, 2].

Cytokines are responsible for endothelial dysfunction. High concentration of the various vasodilatory mediators [prostacyclines, nitric oxide (NO), endocannabinoids, and carbon monoxide (CO)] as well as vasoactive substances (adrenaline, noradrenaline, atrial natriuretic peptide, glucagon, renin, substance P, aldosterone, vasopressin) reach systemic circulation through portosystemic shunts [3].

As the liver disease advances, the compensatory mechanisms for splanchnic vasodilation are exceeded [5].Fluid accumulation in the splanchnic region, contributes to the formation of ascites. The process of bacterial translocation increases the risk of infections, such as spontaneous bacterial peritonitis (SBP), promoting further inflammation and vasodilation. Elevated pressure in the portosystemic shunts raises the likelihood of variceal bleeding. Excessive renal vasoconstriction and hypoperfusion can lead to hepato-renal syndrome (HRS) [4].

Chronotropic and inotropic impairment, characteristic to CCM, result from prolonged and excessive SNS activation. This can lead to direct damage to the myocardium due to noradrenaline exposure, alongside with a desensitization of β-adrenergic receptors [5].

Neurohormonal responses via RAAS and SNS also promote cardiac remodelling (hypertrophy, fibrosis). Also, sodium and water retention and HC generate volume overload which increase LV filling pressures (Fig. 1). These can induce LV DD.

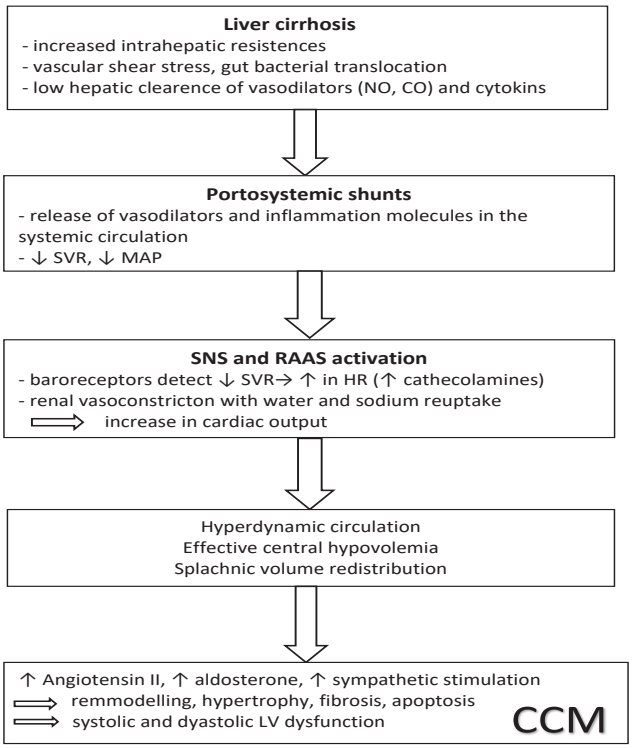

Fig. 1. Cirrhotic cardiomyopathy pathophysiological mechanisms [1-8, 18, 10- 13, 26]; NO: nitric oxide; CO: carbon monoxide; SVR: systemic vascular resistances; MAP: mean arterial pressure; HR: heart rate; CCM: cirrhotic cardiomyopathy.

Alongside neurohormonal activation, proinflammatory state is also a culprit in CCM pathology. Cytokines and vasodilators interact with the myocytes, resulting in contractility impairment through a transition in myosin heavy chain isoform from the α-type to the weaker β-type, as well as by triggering apoptosis [6].

Excess of TNF α, endocannabinoids and NO have negative inotrope effect and reduce cardiac systolic performance in cirrhotic patients with infections [7]. In patients with HRS, a difference between the peripheral vascular response and cardiac response to SNS activation was noted. Even if peripheral vessels contract to maintain the arterial pressure, the hearts response is slower to improve cardiac output. The reasons lie in the reduced venous return due to severe vasodilation, but also involve the chronotropic and inotrope cardiac dysfunction due to long standing SNS over activation and cytokine effects [7].

Nitric oxide and CO play a crucial role in arterial vasodilation by increasing cGMP in the smooth muscle of blood vessels. They impair cardiac contractility by reducing

cAMP (the most important β-adrenergic mediator). Nitric oxide also supresses the sarcolemmal L-type calcium channel [2]. Anandamide, the most prevalent cannabinoid, diminishes myocardial contractility by binding to Cannabinoid-1 receptors [6]. Endotoxin activated macrophages produce TNFα, which promotes the production of NO and enhances the release of anandamide, highlighting the role of inflammation in exacerbating cardiac dysfunction [2].

Beyond neurohormonal and inflammatory injury, elevated bile salts in systemic circulation exert direct cardiotoxicity (apoptosis and β-receptor down-regulation) [8].

QT interval prolongation is present in ~40–50% of cirrhotic patients and reflects autonomic imbalance (SNS overactivity, vagal impairment) [9].

DEFINITION AND DIAGNOSIS CRITERIA

Diagnosis requires a high index of suspicion. Up-front HF symptoms usually relate to stressful situations that determine decompensation. Usually, in cirrhotic patients, such events are infection, TIPS placement or LT [14-16]. The presence of DD influences survival in cirrhosis as mortality rates were positively correlated with LV DD grade [17].

The definition and diagnosis of CCM are still undergoing significant changes as new imaging techniques and biomarkers continue to emerge. The initial diagnostic criteria were established in 2005. They included a diminished contractile response during stress testing and a resting left ventricule ejection fraction (LVEF) of less than 55%. The indicators of DD were prolonged mitral deceleration time, an extended isovolumic relaxation time and an E/A ratio of less than 1.0. Additional criteria encompassed electrophysiological abnormalities, enlarged left atrium (LA) and increased biomarkers (Table I) [18].

In the next years, novel echocardiographic techniques such as tissue Doppler imaging (TDI) and speckle tracking became widely available. In 2016 the American Society of Echocardiography published a new position paper regarding diastolic function evaluation [19].

Using 2D echocardiography a trend towards over diagnosing CCM was noticed. The prevalence of 61% using the 2005 criteria dropped to 45% when adding TDI [20, 21]. The reason was 2D echocardiography and especially the cut – off for the E/A ratio lacked sensitivity in identifying DD and generated false positive diagnoses.

Cirrhotic cardiomyopathy diagnostic criteria were updated in 2019 by an expert multidisciplinary commission (Cirrhotic Cardiomyopathy Consortium). They focused on echocardiography parameters that are less dependent on loading conditions, such as TDI and speckle tracking. Also, they aimed to improve LV subclinical systolic dysfunction detection by introducing global longitudinal strain (GLS). LV systolic dysfunction was characterized by reduced LVEF or low absolute GLS in those patients with apparent normal cardiac function. Left ventricular DD was defined by the presence of at least 3 out of 4 characteristics: low septal e' velocity, high ratio of E/e', LA enlargement and high tricuspid regurgitation (TR) velocity (Table I). Due to a lack of standardised definition of abnormal stress test results, this criterion was left out. Initially higher than normal absolute GLS value (>22%) was also included in the diagnostic, but was later dropped, as high GLS could be a mark of a more severe liver disease and hemodynamic disturbance, but not a clear sign of a myocardial pathology.

The reported prevalence of CCM varies with criteria: 50–70% with 2005 criteria vs. 29–55.7% with 2019 criteria [24, 25]. Future refinements may include standardized stress testing and advanced imaging (cardiac MRI) to better characterize structural myocardial changes.

DIAGNOSTIC TESTS

Symptoms such as breathlessness and fatigue can be present in cirrhotic patients due to ascites and peripheral muscle wasting. They can present with edema and pleural effusion in the context of hypoalbuminemia. This overlap with HF symptoms and the usual absence of symptoms at rest makes the diagnosis difficult.

Tabel II summarises the most important diagnostic tools in CCM.

Table I. CCM diagnostic criteria [8, 10-13, 23, 18, 22, 26, 27]

Cirrhotic Cardiomyopathy Diagnostic Criteria			
2005 World Congress of Gastroenterology		**2019 Cirrhotic Cardiomyopathy Consortium**	
Systolic Dysfunction (any of the following) AND/ OR	Blunted contractile response on stress testing LVEF < 55%	GLS < 18% (absolute) LVEF ≤ 50%	**Systolic Dysfunction** (any of the following) AND/ OR
Diastolic Dysfunction (any of the following)	TDE > 200ms E/A <1 IVRT> 80ms	Septal e'< 7cm/s E/e'≥ 15 LA vol. index> 34ml/m^2 TR velocity> 2.8m/s	**Diastolic Dysfunction (3/ 4 of the following)** 0 or 1/4 – normal 2/4 - indeterminate
Supportive criteria (not diagnostic)	Electrophysiological anomalies: Chronotropic dysfunction Electromechanical uncoupling Prolongued QTc interval Dilated LA Increased LV mass Increased NT proBNP or BNP Increased hsTnI	ECG changes Abnormal chronotropic or inotropic response Electromechanical uncoupling Myocardial mass change Chamber enlargement Serum biomarkers CMR imaging	**Future research** (not diagnostic)

A: atrial contraction peak velocity; BNP: brain natriuretic peptide; E: early diastolic mitral peak velocity; GLS: global longitudinal strain; hs TnI: high sensitive troponin I; LA: left atrium; LV: left ventricle; LVEF: left ventricule ejection fraction; IVRT: isovolumic relaxation time; TDE: deceleration time of E wave; TR: tricuspid valve regurgitation..

Table II Diagnostic investigations in cirrhotic cardiomyopathy [16, 19, 21, 26 - 55]

Diagnostic tools in cirrhotic cardiomyopathy		
Investigation	**Information**	**Advantages/ disadvantages**
Echocardiography	Chamber volumes/diameters Valve function Systolic function LVEF, GLS Diastolic function E, A, E/A, TDE, IVRT, septal and lateral e', E/e' LA volume TR velocity/ sPAP	Available Cost effective Diagnostic criteria information Serial evaluation while on waiting list or prior and after procedures (LT, TIPS) Prognostic information [20, 34] Information regarding other cardiac pathologies (CAD, valve disease)
CMR	Increased extracellular volume fraction - mark of cellular edema and diffuse fibrosis - frequent in CCM - reversible after LT Late gadolinium enhancement - detects focal areas of fibrosis - rare in CCM	Detailed structural information Precise LVEF measurement Not influenced by acoustic window Prognostic information [42] Limited accessibility, reserved for particular cases Expensive Time consuming analysis for diastolic function parameters
ECG	Prolonged QTc Sinus tachycardia/ bradycardia Atrial fibrillation	Limited information Limited prognostic value (A. fib./ sinus tachycardia) [50, 51] CAD probability information in presence of STT abnormalities/ Q waves
NT proBNP/ BNP **Hs TnI**	Myocardial wall stress Hypervolemia	Prognostic information [16, 47, 52] Serial determinations while on waiting list or prior and after procedures (LT, TIPS) CAD probability (hs TnI)
Stress tests		
ECG treadmill test	Chronotropic incompetence Modified heart rate reserve (MHRR)	Prognostic information - low MHRR correlated with increased risk of HF [53] Limited by reduced exercise capacity in cirrhosis
CPET	VO2 max Anaerobic threshold	Prognostic information (VO2max< 60% predicts 1 year mortality on LT waiting list) [54]
Dobutamine stress echocardiography	Diagnostic of DD when resting echocardiography is unclear (increase in E/e') Unmasks systolic dysfunction (<10% increase in LVEF)	Lack of standardised definition of chronotropic and inotrope incompetence No longer included in diagnostic criteria Increased CCM diagnostic from 7.7% to 61.5% [55]

CAD: coronary artery atherosclerotic disease; CCM: cirrhotic cardiomyopathy; CMR: cardiac magnetic resonance; CPET: cardiopulmonary exercise testing; LVEF: left ventricle ejection fraction; GLS: global longitudinal strain; IVRT: isovolumic relaxation time; LA: left atrium; LT: liver transplant; sPAP: systolic pulmonary arterial pressure; TDE: deceleration time of E diastolic wave; TR: tricuspid valve regurgitation; VO2 max – maximal oxygen consumption.

Transthoracic echocardiography (TTE) is the first line investigation for CCM. It is accessible and offers myocardial structural and functional information. Hyperdynamic circulation and reduced SVR lead to an increased cardiac contractility in cirrhotic patients without CCM. An EF below 50% is considered abnormal.

Apart from LVEF, a new parameter, GLS, was introduced to diagnose subclinical systolic LV dysfunction. It represents a percentage of longitudinal shortening performed by the subendocardial LV longitudinal fibres, which are more susceptible than the rest to ischemia and wall stress. They are the first affected in all cardiomyopathies. Global longitudinal strain is represented as a negative number because the myocytes shorten during systole. The normal values are less or equal to -18%. For simplification, the absolute GLS value will be used (normal GLS >18%). A decline in GLS in CCM patients is expected early in the course of the disease. Yet, GLS data from clinical trials in cirrhotic patients is conflicting [26]. Indeed multiple studies demonstrated decreased GLS in cirrhotic patients [28-30]. Still, other authors found no difference in GLS comparing to controls but showed increased LVEF corresponding to the severity of the liver disease [31]. Elevated resting GLS was associated with advanced liver disease in another study. Authors showed that both below and above normal GLS predicted mortality [32]. The systemic vasodilation progresses with liver disease and could explain LV increased contractility [33]. GLS was higher in patients with more advanced cirrhosis, explaining the correlation with a higher risk of death [32]. These results reflect the various haemodynamic effects of cirrhosis in patients with a normal myocardium (increased GLS) and those with CCM (decreased GLS). A reduced GLS was associated with an increase in HF events after LT [34].

Diastolic dysfunction diagnosis was initially based on a mitral pulse wave Doppler profile and included preload dependent parameters that increase with hypervolemia and decrease after diuretic treatment. E/A ratio has a U curve evolution, with similar diastolic pattern in advanced DD and in young healthy adults. The 2019 criteria introduced a more detailed definition with 4 parameters that are less dependent on preload. Tissue Doppler imaging measures tissue velocity, septal and lateral e' represent septal and lateral mitral annulus velocity during early diastole. Septal and lateral e' values below 7 and respectively 10 cm/s are suggestive of impaired LV relaxation and precede the decline in E wave velocity [19]. Decreased septal e' was associated with worse cardiovascular prognosis including risk of death after LT [35]. Tissue Doppler imaging cannot be used in patients with wall motion anomalies or calcification of the mitral annulus. The E/e' ratio correlates with LV filling pressure and pulmonary capillary wedge pressure [36]. Values of E/e' >15 are considered indicative of high LV filling pressure. A study demonstrated that E/e' >9.2 predicted arrhythmias and atrial fibrillation in patients with cirrhosis after LT [34]. TR velocity indicates pulmonary artery systolic pressure (sPAP), a value exceeding 2.8 m/s suggesting DD as sPAP increases due to elevated LV filling pressures that translate to the LA and to the pulmonary vasculature. This parameter alone is not specific and must be used in association with the other parameters. The left atrium dilates in time due to the increased LV filling pressure and a value above 34 ml/m^2 is indicative of DD. Left atrium dilation can be present in cirrhotic patients in the context of the HC, even if DD has not yet developed. Considering these caveats, 3 out of 4 parameters are required in order to diagnose LV DD. Normal diastolic function can be established if only one or none of the criteria is met. When 2 criteria are present, diastolic function cannot be determined and further testing is needed [19].

Cardiac magnetic resonance (CMR) permits for a more reliable LVEF assessment in patients with a difficult acoustic window and provides important information regarding cellular structure not available otherwise [37]. Late gadolinium enhancement (LGE) and extracellular volume fraction calculation (ECV), evaluate the presence of myocardial fibrosis and cellular edema. In CCM patient's focal fibrosis areas are rarely observed [38]. LGE, which is based on comparing relative differences in myocardial recovery times (fibrosis vs. normal), is of limited use in CCM patients who display a diffuse myocardial fibrosis pattern that can be missed entirely with no normal reference myocardium to compare [39]. ECV is a more reliable method to assess diffuse fibrosis and cellular edema in this population [40, 41]. Myocardial ECV fraction is increased in ESLD patients. Patients with more severe liver disease and ascites exhibited higher ECV values. Wiese et al. indicated that an increase in ECV is linked to the progression of liver disease and established a connection between high ECV levels and poorer outcomes [42]. ECV usually reverts to normal at one year after LT, indicating CCM abnormalities are not definitive [43]. End stage liver disease is associated with iron metabolism anomalies that result in elevated myocardial iron levels. T2* imaging is utilized to assess iron accumulation in the heart or liver. One study found that T* values lower than 20ms correspond with advanced liver disease (MELD>25 and Child C), and those with values below 15ms were related to worse outcomes post LT [44].

Stress echocardiography assessment in patients with liver cirrhosis is difficult because they typically exhibit reduced inotropic and chronotropic reactions during physical exertion or pharmacological stress. Even using dobutamine, the cardiac response remains abnormal. A rise in LA filling pressure during physical activity or stress may indicate DD among cirrhotic individuals. A significant limitation is the absence of clear thresholds for determining inotropic and chronotropic impairment. [45].

Brain natriuretic peptide and NT proBNP are the most utilised biomarkers. Cirrhosis implies hypervolemia, LA dilation, increased filling pressure and wall stress, all determining an increase in BNP/ NT proBNP compared to healthy controls. Higher values are noted during acute settings such as decompensation, ascites, encephalopathy, bleeding or BPS [46]. MELD score, Child classification and NT proBNP predict unfavourable outcomes in patients waiting for LT and in a post operatory setting. Bernal et al. showed that cardiac complications occurred in 37% of LT patients with NT proBNP > 2000pg/ml, compared with 9% in the other group [47]. Routine evaluation of BNP/ NT proBNP in cirrhotic patients on transplant list could be an important tool for better risk stratification.

Troponin (hsTnI) also increases due to myocardial wall stress and reflects myocyte damage. Increased troponin in cirrhosis is linked with a risk of adverse events. Coss et al. [48] demonstrated that pretransplant elevated troponin levels are associated with cardiovascular adverse events after LT. Almost half of the cirrhotic patients without known cardiac disease presenting to the emergency room for decompensation, had increased troponin and the value correlated with one year mortality [21, 49].

TREATMENT

Heart failure treatment has seen remarkable progress in the recent years, and the prognosis of patients with reduced EF has improved using the four therapeutic pillars [angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), angiotensin receptor neprilisine inhibitors (ARNi), mineralocorticoid antagonists (MRAs), sodium glucose cotransporter 2 inhibitors (SGLT2i) and betablockers (BB) [56].

No clear treatment recommendations exist for CCM patients. Therapeutic management in end stage cirrhotic patients with ascites consists of sodium and water restriction, paracentesis and high dose MRAs combined with loop diuretics [57].

Regarding the possible application of HF medical treatment guidelines in CCM patients, the clinical and pathophysiological characteristics of cirrhosis must be considered. Angiotensin converting enzyme inhibitors, ARB, ARNi are not tolerated by Child C decompensated cirrhotic patients, despite high RAAS activity due to important peripheral vasodilation. These drugs further decrease SVR reducing renal perfusion and increasing risk of HRS. Angiotensin converting enzyme inhibitors, ARBs, ARNi use is restricted to patients in the initial stages of liver disease [58].

Some drugs already used in cirrhosis may have theoretical advantages in CCM due to an overlap between pathophysiology and therapeutic mechanisms (Table III).

Mineralocorticoid antagonists offer unique advantages in patients with CCM. These drugs counteract the RAAS activation, excess angiotensin II and secondary hyperaldosteronism that are present in cirrhotic patients. Because of that, MRAs reduce water and sodium retention, they improve portal hypertension and display antifibrotic effects in both myocytes and hepatocytes. The use of MRAs helps slow down liver disease progression and prevent decompensation. At cardiac level, MRAs have a positive effect on left ventricular remodeling, reduce hypertrophy and mitigate fibrosis, thus improving diastolic function [59, 60].

Non-selective BB (**propranolol**) have been traditionally used in cirrhotic patients, reducing portal hypertension, and preventing esophageal varices haemorrhage [62]. Beta blockers protect myocytes from SNS over activation by blocking the β1 receptor, also they increase splanchnic vasoconstriction, reduce mesenteric congestion and stimulate intestinal contractility due

Table III. Possible Cirrhotic Cardiomyopathy treatment options [8, 12, 13, 18, 21, 59 – 75, 76- 80]

Possible cirrhotic cardiomyopathy therapeutic options			
Medication	**Class/ Mechanism**	**Key Results**	**Clinical evidence**
Propranolol	NS Betablockers: - Reduce portal gradient - Improve inflammation and -prevent bacterial translocation - Prevent esophageal haemorrhage - Prevent direct myocardial damage due to sympathetic overstimulation	Cirrhotic patients with refractory ascites Survival in propranolol group 19% versus 64% in no BB group Non randomised, selection bias suspected Cirrhotic patients on LT waiting list BB reduced mortality in all patients, including those with refractory ascites	Serste et al. [63] Leithead et al. [74]
Metoprolol	Possible harm in severe patients, the reduction of CO and MAP, resulting in hemodynamic deterioration Should be stopped if MAP< 65mmHg	CCM diagnosis using dobutamine stress echocardiography Metoprolol versus Placebo No difference in diastolic function or other echo parameters	Silvestre et al. [67]
Carvedilol		Retrospective analysis Cirrhotic patients with ascites Improved survival in carvedilol group (24%) versus no BB (2%)	Sinha et al. [65]
Ivabradine	No negative inotrope effect No effect on MAP Reduces HR by blocking sinus node I_f channel Improve DD by HR reduction	Cirrhotic patients with DD Carvedilol ± ivabradine versus no treatment Improved DD, NT pro BNP Improved 1 year mortality, reduced risk of encephalopathy and kidney injury	Premkumar et al. [66]
Spironolactone	MRAs counteract: RAAS activation Angiotensin II excess Aldosterone excess	Child A preascitic cirrhotic patients Potassium canrenoate 200mg versus no MRA treatment Significantly reduced LV wall thickness, LV end diastolic volume, portal gradient No effect on E/A ratio or diastolic function	Pozzi et al. [61]
Eplerenone	Prevent decompensation of liver disease, reduce portal pressure Positive effect on: LV remodelling LV fibrosis LV hypertrophy	Spironolactone 100mg compared to eplerenone 100mg in cirrhotic patients with ascites No difference in weight reduction Lower incidence of gynecomastia and hyperkalemia in eplerenone group	Rishabh et al. [75]
SGLGT2i	Cardiac protective effect in HF across all spectrum of EF Renal protective effects (efferent arteriole vasodilation) Diuretic effects – osmotic and natriuretic Reduction of body sodium Less RAAS and SNS activation (mild hemodynamic effects due to shift from interstitial to intravascular fluid)	Patients with T2DM and NAFLD Reduced liver stiffness (fibroscan) in SGLT2i group In NAFLD patients Dapagliflozin improved ALT, AST, HOMA-IR, lipid profile, body weight and BMI Emplagliflozin improved ascites, edema and pleural effusion in cirrhotic patients (case reports)	Zhou et al. [71] Lei et al. [70] Qin et al. [76] Montalvo-Gordon et al. [77] Kalambokis et al. [78]

CO: cardiac output; BB: beta blocker; EF: ejection fraction; HF: heart failure; LT: liver transplant; LV: left ventricle; MAP: mean arterial pressure; MRA: mineralocorticoid receptor antagonist; NAFLD: non-alcoholic fatty liver disease; RAAS: renin angiotensin aldosterone system; SGLT2i: sodium glucose cotransporter 2 inhibitors; SNS: sympathetic nervous system;T2DM: type 2 diabetes mellitus.

to β2 blockage. BB also reduce the RAAS activation by blocking beta receptors in the juxtaglomerular apparatus.

In 2010, Serste et al. [63] reported that propranolol treatment was associated with worse survival in patients with refractory ascites. Though likely biased by non-randomized design, this raised the concept of a "therapeutic window" for BB use in cirrhosis. Later trials and registry data did not support this hypothesis.

Carvedilol, superior to preventive endoscopic variceal ligation and propranolol in preventing bleeding [64], demonstrated clear mortality benefit that was not influenced by the presence of ascites [65]. As a rule, non-selective BB should be withheld if mean arterial pressure falls under 65mmHg, a threshold below which the risk of HRS increases.

Ivabradine, a molecule that is active at the sinoatrial node by blocking the pacemaker current (If), does not produce a negative inotropic effect or influence blood pressure. Adding ivabradine to carvedilol in cirrhotic patients proved beneficial. Patients who reached the target heart rate had a reduction in E/e' ratio, in opposition to patients in the control group which had an increase in E/e' [66].

Metoprolol use in patients with CCM (diagnosed with dobutamine stress echocardiography) showed no benefit in regard to DD parameters, nor in noradrenaline levels, plasma renin activity or troponin levels. This could be attributed to selection bias, as more severe Child C patients were in the treatment arm, but also to the differences between the effects of a selective and non-selective BB and short study duration [67].

Sodium glucose cotransporter 2 inhibitors are antidiabetic drugs that have been included in the management of HF, displaying cardioprotective effects irrespective of ejection fraction in multiple clinical trials [68, 69]. Apart from the hypoglycemic role, they also have osmotic and natriuretic diuretic effects. There is no data regarding the use of SGLT2i in CCM patients. There are trials with SGLT2i in patients with type 2 diabetes and metabolic dysfunction associated steatotic liver disease (MASLD) that show an improvement of hepatic function tests, insulin resistance, lipid profile and body weight [70]. Fibrosis and steatosis measured by fibroscan improved in diabetic patients without cirrhosis treated with SGLT2i [71]. Because cirrhosis and HF share some common physiopathologic mechanisms such as RAAS and SNS activation there is increasing interest in using SGLT2i in patients with cirrhosis and refractory ascites [72, 73]. Sodium glucose cotransporter 2 inhibitors decrease the sodium retention in the skin and muscles, leading to a reduction in interstitial fluid. After initial reduction of intravascular volume, SGLT2i compensate through a shift of fluid from the interstitial to the intravascular compartment. This limited reduction of intravascular volume protects from further activation of RAAS and SNS. Also, renal hemodynamic through vasodilation in the efferent arteriole and reduction of intra glomerular pressure is improved. This confers a better safety profile compared to MRAs and loop diuretics. Despite this, data for SGLT2i use in cirrhosis is limited to some case reports [72, 76-78].

CLINICAL RELEVANCE OF CCM: LT AND TIPS PATIENTS' SELECTION

Patients diagnosed with CCM do not have an absolute contraindication for LT, as hemodynamic alterations and cardiac dysfunction may improve after surgery. Nevertheless, systematic preoperative cardiac evaluation is crucial. A basic screening including ECG, transthoracic echocardiography, and NT-proBNP measurement is recommended for all candidates. Importantly, patients with a left ventricular ejection fraction (LVEF) <40% despite optimal guideline-directed medical therapy are considered to have an absolute contraindication for LT [81].

Careful monitoring of CCM patients before, during, and after LT can significantly improve prognosis. Invasive hemodynamic assessment and intraoperative transesophageal echocardiography are essential for the timely detection of preload and afterload variations and for assessing cardiac adaptation. Liver transplant surgery itself implies major circulatory stress, particularly hazardous in CCM, as subclinical myocardial impairment reduces the capacity to tolerate abrupt hemodynamic shifts [82].

Cirrhotic cardiomiopathy patients remain at increased risk for HF after LT. Hyperdynamic circulation and its systemic consequences may take months to normalize. Some patients even show transient worsening of LV systolic and diastolic function in the first months after transplantation, which coincides with the highest risk for HF events, followed by gradual recovery at 1 year [83]. Reported incidence of HF post-LT varies, reflecting heterogeneous diagnostic criteria and pre-transplant screening protocols. Sakr et al. [84] found a 14% incidence of HFrEF post-LT, with 33% mortality at 1 year, while Eimer et al. [85] reported new LV systolic dysfunction in 7% of patients, particularly in those older or with higher sPAP. Other cohorts found pulmonary congestion in up to half of ICU patients [30], or newly reduced LVEF <40% in 11% of recipients [86]. Risk factors include sinus tachycardia, elevated filling pressures (dilated LA, increased E/e' ratio), and advanced liver disease (higher MELD) [50].

Transjugular intrahepatic portosystemic shunt is another frequently used procedure in cirrhosis, mainly for refractory ascites and variceal bleeding. While effective in many patients, TIPS may precipitate complications such as hepatic encephalopathy, hepatic function decline, or HF decompensation. Contraindications include severe pulmonary hypertension (mPAP >45 mmHg) and overt HF (LVEF <50%). Up to 20% of patients develop HF post-TIPS, likely reflecting undiagnosed CCM [87]. Literature reports wide variation in HF incidence after TIPS, related to patient selection and diagnostic methods. Structural and diastolic changes (LV dimensions, mitral inflow pattern) are often observed after shunt placement [88]. Reported incidence of HF ranges from 10% to 20%. Elevated NT-proBNP, abnormal E/A and E/e' ratios, LA dilatation, increased sPAP, LV diameters and right atrial size were strong predictors [16, 89, 90].

Accumulating evidence supports the utility of BNP and NT-proBNP in refining cardiac risk stratification. Billey et al. [16] demonstrated that BNP >40 pg/mL or NT-proBNP >125 pg/mL independently predicted post-TIPS HF. For LT candidates, higher thresholds have been identified: BNP >391 pg/mL strongly associated with DD and increased post-transplant mortality, while BNP >567 pg/mL indicated systolic dysfunction and a higher risk of adverse outcomes [52].

Based on international evidence and our institutional expertise, we propose an algorithm integrating ECG,

Table IV. Fundeni centre protocol for cardiac risk stratification before liver transplant and transjugular intrahepatic portosystemic shunt

Fundeni Center protocol – Proposal for a national standard in cardiac risk stratification before LT and TIPS		
Risk assessment	Criteria	Recommendation
Low risk	- BNP < 40 pg/mL or - NT-proBNP < 125 pg/mL - Normal GLS and normal diastolic function - mPAP ≤ 25 mmHg	Proceed directly to TIPS/ LT.
Intermediate risk	- BNP 40–391 pg/mL or - NT-proBNP 125–1000 pg/mL - Mildly reduced GLS (16-18%) or - grade I–II diastolic dysfunction (E/e' 9–14, mild LA dilatation (34- 40ml/m^2)) - mPAP 25-35 mmHg	Consider further testing: - stress echocardiography (dobutamine or exercise) or CPET and/ or - CMR (for tissue characterization, fibrosis and RV function) Optimize volume status, titrate BB, and re-evaluate prior to intervention
High risk	- BNP > 391 pg/mL or - NT-proBNP > 1000 pg/mL - Significantly abnormal GLS (< 16%) or - Advanced diastolic dysfunction (E/e' >15, severe LA dilatation (> 45ml/m^2), restrictive filling pattern (E/A > 2)) - mPAP 35–45 mmHg	Comprehensive cardiology evaluation required, including stress echocardiography, CMR and invasive hemodynamic assessment (right heart catheterization) when indicated Optimization with guideline-directed HF therapy is mandatory before considering LT/TIPS.
Absolute contraindications	- LVEF < 40% despite optimized therapy	contraindication for LT
	- LVEF < 50%	contraindication for TIPS
	- Overt heart failure	contraindication for LT or TIPS
	- mPAP > 45 mmHg (severe PH)	contraindication for LT or TIPS

BNP: brain natriuretic peptide; CMR: cardiac magnetic resonance; GLS: global longitudinal strain; mPAP: mean pulmonary artery pressure; LA: left atrium; LT: liver transplant; LVEF: left ventricle ejection fraction; TIPS: transjugular intrahepatic portosystemic shunt.

echocardiography (including GLS and diastolic indices), and natriuretic peptides (Table IV). This structured approach combines biomarkers with advanced echocardiographic parameters to refine risk stratification and individualize preoperative assessment. By systematically integrating imaging and laboratory data, we aim to minimize post-procedural HF, harmonize evaluation across transplant centres and improve outcomes. As the leading national LT centre, Fundeni Centre proposes this protocol as a reference standard for other Romanian LT centres, thereby promoting uniformity, safety, and excellence in the management of cirrhotic patients requiring high-risk procedures.

CONCLUSIONS

Cirrhotic cardiomyopathy is defined by the presence of LV DD and/ or a subclinical systolic impairment in cirrhotic patients, manifesting as an inability to increase cardiac output and perfusion in stressful situations such as surgery or infection. Hyperdynamic circulation, reduced SVR and hypotension determine the activation of SNS and RAAS and represents the initial driver of CCM. Reduced liver clearance of inflammatory cytokines and vasodilators cause negative inotrope and chronotropic effects.

Diagnosis is based on TTE parameters, but requires the integration of multiple tests (ECG, stress tests, CMR, NT pro BNP, troponin I).

Data regarding medical treatment in CCM is limited. Due to marked vasodilation and reduced SVR the use of RAASi can further aggravate vasodilation and increase the risk of renal impairment. Non-selective BB and MRAs have theoretical advantages by mitigating SNS and RAAS over activation. Other medications, such as ivabradine and SGLT2i, show promising effects but require further research.

The diagnosis of CCM has clinical implications, as these patients are at risk of developing HF after LT or after placing TIPS. Pre procedural cardiac evaluation is mandatory to identify patients at risk. Careful follow-up after the intervention can help manage potential complications and improve survival. The Fundeni protocol provides a structured algorithm for this evaluation and may serve as a national reference model.

Conflicts of interest: None to declare.

Authors' contribution: T.R. conceived and designed the study. All the authors collected relevant literature information. T.R. drafted the manuscript. S.I and L.G. revised the manuscript. All the authors read and approved the final version of the manuscript.

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