Current Concepts of Cirrhotic Cardiomyopathy

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KEYWORDS

• Cirrhotic cardiomyopathy • Diastolic dysfunction • Heart failure
• Liver transplantation • Heart disease • Cardiovascular events • Echocardiogram
• Transjugular intrahepatic portosystemic shunt

KEY POINTS

- The criteria for diagnosis of cirrhotic cardiomyopathy were recently revised in 2020 to reflect the improved performance of echocardiography for diagnosis of abnormal cardiac structure and function.
- Cirrhotic cardiomyopathy may increase the risk for major cardiac events after transjugular intrahepatic portosystemic shunt placement and after liver transplant.
- Echocardiographic follow-up of patients with cirrhotic cardiomyopathy is warranted.

Video content accompanies this article at http://www.liver.theclinics.com.

INTRODUCTION

Cirrhosis accounts for 1.16 million deaths worldwide annually, making it the 11th most common cause of death globally.[1] Cirrhosis deaths are expected to increase over the next decade because of the ongoing epidemics of obesity and alcohol-related liver disease.[1] The primary physiologic complication in patients with cirrhosis is elevated pressure in the portal venous system (ie, portal hypertension). This elevated pressure can manifest as ascites, hepatic hydrothorax, hepatorenal syndrome, or portal hypertensive gastropathy and gastroesophageal varices with bleeding. These complications are markers of hepatic decompensation and are associated with 50% mortality at 1 year, especially in Child C patients.[2]

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The cardiovascular effects of portal hypertension result in hyperdynamic circulation characterized by low systemic vascular resistance and high-cardiac output. Cirrhotic cardiomyopathy (CCM) is characterized by intrinsic subclinical alterations in myocardial structure and function in the absence of overt structural abnormalities owing to other causes (eg, ischemia).[3] CCM is usually latent, but it can become unmasked under stress, such as an acute change in hemodynamic loading conditions, leading to clinical heart failure.[4] CCM is related to both portal hypertension and cirrhosis, irrespective of the underlying cause of end-stage liver disease (ESLD), although some diseases (eg, alcohol, nonalcoholic steatohepatitis, iron overload) may have further impact on cardiac function.[5]

In the following review, the authors discuss the epidemiology, pathophysiology, diagnostic criteria, and clinical implications of CCM. They focus particularly on aspects of clinical care for screening, surveillance, and management of CCM in the context of liver transplantation and transjugular intrahepatic portosystemic (TIPS) placement. Finally, the authors address the major unmet needs and research priorities surrounding CCM.

EPIDEMIOLOGY

There is limited information on the epidemiology of CCM, as its diagnosis is difficult because of near normal cardiac function at rest. Typically, the syndrome is not recognized until clinical decompensation occurs, at which time patients often present with features of high-output heart failure or diastolic heart failure.[6] With regard to heart failure, there are 4 stages for its development; stage A: the presence of risk factors (eg, hypertension, diabetes mellitus); stage B: the presence of structural changes (eg, remodeling) without clinical features; stage C: clinical presentation; and stage D: refractory clinical presentation[7] (**Table 1**). Although accurate identification and staging of heart failure owing to CCM are challenging, echocardiography, which is used

Table 1
Cirrhotic cardiomyopathy in the spectrum of heart failure

	ACCF/AHA HF Stage[7]	CCM Correlate	Therapeutic Target
Early stage	Stage A	Patients with cirrhosis or metabolic syndrome and its components without structural heart disease	Risk factor modification (eg, control blood pressure, weight loss as needed)
	Stage B	LV remodeling and/or systolic or diastolic dysfunction on imaging *without* HF symptoms	Treat structural heart disease to prevent progression to symptomatic HF (stage C)
Late stage	Stage C	LV remodeling and/or systolic or diastolic dysfunction + prior or current HF symptoms	GDMT to prevent progression to stage D HF
	Stage D	Refractory HF requiring specialized interventions	GDMT to reduce mortality

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; GDMT, guideline-directed medical therapy; HF, heart failure; LV, left ventricle.

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clinically to identify cardiac correlates of early-stage heart failure (stage A or B), is operator dependent, and accuracy and reproducibility can be limited by the acoustic window. In late-stage heart failure (stage C or D), clinical heart failure symptoms may be masked or confounded by those of advanced cirrhosis (eg, low functional capacity, shortness of breath, and fluid overload). Therefore, accurate staging of heart failure owing to CCM may require sophisticated investigation beyond standard echocardiography to identify changes in myocardial tissue structure, function, and flow before the onset of cardiac decompensation (see *Diagnosis*).

Because of the latent nature of the disease, the actual prevalence, incidence, and natural history of CCM are largely unknown. Attempts have been made to extrapolate the prevalence of CCM by looking at the prevalence of QT interval prolongation in patients with cirrhosis, which previously was touted as the most common manifestation of CCM.[3,6] The prevalence of QT interval prolongation increases with severity of portal hypertension from 25% in Child A cirrhosis to up to 60% in Child C cirrhosis.[5] However, QT can be prolonged because of a variety of causes (eg, thyroid disease, obesity, medications[8]), which limits its use as an accurate surrogate for CCM. In patients undergoing liver transplantation, up to 50% of waitlist candidates show signs of cardiac dysfunction, and 7% to 24% of early deaths after liver transplantation result from overt heart failure.[5,9–11] Similarly, the leading cause of death after TIPS in patients with cirrhosis is cardiac decompensation, and 20% of patients can have a heart failure hospitalization within 1 year of TIPS.[12]

CLINICS CARE POINTS

- The true prevalence, incidence, and natural history of CCM is unknown.
- Detection of CCM requires a high index of clinical suspicion.

PATHOPHYSIOLOGY

The long recognized characteristic cardiovascular finding in ESLD is hyperdynamic circulation in view of low systemic vascular resistance and high-cardiac-output state (**Fig. 1**).[13] With portal hypertension and cirrhosis, a constellation of changes in vasoactive mediator levels occurs, the result of which is a vasodilatory state; there is also an increased vascular response to vasodilators and a decrease in responsiveness to vasoconstrictors. These changes occur in the systemic circulation and splanchnic circulation but not in the hepatic microcirculation.[14] The vasodilation and associated hypotension lead to activation of vasoconstrictor systems, including the renin-angiotensin system and the sympathetic nervous system, resulting in renal vasoconstriction and sodium and fluid retention. These changes in turn expand circulating volume, further exacerbating the hyperdynamic circulation. With this, structural and functional changes occur in the heart, including left ventricular remodeling.[15] Diastolic dysfunction (DD) develops, as does systolic dysfunction; blunted responses to stress are seen, as is chronotropic incompetence.[5,16] At a structural level, changes consistent with diffuse myocardial fibrosis have been described.[17]

Although patients with cirrhosis often exhibit total body volume overload, increased arterial compliance leads to a functional hypovolemia, and therefore, a decrease in cardiac preload. In CCM, the heart fails to increase cardiac output in response to the decrease in effective circulating volume, which may in part be attributed to high peripheral arterial vasodilation. This cardiac insufficiency may also be masked by

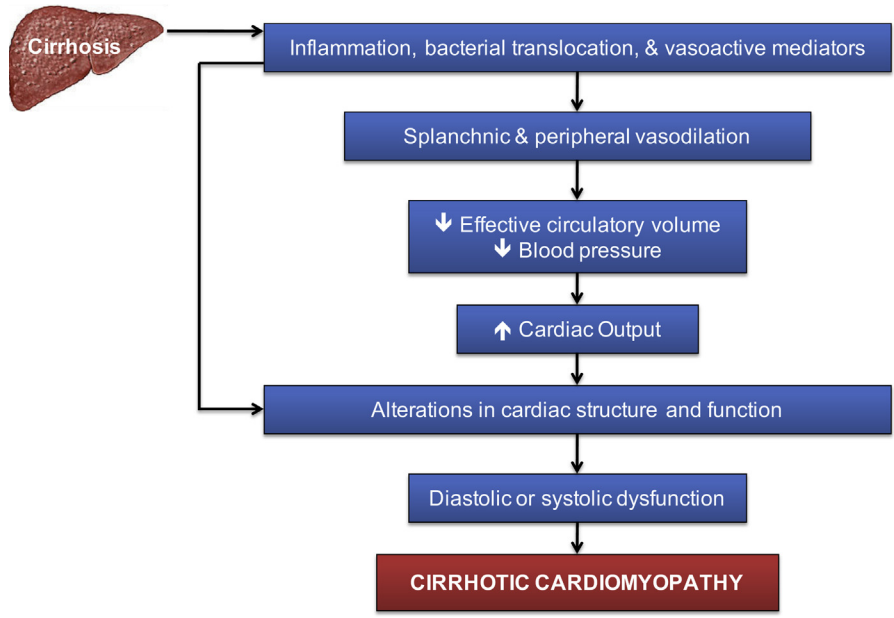

Fig. 1. The role of cirrhosis physiology in the development of CCM.

splanchnic arterial vasodilation, which further unloads the ventricle by increasing splanchnic blood flow. Other contributors to the blunted cardiac response in CCM include autonomic dysfunction and impaired volume and baroreceptor reflexes. In animal models, the cardiac alterations that characterize CCM have been attributed to a variety of molecular causes, including biophysical changes in the cardiomyocyte membrane through altered K^+ channels, altered L-type Ca^{2+} channels, and altered Na^+/Ca^{2+} exchanger, attenuation of the stimulatory β-adrenergic system, and overactivity of negative inotropic systems mediated via increases in cyclic GMP.[18]

CLINICS CARE POINT

- CCM develops over time in response to chronic exposure to hyperdynamic circulation.

DIAGNOSIS

2005 Criteria

The first attempt to devise diagnostic criteria for CCM was in 2005 during the World Congress of Gastroenterology. The proposed criteria at that time described the systolic component of CCM (ie, systolic dysfunction) as having reduced left-ventricular ejection fraction (LVEF) less than 55% or having suboptimal contractile response to pharmacologically or physiologically induced stress. The 2005 criteria described the diastolic component of CCM (ie, diastolic dysfunction) as low early to late diastolic transmitral flow velocity (E/A) less than 1, isovolumetric relaxation time greater than 200 milliseconds, or deceleration time greater than 80 milliseconds (Fig. 2).[4] Although that attempt to characterize CCM was an important first step in the right direction, applying 2005 criteria to clinical practice can be challenging for multiple reasons.

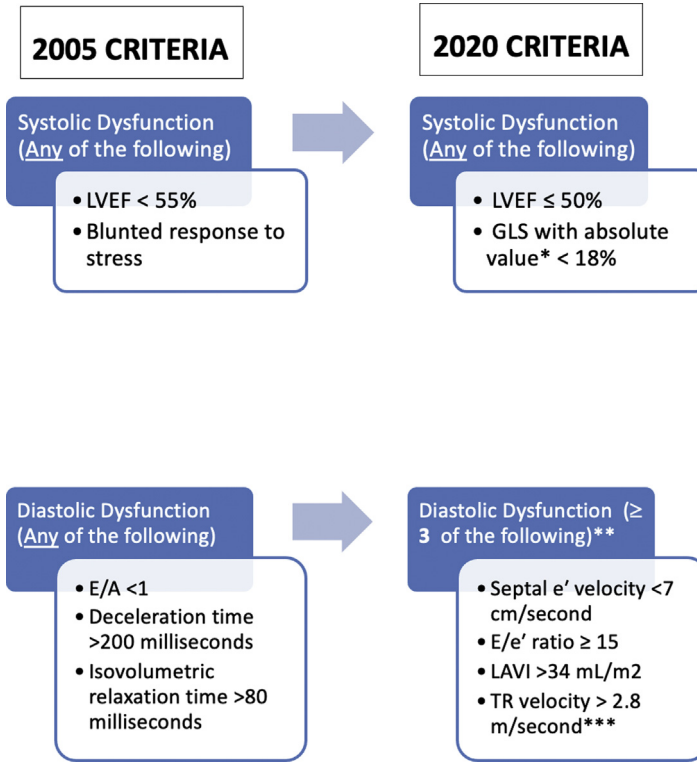

Fig. 2. The Revised Criteria for Cirrhotic Cardiomyopathy. LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; E/A, early to late diastolic transmitral flow velocity; e, early diastolic mitral annular tissue velocity; LAVI, left atrial volume index, TR, tricuspid regurgitation. *GLS is a negative value reflecting myocardial fiber shortening during systole. To avoid confusion, using the absolute value is recommended to describe changes in GLS. **Presence of only 2 abnormalities suggests diastolic dysfunction of indeterminate grade. Further evaluation is needed using E/A ratio change during Valsalva, pulmonary vein velocity, GLS, left atrial strain, and isovolumetric relaxation time. *** This criterion is only applicable in the absence of primary pulmonary hypertension or portopulmonary hypertension.

The remarkable vasodilatory state for patients with ESLD significantly decreases afterload, which can result in an exaggerated, hard-to-interpret LVEF. Therefore, LVEF may not be reliably used as a sole surrogate for detection of systolic dysfunction in these patients. Applying depressed contractile response to stress to daily practice is limited by lack of unanimous definition or characterization of what depressed contractile response to stress entails. Furthermore, the frequent use of nonselective beta-blockers, which lower cardiac output by reducing heart rate, for variceal bleeding prophylaxis in patients with ESLD is another limitation for applying the 2005 CCM criterion. The aforementioned DD criteria have shortcomings as well. They tend to exhibit U-shaped phenomenon where measurements on both ends of the spectrum (ie, in normal DD and in advanced DD) can look alike.[19] In addition, volume overload and its effect on preload impede the utility of the E/A ratio, because it is relatively preload dependent.[3] It is noteworthy that the 2005 criteria included a set of cardiac surrogates to support the diagnosis of CCM, such as prolonged QT interval, which has been the most studied supportive criterion of CCM. However, as mentioned above, QT can be prolonged because of a variety of causes, which limits its diagnostic potential for CCM.

2020 Criteria

The challenges in applying 2005 criteria to clinical practice triggered interest in revising them, and the evolution in echocardiography technology paved the path for the revision. This evolution was most remarkable for clinical implementation of speckle tracking strain imaging and advancing tissue Doppler imaging (TDI). In 2015, the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) recommended considering myocardial strain, specifically global longitudinal strain (GLS), assessment in addition to ejection fraction in the evaluation of left-ventricular contractile function.[20] GLS reflects the myocardial fiber strain defined by proportional shortening in fiber length during systole in relation to diastole, and hence, it is a negative value (Video 1). In 2016, ASE and EACVI revised the DD evaluation criteria, some of which are only obtainable via TDI, which has become a routinely applied technology in clinical practice.[19] In early 2020, the Cirrhotic Cardiomyopathy Consortium (CCMC), an international multidisciplinary consortium, published the revised CCM criteria.[3] The systolic component of CCM was characterized as reduced LVEF ($\leq$50%) or decline in GLS (absolute value <18). The diastolic component was defined by having at least 3 of the following: early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e′) $\geq$15, left atrial volume index (LAVI) greater than 34 mL/m^2, septal e′ less than 7 cm/s, or tricuspid regurgitation maximum velocity greater than 2.8 m/s in the absence of pulmonary hypertension. When DD is diagnosed, the severity can be determined using E/A ratio (0.8–2 = grade II and >2 = grade III). Patients with only 2 out of the 4 criteria need further echocardiographic evaluation to define DD grade. This additional evaluation entails assessing E/A ratio change during Valsalva, pulmonary vein velocity, GLS, left atrial strain, and isovolumetric relaxation time. Although 2020 criteria did not include supportive criteria like those of 2005, the CCMC suggested studying the diagnostic utility of a group of variables (eg, abnormal chronotropic or inotropic response, myocardial mass change, and serum biomarkers) that may have future potential in the management of CCM.[3]

CLINICS CARE POINTS

- GLS needs to be incorporated in systolic function assessment, in addition to LVEF in patients with ESLD.
- E/e′, septal e′, LAVI, and tricuspid regurgitant velocity should be evaluated to determine diastolic function in patients with ESLD.

PRETRANSPLANT IMPLICATIONS

The data are scarce regarding impact of CCM in its new definition on pretransplant outcomes or outcomes in patients with ESLD. However, the individual components of the new CCM criteria have been studied in relation to these outcomes. Lee and colleagues[21] described in 44 patients with decompensated cirrhosis who were prospectively followed for a median of 22 months that E/e′ greater than 10 was associated with reduced survival (28 vs 37 months). Another prospective study evaluated cardiac decompensation within 1 year after TIPS in 100 patients and showed that elevated E/e′ (11 in cardiac decompensation group vs 7 in others) or LAVI (40 vs 29 mL/m^2) pre-TIPS was associated with higher risk of cardiac decompensation post-TIPS.[12] Jansen and colleagues[22] retrospectively reviewed the 2-year clinical course of 114

patients who underwent TIPS and found that decreased left ventricular contractility detected as depressed GLS absolute value less than 16.6% was associated with development of acute on chronic liver failure and impaired survival. These studies demonstrate the prognostic value for the new CCM individual criteria. It is important to note that because these studies predate the new CCM criteria, evaluation of CCM as a whole entity was not possible, and only some of the CCM criteria (eg, LAVI, E/e′, and GLS) were evaluated. It is possible that some of the patients with elevated LAVI or E/e′ in these studies had normal values for the other 3 variables of DD, which, in the presence of normal systolic function, rules out CCM. Therefore, future studies are needed to evaluate the prevalence of the recently redefined CCM and its impact on the clinical course of patients with decompensated cirrhosis, including those undergoing TIPS placement.

Data about utility of other cardiac imaging modalities relating to CCM in pretransplant care are even more limited. Wiese and colleagues[17] showed in 52 patients with cirrhosis that increased myocardial extracellular volume on cardiac MRI, reflecting myocardial fibrosis possibly owing to CCM, is associated with increased risk of death or receiving liver transplant during 2 years of observation. Interestingly, the study showed that increased myocardial extracellular volume corresponds with higher Child-Pugh scores in the cohort, which suggests that CCM can worsen as liver disease progresses.

POSTTRANSPLANT IMPLICATIONS

There have been emerging data about the impact of CCM, DD, or their individual echocardiographic surrogates on posttransplant outcomes. A recently presented retrospective study at the American Transplant Congress (May 2020) showed in 141 patients who were followed for a median of 4.5 years posttransplant that meeting 2020 criteria for CCM increases the risk of major cardiovascular outcomes (coronary artery disease, congestive heart failure, arrhythmia, and stroke) by more than 2-fold.[23] There was a trend toward association between CCM and heart failure occurring more than 90 days posttransplant. It is notable that CCM affected one-third of the study cohort in whom DD was the predominant feature for CCM.[23] Other studies have evaluated the individual criteria of CCM in relation to posttransplant outcomes. Dowsley and colleagues[24] showed that increased LAVI (>40) and increased E/e′ (>10) are associated with posttransplant early heart failure (within 2.6 months). The study also showed that abnormal LAVI predicts poor survival at 1- and 5-year posttransplant. Although CCM was initially thought to reverse after transplant,[25] subsequent studies, using contemporary echocardiographic criteria, did not validate this finding.[9,24]

CLINICS CARE POINTS

- E/e′ greater than 10 can be associated with poor outcomes post-TIPS and posttransplant.
- Reduced GLS may negatively impact TIPS outcomes.

PROPOSED MANAGEMENT

CCM typically indicates subclinical structural and functional cardiac changes in patients with ESLD, which places these patients in stage B on the path toward heart failure, which can become evident as the burden on the heart increases after TIPS placement or after liver transplant. TIPS placement results in increased preload, which

in the setting of CCM may lead to overt heart failure (ie, cardiac decompensation). Therefore, if TIPS is performed in a patient with CCM, it may be beneficial to obtain a surveillance echocardiography within the first few months to ensure that there is no subclinical worsening in cardiac function that may warrant initiation of anti-remodeling therapy.

This risk for heart failure can be further augmented after liver transplant when increasing number of patients develop metabolic syndrome or at least some of its components.[26] At that point, effective management of hypertension, diabetes mellitus, dyslipidemia, and obesity will be critical in mitigating the risk of developing heart failure as well as other major cardiovascular outcomes. To this end, a recent study showed that arterial hypertension was adequately managed in less than one-third of liver transplant recipients and that adequate control was associated with improved survival and decreased incidence of cardiovascular events.[27]

Echocardiographic surveillance of transplant candidates with CCM was recently recommended by the CCMC.[3] The recommended surveillance interval for comprehensive echocardiography is every 6 months among liver transplant candidates on the waitlist. Among liver transplant recipients, surveillance is recommended every 6 months for 2 years following liver transplantation. This surveillance can potentially detect asymptomatic further decline in cardiac function, which can affect candidacy to remain on the waitlist. Conversely, in patients with ESLD without transplant potential, surveillance is unlikely to be of benefit given the poor expected survival and high rate of liver-related decompensation relative to cardiac events.[28,29] In the

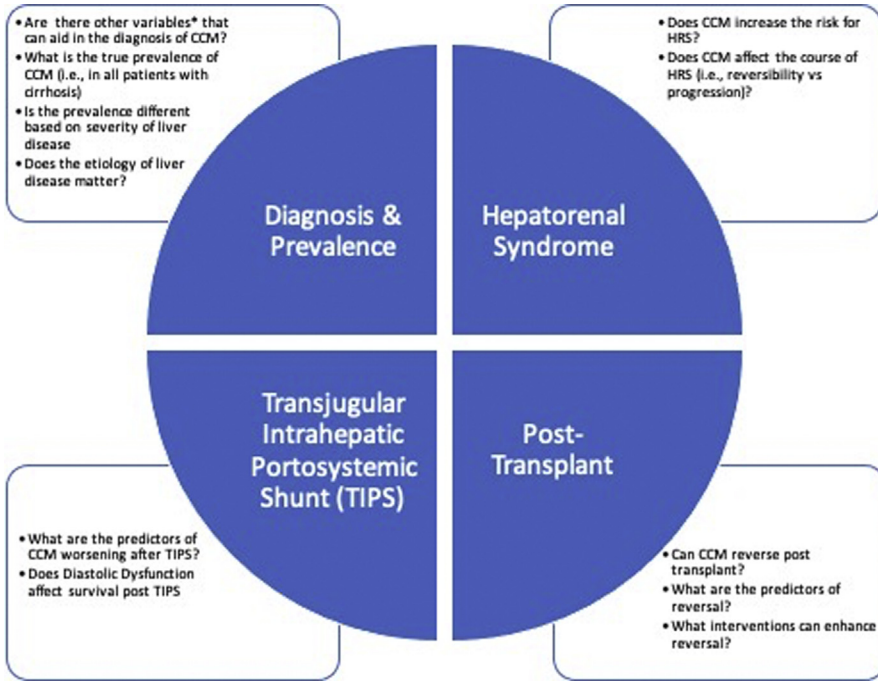

Fig. 3. Topics and questions for future research about Cirrhotic Cardiomyopathy. CCM, cirrhotic cardiomyopathy; HRS, hepatorenal syndrome; TIPS, transjugular intrahepatic portosystemic shunt. *Examples: abnormal chronotropic or inotropic response, electrocardiographic changes, electromechanical uncoupling, myocardial mass change, changes on cardiac magnetic resonance imaging, and serum biomarkers.

posttransplant setting, surveillance can detect subclinical significant decline in systolic for example can trigger therapeutic interventions (eg, angiotensin-converting enzymes inhibitors, beta-blockade) that may improve survival.

CLINICS CARE POINTS

- If TIPS is performed in a patient with CCM, post-TIPS echocardiography may be of benefit.
- Once CCM is diagnosed in a liver transplant candidate, echocardiographic surveillance should be considered every 6 months while on the waitlist and continue until 24 months posttransplant.

FUTURE DIRECTIONS

Although the knowledge of CCM has been advancing over the past few years, multiple unanswered questions remain with multiple opportunities for future investigations (**Fig. 3**). The true prevalence of CCM in all comers with decompensated cirrhosis remains unknown, as studies have focused predominantly on liver transplant candidates. CCM has been historically associated with hepatorenal syndrome[30]; however, this association needs to be reevaluated according to the new criteria. The evolution of CCM after liver transplant and factors predicting reversal versus persistence of CCM need to be explored to potentially identify patients who can benefit from early intervention.

SUMMARY

There are new criteria for CCM which assessment needs to be incorporated in the standard echocardiographic examinations performed in patients with ESLD. CCM and its components appear to negatively impact outcomes in patients while awaiting liver transplant, after TIPS, or after liver transplant. Therefore, close follow-up is warranted in these patients. Prospective studies are critically needed to further evaluate pretransplant and posttransplant outcomes in CCM patients.

DISCLOSURE

M.J. Izzy has nothing to disclose. L.B. Vanwagner receives investigator-initiated grant support and is on the speaker's bureau for W.L. Gore & Associates, is on the speaker's bureau for Salix Pharmaceuticals, and consults for Gilead Sciences outside of the submitted work.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.cld.2021.01.012.

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