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Cirrhotic Cardiomyopathy: Appraisal of the Original and Revised Criteria in Predicting Post-Transplant Cardiac Outcomes

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Abstract

Background & Aims: Cardiovascular disease (CVD) significantly contributes to morbidity and mortality after liver transplant. Cirrhotic cardiomyopathy (CCM) is a risk factor for CVD after transplant. CCM criteria were originally introduced in 2005 with a revision proposed in 2020 reflecting echocardiographic technology advancements. This study assesses the two criteria sets in predicting major adverse cardiac events (MACE) after transplant.

Approach & Results: This single-center retrospective study reviewed adult liver transplant (LT) recipients between 1/1/2009 and 12/31/2018. Patients with insufficient pre-LT echocardiographic data, prior ischemic heart disease, portopulmonary hypertension, or longitudinal care elsewhere were excluded. The primary composite outcome was MACE (arrhythmia, heart failure, cardiac arrest, and/or cardiac death) after transplant. Of 1165 patients, 210 met eligibility criteria. CCM was present in 162 patients (77%) per the original criteria, and 64 patients (30%) per the revised criteria. There were 44 MACE and 31 deaths in the study period. 38.7% of deaths occurred secondary to CVD. CCM defined by the original criteria was not associated with MACE after LT ($p = 0.21$), but the revised definition was significantly associated with MACE (HR 1.93, 95% CI

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1.05–3.56, p = 0.04) on multivariable analysis. Echocardiographic variable analysis demonstrated low septal e' as the most predictive variable for MACE after LT (HR 3.45, p < 0.001).

Conclusions: CCM, only when defined by the revised criteria, was associated with increased risk for MACE after LT, validating the recently revised CCM definition. Abnormal septal e', reflecting impaired relaxation, appears to be the most predictive echocardiographic criterion for MACE after LT.

Keywords

diastolic dysfunction; cirrhosis; liver transplantation; cardiac disease; echocardiography

Despite several advances in therapies and management, cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality among liver transplant recipients (LTR). Within the first 5 years of liver transplant (LT), the incidence of cardiovascular disease can be as high as 20%, with most events occurring within the first post-transplant year (1). Within the first month alone, cardiovascular disease is the leading cause of death and accounts for up to 50% of all deaths overall among LTR (2). Cirrhotic cardiomyopathy, a phenomenon of altered systolic or diastolic function without a relevant pre-existing cardiac disease, has been implicated in development of cardiac disease after LT (3).

Cirrhotic cardiomyopathy was originally characterized in 2005 by a group of experts at the World Congress of Gastroenterology. However, since 2005, important echocardiographic advances have emerged such as the incorporation of tissue doppler imaging (TDI) in the assessment of diastolic dysfunction (DD)(4). To this end, the 2016 joint guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging revised the criteria for diastolic dysfunction among the general population by incorporating measures that reflect utilization of contemporary echocardiographic advancements such as TDI(5). Consequently, the cirrhotic cardiomyopathy consortium, an international multidisciplinary expert panel, revised the criteria for CCM in 2020 to be largely in line with the aforementioned guidelines(6) (Figure 1). It is notable that none of the revised criteria were included in the original definition and characterization for cirrhotic cardiomyopathy set forth in 2005. While CCM prevalence according to the original criteria exceeded 50%, the prevalence according to 2020 criteria appears to be ranging from 28–35% among liver transplant candidates, which is still remarkably high(3, 6–8). Furthermore, although recent data suggest that the revised criteria predict cardiac outcomes after LT, it is unknown if the original criteria, or some of them, still have utility in predicting cardiac outcomes after LT (3, 7). In this study, we aim to assess the utility of the CCM original criteria and that of the revised criteria in predicting major adverse cardiac events (MACE) after liver transplant.

Methods:

Study Design and Sample Selection

This retrospective study includes adult transplant-naïve patients undergoing liver only transplant for either decompensated cirrhosis or cirrhosis complicated by hepatocellular

carcinoma or hepatopulmonary syndrome at Vanderbilt University Medical Center between 01/01/2009 and 12/31/2018 (Figure 2). Cirrhosis etiology was stratified as either non-alcoholic fatty liver disease (NAFLD), alcohol-associated liver disease, Hepatitis C viral infection or other etiologies for cirrhosis. Patients without an accessible pre-transplant echocardiogram or without sufficient data for characterization of cirrhotic cardiomyopathy (CCM) by both diagnostic criteria were excluded. Patients at risk of ischemic cardiomyopathy (i.e., those with prior myocardial infarction or coronary revascularization) and those with portopulmonary hypertension were excluded. There were no patients with alcohol-related cardiomyopathy or heart failure pre-transplant in the cohort. Patients who were followed longitudinally within the Veterans Affairs health system after transplant were excluded due to paucity of after transplant data within our medical records system. Patients' records were reviewed for after transplant outcomes through 12/1/2020. The study was approved by the Institutional Review Board of Vanderbilt University Medical Center.

Echocardiographic Data Collection

Per our transplant center protocol, pre-transplant cardiovascular assessment included a preoperative echocardiogram. For those patients with multiple available echocardiograms within the year prior to LT, the most recent comprehensive echocardiogram was included for analysis in this study. Quantitative and qualitative echocardiographic data on all subjects were obtained from manual adjudication of measurements in echocardiogram reports and/or sonographic images as well as using previously described methods for data extraction from semi-structured echocardiogram reports(9).

Echocardiographic Diagnostic Criteria

By the original diagnostic criteria, CCM-related diastolic dysfunction was defined as any of the following: early to late diastolic transmitral flow velocity (E/A) < 1, mitral valve deceleration time > 200 msec, or isovolumetric relaxation time (IVRT) > 80 msec(10). The IVRT criterion was not available to be retrospectively assessed as it is not routinely performed in standard of care practice. Per the revised diagnostic criteria, diastolic dysfunction was defined as at least two of the following criteria: left atrial volume index (LAVI) > 34ml/m^2, septal e' < 7 cm/sec or lateral e' < 10 cm/sec, tricuspid regurgitant maximum velocity > 2.8 m/sec, or ratio of early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e') ≥ 15(5, 6). If not readily available, the left atrial volume index was calculated using the left atrial end systolic volume and body surface area, and the E/e' ratio was calculated using the mitral inflow E velocity and the lateral and septal early diastolic mitral annular velocity(11, 12). Regarding systolic function, the original CCM criteria defined it by left ventricular ejection fraction (EF) < 55% or by blunted contractile response to stress(6). Although we assessed EF in this study, we were unable to assess the blunted response to stress given the lack of universal objective definition for this criterion(13). The revised criteria for CCM-related systolic dysfunction defined it as EF ≤ 50% or global longitudinal strain (GLS) with an absolute value of < 18%(10). We were unable to assess GLS as it was not available as a standard of care measurement during the study period.

Demographic and Clinical Data Collection

Demographic and clinical data for the patients in the study, including information regarding disease etiology, smoking status, and pre-transplant hepatic decompensation events were obtained through manual adjudication. Additional clinical data were obtained through database extraction methods from Vanderbilt's research data warehouse (RDW). The RDW contains data for patients seen within Vanderbilt University Health System since 1990 (14). At our institution, congruent data can also be extracted through several interfaces including an operational perioperative database and via Epic's (EPIC Systems Corporation, WI) Clarity database. Our institutional electronic record transitioned to Epic Systems in 11/2017, however the source of data for this study remained consistent through this transition within the RDW.

Assessment of Pre-Transplant Comorbidities and After Transplant Cardiac Outcomes

Comorbidities, both prior to and after transplant, were assessed using the international classification of disease code, $9^{th,}$ and 10^{th} revisions (ICD-9-CM/ICD-10-CM). Comorbidities were identified if at least one inpatient or two outpatient administrative codes were present. Regarding outcome assessment, the primary outcome of major adverse cardiac events (MACE) was defined using a combination of ICD-9-CM and ICD-10-CM diagnostic codes for the first occurrence of cardiac events that are relevant to cardiomyopathy such as atrial or ventricular arrhythmia, heart failure, cardiac arrest, or cardiac death after liver transplant(15). Secondary outcomes included occurrence of individual MACE and all-cause mortality. Data regarding mortality was obtained from United Network for Organ Sharing reporting and were augmented by manual adjudication through chart review to minimize missing data.

Statistical Analysis

The association between time to event outcomes and covariates was estimated using separate Cox proportional hazards regression models. Subjects were considered at risk from the time of transplant until they experienced the event of interest or were censored. Censoring occurred at the last follow-up time or having an event that precluded the event of interest (e.g., censored at death for MACE). Model complexity, or the allowed number of degrees of freedom for predictor variables, was limited by the number of events available for each outcome considered. We limited models to no more than one degree of freedom per fifteen available events. When CCM characterization by the original or revised criteria was the predictor of interest, we used inverse probability of treatment weighting to efficiently adjust for confounding. Weights used the propensity score to create a synthetic sample in which the distribution of measured baseline covariates was independent of CCM grouping. Separate propensity score models were created for each CCM definition, with both models including adjustment variables of age, gender, baseline diabetes mellitus and smoking status, and disease etiology. Diagnostics were performed to evaluate balance between exposure groups after weighting(16). Results are presented as hazard ratios with corresponding 95% confidence intervals.

Results:

Patient Characteristics by CCM Status

We identified 1,165 liver transplant surgeries performed at our institution during the study period. Of these, there were 811 patients undergoing their first liver only transplantation for cirrhosis managed within our health system (Figure 2). 716 of these patients had an echocardiogram at our institution prior to liver transplantation, and of these an additional 63 patients were excluded for either ischemic heart disease or portopulmonary hypertension prior to transplant. Of the remaining 653 patients, only 210 patients had sufficient echocardiographic data to adequately define presence or absence of cirrhotic cardiomyopathy status by both the original and the revised criteria (Figure 1). The median study follow-up time was 3.2 years. The baseline characteristics of the study population and their echocardiographic variables are demonstrated in Table 1. All patients included in the study had EF greater than 50% prior to liver transplant (i.e., no patient met the EF threshold of the revised criteria for CCM) and of patients who had ejection fraction 50.1 to 54.9 (i.e., meeting the EF threshold of the original criteria for CCM), all (three patients) qualified for CCM based on their diastolic criteria, as well. Regarding etiology, 33% of patients had non-alcoholic fatty liver disease-related cirrhosis followed by 24% with alcohol-associated liver disease. Hepatitis C accounted for 19.5% of the study population. Cirrhotic cardiomyopathy, largely determined by diastolic dysfunction per the original criteria was present in 162 patients (77%) while only 64 patients (30%) met the revised CCM criteria. CCM presence/absence by original and revised criteria was concordant in only 42% of subjects.

Patients with CCM by the original criteria tended to be older (56 vs 60, $p = 0.002$), diabetic (6% vs 18%, $p = 0.05$), obese (17% vs. 48%, $p < 0.001$), and had a higher prevalence of NAFLD as their etiology for cirrhosis (17% vs 38%, $p = 0.007$) compared to those without CCM. Stratification by the revised diagnostic criteria was associated with an older age at transplant (58 vs 60, $p = 0.03$) and higher female predominance (36% vs 52%, $p = 0.03$) among CCM patients. There were comparable rates of obesity ($p = 0.2$), diabetes mellitus ($p = 0.3$) and NAFLD ($p = 0.3$) prior to transplant in patients with or without CCM by the revised criteria (Table 1). There was no statistically significant difference in the prevalence of pre-transplant smoking between patients with and without CCM by either the original ($p = 0.8$) or revised ($p = 0.2$) definitions. There was a total of 44 major adverse cardiac events throughout the study period (Table 2), with the median time to event among these patients of 53 days after transplant. There was a total of 31 deaths throughout the course of the study, with CVD being the most common cause of death (38.7%).

Association of CCM with Outcomes

Primary Outcome—Table 3 demonstrates the univariable analysis of CCM (by original and revised criteria) as well as potential risk factors in relation to MACE after LT. Age at transplant and pre-transplant diabetes mellitus were associated with MACE after LT on univariate analysis. On multivariable analysis (Table 4), after adjusting for age, gender, diabetes mellitus, smoking, and disease etiology using inverse probability weighting, there was no impact of CCM as characterized by the original criteria on risk of MACE (primary outcome) after liver transplant ($p = 0.21$). Conversely, cirrhotic cardiomyopathy

as characterized by the revised criteria did significantly increase the risk of MACE after controlling for the same risk factors (HR 1.93, 95% CI 1.05–3.56, p = 0.04).

Secondary outcomes—Regarding the secondary outcomes, of the MACE individual components, there was no association with the original CCM definition. However, for the revised CCM definition, there was an association with cardiac death or cardiac arrest that approached statistical significance (HR 2.68, 95% CI 0.97–7.38, p=0.06) (Table 4). There was no impact of CCM (as defined by either definition) on all-cause mortality.

Subgroup analysis of Association of Individual Echocardiographic Components of CCM with Outcomes

Primary Outcome—The echocardiographic variables utilized in each of the definitions were assessed to determine associations with MACE or its subcomponents. Univariable analyses showed decline of septal e' to be associated with increased risk of MACE after LT (p < 0.001; Table 3). After adjusting for diabetes mellitus given that it was the most statistically significant risk factor for MACE in the analysis, low septal e' remained independently associated with MACE after transplant (P = 0.002; Table 5).

Given the noted significance of septal e', we further assessed the impact of septal e' using the diagnostic cutoff of 7 cm/sec as defined by the revised diagnostic criteria for CCM. On univariable analysis, septal e' less than 7 cm/sec was associated with significantly reduced MACE free survival (HR 3.45, 95% CI 1.89–6.31, p < 0.001, Figure 3). After controlling for diabetes mellitus, the risk of MACE after transplant remained significant with a 3-fold increased risk of MACE after LT in patients with septal e' less than 7 cm/sec (HR 3.16, 95% CI 1.78–5.61, p < 0.001).

Secondary Outcome—For heart failure after transplant, decreased septal and decreased lateral e' as well as increased ratio of E/e' conferred a significantly increased risk (Table 5). Decreased septal e', increased peak tricuspid regurgitant velocity, and increased mitral valve deceleration time were all associated with cardiac arrest or cardiac death after transplant. None of the echocardiographic variables were associated with arrhythmia after LT. Septal e' was statistically significant for all-cause mortality.

Discussion:

This study demonstrates that CCM, only when defined by the recently proposed diagnostic criteria as opposed to the original criteria, has significant implications on cardiac disease after transplant even after accounting for known cardiovascular risk factors such as gender, age, pre-transplant diabetes mellitus, smoking, and liver disease etiology (e.g., NAFLD). Patients with the newly defined CCM were at significantly increased risk for major adverse cardiac events after liver transplant. Of the echocardiographic variables between the two definitions, septal e' is the one variable with the most significant associations with the components of MACE after liver transplant.

Cirrhotic cardiomyopathy in this population is predominantly a reflection of diastolic dysfunction which is known to be the hallmark of CCM(6). All patients within our

transplant cohort had normal ejection fraction. This is expected given that patients with reduced ejection fraction are often not considered for liver transplant alone. Further, patients with end stage liver disease tend to have decreased afterload, related to ongoing systemic vasodilation, that often exaggerates the EF. These factors explain the infrequent observation of low EF in this population with unique hemodynamics(6).

There are conflicting data regarding the clinical importance of DD in LTRs(18, 19). Mittal et al found that significant diastolic dysfunction was associated with mortality after transplant(19). Alternatively, Sonny and colleagues were unable to identify an association of DD and MACE or mortality (20). Importantly, none of these studies assessed the association of the revised CCM criteria alone or compared with the original criteria in relation to MACE after LT in the same cohort.

The current study shows that there is no association between CCM according to the original definition, mainly reflecting DD, with major adverse cardiac events after transplant. Importantly, however, it shows that when the revised definition is applied, patients with cirrhotic cardiomyopathy were almost twice as likely to have major adverse cardiac events following liver transplant. This finding mirrors that of a recently published study that showed that presence of CCM, as newly defined, doubles the risk for development of cardiovascular disease after transplant(3). The improvements noted in predicting MACE with the revised CCM definition validate the changes recently made in the criteria for diastolic dysfunction and CCM(5, 6). This improvement reflects more specific criteria that are more representative of the disease process. Namely, the newer diagnostic criteria are largely dependent on tissue Doppler imaging to assess tissue velocities which are essential to accurately assess diastolic dysfunction (i.e., impairment in cardiac relaxation), which is the hallmark of cirrhotic cardiomyopathy. This advancement in echocardiography technology and practice had evolved after the introduction of the original criteria in 2005. Therefore, none of the variables that comprise the newer criteria were included with the original CCM definition which made CCM definition entirely different between the original and revised criteria and hence the discordance between the two definitions in this study. The advancement in the sphere of echocardiography has also demonstrated limitations for the old criteria (e.g., E/A being preload dependent and deceleration time being confounded by multiple factors).

Notably, even after controlling for diabetes mellitus and other well-known risk factors for cardiac events, the revised definition for CCM remained significantly associated with MACE after transplant. Of note, pre transplant exposure to known cardioprotective medications such as statins and beta blockers was comparable between patients with and without CCM by either definition. This may suggest that the development and sequelae of cardiac remodeling in CCM occur independent of known cardiometabolic risk factors or exposure (or lack thereof) to cardioprotective medications.

Diastolic dysfunction-related echocardiographic variables have been associated with post-operative MACE and mortality in non-cardiac and non-hepatic surgery(21–26). Of these variables, those relating to left ventricular filling pressure (septal e', lateral e', E/e' ratio) have all been implicated as the most important variables in this regard(24, 27–29).

Impairments in these measurements have also been correlated with heart failure after liver transplant, likely as sequela of structural abnormalities of the myocardium(30–32). In our study, patients with a lower septal e', specifically below the cutoff of 7 cm/sec, were noted to have a 3.4 times increased risk of MACE after liver transplant. In addition, lower lateral e' values were significantly associated with MACE after transplant. Average E/e' ratio did not have an association with MACE, cardiac arrest or cardiac death or overall mortality in our study. Of the variables that have been involved in redefining cirrhotic cardiomyopathy, septal e' stands out as the most predictive variable for after transplant MACE, heart failure, cardiac arrest or cardiac death and all-cause mortality.

It is noteworthy that some echocardiographic variables in our study did not demonstrate significant associations with MACE unlike prior studies. Dowsley et al have shown elevated LAVI to be associated with mortality, but these findings were not appreciated in our study(27). Other studies have also shown LAVI to be associated with individual or composite MACE whereas our study did not reflect these findings. Kwon et al identified a cutoff value of ejection fraction < 60% to be associated with increased short-term and long-term mortality on subgroup analysis (32) while our study did not identify any association between ejection fraction and mortality. For tricuspid regurgitant maximal velocity, to our knowledge, this study is the first to show its predictability of cardiac arrest or cardiac death in this special population. Studies in other patient populations at high risk of cardiovascular mortality such as patients with sickle cell disease have shown high tricuspid regurgitant velocities to significantly increase the risk of death(33, 34).

Although higher E/A is typically indicative of more advanced DD, in our analysis higher E/A was associated with decreased risk for MACE and some of its components, which may seem illogical (5, 6). However, it serves to support that E/A cannot be used as a sole marker or indicator for DD and it needs to be interpreted in the context of other DD markers. This is supported by two facts: 1) E/A is preload dependent which renders it widely variable in response to fluid shifts in these patients with end stage liver disease and 2) E/A is known to exhibit a U-shaped phenomenon where normal E/A and that of advanced diastolic dysfunction can appear similar, thereby limiting its interpretability(6, 35).

Historically, pre-transplant cardiac risk stratification focuses only on systolic function as measured by left ventricular ejection fraction. Our findings, however, push towards broadening the cardiac risk stratification approach prior to transplant to include diastolic function given the demonstrated significant implications in this study. Specifically, the current study demonstrates important associations of the revised CCM-related DD criteria with the relevant clinical outcomes while it does not show meaningful associations of the original CCM-related DD criteria with clinical outcomes.

Our study has limitations. Despite having many liver transplants performed during our study period, we were limited in sample size given variable echocardiographic practices over the duration of our study. Nonetheless, the study sample size remains the largest to date investigating the impact of the revised criteria of CCM (or new DD criteria) on transplant outcomes. Future prospective studies may overcome this limitation especially now that comprehensive echocardiography with tissue doppler imaging has become the recommended

standard of care in assessing cardiac function in patients with cirrhosis, particularly transplant candidates, as emphasized by the CCM consortium practice guidance(6). The exclusion of patients due to the missing relevant echocardiographic data may have affected the prevalence estimates of CCM in this study; however, the proportion of CCM to non CCM was comparable to what has been reported since the revision of CCM criteria in 2020 (7, 8). In addition, echocardiographic variables like global longitudinal strain (GLS) and isovolumetric relaxation time (IVRT) were not available to be assessed in this study as neither of these variables was part of standard of care echocardiography during the study period. However, the impact of this limitation may be minimal in view of the recent data that showed that impaired GLS is infrequent among patients with end stage liver disease with a prevalence of < 2% and given the limitation of IVRT as a variable influenced by blood pressure which tends to be low in this patient population(3). Despite these limitations, this study identified a cohort of patients with sufficient data to determine their cirrhotic cardiomyopathy status by both the original and the revised criteria. This allowed for two separate analyses of the original and revised criteria with respect to MACE after LT. Our study is further strengthened by a robust review of the echocardiographic results to ensure accuracy and by the multivariable analysis accounting for multiple known cardiac risk factors that have not been accounted for by prior CCM-related studies. Statistical assessment by inverse probability weighting allowed for an unbiased representation of the true impact of CCM as defined by the different criteria.

In conclusion, this study shows that the original definition and characterization for CCM has limited clinical relevance for cardiac events after LT. Conversely, the revised definition of CCM is predictive of a significantly increased risk for MACE after LT. The study validates the 2020 proposed revision of CCM criteria and highlights that comprehensive echocardiography including tissue doppler imaging is critical for LT-related cardiac risk stratification and potentially risk prevention. Importantly, left ventricular filling pressure determined by septal e' is a significant predictor for various major adverse cardiac events after liver transplant. This observation sheds light on the need for a paradigm shift that incorporates diastolic dysfunction in pre-LT risk stratification, which historically has been almost exclusively focused on quantification of ejection fraction and right cardiac pressures. Close monitoring of LTRs with underlying CCM, as recommended by the CCM consortium (6), may have substantial implications on the long-term outcomes and management of these patients (e.g. initiation of anti-remodeling pharmacotherapy in patients with subclinical decline in EF to prevent clinical heart failure).

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List of Abbreviations

CVD	Cardiovascular Disease

CCM	Cirrhotic Cardiomyopathy
MACE	Major Adverse Cardiac Events
LTR	Liver Transplant Recipients
LT	Liver Transplant
RDW	Research Data Warehouse
TDI	Tissue Doppler Imaging
DD	Diastolic Dysfunction
NAFLD	Non-Alcoholic Fatty Liver Disease
IVRT	Isovolumetric Relaxation Time
LAVI	Left Atrial Volume Index
EF	Ejection Fraction
GLS	Global Longitudinal Strain
ICD	International Classification of Diseases

References:

1. Sastre L, García R, Gándara J-G, Ruiz P, Lombardo J, Colmenero J, et al. Incidence, Predictors, and Impact on Survival of Long-term Cardiovascular Events After Liver Transplantation. Transplantation. 2020; 317–325. [PubMed: 31335770]
2. VanWagner LB, Lapin B, Levitsky J, Wilkins JT, Abecassis MM, Skaro AI, et al. High early cardiovascular mortality after liver transplantation. Liver Transplantation.2014;20(11):1306–1316. [PubMed: 25044256]
3. Izzy M, Soldatova A, Sun X, Angirekula M, Mara K, Lin G, et al. Cirrhotic Cardiomyopathy Predicts Post-Transplant Cardiovascular Disease: Revelations of The New Diagnostic Criteria. Liver Transplantation.2021;27(6):876–886. [PubMed: 33533556]
4. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the Mysteries of Diastolic Function. Deciphering the Rosetta Stone 10 Years Later. Journal of the American College of Cardiology.2008;51(7):679–689. [PubMed: 18279730]
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American society of echocardiography and the European association of cardiovascular imaging. European Heart Journal Cardiovascular Imaging.2016;17(12):1321–1360. [PubMed: 27422899]
6. Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, et al. Redefining Cirrhotic Cardiomyopathy for the Modern Era. Hepatology.2020;71(1):334–345. [PubMed: 31342529]
7. Razpotnik M, Bota S, Wimmer P, Hackl M, Lesnik G, Alber H, et al. The prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria. Liver International.2021;41(5):1058–1069. [PubMed: 33342074]
8. Izzy M, Lin G, Watt KD. Cirrhotic cardiomyopathy prevalence according to the new criteria. Liver International.2021;41(5):1170. [PubMed: 33595171]
9. Wells QS, Farber-Eger E, Crawford DC. Extraction of echocardiographic data from the electronic medical record is a rapid and efficient method for study of cardiac structure and function. Journal of Clinical Bioinformatics.2014;4.

10. Izzy M, Oh J, Watt KD. Cirrhotic Cardiomyopathy After Transplantation: Neither the Transient Nor Innocent Bystander. Hepatology.2018;68(5):2008–2015. [PubMed: 29672903]
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. Journal of the American Society of Echocardiography.2005;18(12):1440–1463. [PubMed: 16376782]
12. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler Tissue Imaging: A Noninvasive Technique for Evaluation of Left Ventricular Relaxation and Estimation of Filling Pressures. Journal of the American College of Cardiology.1997;30(6):1527–1533. [PubMed: 9362412]
13. Izzy M, VanWagner LB. Current Concepts of Cirrhotic Cardiomyopathy. Clinics in liver disease.2021;25(2):471–481. [PubMed: 33838862]
14. Danciu I, Cowan JD, Basford M, Wang X, Saip A, Osgood S, et al. Secondary Use of Clinical Data: the Vanderbilt Approach. Journal of biomedical informatics. 2014; 28.
15. Shelton SK, Chukwulebe SB, Gaieski DF, Abella BS, Carr BG, Perman SM. Validation of an ICD code for accurately identifying emergency department patients who suffer an out-of-hospital cardiac arrest. Resuscitation.2018;125:8–11. [PubMed: 29341874]
16. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Statistics in Medicine.2014;33:1242–1258. [PubMed: 24122911]
18. Raevens S, De Pauw M, Geerts A, Berrevoet F, Rogiers X, Troisi RI, et al. Prevalence and outcome of diastolic dysfunction in liver transplantation recipients. Acta cardiologica.2014;69(3):273–280. [PubMed: 25029872]
19. Mittal C, Qureshi W, Singla S, Ahmad U, Huang MA. Pre-transplant Left Ventricular Diastolic Dysfunction Is Associated with Post Transplant Acute Graft Rejection and Graft Failure. Digestive Diseases and Sciences.2013;59(3):674–680. [PubMed: 24323177]
20. Sonny A, Ibrahim A, Schuster A, Jaber WA, Cywinski JB. Impact and persistence of cirrhotic cardiomyopathy after liver transplantation. Clinical Transplantation.2016;30(9):986–993. [PubMed: 27292629]
21. Saito S AT, Kurokawa F, Ashihara K, Hagiwara N. Usefulness of tissue Doppler echocardiography to predict perioperative cardiac events in patients undergoing noncardiac surgery. Heart Vessels.2012;27(6):594–602. [PubMed: 21989863]
22. Cho D-H, Park S-M, Kim M-N, Kim S-A, Lim H, Shim W-J. Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema and cardiovascular complications in patients undergoing noncardiac surgery. Echocardiography.2014;31(1):42–49. [PubMed: 23919453]
23. Wang JN, Biering-Sørensen T, Jørgensen PG, Jensen JS, Mogelvang R. Left ventricular filling pressure by septal and lateral E/e' equally predict cardiovascular events in the general population. The international journal of cardiovascular imaging.2017;33:653–661. [PubMed: 28066866]
24. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality Rate in Patients With Diastolic Dysfunction and Normal Systolic Function. Archives of Internal Medicine.2011;171(12):1082–1087. [PubMed: 21709107]
25. Zhou Y, Liu L, Cheng T, Wang D-X, Yang H-Y, Zhang B-W, et al. Grade 3 Echocardiographic Diastolic Dysfunction Is Associated With Increased Risk of Major Adverse Cardiovascular Events After Surgery: A Retrospective Cohort Study. Anesthesia and Analgesia.2019;129(3):651–658. [PubMed: 31425203]
26. Jun I-J, Kim J, Kim H-G, Koh G-H, Hwang J-H, Kim Y-K. Risk factors of postoperative major adverse cardiac events after radical cystectomy: implication of diastolic dysfunction. Scientific Reports.2019;9(1):14096. [PubMed: 31575918]
27. Dowsley TF, Bayne DB, Langnas AN, Dumitru I, Windle JR, Porter TR, et al. Diastolic dysfunction in patients with end-stage liver disease is associated with development of heart failure early after liver transplantation. Transplantation.2012;94(6):646–651. [PubMed: 22918216]

28. Seko Y, Kato T, Shiba M, Morita Y, Yamaji Y, Haruna Y, et al. Association of the low e′ and high E/e′ with long-term outcomes in patients with normal ejection fraction: a hospital population-based observational cohort study. BMJ Open.2019;9(11):e032663.

29. Eyvazian VA, Gordin JS, Yang EH, Aksoy O, Honda HM, Busuttil RW, et al. Incidence, Predictors, and Outcomes of New-Onset Left Ventricular Systolic Dysfunction After Orthotopic Liver Transplantation. Journal of cardiac failure.2019;25(3):166–172. [PubMed: 30412734]

30. Qureshi W, Mittal C, Ahmad U, Alirhayim Z, Hassan S, Qureshi S, et al. Clinical predictors of post-liver transplant new-onset heart failure. Liver Transplantation.2013;19(7):701–710. [PubMed: 23554120]

31. Sonny A, Govindarajan SR, Jaber WA, Cywinski JB. Systolic heart failure after liver transplantation: Incidence, predictors, and outcome. Clinical transplantation.2018;32(3):e13199. [PubMed: 29323769]

32. Kwon HM, Moon YJ, Jung KW, Park YS, Kim KS, Jun IG, et al. Appraisal of Cardiac Ejection Fraction With Liver Disease Severity: Implication in Post–Liver Transplantation Mortality. Hepatology.2020;71(4):1364–1380. [PubMed: 31464025]

33. Shah P, Suriany S, Kato R, Bush AM, Chalacheva P, Veluswamy S, et al. Tricuspid regurgitant jet velocity and myocardial tissue Doppler parameters predict mortality in a cohort of patients with sickle cell disease spanning from pediatric to adult age groups - revisiting this controversial concept after 16 years of additional evidence. American Journal of Hematology.2021;96(1):31–39. [PubMed: 32944977]

34. Gladwin MT, Barst RJ, Gibbs JSR, Hildesheim M, Sachdev V, Nouraie M, et al. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PloS one.2014;9(7):e99489. [PubMed: 24988120]

35. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology.1997;26(5):1131–1137. [PubMed: 9362352]

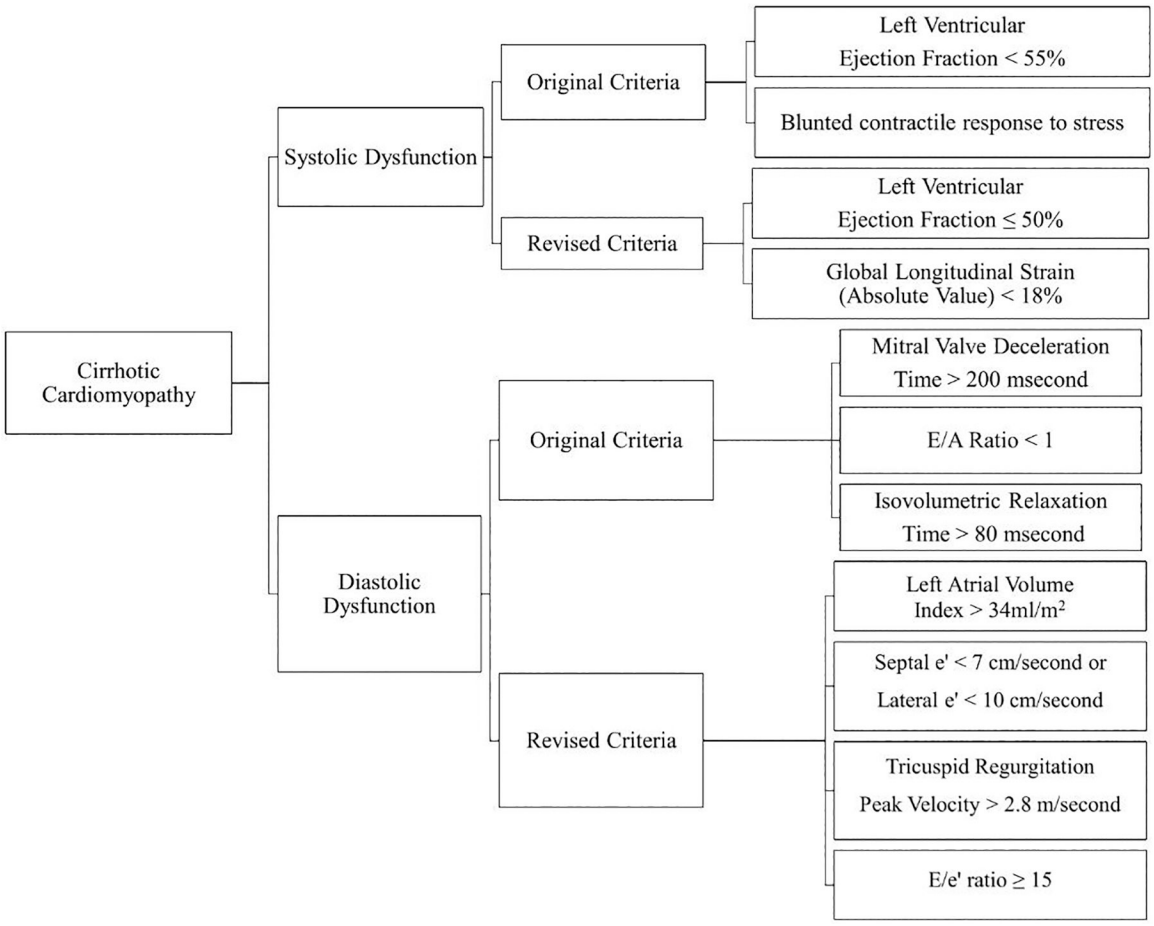

Figure 1:

Defining Cirrhotic Cardiomyopathy by the Original and Revised Criteria. Flowchart diagram detailing the individual criteria for defining systolic and diastolic dysfunction by either the original cirrhotic cardiomyopathy criteria from 2005 or the revised cirrhotic cardiomyopathy criteria from 2020

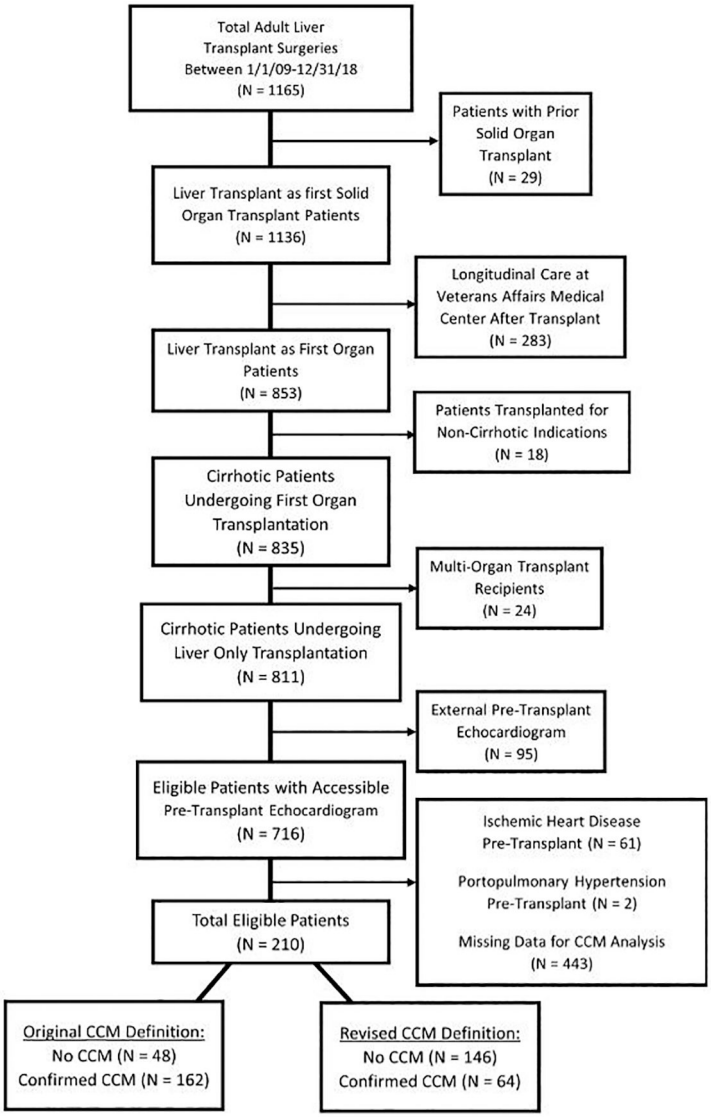

Figure 2:
Study Cohort. Flowchart of patient exclusions and etiologies for exclusion within the study

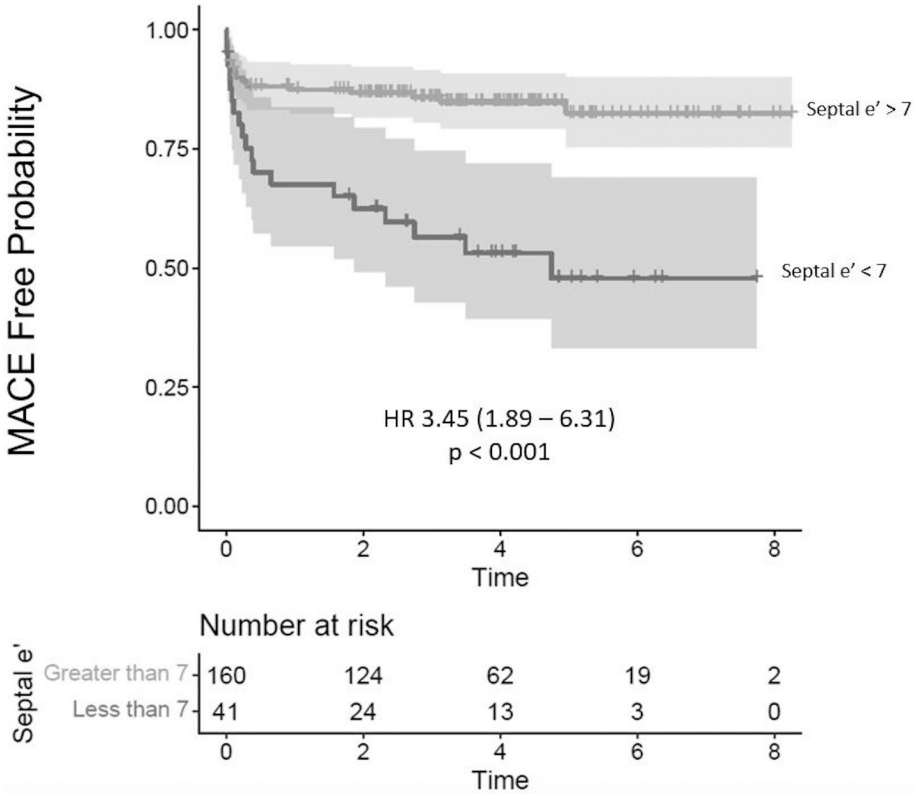

Figure 3:

Kaplan-Meier Curves for Major Adverse Cardiac Event (MACE) Free Survival for Septal e' Diagnostic Cutoff. Unadjusted MACE Free Survival Model Stratified by septal e' diagnostic cutoff of 7 cm/sec per the revised cirrhotic cardiomyopathy criteria

Table 1:

Baseline Characteristics of Patients with and without Cirrhotic Cardiomyopathy (CCM) By the Original and Revised Definition

	Original CCM Definition		Revised CCM Definition	
Demographic Variables	**No CCM (N = 48)**	**CCM (N = 162)**	**No CCM (N = 146)**	**CCM (N = 64)**
Age	56	60	58	60
MELD at Transplant	29	28	28	28
Male Gender	28 (58%)	97 (60%)	94 (64%)	31 (48%)
Race				
White	47 (98%)	153 (94%)	141 (97%)	59 (92%)
Black	--------	6 (4%)	2 (1%)	4 (6%)
Other	1 (2%)	3 (2%)	3 (2%)	1 (2%)
Disease Etiology				
Non-Alcoholic Fatty Liver Disease	8 (17%)	61 (38%)	45 (31%)	24 (38%)
Alcohol-Associated Liver Disease	12 (25%)	39 (24%)	40 (28%)	11 (17%)
Hepatitis C Viral Infection	13 (27%)	28 (17%)	27 (18%)	14 (22%)
Other Etiologies	15 (31%)	34 (21%)	34 (23%)	15 (23%)
Smoking Pre-Transplant	18 (38%)	64 (40%)	53 (36%)	29 (45%)
BMI > 30 Pre-Transplant	8 (17%)	79 (48%)	55 (38%)	30 (47%)
Hypertension	8 (17%)	27 (17%)	25 (17%)	10 (16%)
Diabetes	3 (6%)	29 (18%)	25 (17%)	7 (11%)
Pre-Transplant Statin Use	6 (12%)	37 (23%)	29 (20%)	14 (22%)
Pre-Transplant Antiplatelet Therapy	19 (40%)	71 (44%)	59 (40%)	31 (48%)
Pre-Transplant Beta Blocker Use	34 (71%)	105 (65%)	97 (66%)	42 (66%)
Pre-Transplant Aldosterone Antagonists	47 (98%)	133 (82%)	123 (83%)	57 (89%)
Echocardiographic Variables (median)	**No CCM (N = 48)**	**CCM (N = 162)**	**No CCM (N = 146)**	**CCM (N = 64)**
Septal e' (n = 201)	9.8	8	8.5	7.2
Lateral e' (n = 204)	12	11	12	9.1
Average E/e' Ratio (n = 201)	8.9	9.1	8.5	11.9
Tricuspid Regurgitant Maximal Velocity (n=183)	2.5	2.5	2.4	2.8
Left Atrium Volume Index (n = 202)	33	28	26	38
Mitral Valve Deceleration Time (n = 209)	170	246	218	252
Ejection Fraction (n = 210)	66	66	65	67
E/A Ratio				
E/A ≤ 0.8	------	36 (23%)	23 (16%)	13 (22%)
E/A 0.9–1.9	43 (90%)	110 (71%)	112 (77%)	41 (71%)
E/A ≥2	5 (10%)	9 (6%)	10 (7%)	4 (7%)

Table 2:

Incidence of Major Adverse Cardiac Events (MACE) after Liver Transplant by Cirrhotic Cardiomyopathy (CCM) Definition

	Original CCM Definition		Revised CCM Definition	
Cardiac Events	**No CCM (N = 48)**	**CCM (N = 162)**	**No CCM (N = 146)**	**CCM (N = 64)**
MACE	6 (12%)	38 (23%)	25 (17%)	19 (30%)
Arrhythmia	1 (2%)	18 (11%)	11 (8%)	8 (12%)
Heart Failure	3 (6%)	15 (9%)	10 (7%)	8 (12%)
Cardiac Arrest or Cardiac Death	2 (4%)	14 (9%)	7 (5%)	9 (14%)
All-Cause Mortality	6 (12%)	25 (15%)	19 (13%)	12 (19%)

Table 3:

Unadjusted Hazard Ratios for Variables for Major Adverse Cardiac Events After Liver Transplant

Variable	HR	Confidence Interval	P value
Age (per 10-year difference)	**1.70**	**1.16 – 2.48**	**0.006**
Gender	1.45	0.76 – 2.74	0.26
Diabetes	**3.23**	**1.69 – 6.17**	**<0.001**
Smoking	0.72	0.38 – 1.36	0.31
CCM (Original Definition)	2.22	0.93 – 5.26	0.07
CCM (Revised Definition)	1.73	0.95 – 3.14	0.07
Ejection Fraction	0.99	0.94 – 1.04	0.61
Septal e'	**0.71**	**0.60 – 0.84**	**<0.001**
Lateral e'	0.91	0.82 – 1.01	0.08
Average E/e' Ratio	1.05	0.97 – 1.14	0.26
Tricuspid Regurgitant Maximal Velocity	1.13	0.52 – 2.45	0.76
LAVI	1.02	0.99 – 1.04	0.29
E/A Ratio	**0.28**	**0.11 – 0.70**	**0.006**
Mitral Valve Deceleration Time	1.00	1.00 – 1.01	0.10

Table 4:

Adjusted Hazard Ratios for Major Adverse Cardiac Events (MACE) After Liver Transplant using Cox Proportional Hazards via Inverse Probability Treatment Weighting (Controlled for Diabetes, Age, Gender, Smoking and Liver Disease Etiology)

	Original CCM Definition			Revised CCM Definition		
Cardiac Outcomes	**Hazard Ratio**	**Confidence Interval**	**P value**	**Hazard Ratio**	**Confidence Interval**	**P value**
MACE	1.77	0.73 – 4.31	0.21	**1.93**	**1.05 – 3.56**	**0.04**
Arrhythmia	2.70	0.38 – 19.27	0.32	1.94	0.78 – 4.87	0.16
Heart Failure	1.61	0.47 – 5.56	0.45	2.05	0.75 – 5.62	0.16
Cardiac Arrest or Cardiac Death	2.06	0.44 – 9.67	0.36	2.68	0.97 – 7.38	0.06
All-Cause Mortality	1.15	0.47 – 2.86	0.76	1.25	0.59 – 2.65	0.56

Table 5:

Adjusted Hazard Ratios for Major Adverse Cardiac Events (MACE) After Liver Transplant in Relation to Echocardiographic Variables via Cox Proportional Hazards Using Inverse Probability Treatment Weighting (Controlled for Pre-Transplant Diabetes Mellitus)

	MACE		Arrhythmia		Heart Failure		Cardiac Arrest or Cardiac Death		All-Cause Mortality	
Echocardiographic Variables	**Hazard Ratio**	**P value**	**Hazard Ratio**	**P value**	**Hazard Ratio**	**P value**	**Hazard Ratio**	**P value**	**Hazard Ratio**	**P value**
Ejection Fraction	0.99	0.75	1.04	0.40	0.95	0.39	0.97	0.47	1.02	0.52
Septal e'	**0.71**	**0.002**	0.99	0.93	**0.48**	**<0.001**	**0.62**	**0.006**	**0.79**	**0.02**
Lateral e'	**0.88**	**0.04**	0.98	0.85	**0.76**	**0.02**	0.85	0.11	0.93	0.22
Average E/e' Ratio	1.07	0.17	0.98	0.79	**1.17**	**0.02**	1.11	0.12	1.02	0.66
Tricuspid Regurgitant Maximal Velocity	1.07	0.88	0.79	0.74	0.86	0.82	**3.95**	**0.001**	1.49	0.32
Left Atrial Volume Index	1.02	0.18	1.00	0.89	1.03	0.37	1.04	0.15	1.02	0.22
E/A Ratio	**0.27**	**0.002**	0.48	0.17	**0.10**	**0.02**	0.40	0.12	**0.36**	**0.01**
Mitral Valve Deceleration Time	1.0	0.23	1.01	0.08	1.00	0.76	**1.01**	**0.05**	1.00	0.52