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Cirrhotic Cardiomyopathy: An Evolving Diagnostic Entity with Long-Term Clinical Sequelae

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Abnormal cardiac function in patients with cirrhosis was first described by Kowalski and Abelmann in 1952.(1) These authors described an increased resting cardiac output with concurrent reduction in peripheral vascular resistance, with later accounts indicating an attenuated increase in cardiac output with exercise and stress.(2) As the majority of the initial studies were conducted in patients with alcoholic cirrhosis, this was considered a latent manifestation of alcohol-related cardiomyopathy.(3) However, replication of similar findings in non-alcohol-related liver diseases and in experimental animal models has supported the theory that cirrhosis per se can induce a specific pattern of subclinical cardiac dysfunction that was later termed 'cirrhotic cardiomyopathy' (CCM).

Despite an appreciation of its cellular and pathogenic underpinnings, the diagnosis and management of CCM has been hampered by a lack of universally accepted criteria. The first consensus definition of CCM was proposed during the World Congress of Gastroenterology in 2005.(4) These criteria identified systolic dysfunction indices at rest (left ventricular ejection fraction [LVEF] <55%), blunted contractile response on stress testing, evidence of diastolic dysfunction and prolongation of the QT-interval on ECG as key diagnostic components.(4) However, progress in modern imaging techniques were felt to render these criteria obsolete. New criteria proposed by the Cirrhotic Cardiomyopathy Consortium in 2020 (CCC-2020) include key markers of diastolic and systolic impairment including global longitudinal strain (GLS) - a sensitive and reproducible index of myocardial contractile dysfunction.(5) Contribution of QT-interval prolongation as a supportive criterion was rescinded by the latest definition with a recent study demonstrating no association with structural cardiac abnormalities.(6)

The discrepant evidence linking CCM as an 'all-encompassing entity' to the development of hepatorenal syndrome, post-transplant cardiovascular events and survival likely reflects the uncertainty surrounding the aforementioned diagnostic criteria. Prevalence of CCM itself varied significantly depending on the metrics assessed, ranging from 3.7 to 55.7%.(3, 6) As such, the contemporary CCC-2020 criteria has potential to unify the disparate diagnostic indices that constitute CCM,

under the umbrella of one condition. This, however, requires both a standardized echocardiographic assessment of cirrhotic patients and subsequent follow-up for cardiovascular (CV) events.

In this issue of *Liver Transplantation*, Izzy et al. evaluated the prevalence of CCM by the CCC-2020 criteria and its association with post-transplant CV events.(7) Their study was a single-centre retrospective cohort study of 141 patients with decompensated cirrhosis who underwent echocardiographic assessment prior to liver transplantation. Notably, post-transplant CV events included presentations related to unstable coronary artery disease (CAD), in addition to metrics previously reported in CCM studies including heart failure, arrhythmia and stroke.

The authors estimated the overall prevalence of CCM by the CCC-2020 criteria to be 34.8%. This was diagnosed almost exclusively on the basis of diastolic dysfunction in 47 (96%) with only two patients noted to have impaired GLS. None had resting systolic dysfunction below the diagnostic threshold of LVEF<50% as stipulated by the CCC-2020 criteria. Prevalence of CCM was higher in patients with non-alcoholic steatohepatitis (NASH) and alcohol-related liver disease.

CV events occurred in 27 (19.1%) of recipients. Although CCM was associated with a 2-fold (HR 2.57 95%CI 1.19-5.54) higher risk of cardiovascular events, there was no impact on mortality. Conventional risk factors including diabetes and NASH did not predict occurrence of the CV events, although hypertension conferred a 3-fold higher adjusted risk. Alternative cut-point estimation of echocardiographic indices were explored, with the most notable finding of an alternative GLS cut-off less than -20.6 that was associated with a 6-fold higher risk of heart failure and CAD. It was of interest to note that in a small subset of patients that underwent repeat echocardiography, reversal of CCM was not observed in the majority following LT.

This study is timely as it provides validation of the new CCC-2020 guidelines.(5) CCM being present in over a third of patients undergoing LT is an important point of consideration, particularly with recent data indicating a lack of reversibility of the condition.(8) Study strengths include blinded echocardiographic assessment, well phenotyped patient population, individual chart verification of CV outcomes and long-

term follow-up (mean 4.5 ±2.8 years). Main limitations include the retrospective, single-centre analysis and modest event numbers.

An important point of discussion raised by this study is whether current guidelines adequately addresses assessment of systolic dysfunction in CCM. This is clearly evidenced by the fact that over 96% of CCM was diagnosed on the basis of diastolic dysfunction. Two questions are raised. First, can reference echocardiographic indices from the general population adopted by the CCC-2020 guidelines be applied in a cirrhotic population? Second, does assessment of resting systolic function adequately risk stratify patients at risk of post-transplant CV events? Resting cardiac output often exceeds 8L/min in this cohort, with loading conditions that vary substantially from the general population.(9) As such, we agree with the authors that validation of alternative cirrhosis-specific echocardiographic cut-offs may be needed. Further, stress testing, which offers insights into cardiac inotropic and chronotropic response, should be considered in those with normal resting systolic function. Impaired cardiac reserve has been associated with complications of CCM and efforts are needed to assess whether it can improve prediction of post-transplant CV events.(9)

Inclusion of unstable CAD as a potential complication of CCM is of interest, although not without controversy. The authors highlight the pathophysiologic relationship linking hepatic fibrosis with vascular inflammation and oxidative stress- both potent drivers of accelerated atherosclerosis. However, this association should be interpreted with caution for two reasons. First, it can be argued that LT would reverse the cirrhotic milieu that potentiates adverse vascular remodelling. Second, numerous factors such development of post-transplant metabolic syndrome and diabetes have not been adjusted for in this analysis. As such, replication of these findings is needed to better understand the effect of CCM on CAD-related outcomes.

Other questions remain. What is the utility of GLS in establishing a diagnosis of CCM? Will addition of CCM to LT-specific risk indices such as the CAR-OLT score improve perioperative risk stratification?(10) Should a diagnosis of CCM impact perioperative care of patients undergoing transplantation? Does the CCM reverse

following LT? Utilizing multi-modality imaging including cardiac magnetic resonance imaging may be essential to provide answers to the last question.

The study by Izzy and colleagues have presented important evidence, supporting the use of the new diagnostic criteria of CCM whilst also raising the possibility of establishing cirrhosis-specific echocardiographic cut-offs. These findings provide a rationale to extend research in this field, encouraging the launch of prospective multicentre collaborations to further refine these diagnostic indices and with a focus on improving prediction of CV events. This could ultimately facilitate trials of therapeutic agents for this condition.

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