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EDITORIAL COMMENT

Hearts of Steel

Preoperative Cardiovascular Risk Assessment in Liver Transplant Recipients*

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In the United States, liver transplant volumes are on the rise. Despite the setbacks encountered in the face of the COVID-19 pandemic, 8,906 liver transplants were performed in 2020, an all-time high.[1] Alcohol-associated and nonalcoholic steatohepatitis are currently the 2 leading indications for liver transplantation.[1] Hereditary hemochromatosis, a familial iron overload syndrome, is a much less common causes of cirrhosis. When hepatic iron overload is diagnosed before liver transplantation, the cardiac evaluation is typically very thorough, as iron overload is a well-established cause of cardiomyopathy, predisposing patients to clinical heart failure and arrythmias. Acquired iron overload may occur concomitantly with other etiologies of cirrhosis, and as such, it is not always recognized in the pretransplant setting.

In this issue of *JACC: Case Reports*, Rhee et al[2] report a series of 4 patients with myocardial iron overload who developed acute heart failure (HF) in the setting of liver transplantation. This group of patients was somewhat heterogeneous: different primary etiologies of end-stage liver disease were present, and hepatic iron overload was not appreciated before transplantation in 2 patients, as liver biopsy was not performed. Myocardial iron overload was recognized before liver transplantation in 3 patients, based on cardiac magnetic resonance imaging (CMR) with a T2*-based sequence, and 2 patients had mild or borderline left ventricular (LV) and right ventricular systolic dysfunction. All patients developed marked LV systolic dysfunction postoperatively, with 3 manifesting cardiogenic shock, which was ultimately fatal in 2 cases.

Although preoperative cardiovascular workup and management practices are highly institution dependent, moderate or greater LV systolic dysfunction is an exclusion criterion for liver transplantation in many centers.[3] It is important to note that iron overload typically causes profound LV diastolic dysfunction before systolic dysfunction develops; that is, reduction in the ejection fraction is a relatively late-stage finding in iron overload cardiomyopathy.[4] Transthoracic echocardiography (TTE) to screen for LV dysfunction and pulmonary hypertension is typically a component of pretransplant workup,[5] and diastolic function assessment is a critical component of a comprehensive TTE protocol. However, patient-level and technical factors, such as tachycardia and poor quality of mitral annular tissue Doppler images, can confound diastolic function assessment on TTE, potentially leading to underrecognition of restrictive physiology.

It is prudent to maintain an increased index of suspicion for subclinical myocardial dysfunction in patients with evidence of iron overload in other organs and to consider advanced imaging, namely, CMR with a T2*-based sequence, to clarify whether myocardial iron overload is present. Notably, T2* imaging is not part of the standard CMR protocol for cardiomyopathy at many institutions, so it is important to specify the clinical concern for myocardial iron overload when ordering these studies. The prognostic value of myocardial T2* values is evident in

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transfusion-dependent patients with thalassemia, in whom lower T2* values (indicative of greater iron overload) have been associated with decreased survival, particularly when T2* is <10 ms. Chelation therapy can lead to improvement in T2* values, and serial CMR with T2* can be used to guide chelation therapy in this population.[6]

Considering the pool of liver transplant candidates as a whole, iron overload cardiomyopathy may be relatively uncommon, but LV diastolic dysfunction is not. As the mean age of liver transplant recipients increases, and as more patients are transplanted for nonalcoholic steatohepatitis,[7] the cardiovascular risk profile of this population is becoming increasingly complex. Comorbid diabetes, obesity, hypertension, and chronic kidney disease contribute to increased risk of cardiac structural changes, including LV hypertrophy and chamber dilation. Even in the absence of overt cardiac remodeling, cirrhosis is often associated with a high-output state with elevated intracardiac filling pressures. Current echocardiographic diagnostic criteria for cirrhotic cardiomyopathy include: 1) LV systolic dysfunction, with LV ejection fraction ≤50% or global longitudinal strain absolute value <18%; or 2) LV diastolic dysfunction as evidenced by 3 or more of the following findings: left atrial volume index >34 mL/m^2, septal mitral annular e' velocity <7 cm/s, mitral inflow to septal mitral annular e' velocity ratio (E/e') ≥15, and peak tricuspid regurgitation velocity >2.8 m/s.[8] Practically speaking, many patients with subclinical LV diastolic dysfunction have equivocal TTE findings, and further investigation may be needed to clarify the situation.

A comprehensive cardiovascular evaluation before solid organ transplantation should always include a thorough history and physical examination. It can be challenging to determine whether volume overload is entirely attributable to cirrhosis, and high-dose diuretics prescribed for ascites could potentially mask HF symptoms. Particularly when patients receive care in multiple hospital systems, careful review of records is essential to determine whether HF has ever been clinically diagnosed. In addition to workup for myocardial ischemia, which is standard practice in most transplant centers, clinicians should perform testing tailored to the patient's history and symptomatology. When clinical volume status assessment is challenging because of factors such as obesity, or when the diagnosis of HF is in question, right heart catheterization can be invaluable. Particularly if the etiology of end-stage liver disease is unclear, liver biopsy may provide guidance regarding the need for subspecialized cardiac testing (for instance, technetium pyrophosphate scanning to assess for cardiac amyloidosis, or CMR to assess for iron overload or cardiac sarcoidosis).

Given the intense hemodynamic stresses associated with liver transplant surgery, interdisciplinary discussion before transplantation is essential to develop management plans for patients with complex cardiac problems. In our center, we have a monthly conference focused on liver transplant candidates with clinical cardiovascular disease or abnormal cardiovascular test results. Our team includes transplant hepatologists, anesthesiologists, surgeons, and advanced practice providers, as well as cardiovascular consultants with expertise in echocardiography, nuclear cardiology, CMR, pulmonary hypertension, inherited cardiomyopathies, and interventional cardiology. Often, we must make decisions based on limited literature. Considering that some patients evaluated by the group ultimately do not undergo transplantation, often because of competing comorbidities, a judicious approach to testing and intervention is appropriate.

To establish best practices for preoperative cardiovascular evaluation in liver transplant candidates, particularly for less common conditions such as hepatic iron overload, multicenter studies are needed. As transplant recipients are living longer, prevalent and incident cardiovascular disease is becoming an increasingly important determinant of long-term outcomes,[9] and defining the extent of cardiovascular pathology before transplantation is helpful in anticipating follow-up plans. For transplant recipients with established cardiovascular disease, application of evidence-based therapies for HF and coronary artery disease is of the utmost importance. When following transplant recipients, clinicians must remain vigilant for development of new cardiovascular symptoms and have a low threshold for expert consultation. Ultimately, interdisciplinary collaboration in both clinical work and research will be key to improving longevity and quality of life in this complex patient population.

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