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REVIEW

Cardiac risk stratification of the liver transplant candidate: A comprehensive review

Sanjana Nagraj, Spyros Peppas, Maria Gabriela Rubianes Guerrero, Damianos G Kokkinidis, Felipe I Contreras-Yametti, Sandhya Murthy, Ulrich P Jorde

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Abstract

Cardiovascular diseases (CVD) form a principal consideration in patients with end-stage liver disease (ESLD) undergoing evaluation for liver transplant (LT) with prognostic implications in the peri- and post-transplant periods. As the predominant etiology of ESLD continues to evolve, addressing CVD in these patients has become increasingly relevant. Likewise, as the number of LTs increase by the year, the proportion of older adults on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve with parallel increases in their CVD risk profiles. The primary goal of cardiac risk assessment is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability. This review focusses on cardiac assessment of LT candidates in a stepwise manner with special emphasis on preoperative patient optimization. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

Key Words: Cardiovascular risk; Liver transplantation; End stage liver disease; Liver cirrhosis; Cardiovascular diseases; Cardiovascular diagnostic techniques

Core Tip: Liver transplantation is high-risk invasive procedure with an increased likelihood of cardiovascular mortality in the perioperative and postoperative periods. As the predominant etiology of end-stage liver disease and attributes of transplant candidates continue to evolve, cardiac risk stratification of these patients is becoming increasingly relevant. This review aims to reach providers seeking to learn about the current state of cardiac assessment of liver transplant candidates, commonly encountered cardiovascular conditions, preoperative diagnostic testing, and patient optimization. We also highlight areas requiring further investigation.

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INTRODUCTION

Patients with end-stage liver disease (ESLD) often have multiple comorbidities, of which cardiovascular diseases (CVD) form a principal consideration with prognostic implications in the peri- and post-transplant periods[1]. Nearly 36000 liver transplants (LTs) per million population were performed globally in 2019, a 5% increase since 2018, and an additional 13000 patients were added to the waiting list[2]. CVD which is a well-established risk factor of increased mortality in both the early and late periods after LT, accounts for > 40% of deaths in the first 30 d after transplant[3-5]. Additionally, CVD is the leading cause of death at 1-yr follow-up[3-5].

As the predominant etiology of ESLD continues to shift towards non-alcoholic steatohepatitis (NASH) with corroborating increases in obesity (body mass index ≥ 30 kg/m^2 in 40% of LT recipients) and diabetes mellitus (30% of LT recipients), addressing CVD in these patients has become increasingly relevant[6-9]. Likewise, as the number of LTs increase by the year, the proportion of older adults (age ≥ 65 years old) on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve, they parallel increases in their CVD risk profiles. Therefore, cardiac risk stratification and timely management of CVD is important to ensure favorable outcomes in LT candidates.

The primary goal of cardiac risk assessment in patients awaiting LT is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. Currently, there exist no validated models to predict cardiovascular mortality in LT recipients. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability[8]. Moreover, there is a paucity of guidelines for adverse cardiac events unrelated to perioperative myocardial ischemia in LT recipients[10]. Recognizing these limitations, this review aims to reach providers seeking to learn about the current state of cardiac assessment of LT candidates. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

HEMODYNAMIC CHANGES DURING LT

Significant hemodynamic alterations occur during the LT procedure and invasive hemodynamic monitoring is necessary to guide intraoperative management[11]. The most significant periods of hemodynamic instability arise while clamping the portal vein and inferior vena cava (IVC) during the anhepatic stage, and again at the time of reperfusion of the donor graft called the neohepatic stage[12, 13]. During the anhepatic stage, an abrupt cessation of blood flow to the native liver results in a significant reduction in the preload and subsequently, in the cardiac output predisposing to cardiac dysfunction[12]. In anticipation of this complication, intravenous administration of fluids is recommended prior to vessel clamping to prevent sudden reductions in intravascular volume. Alternative options include partially occluding the IVC or creating a temporary portocaval shunt[11,14].

During the neohepatic stage, reperfusion of the donor graft predisposes to post-reperfusion syndrome (PRS), defined as a > 30% decline in mean arterial pressure that lasts for at least 1 min and occurs within 5 min of reperfusion of the donor liver[15]. PRS complicates 8%-30% of LT and manifests as dramatic reductions in the heart rate, cardiac output and systemic vascular resistance, leading to systemic hypotension, and in some cases dysrhythmias or even cardiac arrest[16]. Although the pathogenesis of PRS remains unclear, different mechanisms have been implicated with most important being the rapid release of vasoactive substances and pro-inflammatory cytokines [tumor necrosis factor (TNF)-1α, interleukin (IL)-6] from both the donor graft and the recipient's immune system[16,17].

A subset of patients undergoing LT develop an abnormal cardiac response characterized by a decrease in stroke work despite an increase in preload[18]. This is associated with a longer post-operative intubation time and poor surgical outcomes[18,19]. Although these cardiovascular complications can be anticipated, the cardiac response during LT tends to vary significantly between individuals depending on competing comorbidities and presence of preexisting cardiomyopathy[20]. Therefore, careful monitoring of hemodynamic parameters during LT is essential to lower the risk of perioperative adverse outcomes and increase the likelihood of graft survival. Similarly, recognition of underlying CVD and optimization prior to LT is imperative in reducing the risk of perioperative complications and mortality. A comprehensive review of CVD encountered in LT candidates, including their pathophysiology, pretransplant evaluation, and management is detailed below and outlined in Table 1.

CLINICAL ENTITIES

Coronary artery disease

Epidemiology: Patients with ESLD and concomitant coronary artery disease (CAD) undergoing LT have higher morbidity and mortality rates compared to recipients without CAD[21,22]. The incidence of CAD in LT candidates varies widely, ranging 2%-38% depending on the etiology of ESLD, investigation modality used for diagnosis, criteria for significant CAD used in different studies (defined as either ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels *vs* ≥ 70% stenosis), and heterogeneity of the surveyed populations[4,10,21,23]. Among ESLD patients without symptoms of CAD, prevalence of obstructive CAD (defined as ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels) is similar to that of the general population[24]. Besides the well-established implications of obstructive CAD, nonobstructive CAD plays an important role in LT candidates. Patients with ESLD have a significantly higher prevalence of silent nonobstructive CAD in comparison with matched subjects without liver disease[21,24]. This is relevant as any degree of CAD, obstructive or non-obstructive, has been associated with a significantly higher risk of major adverse cardiac events (MACE) after transplant[21,24,25]. Additionally, the prevalence of CAD in ESLD from NASH/cryptogenic etiology is higher compared to other etiologies of ESLD and parallels the increased risk of postoperative myocardial ischemia in this subset of transplant recipients[4].

Pathophysiology: Patients with ESLD may not manifest symptoms of CAD due to the mal-adaptive hemodynamic changes that occur in liver disease[26]. Splanchnic vasodilation in response to high portal pressures reduce the peripheral vascular resistance and increases the cardiac output. The resulting hyperdynamic circulation leads to increased blood flow through systemic and pulmonary circulations [26]. Therefore, in the presence of a reduced afterload from a low peripheral vascular resistance, both CAD and cirrhotic cardiomyopathy may remain silent for prolonged durations. As described previously, intraoperative hemodynamic changes during LTs are significant and impose immense stress on the cardiovascular system, wherein a sudden reduction in preload, precipitated by acute blood loss or clamping of the portal vein and IVC, a reduction in the cardiac output, and an increase in systemic vascular resistance can rapidly precipitate overt myocardial ischemia in patients with preexisting CAD [23].

Pre-operative evaluation: The rationale behind screening for CAD in LT candidates is to determine the ability of the cardiovascular system to handle hemodynamic stress peri- and post-transplant without sustaining ischemic damage. Therefore, screening helps with cardiac risk stratification and identification of those patients who would benefit from pre-operative optimization, including revascularization of their CAD[27]. Considering the high prevalence of CAD in these patients, basic cardiac workup consisting of an electrocardiogram (ECG), chest X-ray, and transthoracic echocardiogram should be obtained routinely in all LT candidates, with further workup pursued on a case-specific basis[28]. As per American Heart Association (AHA) guidelines, screening for CAD should be pursued only if diagnosis would change management with a discernable improvement in patient outcomes[8]. Specifically, screening asymptomatic individuals should take into consideration patient eligibility for downstream intervention(s) if indicated, cost of the screening procedure and intervention, and the likelihood of preventing adverse cardiac events in the context of LT. However, decision to screen and treat asymptomatic patients is often challenging as predicting which subset will develop intraoperative or postoperative complications is difficult. Therefore, a detailed history and examination that explore

Table 1 Preoperative assessment of common cardiac diseases and relationship with liver transplant outcomes

	Pretransplant	During transplant	Post-transplant
Coronary artery disease	Prevalence 2%-38%. Screening: DSE (high NPV), SPECT myocardial perfusion, conventional coronary angiography (gold standard)		Cumulative 3-yr post-LT MACE incidence: 37.5%. All-cause mortality: 13%
Cirrhotic cardiomyopathy	Prevalence 40%-50%. TTE is the preferred method for the diagnosis of systolic or diastolic dysfunction preoperatively	23% abnormal cardiac response	Pretransplant diastolic dysfunction increase the risk for acute graft rejection or failure, and all-cause mortality
Valvular heart disease	27.5% with cardiac valve dysfunction. Routine TTE screening is recommended prior to LT	Severe aortic stenosis associated with 31% risk of perioperative complications	Pretransplant AV replacement or AS increase the likelihood for significant cardiac complications 1-3 yr post-LT
Portopulmonary hypertension	Prevalence 5%-8.5%. Preoperative screening with TTE is recommended to all LT candidates. Patients with RVSP > 45 mm Hg needs confirmation with RHC	MPAP > 50 mm Hg: 100% mortality. MPAP 35-50 mm Hg: Increased morbidity and mortality. MPAP < 35 mm Hg and MPAP > 35 mm Hg due to volume overload or hyperdynamic state: No increase in mortality	
Conduction abnormalities	Routine ECG should be performed in all LT candidates independently of a cardiac abnormality history		AF is the most common MACE in the first 90 d post-transplant (-43%). AF is an independent risk factor for MACE 30- and 90-d after LT
QTc prolongation	Common ECG finding in ESLD patients with CCM; no sex-based differences exist as in general population. Reversible causes of QTc prolongation should be identified and corrected preoperatively		Conflicting data exist regarding QTc prolongation as an independent predictor of mortality and its reversibility post-LT

LT: Liver transplantation; DSE: Dobutamine stress echocardiogram; NPV: Negative predictive value; SPECT: Single-photon emission computerized tomography; MACE: Major adverse cardiac events; TTE: Transthoracic echocardiogram; AV: Aortic valve; AS: Aortic stenosis; RVSP: Right ventricular systolic pressure; RHC: Right heart catheterization; MPAP: Mean pulmonary arterial pressure; ECG: Electrocardiogram; AF: Atrial fibrillation; ESLD: End-stage liver disease; CCM: Cirrhotic cardiomyopathy; QTc: Corrected QT.

the presence of both traditional and non-traditional risk factors of CAD, and presence of CAD equivalents such as peripheral artery disease should be obtained in all patients to determine the need of screening and the choice of investigation. Presence of ≥ 1 risk factors of CAD has been found to be highly predictive of angiographically significant stenosis and can be used to guide decision-making[24,25]. Similarly, the absence of CAD risk factors serves as a reliable clinical marker in ruling out significant CAD[24]. Specifically, age > 60 years, hypertension, left ventricular hypertrophy, diabetes, smoking, dyslipidemia, prior history of CAD, and high model for ESLD scores have been identified as significant risk factors of CAD in LT candidates[4,8]. Non-traditional risk factors of CAD pertinent to LT candidates should also be identified and integrated into decision-making. These include familial amyloid polyneuropathy, hereditary hemochromatosis, and NASH, each of which is associated with CAD apart from causing ESLD[29,30].

Despite studies reporting the presence one or more risk factors of CAD to be highly predictive of angiographically significant stenosis, there is a lack of consensus between guidelines on the number of risk factors needed to pursue noninvasive testing and the role of functional status in determining the need for screening for CAD. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend noninvasive testing in the presence of more than two risk factors of CAD and poor functional capacity while the AHA/American College of Cardiology (ACC) guidelines consider three or more risk factors to warrant testing irrespective of patients' functional status[8,31]. Generally, candidates should be perceived as high risk in the presence of a prior history of CAD, diabetes mellitus or ≥ 2 risk factors of CAD.

Noninvasive testing: Noninvasive testing which has a well-established role in detecting CAD in the general population is unfortunately suboptimal in patients with ESLD who tend to have a higher pre-test probability. In these patients, noninvasive tests are further limited by the hemodynamic changes of liver disease, poor coronary flow reserve, microvascular dysfunction, and carry a poor sensitivity[32-34]. However, they have been found to accurately predict development of adverse cardiac events in the post-transplant period[32-34]. Patients with nondiagnostic or abnormal noninvasive testing should undergo coronary angiography (CAG) to corroborate findings, determine the need for intervention, and whether revascularization will improve LT outcomes on an individual basis.

Noninvasive testing with stress echocardiography, typically dobutamine stress echocardiography (DSE) is a class 1B recommendation of the American Society of Transplantation for routine evaluation of CAD in all LT candidates[27]. Cardiac catheterization is recommended if DSE is nondiagnostic or abnormal. Over the years, conflicting data regarding the sensitivity and predictive value of noninvasive stress tests have been reported. In a meta-analysis evaluating the diagnostic accuracy of DSE for detecting CAD in ESLD patients awaiting LT, DSE demonstrated a poor sensitivity (32%) but excellent negative predictive value (NPV) (98%) for perioperative and long-term cardiac events[33]. Multiple other studies have found DSE to have a low sensitivity and positive predictive values and intermediate to high NPVs[4,34-36]. A frequently encountered limitation of DSE in patients with ESLD is the inability to achieve target heart rates and thereby rate-pressure products.

Myocardial perfusion imaging with single positron emission tomography (SPECT) is another modality with established role in diagnosing CAD in the general population. However, its diagnostic accuracy in ESLD patients is unclear due to conflicting results reported by different studies[28,37,38]. A high number of false positives may be secondary to the chronic vasodilatory state characteristic of ESLD and a low coronary flow due to microvascular dysfunction rather than epicardial vessel stenosis, encountered frequently in patients with NASH cirrhosis[28,37,38].

Coronary computed tomography (CT) is another option with excellent diagnostic accuracy for detect significant CAD in the general population and can serve as a viable option in ESLD patients as well[39]. Considering the questionable sensitivity of stress tests and specificity of perfusion testing such as SPECT, coronary CT can serve as an accurate and noninvasive alternative. However, there are limitations associated with it just like any other test. As per the 2018 American Society of Transplantation Liver and Intestinal and Thoracic and Critical Care Community of Practice guidelines, coronary CT maybe considered as an alternative to CAG in patients with ESLD who are able to tolerate lying flat, do not have severely impaired renal function, have low heart rates without irregularities in the rhythm, although newer gating techniques allow interpretation of coronary CT even in patients with atrial fibrillation (AF)[40,41].

Invasive testing: CAG is the gold standard diagnostic modality for detecting coronary artery stenosis and is relatively safe in patients with ESLD[28,40]. It is indicated in patients with a prior history of CAD, myocardial infarction, or a coronary intervention, in those with high pre-test probability of CAD, and in patients with abnormal or nondiagnostic noninvasive test results. On detecting significant stenosis, the decision to revascularize should be guided by whether it will improve transplant outcomes. Notably, the study conducted by Snipelisky *et al*[42] showed that patients with severe CAD continued to have an elevated cardiac mortality after LT despite revascularization preoperatively, thus questioning the benefit of pre-transplant coronary interventions. However, revascularization should be pursued if obstructive CAD is the primary precluding factor for LT[28,43]. Studies investigating the feasibility of percutaneous coronary intervention and stenting in LT candidates have found it to be feasible with a preference for bare metal stents considering the shorter dual antiplatelet therapy compared to drug eluting stents[44,45].

Cirrhotic cardiomyopathy

Epidemiology: Impaired cardiac contractility secondary to sympathetic stress and altered diastolic function in patients with ESLD is termed cirrhotic cardiomyopathy[26,46,47]. Although there are limited data citing the prevalence of cirrhotic cardiomyopathy, attributable in part to the indolent nature of the disease, nearly 40%-50% of ESLD patients have cardiac changes consistent with cardiomyopathy[48,49]. This is relevant as nearly 20% of mortality in LT recipients over a 20 years post-transplant follow up period and 40% of early postoperative deaths after LT are cardiovascular-related[50].

Pathophysiology: Cirrhotic cardiomyopathy predisposes to reduced survival, and complications such as renal failure and hepatorenal syndrome in patients undergoing LT[47]. Cardiac dysfunction in ESLD occurs secondary to maladaptive alterations in the systemic and splanchnic circulations leading to an increased cardiac output and heart rate[51,52]. Pooling of blood in the splanchnic vascular bed leads to a lower central blood volume termed “central” or “effective” hypovolemia. This results in baroreceptor-induced activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)[47]. SNS stimulation leads to overactivation of the β-adrenergic system resulting in receptor desensitization and cardiac dysfunction[53].

Systolic dysfunction: At rest, systolic dysfunction in patients with ESLD remains subclinical due to a reduced afterload and low systemic vascular resistance. However, it manifests overtly when the cardiovascular system is challenged with stressors such us LT, TIPS, and exercise[26,46,47,53]. Four possible mechanisms have been proposed to explain the systolic dysfunction in patients with ESLD: (1) Impaired beta-adrenergic receptor signaling secondary to sympathetic hyperactivity, which has also been shown to cause direct myocyte damage; (2) Decreased cardiac contractility and increased cardiomyocyte apoptosis mediated by endocannabinoids, levels of which have been shown to be increased in murine cirrhotic hearts; (3) The presence of cardio-depressant substances such as nitric oxide and carbon monoxide; and (4) Abnormalities of the sodium/calcium (Na/Ca) exchanger that result in the excess Ca influx leading to cardiomyocyte apoptosis[26,53].

Diastolic dysfunction: Diastolic dysfunction in patients with ESLD occurs due to an increased stiffness of the myocardial wall from a combination of myocardial hypertrophy, fibrosis and subendothelial edema. Activation of RAAS has been implicated in myocardial hypertrophy, myocardial fibrosis and development of diastolic heart failure in patients with portal hypertension irrespective of the presence of cirrhosis[54]. Additionally, increased levels of plasma aldosterone, a byproduct of RAAS activation have been associated with a reduced ratio of early to late (atrial) phases of ventricular filling (E:A ratio) in ESLD[54]. Therefore, it is likely that activation of RAAS leads to diastolic dysfunction by multiple direct and indirect pathophysiologic mechanisms[55-58]. Other proposed mechanisms for diastolic dysfunction in ESLD involve alteration in collagen configuration and sodium retention[59,60].

Pretransplant evaluation: Patients with ESLD can be screened for cirrhotic cardiomyopathy through biological markers and imaging modalities, wherein they supplement data obtained from history and physical examination[61]. Imaging appears to provide maximum diagnostic value when used in the appropriate clinical context.

Biological markers: Biomarkers for subclinical and clinical heart failure (HF) include brain natriuretic peptide (BNP), propeptide, N-terminal pro-BNP (NT-proBNP), and cardiac troponins[53,62,63]. BNP and NT-proBNP have been associated with the severity of ESLD and portal hypertension. Henriksen *et al*[64] demonstrated a significant correlation between proBNP and BNP levels and Child score. Moreover, they reflect the severity of diastolic and systolic cardiac abnormalities as well as mortality in clinical HF and in cirrhotic cardiomyopathy (CCM)[63,65,66]. A major consideration and limitation to setting cut-off values for any biomarker including BNP and NT-proBNP is the heterogeneity in assays used across institutions, timing of measurement, and the different thresholds/cut-offs used by individual labs. Therefore, at this time there are no cut-off points for biomarkers indicating that the patient should be removed from the transplant waiting list.

Cardiac remodeling may be measured by levels of galectin-3 and soluble suppression of tumorgenicity-2 (ST-2), member of the IL-1 family, directly interacting with cardioprotective IL-33. These markers have been shown to reflect cardiac inflammatory and fibrotic remodeling[67,68]. However, galectin-3, and soluble ST-2 are also markers for liver inflammation and fibrosis, which may limit their applicability to CCM[69]. In addition to highly sensitive C-reactive protein associated with cardiac disease (and other inflammatory conditions), other inflammatory markers have been studied in HF and CCM including IL-6, IL-8, TNF-α, lipopolysaccharide binding protein, vascular endothelial growth factor, and soluble urokinase-type plasminogen activator receptor, some of which may worsen the circulatory dysfunction of portal hypertension[47,53,61,63].

Imaging

Transthoracic echocardiography: Transthoracic echocardiography (TTE) is the preferred imaging modality although cirrhotic cardiomyopathy is largely a clinical diagnosis and there are no specific TTE features distinguishing a cirrhotic etiology[47]. Systolic dysfunction is characterized by either left ventricular ejection fraction (LVEF) ≤ 50% or global longitudinal strain (GLS) < 18% even in the presence of a normal LVEF[47,53]. Some studies have recommended a higher a cut-off value of LVEF 55%-60% in patients with ESLD due to the decreased afterload and increased preload, which could falsely normalize the LVEF in this subset[61]. GLS is particularly useful as the longitudinally oriented subendocardial fibers are highly susceptible to damage making longitudinal left ventricular function the first manifestation of cardiac impairment[53]. Diastolic dysfunction characterized by TTE should meet three or more of the following diagnostic criteria: (1) Diastolic tissue velocity of mitral annulus (septal E′ velocity) < 7 cm/s; (2) Ratio of velocity of the left ventricle inflow during early, rapid passive filling (E wave) compared to E′ (E/E′ ratio) ≥ 15. E:E′ ratio has been found to reflect left ventricular filling pressure, and this ratio increases as diastolic function worsens; (3) Left atrial volume index > 34 mL/m^2; and (4) Tricuspid regurgitation velocity > 2.8 m/s[47,53,61]. Tissue doppler imaging is a well validated imaging technique for diastolic dysfunction evaluation[61].

Cardiac magnetic resonance imaging: Structural changes in cirrhotic cardiomyopathy as seen on cardiac magnetic resonance imaging (MRI) appear similar to those of myocarditis with a non-specific patchy distribution[70]. Considering the non-specific changes, the practical applicability of cardiac MRI for diagnosing cirrhotic cardiomyopathy is low[61]. However, it can be used to visualize edema and myocardial fibrosis seen as late gadolinium enhancement, especially pronounced in patients with alcoholic liver cirrhosis, to measure LVEF and chamber volumes[39,61,71,72].

Management and prognosis: Currently there exist no guidelines for the diagnosis and treatment of cirrhotic cardiomyopathy. Management of heart failure in patients with ESLD is built on principles similar to that of non-cirrhotic patients, consisting of strict sodium and fluid restriction, use of diuretics to decongest, and afterload reduction[26]. However, afterload reduction in patients with ESLD can be challenging as they have arterial hypotension at baseline[26]. Additionally, the benefit of beta-blockers in ESLD patients is not as clear as in other groups. While nonselective beta-blockers can help improve electromechanical coupling, data from clinical trial report a reduction in cardiac output which can have

detrimental consequences during periods of stress such as infection[73].

LT remains the gold standard treatment as it normalizes hepatic metabolism and reduces the adverse effects of hyperdynamic circulation, thus improving cardiac function[53,74]. Despite undergoing LT, recipients seldom remain complication free as the presence of cirrhotic cardiomyopathy increases their likelihood of acute graft rejection and mortality. This unfavorable effect of cirrhotic cardiomyopathy on post-transplant outcomes was illustrated in a study by Mittal *et al*[75] of 970 LT recipients evaluated over a mean duration of 5.3 years. Patients with diastolic dysfunction pretransplant had a significantly higher risk of acute cellular rejection [hazard ratio (HR) = 10.56; P = 0.0001)], graft failure (HR = 2.09; P = 0.007), and all-cause mortality (HR = 1.52; P = 0.01) compared to recipients without cardiac dysfunction. Notably, the risk of complications increased with worsening diastolic dysfunction. Although point-based scoring systems such as the cardiovascular risk in orthotopic liver transplantation score to predict adverse cardiovascular events after LT have been proposed, till date there exist no validated and standardized models to quantitatively risk-stratify patients based on their risk of developing perioperative cardiac complications[76].

Portopulmonary hypertension

Epidemiology and pathophysiology: Portopulmonary hypertension (PoPH) is the presence of pulmonary arterial hypertension associated with portal hypertension of hepatic or extrahepatic origin and is currently classified as World Health Organization group 1 PH[77,78]. Prospective studies evaluating PoPH have reported a prevalence of 5 to 8.5% in patients awaiting LT[78-80]. No specific etiology of portal hypertension or chronic liver disease is associated consistently with the development of PoPH[81,82]. Similarly, the severity of liver disease has not been found to be predictive of PoPH[81,82]. However, presence of severe PoPH has been associated with a worse prognosis in patients undergoing LT compared to recipients without PoPH[83,84]. Although the pathophysiology of PoPH remains unclear, the most widely accepted mechanism is an imbalance of vasoconstrictive and vasodilatory mediators, wherein humoral substances such as endothelin-1 bypass hepatic metabolism and reach the pulmonary circulation through portosystemic shunts, leading to pulmonary arterial hypertension[85,86].

Preoperative evaluation and management: PoPH most commonly presents with exertional dyspnea but symptoms may be absent or subtle in the initial stages[87,88]. Currently, the ESC and ERS recommend echocardiographic assessment for PH in symptomatic patients with chronic liver disease or portal hypertension and in all LT candidates (Class I/Grade B)[89]. Screening with TTE is geared at estimating the right ventricular systolic pressure (RVSP). Additional information obtained from TTE include right ventricular dilatation or dysfunction and presence and severity of tricuspid regurgitation[90,91]. Patients with RVSP > 45-50 mmHg should be evaluated further with right heart catheterization (RHC) which is the gold standard investigation for diagnosing PoPH. The updated RHC criteria for diagnosing PoPH are: Mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary vascular resistance (PVR) ≥ 240 dyne $s^{-1} \cdot cm^{-5}$ or 3 Wood Units (WU) and pulmonary capillary wedge pressure ≤ 15 mmHg[92]. Importantly, PoPH with severe hemodynamic impairment (*i.e.*, mPAP > 45-50 mmHg or PVR > 3 WU) is associated with excessive mortality and is considered an absolute contraindication for LT[93,94]. Patients with mPAP ranging from 35-50 mmHg should be referred to a PoPH specialist for pulmonary arterial hypertension-specific-therapy with the goal of lowering mPAP to < 35 mmHg and becoming eligible for LT in the future[93,94]. It is important to note that mPAP may be elevated in conditions other than PoPH such as volume overload and a hyperdynamic state encountered in ESLD patients. Therefore, optimization of volume status is important and a complete assessment during RHC to ensure PVR is > 3 WU is necessary to diagnose PoPH[95,96].

Hypertension: Systemic hypertension is not a common finding among patients with ESLD who most often have low arterial blood pressure (BP), pathognomonic of splanchnic vasodilation and portal hypertension in liver cirrhosis[97,98]. The release of vasodilators and SNS-mediated vasodilation of splanchnic vessels lead to reductions in the afterload and systemic vascular resistance[97,99]. Also, patients with ESLD have a blunted response to vasopressors, and an increased arterial compliance, all of which result in low systemic BPs[99]. Often, patients with arterial hypertension become "normotensive" during the course of developing chronic liver disease. In clinical practice, determining the etiology of an inappropriately normal BP should take into consideration secondary causes of hypertension such as severe renovascular disease, a previous history of arterial hypertension, and mechanisms counteracting vasodilation. In ESLD, release of nitric oxide, calcitonin gene-related peptide, and adrenomedullin results in splanchnic vasodilation, while counteractive activation of renin angiotensin aldosterone system leads to vasoconstriction and an increase in BP[97,98]. Additionally, these counteractive mechanisms are influenced by agents such as beta blockers and aldosterone antagonists which are often used in these patients to mitigate other manifestations of ESLD and also provide antihypertensive effects.

Valvular diseases: The prevalence of valvular heart disease in patients with ESLD is currently unknown and there is a paucity of literature and guidelines about management of structural heart disease in LT

candidates[100]. The presence of valvular diseases such as severe aortic stenosis can pose a prohibitive risk to live transplant due to an increased risk of intraoperative complications and a risk of perioperative mortality greater than 30%[101,102]. Similarly, the hemodynamics of ESLD can preclude candidacy for valve surgery making these patients extremely high-risk for both procedures[101]. Additionally, the severity of aortic stenosis has been found to correspond with perioperative mortality in patients undergoing noncardiac surgery[102]. Additionally, patients with uncorrected severe aortic stenosis undergoing LT have been found to have a higher rate of cardiac complications, including cardiac death, myocardial infarction, and requirement of aortic valve replacement in the post-transplant period compared to patients without valvular disease[101,103]. As per the AHA/ACC 2014 guidelines, elevated-risk elective noncardiac surgery is reasonable to perform in patients with either severe asymptomatic aortic stenosis, mitral regurgitation, or severe asymptomatic aortic regurgitation with normal LVEF[104]. Since exercise tolerance is often poor in patients with ESLD, assessment of severity of valvular heart disease is primarily made based on imaging. However, a detailed history of symptoms of valvular heart disease or heart failure, clinical examination including cardiac examination for murmurs, and transthoracic echocardiogram is recommended routinely in all LT candidates to detect ESLD valvular heart disease, determine its severity, and assess left ventricular function[100,104,105]. This allows for risk stratification and timely planning of valvular intervention if indicated based on clinical or radiological findings.

Conduction abnormalities: A routine 12-lead ECG should be performed irrespective of a history of cardiac disease in all patients undergoing evaluation for LT[8,27].

AF: AF has a prevalence of around 10% in patients with ESLD and is the most common arrhythmia after liver transplantation[106]. It has been found to be associated with a poor prognosis, especially higher in-hospital mortality, length of hospital stay, increased perioperative cardiac complications, and MACE after liver transplantation[106-109]. Presence of AF in the pre-transplant period is a strong independent predictor of MACE at both 30- and 90-d after LT. In LT recipients, it is also the most common major adverse cardiac event in the first 90 d after transplant and constitutes nearly half of MACE (43%) in these patients[107]. Therefore, detection of AF with 12-lead ECG, telemetry monitoring, or ambulatory monitoring devices in those with a suspicion of paroxysmal AF is important as a part of cardiac evaluation of LT candidates.

QT interval prolongation: QT interval prolongation, considered a hallmark of cirrhotic cardiomyopathy, occurs in 30%-50% of patients with ESLD[110-112]. The mechanism for QT prolongation in ESLD can be multifactorial but only the Child-Pugh score has been found to be an independent predictor, with changes in plasma norepinephrine contributing to corrected QT (QTc) interval variability[110,113]. Individual components of the Child-Pugh score have not been found to prolong QTc interval significantly[110,112]. Sex-specific differences in the duration of QT interval which are well-established in the general population do not exist in patients with ESLD, whereby a QTc ≥ 440 ms is considered elevated in both women and men[112,113]. The lack of sex-based differences in the duration of QTc interval in patients with ESLD persists in the post-transplant period[113]. Although men with ESLD have a relative androgen deficiency, levels of sex hormones have not been found to correlate with durations of QTc interval in men and women in the pre-transplant period[113]. Assessment and management of prolonged QTc interval is important as it has been associated with an increased risk of mortality, especially in alcoholic liver cirrhosis, and in Child-Pugh Class A patients with any etiology of ESLD[110,114]. However, conflicting data have been reported on the effect of prolonged QT interval on mortality and its reversibility with LT[110,112,114]. Ko *et al*[112] their study of LT candidates did not find an association between QTc interval prolongation and mortality or complications in the post-transplant period. In this study, patients who underwent LT demonstrated a significant rise in QTc intervals in the early-post transplant period followed by a significant reduction within the first six months of LT. On the contrary, Kim *et al*[114] did not find significant reversibility of the QTc interval after LT, and rather found it to be an independent predictor of mortality. Also, the threshold value set for usually defined in the general population and the investigators found male sex to be an independent predictor of prolongation. This is contrary to the study by Adigun *et al*[113] who found no sex-based differences in QTc prolongation among patients with ESLD and did not find male gender to be independently associated with the duration of the QT interval.

A QT interval of ≥ 500 ms has been found to be associated with a greater risk of developing torsade de pointes in the general population but there exists no established cut-off threshold below which a prolonged QT interval confers freedom from a risk of arrhythmias in both LT recipients and the general population[115]. There is also a lack of consensus on the cut-off threshold warranting drug discontinuation in drug-induced QT prolongation[115]. Beta blockers which are frequently used in patients with ESLD have been found to shorten the QT-interval in those with prolonged durations and increase the duration of QT-interval without prolonging it in those with normal values at baseline[116,117]. Although prolonged QTc interval is prevalent in LT candidates, reversible causes such as QT-interval prolonging medications and electrolyte abnormalities should be sought and corrected promptly due to the possibility of life-threatening ventricular arrhythmias. Also, a prolonged QTc interval is not a

contraindication to LT.

Pericardial diseases

Pericardial effusion: Pericardial effusions can occur both before and after LT and require careful evaluation to detect tamponade. Hepatitis C infection with or without cryoglobulinemia has been associated with pericardial effusions both in patients with ESLD and in transplant recipients[118-120]. Although cryoglobulinemia is a well-established complication of hepatitis C infection, pericardial effusions and myopericarditis occurring as a multiorgan manifestations of cryoglobulinemia are rare with only a few reported cases worldwide[120]. Physical examination and bedside TTE should be performed to exclude tamponade. Presence of tamponade or significant pericardial effusion requires timely pericardiocentesis or pericardial window prior to LT and follow-up with repeat echocardiogram to evaluate for recurrence[28].

Constrictive pericarditis: In the context of patients with ESLD awaiting LT, constrictive pericarditis occurs as an etiology of chronic liver disease whereby longstanding hepatic congestion can lead to cardiac cirrhosis. A high degree of clinical suspicion is required as symptoms of constrictive pericarditis such as ascites, hepatomegaly and peripheral edema are often misdiagnosed as primary chronic liver disease[121]. TTE with doppler is the initial recommended test which may reveal characteristics suggestive of constrictive pericarditis such as ventricular septal shift with respiration, variation in mitral annular inflow velocity, a thickened pericardium, and rapid early diastolic filling[122]. Cardiac MRI and cardiac catheterization provide additional information to aid with diagnosis. Management involves pericardiectomy but cannot reverse ESLD, which in turn renders this procedure very high risk due to coagulopathy[123].

CONCLUSION

Comprehensive and yet patient-directed cardiovascular assessment consisting of risk factor evaluation, clinical examination, diagnostic testing with laboratory parameters, imaging, and invasive testing when medically indicated is essential for risk stratifying patients being considered for LT. Considering the high-risk nature of this invasive procedure, limited number of donor grafts available, and the high likelihood of cardiovascular mortality in the postoperative period, identifying those at highest risk of adverse events who will also benefit from preoperative optimization is imperative. This will help maximize the chances of a successful LT and avoid futile transplants in those with severe CVD not amenable to mitigation or repair. Routine cardiac workup consisting of basic tests is indicated in all LT candidates. Further workup should be guided by clinical judgement and results of the preliminary workup. Despite the high prevalence of CVD among patients with ESLD, current guidelines fall short of meeting clinical need. Areas of future research include developing validated predictive models for cardiac risk stratification in patients with ESLD, improving the diagnostic accuracy of noninvasive tests for evaluation of CAD, and development of standardized guidelines for nonischemic CVD in patients with ESLD.

FOOTNOTES

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