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STATE-OF-THE-ART PAPER

Cardiovascular Risk Assessment of the Liver Transplant Candidate

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Liver transplantation (LT) candidates today are increasingly older, have greater medical acuity, and have more cardiovascular comorbidities than ever before. Steadily rising model for end-stage liver disease (MELD) scores at the time of transplant, resulting from high organ demand, reflect the escalating risk profiles of LT candidates. In addition to advanced age and the presence of comorbidities, there are specific cardiovascular responses in cirrhosis that can be detrimental to the LT candidate. Patients with cirrhosis requiring LT usually demonstrate increased cardiac output and a compromised ventricular response to stress, a condition termed cirrhotic cardiomyopathy. These cardiac disturbances are likely mediated by decreased beta-agonist transduction, increased circulating inflammatory mediators with cardiodepressant properties, and repolarization changes. Low systemic vascular resistance and bradycardia are also commonly seen in cirrhosis and can be aggravated by beta-blocker use. These physiologic changes all contribute to the potential for cardiovascular complications, particularly with the altered hemodynamic stresses that LT patients face in the immediate post-operative period. Post-transplant reperfusion may result in cardiac death due to a multitude of causes, including arrhythmia, acute heart failure, and myocardial infarction. Recognizing the hemodynamic challenges encountered by LT patients in the perioperative period and how these responses can be exacerbated by underlying cardiac pathology is critical in developing recommendations for the pre-operative risk assessment and management of these patients. The following provides a review of the cardiovascular challenges in LT candidates, as well as evidence-based recommendations for their evaluation and management. (J Am Coll Cardiol 2011;58:223–31) © 2011 by the American College of Cardiology Foundation

Liver transplantation (LT) candidates today are older, have greater medical acuity, and have more comorbidities, including cardiovascular disease, than ever before (1). Steadily rising model for end-stage liver disease (MELD) scores at the time of transplant, resulting from high organ demand, reflect the escalating risk profiles of LT candidates (1). In addition to advanced age and the presence of comorbidities, there are specific cardiovascular responses in end-stage liver disease (ESLD) that can be detrimental to the LT candidate. Patients with ESLD requiring LT usually demonstrate increased cardiac output and a compromised ventricular response to stress, a condition termed cirrhotic cardiomyopathy. These cardiac disturbances are likely mediated by decreased beta-agonist transduction, increased circulating inflammatory mediators with cardiodepressant properties, and repolarization changes (2–7). Low systemic vascular resistance and bradycardia are also commonly seen in cirrhosis and can be aggravated by beta-blocker use. These physiologic changes all contribute to the potential for cardiovascular complications, particularly with the altered hemodynamic stresses that LT patients face post-operatively.

The hemodynamic stress of LT is greatest after reperfusion of the transplanted liver and is characterized by a sudden increase in pre-load. In the setting of a cardiomyopathy, elevation in pulmonary capillary wedge pressure and/or reduction in mean arterial pressure can herald profound post-reperfusion hemodynamic instability and hepatic congestion. Post-transplant reperfusion may result in cardiac death due to a multitude of causes, including

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Abbreviations and Acronyms

CAD = coronary artery disease
CT = computed tomography
DM = diabetes mellitus
DSE = dobutamine stress echocardiography
ESLD = end-stage liver disease
HPS = hepatopulmonary syndrome
LT = liver transplantation
LVOTO = left ventricular outflow tract obstruction
MELD = model for end-stage liver disease
mPAP = mean pulmonary arterial pressure
NPV = negative predictive value
PFO = patent foramen ovale
POPH = portopulmonary hypertension
QTc = corrected QT interval
SPECT = single-positron emission computed tomography
TTE = transthoracic echocardiography

arrhythmia, acute heart failure, and myocardial infarction (8,9). Recognizing the hemodynamic challenges encountered by LT patients post-operatively, and how these responses can be exacerbated by underlying cardiac pathology, is critical in developing recommendations for the pre-operative risk assessment and management of these patients. The following provides a review of the cardiovascular challenges presented by ESLD patients, as well as evidence-based recommendations for their evaluation and management.

Coronary Artery Disease

Patients with established coronary artery disease (CAD) who undergo LT have worse outcomes than do patients without CAD (10,11). A 1-year mortality rate of approximately 40% has been reported after LT for patients with CAD (12). Coronary atherosclerosis is common in this population and often goes undiagnosed. In a study of 161 LT candidates at risk for CAD referred for coronary angiography, >25% of patients had at least 1 moderate or severe (≥50%) coronary stenosis. Obstructive CAD was most common among patients with ≥2 traditional cardiac risk factors (13). Nonobstructive lesions (coronary artery stenosis <50%) are unlikely to be detected by stress imaging, but can also be responsible for acute coronary syndromes (unstable angina, myocardial infarction, or sudden cardiac death) (14,15). In fact, it is thought that acute coronary syndromes often result from rupture of coronary plaques with <50% stenosis (16,17).

Traditional coronary risk factors (Table 1) remain important for pre-operative risk stratification in patients with ESLD. Diabetes mellitus (DM) and age >50 years are particularly predictive of post-operative ischemic complications (12,18–21). By 1 estimate, 5-year survival is approximately 40% lower among persons with insulin-dependent DM or known CAD than among persons without these conditions (22). The LT recipients display higher Framingham risk scores than age- and sex-matched non-LT patients (23). The relative predictive value of Framingham risk score for cardiac events is an area of ongoing research. Although 1 retrospective cohort study did report a low incidence of ischemic events at 4-year follow-up, most analyses reveal higher event rates than predicted by Framingham scores, possibly reflecting more comorbidities or a greater severity of illness compared to patients without ESLD (23). The presence of other traditional risk factors, specifically hypertension and hyperlipidemia, has also been shown to be independently associated with worse outcomes after LT (24).

Nontraditional coronary risk factors have also been studied. One retrospective case-control study showed an increased prevalence of CAD among patients with cirrhosis due to nonalcoholic steatohepatitis. In this study, patients with nonalcoholic steatohepatitis cirrhosis were more likely to have traditional CAD risk factors and the metabolic syndrome than were patients with other etiologies of cirrhosis (25). Whether nonalcoholic steatohepatitis cirrhosis is an independent CAD risk factor with incremental predictive value over these traditional risk factors remains to be determined (26–28). Coronary calcium is also strongly associated with traditional CAD risk factors in the cirrhotic population (29). In addition, concomitant renal dysfunction in the setting of ESLD is associated with increased cardiovascular risk (30). Although elevated C-reactive protein is associated with increased cardiovascular events, it has only been studied post-operatively in the ESLD population (31). C-reactive protein appears to peak and slowly fall within 1 week after LT, and delayed elevations may indicate inflammatory complications such as post-operative infection or rejection (32).

The significant hemodynamic stress of LT and prevalence of underlying CAD in ESLD patients warrants a routine pre-operative cardiac assessment (Table 1). However, noninvasive functional testing for ischemia may have limited predictive value for obstructive CAD in this population (Table 1). Most patients cannot undergo exercise testing. Dobutamine stress echocardiography (DSE) has been shown to have a poor sensitivity and a low negative predictive value (NPV) among LT candidates, possibly secondary to an inability to achieve target heart rate and peak double product (heart rate multiplied by blood pressure). A retrospective study of 105 ESLD patients who underwent both DSE and coronary angiography found DSE to have a sensitivity of 13% and NPV of 75% for obstructive CAD (33). Although there are limited data on the predictive value of DSE for post-operative cardiovascular events, 1 study suggests that a low peak double product and chronotropic incompetence are predictive of cardiovascular events (34). The negative predictive value for DSE in LT candidates has been estimated to be >85% in some studies (35,36). Recently, a large retrospective study of 400 LT patients examined the association between pre-operative DSE and adverse cardiac events (death/nonfatal myocardial infarction) at 30 days. They found that DSE had a fairly strong NPV of 89%, but a positive predictive value of only 27% for the identification of post-transplant cardiac events (37). However, the majority of patients in this study had relatively low MELD scores (<15); thus, these findings

Table 1 Pre-Operative Cardiovascular Assessment and Management

Potential CV Pathophysiology	Diagnostic Findings and Test Operating Characteristics	Recommendations
Low HR	Noninvasive stress imaging*	CAD
Chronic vasodilatory state Low SVR, low BP	Low sensitivity, low NPV of DSE (inability to reach target HR × BP) Low PPV, false positives of SPECT (decreased microvascular reserve)	Consideration of invasive or CT coronary angiography if known CAD, abnormal noninvasive test or a high pre-test probability of CAD (DM or ≥2 traditional risk factors)†
High cardiac output LVH Systolic/diastolic dysfunction LVOTO	Echocardiography Subclinical cardiomyopathy (LVH) Inducible LVOTO on DSE Early, reversible systolic dysfunction post-operatively	Cardiomyopathy/heart failure Pre-operative TTE to assess systolic and diastolic cardiac function, valves, and left ventricular outflow tract obstruction if LVH; treatment of HF and LVOTO as appropriate
Portopulmonary hypertension (pulmonary arterial HTN)	Echocardiography: elevated right-sided and pulmonary pressures. Right-side heart catheterization: mean PAP >25 mm Hg, PVR >3 Wood units in the setting of PCWP <15 mm Hg	Pulmonary heart disease: TTE to assess for pulmonary hypertension, with referral to RHC if elevated PASP or RV systolic dysfunction found on TTE (to differentiate pulmonary venous and pulmonary arterial hypertension) RHC to assess response to medical therapy of confirmed POPH
Pericardial effusions	Echocardiography: potentially decreased PPV for tamponade in setting of POPH ± elevated right-sided pressures	Pericardial disease: TTE to assess for pericardial fluid and signs of tamponade
Prolonged QTc interval	Electrocardiography: long QTc, potentially reversible sex differences in QTc abolished	Arrhythmia: electrocardiogram to assess baseline QTc interval; treat reversible causes of long QTc
Pre-existing intracardiac shunt	Echocardiography: PFO or other intracardiac shunts	Intracardiac shunts: TTE to assess for PFO and other intracardiac shunts; precaution against venous air emboli during transplant procedure

*Utility of noninvasive testing for coronary artery disease (CAD) detection in liver transplantation candidates (using coronary angiography as the gold standard): positive/negative predictive values for dobutamine stress echocardiography (DSE) = 22%/75%, respectively (Harinstein et al. [33]), 33%/100% (Donovan et al. [36]), 0%/86% (Williams et al. [35]). Positive/negative predictive values for single-photon emission computed tomography (SPECT) = 22%/77%, respectively (Davidson et al. [38]), 15%/100% (Aydinalp et al. [39]). †Traditional risk factors for CAD include age (male >45 years/female >55 years), hypercholesterolemia, hypertension, tobacco use, and family history of early CAD (first-degree relative male <55 years/female <65 years).

BP = blood pressure; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; LVH = left ventricular hypertrophy; LVOTO = left ventricular outflow tract obstruction; NPV = negative predictive value; PAP = pulmonary arterial pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PFO = patent foramen ovale; POPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; QTc = corrected QT interval; RHC = right heart catheterization; RV = right ventricular; SVR = systemic vascular resistance; TTE = transthoracic echocardiography.

may not be applicable to patients with more severe illness or higher MELD scores.

Similarly, it has been suggested that the predictive value of nuclear single-photon emission computed tomography (SPECT) stress imaging is limited by the chronic vasodilatory state exhibited by patients with ESLD (38). In a recent prospective study, the specificity of abnormal SPECT findings for obstructive CAD by coronary angiography was only 61% (39). This low specificity may be due to the fact that ESLD patients often exhibit impaired coronary flow reserve, which is typically the result of coronary microvascular dysfunction rather than epicardial lesions (40,41). One retrospective review of 339 patients found an excellent NPV of 99% for SPECT in patients with cirrhosis, but this was in a low-risk cohort (42).

Therefore, on the basis of available data, either an abnormal noninvasive test or a high pre-test probability of CAD should prompt consideration for coronary angiography (Table 1). Obstructive CAD not amenable to revascularization (either percutaneous or surgical) can form the basis for denial of LT in some centers (43). However, successful coronary revascularization for obstructive CAD has been used before LT in otherwise suitable candidates (44,45). In general, drug-eluting stents are not recommended in this population because of the requirement for prolonged dual antiplatelet therapy and increased risk of bleeding.

Coronary angiography has been associated with an acceptable safety profile in LT candidates, who often have coagulopathies that render them at higher risk for bleeding complications, or concomitant renal dysfunction that increases the risk of contrast-induced nephropathy (46,47). A transradial approach to invasive angiography may prove useful in the ESLD population to further reduce bleeding complications (48). Cardiac computed tomography (CT) angiography is emerging as an attractive noninvasive alternative to invasive coronary angiography for the assessment of CAD in select LT candidates (49). Favorable patient features for cardiac CT angiography include normal renal function, a nontachycardic regular cardiac rhythm, normal body habitus, and the ability to lie still and perform breath-holding maneuvers.

It is unknown whether contemporary revascularization therapy improves outcomes of LT candidates (50). However, revascularization should be considered in carefully selected patients when the lack of revascularization is deemed to present a prohibitive risk for LT. Therefore, when possible, it is important make an assessment of CAD risk in the ESLD patient before revascularization becomes contraindicated (usually an excessive bleeding risk due to coagulopathy and/or thrombocytopenia).

Heart Failure and Cardiomyopathy

Cirrhosis is associated with a high cardiac output, increased left ventricular wall thickness, cardiac chamber enlargement, and significantly impaired systolic and diastolic response to stress, especially in the setting of volume overload. The degree of left ventricular hypertrophy seen on pre-operative transthoracic echocardiography (TTE) is typically high,

even when corrected for height, sex, and hemodynamic load, suggesting a component of intrinsic subclinical cardiomyopathy in LT candidates (termed cirrhotic cardiomyopathy) (51).

Cirrhotic cardiomyopathy, however, has been shown to involve more than just left ventricular hypertrophy (52). It appears to be a complex condition that is also characterized by a diminished contractile responsiveness to stress, impaired diastolic relaxation, and electrophysiological abnormalities, all in the absence of known cardiac disease. The blunted cardiac response to stress is thought to be due to autonomic dysfunction, together with impaired baroreceptor and volume reflexes. Animal models of cirrhosis have demonstrated both a decrease in beta-adrenoceptor density as well as decreased beta-adrenoceptor–stimulated cyclic-adenosine monophosphate production (53). Diastolic dysfunction is likely related to increased ventricular stiffness in the setting of left ventricular hypertrophy (as noted above), as well as impaired myocardial relaxation, possibly related to abnormalities in calcium exchange through the sarcoplasmic reticulum (54). The electrophysiologic abnormalities found in cirrhotic cardiomyopathy include QT-interval prolongation, electrical and mechanical dyssynchrony, and chronotropic incompetence (55–57).

The clinical ramifications of cirrhotic cardiomyopathy may not manifest until normal vascular tone is restored post-operatively. Thereafter, patients may be at risk of having acute decompensated heart failure develop in certain situations (58–60). In a retrospective study of 86 LT recipients who underwent both TTE and right-side heart catheterization pre-operatively, new systolic heart failure was significantly more likely to develop post-operatively among patients with elevated pulmonary artery or right-heart pressures pre-operatively (61). Elevated pulmonary pressures and post-operative myocardial depression can be detrimental in LT patients, given their underlying cardiomyopathic physiology, and have the potential to cause significant cardiovascular complications. Both survivors and nonsurvivors of LT exhibit early myocardial depression, with nonsurvivors showing less cardiac reserve pre-operatively and a very early drop in cardiac index and oxygen delivery post-operatively. Very early cardiac depression (within 12 h) after transplant is associated with subsequent multiorgan failure and death (62).

A pre-operative TTE should be performed routinely for the assessment of left ventricular, right ventricular, and valvular function. Pre-transplant heart failure, regardless of underlying left ventricular ejection fraction, may resolve post-operatively in LT patients (63). Thus, the presence of pre-operative left ventricular dysfunction is not an absolute contraindication to LT, but is a risk factor for perioperative cardiovascular complications. Successful LT in patients with ejection fraction as low as 10% has been reported with aggressive medical management (64). Volume status and symptoms of heart failure should be monitored and optimized before transplantations. A high index of suspicion should always be maintained for post-LT heart failure, especially when a patient exhibits signs and symptoms consistent with volume overload including weight gain, elevated jugular venous pressure, crackles on lung examination, dyspnea, orthopnea, and increased lower extremity edema.

Optimal medical therapy for heart failure in the setting of left ventricular systolic dysfunction, including beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone-blocking agents should be maintained in the perioperative period, unless there is a contraindication to therapy such as hypotension or renal failure (65). The renal toxicity of calcineurin inhibitors can limit the use of angiotensin-converting enzyme inhibitors and aldosterone-blocking agents in LT recipients. Carvedilol may be the optimal choice for beta-blockade in patients with ESLD. It has been demonstrated to cause a reduction in portal pressure through decreased splanchnic blood flow and decreased portocollateral resistance (66,67). Carvedilol has also been shown to be superior to other beta-blocking agents in reducing the hepatic venous pressure gradient (66,68).

The assessment for left ventricular outflow tract obstruction (LVOTO) by TTE is an important component of the pre-operative cardiovascular assessment of LT candidates with left ventricular hypertrophy. Left ventricular hypertrophy and hyperdynamic systolic function in ESLD may result in hemodynamically significant LVOTO. One retrospective review of 106 transplant recipients found inducible LVOTO on pre-operative DSE in >40% of patients (69). In this study, an outflow gradient of >36 mm Hg was significantly associated with intraoperative hypotension. Although there was no significant mortality risk associated with LVOTO in this study, this condition has led to the denial of transplantation at certain centers (69). Patients with LVOTO can exhibit poor tolerance of the hemodynamic stresses associated with ESLD and transplantation. Careful intraoperative monitoring, however, with avoidance of tachycardia, limited use of inotropic agents, and transesophageal echocardiography-guided volume administration can facilitate safe transplantation in patients with significant LVOTO (70–72). Patients with LVOTO due to underlying hypertrophic cardiomyopathy who also have ESLD can be considered for alcohol septal ablation if they have symptomatic heart failure that would otherwise contraindicate LT (73,74).

Pulmonary Heart Disease

End-stage liver disease has a causal role in 2 main pulmonary syndromes: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). Hepatopulmonary syndrome is characterized by abnormal intrapulmonary vascular dilation in patients with liver disease, leading to physiologic shunting, ventilation-perfusion mismatch, and hypoxemia (75). Patients with HPS typically have normal or only mildly elevated pulmonary artery pressures, and LT

may be curative. POPH is a form of pulmonary arterial hypertension with increased pulmonary vascular resistance due to vasoconstriction and progressive pulmonary vascular remodeling. Patients with this condition by definition have concomitant portal hypertension (75). In POPH, as opposed to HPS, hypoxemia occurs late and LT is often contraindicated if it is left untreated. POPH is present in approximately 5% to 10% of LT candidates (76). Roughly 5% of LT candidates have moderate to severe POPH, with a mean pulmonary arterial pressure (mPAP) ≥35 mm Hg, which has traditionally been considered a contraindication to LT. A pre-operative mPAP of 35 to 50 mm Hg has been associated with a 50% risk of mortality after LT in patients with POPH (77). In 1 study, mortality approached 100% among patients with POPH and mPAP >50 mm Hg (78). The accurate diagnosis of POPH, therefore, is a crucial part of the selection and perioperative management of LT candidates. POPH can present a diagnostic challenge in ESLD; pulmonary artery systolic pressure on TTE may be elevated for many reasons aside from POPH, including pulmonary venous hypertension from left ventricular dysfunction, volume overload, or increased cardiac output.

Pulmonary artery systolic pressure should first be evaluated by TTE in all LT candidates. If pulmonary artery systolic pressure is elevated or if there is right ventricular dysfunction, right-side heart catheterization should be performed. If the mPAP is ≥35 mm Hg, but the pulmonary capillary wedge pressure is high (>15 mm Hg), repeat right-side heart catheterization should be performed after diuresis. If the mPAP is ≥35 mm Hg and the pulmonary vascular resistance is >3 Wood units in the setting of a pulmonary capillary wedge pressure of ≤15 mm Hg, clinically significant pulmonary arterial hypertension is present. In the absence of underlying lung disease (or other risk factors for pulmonary arterial hypertension) in a patient with ESLD, this should be considered moderate to severe POPH.

Mild POPH (mPAP 25 to 34 mm Hg) is not an absolute contraindication for LT, especially if right ventricular function is preserved. However, moderate to severe POPH (mPAP ≥35 mm Hg) warrants consideration for treatment with pulmonary vasodilators before transplantation. Recent case reports and series have demonstrated that pharmacological therapy for moderate to severe POPH (i.e., prostanoids, phosphodiesterase inhibitors, endothelin-receptor antagonists, and so forth) can lower pulmonary pressures to safely facilitate LT (79–82).

Pericardial Effusions

Pericardial effusions resulting in cardiac tamponade can develop in ESLD patients and are associated with hepatitis C infection and cryoglobulinemia. Pericardial effusions have also been associated with ascites, a condition known as hepatohydropericardium, and can occur after LT (83–86). An assessment for pericardial fluid and tamponade physiology is an important part of the pre-operative TTE in LT candidates. It has been observed that the sensitivity of TTE to detect tamponade in the setting of portopulmonary hypertension may be decreased. This is mainly due to the possibility of elevated right-sided pressures delaying or reducing right ventricular collapse, despite the underlying existence of tamponade physiology (87). Therefore, in addition to echocardiographic findings, it is important to do a complete bedside assessment and physical examination to accurately diagnose tamponade in ESLD patients. The presence of a significant pericardial effusion or tamponade should be treated by pericardiocentesis or a pericardial window before or at the time of LT. Because the causes of these effusions are often related to the underlying ESLD, LT candidates require close clinical and echocardiographic follow-up for recurrence.

Patent Foramen Ovale

A patent foramen ovale (PFO) is present in approximately 25% of adults in the general population and is associated with paradoxical embolism (88,89). There are case reports of iatrogenic venous air embolism, with right-to-left shunting of emboli across a PFO during LT (90,91). The overall incidence of this complication appears to be quite low (isolated case reports), and liver transplantation for the most part can be performed safely in patients with a PFO and other types of intracardiac shunts (92). Although the presence of a PFO is not a contraindication to LT, extra care should be taken to prevent thrombus formation and air entry into the venous system during surgery. Further studies are needed to determine the ultimate clinical significance of the presence of a PFO during LT and the potential role, if any, for percutaneous PFO closure in LT candidates.

QT Interval Prolongation

The presence of a prolonged corrected QT interval (QTc) on an electrocardiogram (>440 ms) can be associated with an increased risk of ventricular arrhythmias. Although QTc prolongation is common in patients with ESLD, it often resolves after transplantation (93,94). In a retrospective cohort, nearly one-half of 600 ESLD patients studied had a QTc >440 ms pre-operatively, with resolution in approximately one-half of these patients after transplantation. Advanced age, alcoholic cirrhosis, and Childs class were independent predictors of prolonged QTc. There was, however, no association between prolonged QTc and increased mortality (95). Of note, the physiologic differences in QTc between males and females are abolished in cirrhosis (decreased impact of estrogen/sex-specific hormone levels on QT interval physiology in these patients) (96). A prolonged QTc is not a contraindication to LT, but should prompt a search for reversible causes, such as electrolyte disturbance (e.g., hypokalemia or hypomagnesemia) or the use of QT interval-prolonging drugs.

Acute Hepatic Failure

The recommendations in the preceding text apply specifically to patients with ESLD from chronic hepatic failure. Patients who require LT because of acute hepatic failure have underlying cardiac and physiologic states that differ from patients who have chronic liver disease, and should thus be risk stratified accordingly (97). In most cases, the pre-transplant cardiac risk stratification for these patients can be done in a fashion similar to that for other noncardiac surgeries. Two of the most commonly used algorithms for estimating cardiac risk before surgery are the 2007 American College of Cardiology/American Heart Association guidelines and the Goldman revised cardiac risk index (98,99). These methods differ in their approach, but their emphasis is on defining the urgency of surgery (which may supersede risk stratification), determining the presence of high-risk conditions that could delay surgery, and making further recommendations based on functional status and other clinical risk factors.

All patients with acute hepatic failure being evaluated for LT should undergo TTE to assess left and right ventricular function, valvular function, and to identify any significant pulmonary hypertension (the etiology of which would likely be independent of acute liver failure). Given the extensive fluid shifts and hemodynamic stresses associated with LT, patients with ventricular dysfunction should be closely monitored for volume overload in the perioperative period (e.g., with Swan-Ganz catheter for pressure/hemodynamic monitoring). Furthermore, patients with pulmonary hypertension in the setting of elevated pulmonary capillary wedge pressures (pulmonary venous hypertension) should undergo diuresis before surgery. Patients with pulmonary arterial hypertension should ideally undergo a trial of medical therapy before any surgical intervention (similar to patients with chronic liver disease and pulmonary arterial hypertension).

Recommendations

The American College of Cardiology and the American Heart Association do not provide specific recommendations for the pre-operative cardiovascular assessment of LT candidates. The American Association for the Study of Liver Diseases recommends an evaluation for CAD in LT candidates who are chronic smokers, have a personal or family history of CAD, or have DM (100). These guidelines recommend DSE followed by coronary angiography when appropriate. Because of the already discussed limitations of pharmacologic stress testing in LT candidates, we do not recommend routine noninvasive stress imaging (Table 1). In patients with known CAD, DM, or ≥2 other cardiovascular risk factors, we recommend coronary angiography to assess the extent and severity of CAD. Cardiac CT angiography may be an acceptable alternative in select patients. Coronary revascularization should be considered in LT candidates with obstructive CAD if the extent of CAD contraindicates transplantation. The bleeding risk for any procedure should be taken into consideration. For patients undergoing percutaneous coronary intervention, bare-metal

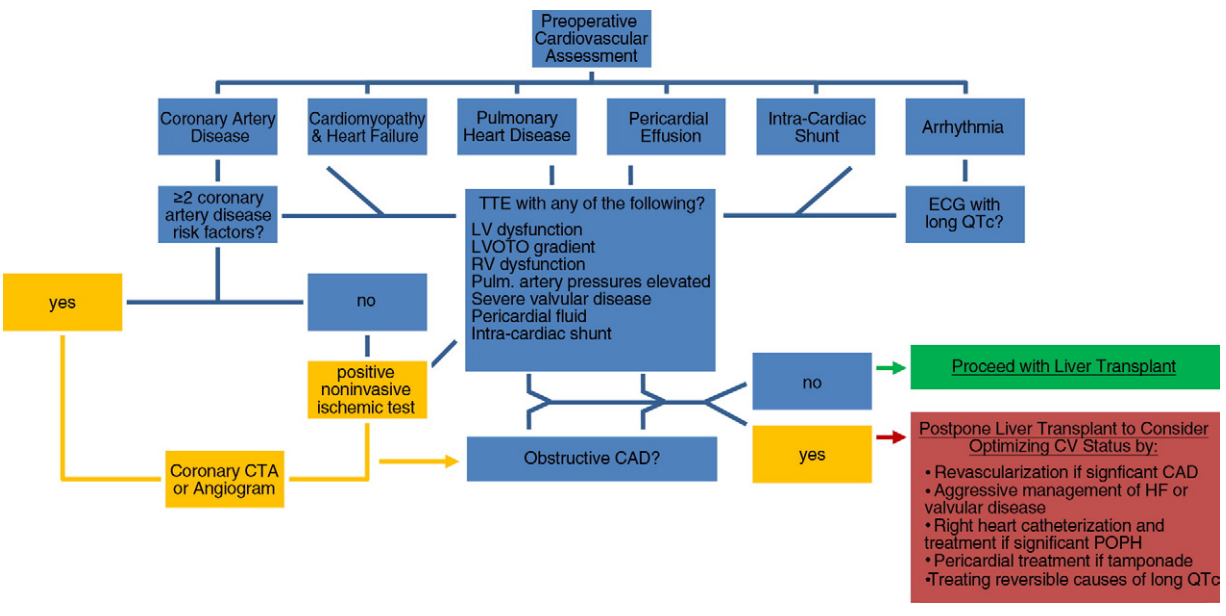

Figure 1 **Suggested Strategy for Pre-Operative Cardiac Assessment of Liver Transplant Candidates**

CAD = coronary artery disease; CTA = computed tomography angiogram; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; LVOTO = left ventricular outflow tract obstruction; POPH = portopulmonary hypertension; Pulm. = pulmonary; QTc = corrected QT interval; RV = right ventricular; TTE = transthoracic echocardiography.

stents are preferred because of the increased risk of bleeding from the prolonged duration of dual antiplatelet therapy required for drug-eluting stents.

The American Association for the Study of Liver Diseases recommends TTE with Doppler for all LT candidates. Echocardiography is necessary to assess left and right ventricular size and function, valvular function, and pulmonary artery pressure, and to exclude the presence of a significant LVOTO or pericardial effusion. Mild-to-moderate heart failure is not an absolute contraindication to LT, but should be monitored and aggressively treated in the perioperative period. There are currently no guidelines for the management of LT candidates with significant LVOTO. Transesophageal echocardiography and/or pulmonary artery catheterization may be used intraoperatively to allow for real-time hemodynamic monitoring and volume management.

Patients with elevated pulmonary arterial systolic pressure on TTE or right ventricular systolic dysfunction should be referred for right-side heart catheterization. Elevated pulmonary artery pressure alone should not be a contraindication to transplantation; rather, a careful evaluation of invasive hemodynamics should be used to identify patients who simply have volume overload and/or high-output state, in which case pulmonary vascular resistance is typically normal. Patients with moderate to severe POPH (POPH with mPAP $\geq$35 mm Hg and elevated pulmonary vascular resistance) should be referred to a cardiologist or pulmonologist with expertise in the administration of pulmonary vasodilator therapy. After a trial of vasodilator therapy, right-side heart catheterization should be repeated before proceeding with LT. If the decision is made to proceed with LT in a patient with significant POPH (medical therapy responders), transesophageal echocardiography to monitor for right ventricular dysfunction, venovenous bypass to prevent sudden right ventricular overload after reperfusion, and use of inhaled nitric oxide therapy to lower pulmonary artery pressures are intraoperative strategies to minimize the risk of cardiogenic shock due to fulminant right ventricular failure after LT.

Any significant pericardial effusion should be treated by either pericardiocentesis or a pericardial window before or at the time of LT. In addition, the presence of a PFO is not a contraindication to LT, but extra care should be taken to avoid air entry into the venous system or thrombus formation during the transplant procedure. Finally, reversible causes of electrocardiographic QTc prolongation should be addressed before LT.

These recommendations (Fig. 1) are based upon the available body of evidence regarding the diagnosis and treatment of cardiovascular disease in patients with ESLD. There is still a significant knowledge gap in the study of cardiovascular outcomes, including quality-of-life outcomes, in patients undergoing LT. The unique physiology of ESLD can profoundly influence accurate diagnosis, management, and outcomes of underlying cardiac pathology, and requires a careful evidence-based approach to the perioperative cardiovascular management of LT candidates.

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