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Pre-liver transplantation cardiac assessment

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Rezumat

Evaluarea cardiovasculară la candidatul pentru transplant hepatic

Transplantul hepatic efectuat pentru pacienții cu disfuncție hepatică avansată reprezintă un stres hemodinamic important pentru aparatul cardiovascular. Evaluarea statusului hemodinamic şi cardiovascular la pacientul cu ciroză este de o importanță crucială în identificarea pacienților fezabili pentru intervenție. În afară de vârsta avansată şi prezența comorbidităților, există numeroase mecanisme adaptative cardiovasculare la pacientul cirotic care pot fi în detrimentul candidatului pentru transplant hepatic. În general, pacienții cu ciroză candidați pentru transplant hepatic prezintă creşterea debitului cardiac, un răspuns ventricular slab la stresul hemodinamic, rezistență vasculară periferică scăzută şi bradicardie. Reperfuzia post-transplant poate duce la deces cardiovascular din numeroase cauze, aritmice, insuficiență cardiacă acută şi infarct miocardic. Acest review dezbate strategiile de screening pentru bolile cardiovasculare la pacienții candidați pentru transplant hepatic şi detaliază valoarea prognostică a testelor frecvent utilizate pentru identificarea bolii cardiace ischemice, insuficienței cardiac şi a hipertensiunii porto-pulmonare. De asemenea, sunt prezentate recomandările bazate pe dovezi pentru evaluarea şi managementul acestor afecțiuni la candidatul pentru transplant hepatic.

Cuvinte cheie: transplant hepatic, evaluare cardiovasculară, hipertensiune portopulmonară

Abstract

Liver transplantation (LT) is a stressful condition for the cardiovascular system of patients with advanced hepatic disease. The underlying hemodynamic and cardiac status of patients with cirrhosis is crucial to determine which patients should became recipients. 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, a compromised ventricular response to stress, low systemic vascular resistance and bradycardia. Post-transplant reperfusion may result in cardiac death due to a multitude of causes, including arrhythmia, acute heart failure and myocardial infarction. This review examines screening strategies for transplant candidates and details the prognostic value of common test used to identify ischemic heart disease, heart failure, portopulmonary hypertension. There are discused evidence-based recommendations for their evaluation and management.

Key words: liver transplantation, cardiac assessment, portopulmonary hypertension

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Introduction

The number of liver transplantations (LT) done each year continues to grow, with improvement in outcomes yielding a greater treatment demand. LT candidates today have a higher cardiovascular risk because they are older and have more comorbidities (1). The cardiac risk stratification is of great interest in LT surgery patients as those with known CAD have worse outcomes, there is a paucity of organ donation, and there is a greater resource expenditure for the entire process (6).

The severity of the hepatic disorder in adults is assesed by Model End Stage Liver Disease Score (MELD score). The pediatric version of this score is called PELD. The MELD score replaces the Child-Turcotte-Pugh (CTP) score as a disease severity index. This change is designed to improve the organ allocation system in liver transplantion to ensure that available organs are directed to transplant candidates based on the severity of their liver disease rather than the length of time they have been on the waiting list (2,3,4). MELD has been prospectively validated in several patient populations and is currently used by the United Network for Organ Sharing (UNOS) to prioritize candidates with chronic liver failure for organ allocation. MELD score is calculated using a relatively simple formula that relies on three readily available objective variables: serum creatinine, total bilirubin and INR (international normalized ratio). The Meld data must be recertified at certain intervals as indicated in *Table 1*. The MELD score can estimate likelihood of three-month survival. Higher MELD scores have been associated with decreased survival rates. Three-month survival is less than 20 percent in patients with a MELD score of 40. Implementation of MELD for organ allocation has decreased pretransplant mortality without having a negative impact on post-transplant mortality (5).

Indications and contraindications for liver transplantation

Liver transplantation is indicated for acute or chronic liver failure from any cause. The major conditions that lead to the need for transplantation in adults and children are summarized in *Table 2* (40,41), together with the most important absolute and relative contraindications (7,37).

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension(POPH)

In LT canditates, it is important to distinguish between two different entities with different therapeutic management

Table 1. *Recertification intervals of the MELD data*

Score	Recertify every	Lab Values
≥ 25	7 days	≤ 48 hrs old
24 - 19	30 days	≤ 7 days old
18 - 11	90 days	≤ 14 days old
≤10	year	≤ 30 days old

Table 2A. *Indications for liver transplantation*

Chronic noncholestatic liver disorders
• Chronic hepatitis C • Chronic hepatitis B • Autoimmune hepatitis • Alcoholic liver disease
Cholestatic liver disorders
• Primary biliary cirrhosis • Primary sclerosing cholangitis • Biliary atresia • Alagille syndrome • Nonsyndromic paucity of the intrahepatic bile ducts • Cystic fibrosis • Progressive familial intrahepatic cholestasis
Metabolic disorders causing cirrhosis
• Alpha-1-antitrypsin deficiency • Wilson disease • Nonalcoholic steatohepatitis and cryptogenic cirrhosis • Hereditary hemochromatosis • Tyrosinemia • Glycogen storage disease type IV • Neonatal hemochromatosis
Metabolic disorders causing severe extrahepatic morbidity
• Amyloidosis • Hyperoxaluria • Urea cycle defects • Disorders of branch chain amino acids
Primary malignancies of the liver
• Hepatocellular carcinoma • Hepatoblastoma • Fibrolamellar hepatocellular carcinoma • Hemangioendothelioma
Miscellaneous conditions
• Budd-Chiari syndrome • Metastatic neuroendocrine tumors • Polycystic disease
Retransplantation Fulminant hepatic failure

Table 2B. *Contraindications to liver transplantation surgery*

Absolute contraindications
• Brain death • Extrahepatic malignancy • Active uncontrolled infection • Active alcoholism and substance abuse • AIDS • Severe cardiopulmonary disease • Uncontrolled sepsis • Inability to comply with medical regimen • Lack of psychosocial support • Anatomic abnormalities precluding liver transplantation • Compensated cirrhosis without complications (Child-Turcotte-Pugh score, 5–6)
Relative contraindications
• Advanced age • Cholangiocarcinomaa • HIV infectiona • Portal vein thrombosis • Psychologic instability

Table 3. *Diagnostic Criteria for the Hepatopulmonary Syndrome and Degree of severity*

A. Diagnostic Criteria for the Hepatopulmonary Syndrome	
Variable	**Criterion**
Oxygenation defect	Partial pressure of oxygen <80 mm Hg or alveolar–arterial oxygen gradient ≥ 15 mm Hg while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography
Liver disease	
B. Degree of severity	
Mild	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 80 mm Hg
Moderate	Alveolar–arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 60 to <80 mm Hg
Severe	Alveolar-arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen ≥ 50 to <60 mm Hg
Very severe	Alveolar-arterial oxygen gradient ≥ 15 mm Hg, partial pressure of oxygen <50 mm Hg (<300 mm Hg while the patient is breathing 100% oxygen)

and response to liver transplantation: hepatopulmonary syndrome and portopulmonary hypertension (41).

Hepatopulmonary syndrome is characterized by abnormal intrapulmonary vascular dilation in patients with liver disease, leading to physiologic shunting, ventilation-perfusion mismatch, and hypoxemia (11,12). Less commonly, there are pleural and pulmonary arteriovenous communications. A classification of the severity of the hepatopulmonary syndrome based on abnormalities in oxygenation is vital because severity influences survival and is useful in determining the timing and risks of liver transplantation (*Table 3*). We need for this classification the partial pressure of oxygen and the alveolar–arterial oxygen gradient (11). In patients with the hepatopulmonary syndrome, pulmonary angiography should be performed only when the hypoxemia is severe (i.e., the partial pressure of oxygen is <60 mm Hg [8.0 kPa]), poorly responsive to administration of 100% oxygen, and when there is a strong suspicion (on the basis of a chest computed tomographic scan) of direct arteriovenous communications that would be amenable to embolization (13).

Contrast-enhanced transthoracic echocardiography with saline (shaken to produce microbubbles >10 μm in diameter) is the most practical method to detect pulmonary vascular dilatation. After the administration of agitated saline in a peripheral vein in the arm, microbubble opacification of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed; microbubbles do not pass through normal capillaries (normal range of the capillary diameter, <8 to 15 μm) (8,9,10).

Patients with HPS typically have normal or only mildly elevated pulmonary artery pressures, and LT may be curative, and it is not a contraindication to LT surgery (11). Because of the poor outcome without liver transplantation, the diagnosis of the hepatopulmonary syndrome associated with a partial pressure of oxygen of less than 60 mm Hg is considered to be an indication for liver transplantation, and patients with this syndrome are given a higher priority for transplantation than patients with other disorders (8).

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 (11,12). In the recent Dana Point classification of pulmonary hypertension, POPH is classified in group 1 - pulmonary artery hypertension (PAH) (38). POPH is defined as an increase in mean pulmonary arterial pressure (mPAP) above 25 mmHg associated with normal capillary wedge pressure and a pulmonary vascular resistance (PVR) above 240 dyn/s/cm - 5 in the settings of portal hypertension (15). In a Romanian study, Rugina Mihaela et all. showed that the prevalence of POPH in patients with liver cirrhosis who are candidates for orthotopic liver transplantation is 3.2% (14). 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 (16). In 1 study, mortality approached 100% among patients with POPH and mPAP >50 mm Hg (17). The accurate diagnosis of POPH, therefore, is a crucial part of the selection and perioperative management of LT candidates (14).

Diagnosing POPH is not easy in patients with cirrhosis, because pulmonary artery pressure can be increased in many disorders: diseases of the left heart, lung diseases or volume overload common in patients with cirrhosis.

Investigation of pulmonary arterial hypertension begins with transthoracic echocardiography (TTE). If mPAP is increased right heart catheterization is indicated. *Figure 1* highlights the investigation and managemant algorithm of POPH (11). Mild POPH (mPAP = 25-34 mmHg) is not a major contraindication to LT, while moderate and severe POPH (mPAP $\geq$ 35 mmHg) is an absolute contraindication for LT and require treatment with vasodilators to decrease pulmonary artery pressure in order to allow LT surgery in reasonable risk conditions (11). The target for vasodilator therapy would be an mPAP <35 mmHg and a PVR <400 dyn/s/cm-5 as these values do not associate additional operative risk (15). Recent case reports and series have demonstrated that pharmacological therapy for moderate to

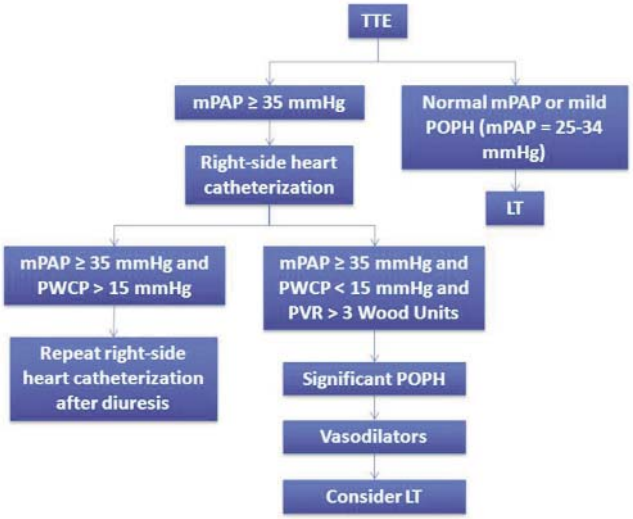

Figure 1. *Investigation and management algorithm of POPH*
TTE - Transthoracic echocardiography, PWCP - pulmonary capillary wedge pressure

severe POPH (i.e., prostanoids, phosphodiesterase inhibitors, endothelin-receptor antagonists, and so forth) can lower pulmonary pressures to safely facilitate LT (18).

Coronary artery disease (CAD)

Evidence suggests that CAD is more prevalent in transplant candidates. Studies show that at least one critical coronary artery lesion occurs in 5% to 26% of all liver transplant candidates who are asymptomatic. Up to 50% of patients with significant CAD will die perioperatively from cardiac complications. However, the challenge remains in identifying those patients who are asymptomatic, but have significant CAD (19,20).

Traditional coronary risk factors remain important for preoperative risk stratification in patients with ESLD. Diabetes mellitus and age >50 years are the most important risk factors that are associated with post-operative ischemic complications (11). The LT recipients display higher Framingham risk scores than age- and sex-matched non-LT patients (21). Cirrhotic patients with 0-1 risk factors have a low likelihood for CAD. However, the presence of two or more factors (other than age) places patients at moderate to severe risk of CAD (19). A diagnosis of non-alcoholic steatohepatitis independently increases the risk of CAD. Critical CAD occurs in approximately 23% of patient with non-alcoholic steatohepatitis. Even though non-alcoholic steatohepatitis patients have additional risk factors including obesity and diabetes, the prevalence of CAD is greater than the sum of associated risk factors (22). Coronary calcium is also strongly associated with traditional CAD risk factors in the cirrhotic population (23).

Noninvasive functional testing for ischemia may have limited predictive value for obstructive CAD in this population. Most patients cannot undergo exercise testing. Dobutamine stress echocardiography (DSE) has been shown to have a poor sensitivity and a low negative predictive value among LT candidates, possibly secondary to an inability to achieve target heart rate and peak double product (heart rate multiplied by blood pressure). 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. SPECT has a low specificity (61%). This 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. Cardiac computed tomography angiography is emerging as an attractive noninvasive alternative to invasive coronary angiography for the assessment of CAD in select LT candidates (11).

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. Although, LT candidates often have coagulopathies that can increase the risk of bleedings during and after coronary angiography, this procedure is consider safe. A transradial approach to invasive angiography may prove useful in the ESLD population to further reduce bleeding complications (24). Successful coronary revascularization for obstructive CAD has been used before LT in otherwise suitable candidates. 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 (11).

Heart failure and cardiomyopathy

"Cirrhotic cardiomyopathy" is formally described as cirrhotic cardiomyopathy, which is defined as chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease and irrespective of the causes of cirrhosis, although some etiologies (e.g., iron overload and alcohol consumption) further impact on myocardial structure and function (*Table 4*). This syndrome is considered to be related to both portal hypertension and cirrhosis and is characterized by intrinsic alterations in myocardial function (25,26).

Table 4. *Cirrhotic cardiomyopathy*

Electrophysiologic changes
- QT-interval prolongation,
- Electrical dyssynchrony,
- Chronotropic incompetence
Myocardial changes
- Inotropic incompetence
- Sistolic dysfunction
- Diastolic dysfunction, frequently due to left ventricular hypertrophy
- Mechanical dyssynchrony
- Disturbances of excitation-contraction coupling

The actual prevalence of this condition is unknown. Therefore, not much is known also regarding the natural history of the disease. The condition is undoubtedly well tolerated and asymptomatic for months to years, and in many cases the symptoms are not easily distinguished from those of the underlying disease. Similarly, the natural history in terms of response to treatment and prognosis is unclear. Increased arterial compliance in cirrhosis leads to a functional hypovolemia (decreased pre-load) despite a volume overload in absolute terms. The blunted cardiac response of cirrhotic cardiomyopathy fails to overcome the decrease in effective circulating volume because of arterial vasodilation. Conversely, splanchnic arterial vasodilation unloads the ventricle and may mask the presence of ventricular insufficiency. Autonomic dysfunction and impaired volume and baroreceptor reflexes may also contribute to the blunted cardiac response. Therefore, the presence of a reduced cardiac workload, favored by splanchnic arterial vasodilation, which is in turn caused by progressive hepatic decompensation, may mask cardiac insufficiency. In fact, echocardiography often shows that patients with decompensated cirrhosis have normal cardiac function; however, physiologic or pharmacological stress, bacterial infections (e.g., spontaneous bacterial peritonitis), transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation may unmask alterations in myocardial function, thus revealing the presence of cirrhotic cardiomyopathy (11,26).

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 after LT surgery.

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 (27). 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 (28). Volume status and symptoms of heart failure should be monitored and optimized before transplantations. Optimal medical therapy for heart failure in the setting of left ventricular systolic dysfunction, including beta-blockers, angiotensin-converting enzyme inhibitors, and aldosteroneblocking agents should be maintained in the perioperative period, unless there is a contraindication to therapy such as hypotension or renal failure (11). 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. Carvedilol has also been shown to be superior to other beta-blocking agents in reducing the hepatic venous pressure gradient (29,30).

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. Patients with LVOTO can exhibit poor tolerance of the hemodynamic stresses associated with ESLD and transplantation, but the presence of LVOTO is not an absolute contraindication of LT surgery, but it may be regard with caution (11).

Pericardial effusions, QT interval prolongation and patent foramen ovale

Pericardial effusions in ESLD patients are associated with hepatitis C infection, cryoglobulinemia, ascites (hepatohydropericardium) and can occur after LT (31,32,33). So, it is very important to asses the presence of pericardial fluid by TTE, before LT surgery. The biggest problem is that the signs of iminent tamponade in the presence of pericardial fluid are masked by the presence of POPH. 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 (34). When TTE shows significant pericardial effusion, the recommendation is to do a pericardiocentesis or a pericardial window before or at the time of LT. We should not forget to repete periodically the TTE because there is a risk of pericardial effusion recurrence, giving the fact that these effusions are often related to the underlying ESLD.

QT interval prolongation is a frequent finding in patients with ESLD. It is well known that QT interval prolongation predispose to ventricular arrhythmias. In a retrospective study it was found that QT interval prolongation was resolve in one-half of patients after liver transplantation (35). Advanced age, alcoholic cirrhosis, and Childs class were independent predictors of prolonged QTc. There was,however, no association between prolonged QTc and increased mortality (35). It is important to treat reversible causes of QT interval prolongation, before liver transplantation: hypokalemia, hypomagnesemia and withdrawal of QT interval-prolonging drug. We should mention that QT interval prolongation it not a contraindication of liver transplant surgery (11).

A patent foramen ovale (PFO) is present in approximately 25% of adults in the general population and is associated with paradoxical embolism (36). PFO is not a contraindication of liver transplant surgery, although it is associated with a low risk of iatrogenic venous air embolism. Liver transplantation can be performed safely in patients with a PFO (11).

Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery

The cardiac perioperative risk assessment of LT candidates is an increasingly important clinical requirement before transplantation surgery and will likely have a strong impact on postoperative outcomes (6). There is a lack of trial about cardiac perioperative risk assessment of LT candidates, so the datas are limited. Safadi et all. have conducted a study on 403 patients who had liver transplantation surgery. The outcomes analyzed were nonfatal myocardial infarction, death, and either out-

come within the first 30 days after the liver transplantation surgery. From the final multivariate model, history of coronary artery disease, prior stroke, and postoperative sepsis predicted greater risk (P=0.014; odds ratio [OR], 4.0; 95% confidence interval [CI], 1.3 to 11.8; P=0.025; OR, 6.6; 95% CI, 1.3 to 33.8; and P<0.001; OR, 7.5; 95% CI, 3.3 to 17.1, respectively). Use of perioperative β-blockers was protective (P=0.004; OR, 0.20; 95% CI, 0.1 to 0.6) for combined cardiac outcomes. For the outcome of death on multivariate analysis, postoperative sepsis and increased interventricular septal thickness predicted risk (P<0.001; OR, 8.6; 95% CI, 3.5 to 20.9; and P=0.027; OR, 2.8; 95% CI, 1.1 to 7.2, respectively), whereas the use of perioperative β-blockers was again protective (P=0.012; OR, 0.07; 95% CI, 0.01 to 0.56) (6).

Recently, Coss E et all. published a study that included 230 LT candidates. The results showed that the main risk factors (univariate analysis) for first cardiac events included age in decades [hazard ratio (HR)=1.31, P=0.047], diabetes (HR=2.20, P=0.004), prior cardiovascular disease (HR=4.77, P<0.0001), a troponin I level > 0.07 ng/mL (HR=2.00, P=0.023), left ventricular hypertrophy (HR=2.06, P=0.047), stress wall abnormalities (HR=2.25, P=0.018), and ischemia on stress imaging (HR=2.89, P=0.015). Multivariate analysis confirmed age, diabetes, a troponin I level > 0.07, and prior cardiac disease as independent risk factors for posttransplant cardiac events (39).

These findings provide insight into this specific population, and additional prospective, randomized studies are needed before any firm conclusions or recommendations can be made.

General recommendations for pre-liver transplant cardiovascular assessment

All patients who are candidates to liver transplantation should undergo a careful history, focused on the identification of cardiovascular risk factors, a complete physical examination, a set of common blood tests that it will be used to evaluate the bleeding risk of patients given the fact that sometimes it is indicated antiplatelet therapy or percutaneous coronary intervention for CAD. Also, it is mandatory an electrocardiogram and a TTE. (*Fig. 2*)

In patients with known CAD, diabetes mellitus, or ≥ 2 other cardiovascular risk factors, it is recommended coronary angiography to assess the extent and severity of CAD. Cardiac CT angiography may be an acceptable alternative in select patients.

Patients will undergo revascularization procedures according to the severity of CAD and especially if they have severe enough CAD to significantly increase the risk of liver transplantation surgery, but we should take into account the costs and the risk of bleeding of percutaneous intervention. Radial approach is preferred to the femural approach, because it was associated with lower bleeding risk. Drug eluting stents are not indicated because they need administration of dual antiplatelet therapy for a longer period of time.

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.

Heart failure is not an absolute contraindication to LT, but prone to aggressive preoperative treatment.

Any significant valvular dysfunction need careful judgment.

If there is significant pericadial effusion, pericardiocentesis or pericardial window is indicated. No clear indications are for the management of LVOTO.

Patients with elevated pulmonary arterial systolic pressure on TTE or right ventricular systolic dysfunction should be

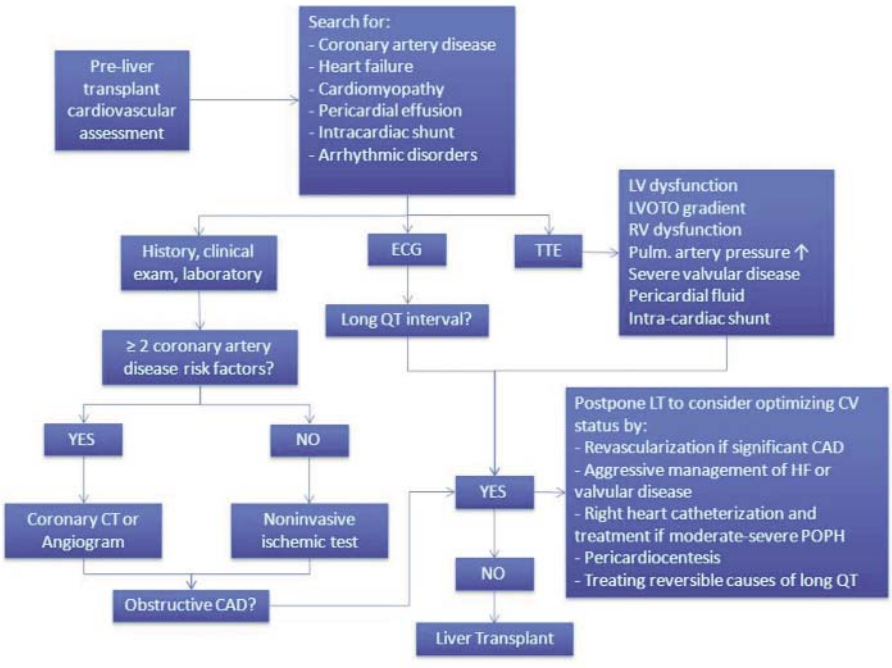

Figure 2. *Pre-liver transplant cardiovascular assessment algorithm (11)*

referred for right-side heart catheterization. Mild POPH (mPAP = 25-34 mmHg) is not a contraindication to LT. Patients with moderate to severe POPH (POPH with mPAP ≥35 mm Hg) should be treated with vasodilators. 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.

There is still a significant knowledge gap in the study of cardiovascular outcomes, including quality-of-life outcomes, in patients undergoing LT. New trials are needed to give standardised recommendations.

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