Journal of Liver Transplantation 10 (2023) 100153

Contents lists available at ScienceDirect

Journal of Liver Transplantation

journal homepage: www.elsevier.com

Review

Cardiovascular assessment of candidates for liver transplant

Manuel Lozano[a], Miguel Molina[a], Jesús Zarauza[a], Federico Castillo[b], Roberto Fernández-Santiago[b], Edward J. Anderson[b], Emilio Fábrega[c], Juan C. Rodríguez-Sanjuán[b,*]

[a] The Departments of Cardiology, University Hospital Marqués de Valdecilla. University of Cantabria. Avenida de Valdecilla S/N 39008-Santander. Spain
[b] The Departments of General Surgery, University Hospital Marqués de Valdecilla. University of Cantabria. Avenida de Valdecilla S/N 39008-Santander. Spain
[c] The Departments of Digestive Medicine, University Hospital Marqués de Valdecilla. University of Cantabria. Avenida de Valdecilla S/N 39008-Santander. Spain

ARTICLE INFO

Article History:
Received 15 February 2023
Revised 12 April 2023
Accepted 13 April 2023
Available online 14 April 2023

Keywords:
Liver transplant
Cardiovascular assessment
Cardiovascular risk

ABSTRACT

Cardiovascular events are the most important cause of morbidity and mortality after liver transplant (LT), since many recipients are older with cardiovascular risk factors and pathophysiology particular to end stage liver disease. Moreover, the LT procedure is associated with a unique cardiac risk. Detection of cardiovascular disease and stratification of risk have, therefore, an important impact on the prognosis of these patients.

Abbreviations

LT	Liver transplant
ESLD	End-stage liver disease
MAFLD	metabolic-associated fatty liver disease
ACC	American College of Cardiology
AHA	American Heart Association
ECG	Electrocardiogram
LVEF	Left ventricular ejection fraction
CAD	coronary artery disease
CTCA	computed tomography coronary angiography
CACS	Coronary Artery Calcium Score
CA	coronary angiography
CABG	coronary artery bypass graft
PCI	percutaneous coronary intervention
CCM	cirrhotic cardiomyopathy
NO	nitric oxide
LVEF	left ventricular ejection fraction
LVGLS	left ventricular global longitudinal strain
TR	Tricuspid regurgitation
LAVI	left auricular volume indexed
CMR	cardiac magnetic resonance
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation
MELD	model for end-stage liver disease
PASP	pulmonary arterial systolic pressure
PoPH	portopulmonary hypertension
mPAP	mean pulmonary arterial pressure
HPS	hepatopulmonary syndrome

1. Introduction

Liver transplants (LT) are on the rise, and candidates are older, more complex, with more cardiovascular risk factors. End-stage liver disease (ESLD) is increasingly due to metabolic-associated fatty liver disease (MAFLD), which is associated with a higher incidence of cardiac events, both before and after LT. In fact, cardiac events have become the leading cause of morbidity and mortality after LT, accounting for over 40% of deaths in the first 30 days after transplant [1].

The cardiovascular evaluation is usually implemented in different centers according to the decisions of a multidisciplinary team. To create some common recommendations and disseminate best practices, in 2012 the American College of Cardiology (ACC) and the American Heart Association (AHA) developed specific guidelines on cardiac disease evaluation and management for kidney and LT candidates [2].

LT is a high-risk procedure where an adequate pre-operative evaluation can reduce the risk of the surgery. Cardiac studies might not all be feasible in the case of critical liver failure, and adaptation to each patient's unique clinical situation is needed.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author at: Violeta 7- 3, 39010-Santander (Spain).
E-mail address: juancarlos.rodriguezs@scsalud.es (J.C. Rodríguez-Sanjuán).

https://doi.org/10.1016/j.liver.2023.100153

We present a review of the cardiovascular evaluation of the liver transplant candidate based on the recent evidence.

2. Screening and main objective

Tests used for cardiovascular screening can be misleading. All are associated with false-positive and false-negative results. Screening in asymptomatic patients should be used wisely. In LT, cardiac evaluation can help to guide candidacy and to allocate organs to recipients who are more likely to survive. This does not mean that high cardiovascular risk patients are not candidates for transplantation. Severe cardiovascular disease can sufficiently shorten life expectancy to preclude transplantation, but studies have shown that survival is generally improved by transplantation even among high-risk patients. In each center results in high- and low-risk cardiovascular patients must be analysed to guide decisions based on objective data [2].

3. What cardiovascular syndromes should we look for?

The objective is to prevent cardiovascular morbidity/mortality and the assessment should be based on determining CV risk factors and establishing the presence of cardiovascular disease. All patients should have a detailed history, physical examination, electrocardiogram, and transthoracic echocardiogram with infusion of agitated saline contrast. Subsequently coronary artery disease (CAD), heart failure, arrhythmias, severe valvular disease, pericardial involvement, pulmonary hypertension, or relevant intrapulmonary shunts should be ruled out. Depending on the results of this initial evaluation the need for other advanced complementary tests should be assessed. [2,3].

4. Cardiovascular system in end stage liver disease

Cardiovascular diseases are of capital importance both in the peri-transplant and post- transplant period. MAFLD continues to grow as a cause of ESLD, and diabetes mellitus is present in 30% of LT recipients; moreover, the increase in the proportion of older adults (aged 65 years or older) on the transplantation waiting list is associated with parallel increases in their cardiovascular risk profiles. Also, there are less-common genetic diseases (such as Wilson's disease, hereditary haemochromatosis, primary hyperoxaluria, familial amyloid polyneuropathy) that are associated with a risky cardiovascular profile [1,2].

Patients with cirrhosis and portal hypertension usually develop a hyperdynamic state, with an increase in cardiac output and a decrease in vascular resistance because of splanchnic and peripheral vasodilatation due to an increased production of vasodilators, such as nitric oxide, and decreased vascular reactivity to vasoconstrictors [4]. In end-stage cirrhosis, there is a marked reduction in systemic vascular resistance that cannot be compensated by a further increase in cardiac output, leading to low arterial pressure. To compensate this, vasoconstrictor systems, such as renin- angiotensin, the sympathetic nervous system and antidiuretic hormone, are activated. These compensatory systems are the cause of sodium and water retention responsible for ascites formation. The prolonged activation of these systems eventually leads to severe renal vasoconstriction, with reduced glomerular filtration and progressive renal insufficiency, a condition termed hepatorenal syndrome [5,6].

Left ventricular ejection fraction (LVEF), an indirect parameter of systolic function, is usually normal at rest in cirrhotic patients. However, with exercise there is evidence of attenuation of LVEF that is in relation to a reduced myocardial reserve and impaired muscular oxygen extraction. Diastolic dysfunction with impairment of passive and active filling of the ventricle during diastole makes it impossible to increase stroke volume when needed, leading to heart failure. Electromechanical dissociation (dispersion between electrical and mechanical systole), and alterations of potassium channels in cardiac membranes can prolong QT, with increased risk of ventricular arrhythmias and sudden cardiac death. Although these events are rare, the significance in these patients is undefined. Deficit of chronotropic response to physical and pharmacological stimuli is well known in patients with cirrhosis [5].

5. Electrocardiography and transthoracic echocardiography

An electrocardiogram (ECG) and a transthoracic echocardiogram should be realized in all LT candidates. Electrocardiograms can identify arrythmias, conduction problems, QT prolongation, cavity enlargement, ventricular hypertrophy, or ischaemia. The echocardiogram is performed to assess cardiac chamber size, myocardial mass, biventricular function, valvular disease, pericardial disease and to estimate pulmonary artery pressure. Infusion of agitated saline contrast allows the identification of shunts [7].

6. Evaluation for ischemic heart disease and coronary artery disease (CAD)

Concomitant CAD in patients with ESLD undergoing LT is associated with higher morbidity and mortality than in recipients without CAD. The prevalence varies between 2% and 38% depending on the etiology of ESLD and on the diagnostic methods used. Candidates for LT usually have sedentary lives, and they may present without any symptoms, making the prevalence of obstructive CAD significantly higher in comparison with patients without liver disease; moreover, the prevalence of CAD in ESLD due to MAFLD is higher than other causes of ESLD [8].

The relevant traditional risk factors are age over 60 years, hypertension, left ventricular hypertrophy, diabetes, smoking, dyslipidaemia, prior history of CAD, peripheral vascular disease and family history of CAD. Non-traditional risk factors of CAD in LT candidates should also be considered. These include familial amyloid polyneuropathy, hereditary hemochromatosis and MAFLD. Despite studies reporting that the presence of one or more risk factors of CAD be highly predictive of angiographically significant stenosis, there is a lack of consensus among guidelines on the number of risk factors needed to pursue non-invasive testing, as well as the role of functional status in determining the need for screening for CAD. In general, candidates should be perceived as high risk in the presence of a prior history of CAD, diabetes mellitus or 2 or more risk factors of CAD [8,9].

Some authors argue that there is no difference in asymptomatic obstructive CAD between cirrhotic and non-hepatic patients, yet those with cirrhosis usually have more extensive non-obstructive CAD than healthy individuals [10]. Haemodynamic changes can cause myocardial ischaemia in areas distal to non-critical stenosis. Liver disease often increases the risk of coronary complications post-transplant even without non- obstructive lesions [11]. Plaque rupture occurs usually in non-critical coronary stenosis and the perioperative period is characterized by vascular stress and a hypercoagulable state that can favor thrombosis [12].

Debate still exists concerning which is the best way to detect significant coronary disease, whether through non-invasive imaging tests (computed tomography coronary angiography –CTCA-) or stress tests (exercise or pharmacological echocardiography). Coronary angiography remains the reference standard for the diagnosis and quantification of CAD.

Methods of cardiovascular stress testing do not usually identify patients with non-obstructive coronary plaques and are focused on obstructive lesions that cause ischaemia. Many centres use pharmacological ischaemia detection with regadenoson, dipyridamole, dobutamine or adenosine because most LT candidates cannot complete an exercise test. Less than 10% of these tests are positive and

there is a poor correlation between the tests used, angiography and postoperative complications occurring from CAD. [13]. Candidates for LT have a particular limitation in target high heart rates because of reduced chronotropy and reduced cardiorespiratory fitness; therefore, exercise and pharmacological stress testing, respectively, result in low sensitivity (13- 22%) and low negative predictive values (75 −80%). The state of vasodilation present in cirrhotic patients results in a limited response to pharmacological agents used in stress perfusion studies [14−16]. Despite this, non-invasive 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 [8].

CTCA is a growing alternative to study CAD in candidates to LT with normal body habitus who are able to lie flat, can perform required breath-holding manoeuvres, and have a regular non-tachycardic rhythm. Renal failure, severe ascites, orthopnoea and hepatic encephalopathy should be considered contraindications [2]. The Coronary Artery Calcium Score (CACS) has a strong negative predictive value for CAD, and some authors include this item in algorithms as a risk factor. The utilization of CACS has demonstrated that 30% of LT candidates have at least moderate (stenosis of 50% or greater) asymptomatic CAD. A CACS higher than 400 Hounsfield Units is predictive of significant CAD requiring revascularization as well as increased 1-month post-LT cardiovascular complications [17]. The additional use of contrast has a high accuracy to predict the absence of obstructive CAD and can replace invasive coronary angiography (CA) that, although infrequently, can have serious adverse complications. Due to the poor predictive value of stress imaging and improvements in the use of coronary CT, non-invasive coronary angiography with CTCA can be the ideal test for screening of obstructive CAD in LT candidates, reserving CA as the gold standard in case of doubt [18]. In LT candidates with coronary artery stenosis of 70% or greater on CTCA or in cases of CACS over 400, CA is mandatory, to quantify the stenosis and to define the need for interventional procedures [8]. A proposed diagnostic algorithm is shown in the Fig. 1.

LT candidates have a high rate of myocardial injury and 30-day mortality (50%) after transplantation if asymptomatic lesions are not treated, so it is accepted that if there are obstructive lesions, they should be revascularized [19]. The modality of revascularization recommended is the percutaneous coronary intervention (PCI) although there is not much information in the literature. This is because coronary artery bypass graft (CABG) surgery is associated with high morbidity and mortality in patients with ESLD [20,21]. The most reasonable modality of revascularization in acute coronary syndromes is also PCI, taking into consideration that these patients have increased bleeding risk from antiplatelet therapy [2].

More difficult is the decision to evaluate and treat CAD in patients who need an urgent transplant because of an acute liver failure. The decision in this scenario should be individualized based on the patient condition and the probability to tolerate invasive procedures in the presence of organ failures. We must keep in mind that coronary revascularization can be planned electively post-transplant if needed [22].

7. Evaluation for cardiomyopathy and heart failure

LT candidates can be asymptomatic and not present the typical semiology of heart failure, because chronic vasodilation reduces cardiac afterload so patients remain compensated at rest. Assessment of both ventricular function and screening for cardiomyopathies using transthoracic echocardiography should be performed in all LT candidates. There is no evidence for repeated routine echocardiograms after listing for transplantation if no pathology has been identified [1]. Heart failure is common in patients evaluated for LT. They can develop systolic and diastolic dysfunction. There is a specific condition recognized in those patients called cirrhotic cardiomyopathy (CCM). It is mediated by peripheral and splachnic vasodilation with low systemic resistance and a hyperdynamic volume state, reduced chronotropism and inotropism and changes in myocardial structure [23].

Systemic inflammation is related to the pathogenesis of cirrhotic cardiomyopathy. Because of increased intestinal permeability, bacteria and pathogen-associated molecular patterns migrate to extra-intestinal organs activating immune systems which produce cytokines and vasodilators like nitric oxide (NO). Although NO is normally cardioprotective, this NO has a cardiotoxic effect, and activates cGMP-dependent protein kinases with negative ionotropic and apoptotic effects.

Other molecules are carbon monoxide and endocannabinoids. They influence excitation-contraction coupling and alter β-adrenergic receptor signaling, increasing the cardiodepressant effect on the heart.

Diastolic dysfunction is related with activation of vasoconstrictor (renin-angiotensin-aldosterone system, sympathetic nervous system) and inflammation systems with activation of the TGF-β pathway. TGF-β is known as a potent pro-apoptogenic and pro-fibrogenic cytokine, leading to hypertrophy and fibrosis with decreased ventricular compliance.

CCM was first described during the 2005 Montreal World Conference of Gastroenterology. Since then, diagnostic criteria have been updated and the latest parameters were proposed in 2019. These new criteria were created because the Montreal criteria were based on load-dependent measures of diastolic function and overdiagnosed diastolic dysfunction.

Treatment resembles the treatment of other causes of heart failure, although it has some particularities. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not recommended because they can reduce afterload in presence of hypotension. Non-selective β-blockers used in the treatment of portal hypertension and in the prevention of variceal bleeding shorten QT interval and improve electro-mechanical dyssynchrony. Diuretics are the main treatment to remove excess volume and aldosterone antagonists also inhibit myocardial fibrosis and activation of the sympathetic nervous system. Ultimately, LT is the only treatment that can restore cardiac function [24].

The diagnostic criteria are shown in Table 1 [25].

There is no established LVEF cut off to preclude LT, although a LVEF of less than 40% is an absolute contraindication. Peri-operative management can be challenging so we must identify and properly treat these patients [23].

Iron overload is frequent in cirrhosis and can cause iron overload cardiomyopathy, making these patients prone to heart failure and arrhythmias. These patients have important left ventricular diastolic dysfunction before systolic dysfunction. Advanced imaging sequencing of cardiac magnetic resonance (CMR) called T2* diagnoses the myocardial iron overload. This sequence is not part of the standard CMR protocol, and its acquisition should be specified when indicated [26]. Dietary changes, phlebotomies and iron chelating therapy ought to be considered in combination with heart failure therapy. Early treatment is a key factor in preventing end-organ damage [27].

8. Evaluation for valvular heart disease

Mild to moderate valvular heart disease is well tolerated in the perioperative period. Aortic stenosis is estimated in 2−7% of the population over 65 years [28]. Aortic stenosis is associated with haemodynamic instability and reduced myocardial perfusion and precludes LT [16]. There is high mortality in cardiac surgery in patients with cirrhosis and there are no guidelines to choose between surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) in these patients. In general, most studies have favourable results for the TAVI group. These studies do not include patients with

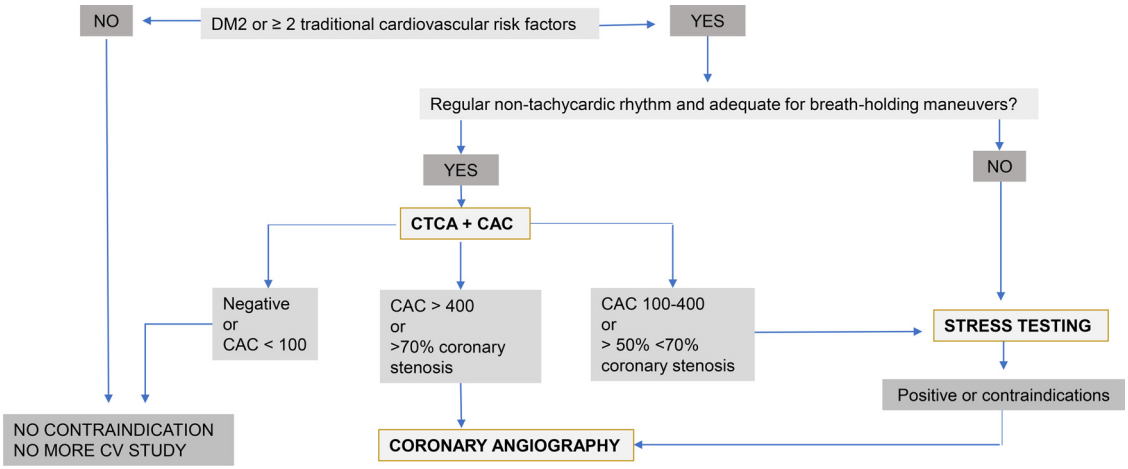

Fig. 1. Evaluation for ischemic heart disease and CAD.

high MELD scores, which are normally the patients who need liver transplant, so further research is needed. In patients post-TAVI, without indication for anticoagulation or dual antiplatelet therapy, aspirin 75−100 mg per day is typically recommended [28].

Severe mitral regurgitation can lead to increased morbidity and mortality and early intervention resulted in better outcomes; if the surgical risk is very high treatment with MitraClip (Abbot Vascular, Minneapolis, MN) in selected patients is a currently available percutaneous treatment option [30,31].

9. Evaluation for arrhythmias

The recommendation is to perform a baseline ECG in the evaluation, without the need for repeated ECGs or ambulatory rhythm monitoring. The most frequent arrhythmia is atrial fibrillation which has a similar prevalence to that of the general population [1]. There is evidence of poor clinical outcomes post LT in pre-existing atrial fibrillation with cerebrovascular events, post-transplant acute kidney injury and increased risk of graft failure [32]. New apparition of postoperative atrial fibrillation (POAF) is related to preoperative non-modifiable variables, mainly pulmonary hypertension, age, MELD (model for end-stage liver disease score), and white race. In a study by Rivas et al. POAF was associated with increased 1-year mortality, but not with in-hospital mortality or long-term mortality [33]. However, in a recent metanalysis by So et al., it is associated with higher mortality and graft failure [34].

For anticoagulation in atrial fibrillation the use of direct oral anticoagulants is preferred over vitamin K antagonists. In patients with high bleeding risk, anticoagulants with an approved antidote are recommended [35]. Atrial left appendage occlusion in liver transplant recipients is associated with higher cardiovascular complications so it is not contemplated [36].

Chronotropic incompetence is the inability to increase heart rate when there is a physical or pharmacological stimulus. It is very high in transplant recipients. The pathophysiologic mechanism is related to autonomic neuropathy and the severity of the response alteration is related with the severity of the liver disease and with Child-Pugh and MELD scores [37].

The QT interval is increased in patients with cirrhosis. Long QT syndrome is defined as a QTc greater than 440 milliseconds and occurs in 30−50% of patients with ESLD. The mechanism for QT prolongation is multifactorial in ESLD and causes such as QT interval prolonging drugs and electrolyte abnormalities should be investigated.

There are no specific recommendations for prevention of sudden cardiac death or ventricular arrhythmias for this population, although β-blockers can improve the QT interval they have not been associated with fewer events [37,38].

10. Evaluation for pericardial disease

Pericardial effusion can appear in ESLD, especially in patients with ascites. If it is significant enough it can cause cardiac tamponade. This condition should be treated with pericardiocentesis or pericardial window before LT. It requires close clinical and echocardiographic monitoring because recurrences are common [39].

11. Evaluation for pulmonary hypertension and intrapulmonary shunts

Pulmonary hypertension has a high prevalence in ESLD [40]. The screening includes a transthoracic echocardiography to identify tricuspid regurgitation and estimate the pulmonary arterial systolic pressure (PASP). If there is suspicion of significant pulmonary hypertension (PASP > 40 mmHg), confirmation with right heart catheterization should be done to calculate pulmonary pressures, pulmonary capillary wedge pressure and pulmonary vascular resistances to guide treatment [7]. Diagnosis of pulmonary arterial hypertension has changed with mean pulmonary artery pressure >20 mm Hg rather than >25 mm Hg and pulmonary vascular resistance is now thought to be < 2 Wood units rather than 3 Wood units [40−43].

A particular type of pulmonary hypertension in liver patients is portopulmonary hypertension (PoPH); it is a cause of pre-capillary pulmonary hypertension that occurs in end stage liver disease [44]. It affects 5 − 6% of these patients and is associated with significantly worse survival that idiopathic pulmonary arterial hypertension [45]. this syndrome is caused by a lack of clearance by the liver of vasoactive substances produced in the splanchnic territory causing pulmonary vascular remodeling and vasoconstriction, with elevation of pulmonary pressure and right ventricular dysfunction. The presence of severe pulmonary hypertension is associated with a marked decrease in post- transplant survival and is considered an absolute contraindication for LT. Patients with moderate to severe PoPH should be treated and pulmonary vasodilators should be used to lower the mean pulmonary arterial pressure (mPAP) in order to make the patient eligible for LT. Previously only mPAP <35 mmHg was acceptable for transplant listing, now candidates with mPAP 35 −45 mmHg, low pulmonary vascular resistance (PVR) and good right heart function can also be contemplated [46]. Vasodilator therapies are based on the treatment of idiopathic pulmonary hypertension. When comparing patients with vasodilator therapy and with a combination of vasodilators and LT, the latter group has the best

Table 1
Proposed criteria [25]. CCM: cirrhotic cardiomyopathy. LV: left ventricular. LVGLS: left ventricular global longitudinal strain. E/e' ratio: early mitral inflow velocity to mitral annular early diastolic velocity ratio. Septal e' velocity: septal mitral annulus velocity. TR: tricuspid regurgitation. LAVI: left auricular volume index.

Diagnostic Criteria for CCM	
Systolic dysfunction	Diastolic dysfunction
LV ejection fraction ≤ 50% or LVGLS < 18%	≥ 3 of the following: E/e' ratio ≥ 15 Septal e' velocity< 7 cm/s TR velocity > 2,8 m/s LAVI > 34 ml/m^2

outcomes. There are three pathways on which target drugs for treatment act: endothelin (endothelin receptor antagonists: bosentan, ambrisentan, macitentan); nitric oxide (phosphodiesterase-5 inhibitors: sildenafil, tadalafil, guanylate cyclase stimulators: riociguat); and prostacyclins (prostacyclin derivates: epoprostenol, treprostinil, iloprost, and prostacyclin agonist receptors: selexipag) [47].

Echocardiography with infusion of agitated saline contrast should also be done to detect intrapulmonary shunts. This is a common finding in hepatopulmonary syndrome (HPS), defined by the presence of hypoxaemia and intrapulmonary shunts in a patient with ESLD, and with a prevalence of 5−32% among LT candidates. In this syndrome it seems there is an imbalance of vasoactive substances that favours vasodilatation. In fact, the mechanism of pulmonary hypoxic vasoconstriction is inhibited. Microbubbles that appear late in the left side of the heart after an injection of bubbles in the venous system (4−8 cardiac cycles) are compatible with this diagnosis. Earlier apparition of microbubbles (1−4 cardiac cycles) is more compatible with an atrial septal defect or a patent foramen ovale. If there are doubts after the transthoracic study, a transoesophageal study can provide better visualization of the atrial septum and the pulmonary veins with a direct visualization of bubbles entering the left atrium [48]. Technetium macroaggregated albumin (99mTc MAA) lung perfusion scans can also detect shunts, but do not differentiate from intracardiac and intrapulmonary shunts.

It is necessary to identify other respiratory conditions and bear in mind that cirrhotic patients usually suffer from concomitant respiratory diseases. Blood gas analysis, pulmonary function tests, chest X-rays and pulmonary angiography can be useful to rule out other causes of hypoxemia.

There are no therapies available and liver transplant is the only effective therapeutic alternative. If the condition becomes severe, patients should be prioritized on the waiting list. The definitive treatment is LT and 85% of cases are cured 6 to 12 months after transplant [49]. There is no evidence concerning when not to transplant these patients. The MELD exception standard is limited to patients with $PaO_2 < 60$ mmHg, but there is a study from the United Network for Organ Sharing database (2002 − 2012) that observed that survival to LT was not different between patients with PaO2 <45 mmHg, 45 to < 60 mmHg and ≥ 60 mmHg. As a result, the decision depends on center outcomes. 6−21% of patients present severe post-transplant hypoxemia, defined as the need for 100% FiO2 supplementation to keep blood-oxygen saturation ≥85%, which is associated with a peritransplant mortality of 45%. Treatment options include the Trendelenburg position, inhaled epoprostenol, inhaled NO and intravenous methylene blue. If these therapies fail, coil embolization of arteriovenous malformations and extracorporeal membrane oxygenation can be used [50].

12. Conclusions

LT candidates have more cardiovascular risk factors, and cardiac events are the leading cause of death post-transplant. Appropriate cardiac evaluation should be done to reduce surgical risk. Each hospital must decide which patients to include on the waiting list and how to best manage their comorbidities according to local practices. There is evidence for some recommendations to improve results. However, randomized clinical trials are necessary to develop stratification tools to predict cardiovascular complications following liver transplant.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Levy PE, Khan SS, VanWagner LB. Cardiac evaluation of the kidney or liver transplant candidates. Curr Opin Organ Transplant 2021;26:77–84. doi: 10.1097/MOT.0000000000000838.
[2] Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, Carithers RL, Ragosta M, Bolton K, Auerbach AD, Eagle KA. American Heart Association Council on the Kidney in Cardio- vascular Disease and Council on Peripheral Vascular Disease. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2012;60:434–80. doi: 10.1016/j.jacc.2012.05.008.
[3] Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, De Hert S, de Laval I, Geisler T, Hinterbuchner L, Ibanez B, Lenarczyk R, Mansmann UR, McGreavy P, Mueller C, Muneretto C, Niessner A, Potpara TS, Ristić A, Sade LE, Schirmer H, Schüpke S, Sillesen H, Skulstad H, Torracca L, Tutarel O, Van Der Meer P, Wojakowski W, Zacharowski K, Scientific Document Group ESC. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J 2022;43:3826–924 PMID: 36017553. doi: 10.1093/eurheartj/ehac270.
[4] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vas- odilation hypothesis: a proposal for the initiation of renal sodium and water retention in cir- rhosis. Hepatology 1988;8:1151–7. doi: 10.1002/hep.1840080532.
[5] Fede G, Graziella P, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in pa- tients with liver cirrhosis. Ann Gastroenterol 2015;28:31–40 PMCID: PMC4290002.
[6] Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease. cardio- hepatic Interactions. JACC Heart Fail 2019;7:87–97. doi: 10.1016/j.jchf.2018.10.007.
[7] Lee MS, Wadia S, Yeghiazarians Y, Matthews R, White CJ, Herrmann HC, O'Donnell W, McPherson J, Leesar MA, Kreutz RP, Brandman D, Gupta A, Mandras S, Kandzari DE. Cardiology assessment of patients undergoing evaluation for orthotopic liver transplantation. J Soc Cardiovasc Angiogr Intervent 2023;2:100528. doi: 10.1016/j.jscai.2022.100528.
[8] Nagraj S, Peppas S, Rubianes Guerrero MG, Kokkinidis DG, Contreras-Yametti FI, Murthy S, Jorde UP. Cardiac risk stratification of the liver trans- plant candidate: a comprehensive review. World J Transplant 2022;12:142–56. doi: 10.5500/wjt.v12.i7.142.
[9] Mohebali D, Anagnostopoulos AM, Estrada-Roman A, Pavlakis M, Curry MP, Gavin MC. Car- diovascular risk assessment in renal and liver transplant candidates: a multidisciplinary institu- tional standardized approach. Cardiol Rev 2019;27:286–92. doi: 10.1097/CRD.0000000000000282.
[10] An J, Shim JH, Kim SO, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Prevalence and prediction of coronary artery disease in patients with liver cirrhosis: a registry-based matched case-control study. Circulation 2014;130:1353–62. doi: 10.1161/CIRCULA-TIONAHA.114.009278.
[11] Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal peri- operative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57:37–44. doi: 10.1016/s0167-5273(96)02769-6.
[12] Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, Chesebro JH. Atherosclerotic plaque rupture and thrombosis: evolving concepts. Circulation 1990;82(Suppl 3):47–59 PMID: 2203564.
[13] Donovan CL, Marcovitz PA, Punch JD, Bach DS, Brown KA, Lucey MR, Armstrong WF. Two- dimensional and dobutamine stress echocardiography in the preoperative assessment of pa- tients with end-stage liver disease prior to orthotopic liver transplantation. Transplantation 1996;61:1180–8. doi: 10.1097/00007890-199604270-00011.
[14] Harinstein ME, Flaherty JD, Ansari AH, Robin J, Davidson CJ, Rossi JS, Flamm SL, Blei AT, Bonow RO, Abecassis M, Gheorghiade M. Predictive value of dobutamine stress echocardiog- raphy for coronary artery disease detection in liver transplant candidates. Am J Transplant 2008;8:1523–8. doi: 10.1111/j.1600-6143.2008.02276.x.
[15] Davidson CJ, Gheorghiade M, Flaherty JD, Elliot MD, Reddy SP, Wang NC, Sundaram SA, Flamm SL, Blei AT, Abecassis MI, Bonow RO. Predictive value of stress myocardial perfusion im- aging in liver transplant candidates. Am J Cardiol 2002;89:359–60. doi: 10.1016/s0002-9149(01)02244-5.

[16] De Gasperi A, Spagnolin G, Ornaghi M, Petrò L, Biancofiore G. Preoperative cardiac assess- ment in liver transplant candidates. Best Pract Res Clin Anaesthesiol 2020;34:51–68. doi: 10.1016/j.bpa.2020.02.002.
[17] Su A, Almazan E, Sakulsaengprapha V, Shay J, Wittstein I, Hammami M, Pustavoitau A, Rizkalla N, Alqahtani S, Woreta T, Hamilton JP, Kohli R, Ottmann SE, Gurakar A, Chen PH. High coronary artery calcium score is associated with increased major adverse cardiac events after liver transplantation. Transplant Direct 2023;9:e1426 PMID: 36700067; PMCID: PMC9820787. doi: 10.1097/TXD.0000000000001426.
[18] VanWagner LB, Harinstein ME, Runo JR, Darling C, Serper M, Hall S, Kobashigawa JA. Ham- mel LL. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations. Am J Transplant 2018;18:30–42. doi: 10.1111/ajt.14531.
[19] Moon YJ, Kwon HM, Jung KW, Jeong HW, Park YS, Jun IG, Song JG, Hwang GS. Risk stratification of myocardial injury after liver transplantation in patients with computed tomographic coronary angiography-diagnosed coronary artery disease. Am J Transplant 2019;19:2053–66. doi: 10.1111/ajt.15263.
[20] Bizouarn P, Ausseur A, Desseigne P, Le Teurnier Y, Nougarede B, Train M, Michaud JL. Early and late outcome after elective cardiac surgery in patients with cirrhosis. Ann Thorac Surg 1999;67:1334–8. doi: 10.1016/s0003-4975(99)00226-x.
[21] Klemperer JD, Ko W, Krieger KH, Connolly M, Rosengart TK, Altorki NK, Lang S, Isom OW. Cardiac operations in patients with cirrhosis. Ann Thorac Surg 1998;65:85–7. doi: 10.1016/s0003-4975(97)00931-4.
[22] Sing SA, Pampaniya H, Yadav V, Subnash Gupta. Coronary artery revascularization before liver transplant –is it putting the cart before the horse? J Liver Transpl 2022;8:10030. doi: 10.1016/j.liver.2022.100130.
[23] Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, Watt KD, Lee SS. Cirrhotic cardio- myopathy consortium. redefining cirrhotic cardiomyopathy for the modern era. Hepatology 2020;71:334–45. doi: 10.1002/hep.30875.
[24] Kalluru R, Gadde S, Chikatimalla R, Dasaradhan T, Koneti J, Cherukuri SP. Cirrhotic cardiomyopathy: the interplay between liver and heart. Cureus 2022;14:e27969 PMID: 36120195; PMCID: PMC9467492. doi: 10.7759/cureus.27969.
[25] Liu H, Lee SS. Diagnostic criteria of cirrhotic cardiomyopathy: out with the old, in with the new? Hepatology 2021;74:3523–5 PMID: 34152621. doi: 10.1002/hep.32021.
[26] Bhave NM, Sharma P, Eagle KA. Hearts of steel: preoperative cardiovascular risk assess- ment in liver transplant recipients. JACC Case Rep 2022;4:682–4. doi: 10.1016/j.jac-cas.2022.04.008.
[27] Habib A, Shaaban A, Thompson J, Chinnakotla S, Martin CM, Vercellotti GM. Sudden onset iron overload cardiomyopathy after liver transplantation. J Investig Med High Impact Case Rep 2023;11 23247096231159812PMID: 36914978; PMCID: PMC10017927. doi: 10.1177/23247096231159812.
[28] Duong N, Nguyen V, De Marchi L, Thomas A. Approach to the patient with decompensated cirrhosis and aortic stenosis during liver transplantation evaluation. Hepatol Commun 2022;6:3291–8 PMID: 36166191; PMCID: PMC9701479. doi: 10.1002/hep4.2094.
[29] Ahmed T, Misumida N, Grigorian A, Tarantini G, Messerli AW. Transcatheter interventions for valvular heart diseases in liver cirrhosis patients. Trends Cardiovasc Med 2021;30 S1050- 1738(21)00164-X. doi: 10.1016/j.tcm.2021.12.014.
[30] Sharma V, Kleb C, Sheth C, Verma BR, Jain V, Sharma R, Parikh P, Cywinski J, Menon KVN, Esfeh JM, Eghtesad B, Quintini C, Uso TD, Tong MZY, Nair R, Bhargava A, Fares M. Cardiac con- siderations in liver transplantation. Cleve Clin J Med 2022;89:46–55. doi: 10.3949/ccjm.89a.21006.
[31] Chokesuwattanaskul R, Thongprayoon C, Bathini T, Ungprasert P, Sharma K, Wijarn- preecha K, Pachariyanon P, Cheungpasitporn W. Liver transplantation and atrial fibrillation; a meta-analysis. World J Hepatol 2018;10:761–71. doi: 10.4254/wjh.v10.i10.761.
[32] Rivas E, Sasaki K, Liang C, Wang J, Quintini C, Maheshwari K, Turan A, Fares M, Cywinski JB. New-onset atrial fibrillation in patients undergoing liver transplantation: retrospective analysis of risk factors and outcomes. J Cardiothorac Vasc Anesth 2022;36:4100–7 PMID: 35999113. doi: 10.1053/j.jvca.2022.07.013.
[33] So WZ, Tan FL, Tan DJH, Ng CH, Yong JN, Syn N, Tang ASP, Wong RC, Lin W, Tan EXX, Huang DQ, Dan YY, Chew NWS, Siddiqui MS, Muthiah MD. A systematic review and meta-analysis on the impact of pre-existing and new-onset atrial fibrillation on outcomes before and after liver transplantation. Dig Liver Dis 2022;54:614–21 PMID: 34896025. doi: 10.1016/j.dld.2021.11.011.
[34] Vandenberk B, Altieri MH, Liu H, Raj SR, Lee SS. Review article: diagnosis, pathophysiology and management of atrial fibrillation in cirrhosis and portal hypertension. Aliment Pharmacol Ther 2023;57:290–303 PMID: 36571829. doi: 10.1111/apt.17368.
[35] Zahid S, Sanchez-Nadales A, Hashem A, Sarkar A, Sleiman J, Lewis A, Uppal D, Nimmagadda M, Ullah W, Leiby B, Snipelisky D, Baez-Escudero J, Asher C. Trends and outcomes of left atrial appendage occlusion in renal and liver transplant recipients: insights from the United States National Inpatient and Readmission Database. Curr Probl Cardiol 2023;48:101488 PMID: 36351464. doi: 10.1016/j.cpcardiol.2022.101488.
[36] Główczyńska R, Borodzicz-Jażdżyk S, Peller M, Raszeja-Wyszomirska J, Milkiewicz P, Zieniewicz K, Opolski G. Chronotropic incompetence in end-stage liver disease. PLoS ONE 2022;17:e0270784 PMID: 35913923; PMCID: PMC9342738. doi: 10.1371/journal.pone.0270784.
[37] Ko J, Koshy AN, Han HC, Weinberg L, Gow P, Testro A, Lim HS, Farouque O, Teh AW. Effect of QT interval prolongation on cardiac arrest following liver transplantation and derivation of a risk index. Int J Cardiol 2021;326:158–63. doi: 10.1016/j.ijcard.2020.11.017.
[38] Raval Z, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. J Am Coll Cardiol 2011;58:223–31 PMID: 21737011. doi: 10.1016/j.jacc.2011.03.026.
[39] Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmo- nary syndrome. Lancet 2004;363:1461–8. doi: 10.1016/S0140-6736(04)16107-2.
[40] Porres-Aguilar M, Zuckerman MJ, Figueroa-Casas JB, Krowka MJ. Portopulmonary hyper- tension: state of the art. Ann Hepatol 2008;7:321–30 PMID: 19034231.
[41] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913 PMID: 30545968; PMCID: PMC6351336. doi: 10.1183/13993003.01913-2018.
[42] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, A Vonk Noordegraaf, Delcroix M, Rosenkranz S, ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618–731 Erratum in: Eur Heart J. 2023 Feb 23;: PMID: 36017548. doi: 10.1093/eurheartj/ehac237.
[43] Bart NK, Liu K, Kotlyar E, Keogh AM. Portopulmonary hypertension: the interplay between the liver and pulmonary arteries. Heart Lung Circ 2022;31:1185–7 PMID: 36028294. doi: 10.1016/j.hlc.2022.07.010.
[44] DuBrock HM. Portopulmonary hypertension: management and liver transplantation evaluation. Chest 2023 S0012-369200043-0Epub ahead of printPMID: 36649754. doi: 10.1016/j.chest.2023.01.009.
[45] Krowka MJ, Kamath PS. Portopulmonary hypertension: may we agree to disagree? Liver Transpl 2023;29:349–50 PMID: 36724441. doi: 10.1097/LVT.0000000000000078.
[46] Tokushige K, Kogiso T, Egawa H. Current therapy and liver transplantation for portopulmonary hypertension in Japan. J Clin Med 2023;12:562 PMID: 36675490; PMCID: PMC9867251. doi: 10.3390/jcm12020562.
[47] Rollán MJ, Muñoz AC, Pérez T, Bratos JL. Value of contrast echocardiography for the diagnosis of hepatopulmonary syndrome. Eur J Echocardiogr 2007;8:408–10. doi: 10.1016/j.euje.2006.07.005.
[48] Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver trans- plantation. Hepatology 2003;37:192–7. doi: 10.1053/jhep.2003.50023.
[49] Raevens S, Boret M, Fallon MB. Hepatopulmonary syndrome. JHEP Rep 2022;4:100527. doi: 10.1016/j.jhepr.2022.100527.