LTSI Consensus Guidelines: Preoperative Pulmonary Evaluation in Adult Liver Transplant Recipients

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The relationship between chronic liver disease and respiratory symptoms and hypoxia is well recognized. Over the last century, three pulmonary complications specific to chronic liver disease (CLD) have been characterized: hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax. Apart from that coexisting pulmonary disease like chronic obstructive lung disease and interstitial lung disease also complicate the outcomes after liver transplantation (LT).

Assessment for evaluation of underlying pulmonary disorders is essential to improve outcomes in patients with CLD, posted for LT. This consensus guideline of the Liver Transplant Society of India (LTSI) provides a comprehensive review of pulmonary issues in CLD, related and unrelated to underlying liver disease and gives recommendations for pulmonary screening in specific clinical scenarios in adults with chronic liver disease planned for LT.

This document also aims to standardize the strategies for preoperative evaluation of these pulmonary issues in this subset of patients. Proposed recommendations were based on selected single case reports, small series, registries, databases, and expert opinion. The paucity of randomized, controlled trials in either of these disorders was noted. Additionally, this review will highlight the lacunae in our current evaluation strategy, challenges faced, and will provide direction to potentially useful futuristic preoperative evaluation strategies. (J Clin Exp Hepatol 2023;13:523–531)

Practice guideline

Pulmonary disease significantly impacts short-term as well as long-term outcomes after liver transplantation (LT) and has important implications regarding prognostication and transplant candidacy. Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PoPH) are two distinct pulmonary vascular disorders that occur because of liver parenchymal or vascular abnormalities.

Preoperative pulmonary evaluation of LT candidates should include evaluation for these as well as an adequate screening of concomitant respiratory disorders like chronic obstructive pulmonary disease (COPD), asthma, interstitial

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Abbreviations: ABG: arterial blood gas; CTEE: contrast-enhanced transesophageal echocardiography; CTTE: contrast-enhanced transthoracic echocardiography; COPD: chronic obstructive pulmonary disease; DLCO: diffusion capacity for carbon monoxide; eNOS: endothelial nitric oxide synthase; ERA: endothelin receptor antagonist; HH: hepatic hydrothorax; HPS: hepatopulmonary syndrome; iNOS: inducible nitric oxide synthase; IPVD: intrapulmonary vascular dilatation; LT: liver transplantation; NO: nitric oxide; MAA: technetium-labeled macroaggregated albumin; MELD: model for end-stage liver disease; mPAP: mean pulmonary artery pressure; PAH, pulmonary arterial hypertension: P[A-a]O_2; alveolar-arterial oxygen gradient: PaO_2; partial pressure of oxygen: PAOP; pulmonary artery occlusion pressure: POPH; portopulmonary hypertension: PMN, polymorphonuclear cell count; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RVSP: right ventricular systolic pressure; SBPL: spontaneous bacterial pleuritis; SBP: spontaneous bacterial peritonitis; SPAG: serum-to-pleural fluid albumin gradient; SpO_2: oxygen saturation; TPG: transpulmonary pressure gradient; TRV: tricuspid regurgitant velocity transpulmonary pressure gradient; TIPS: transjugular intrahepatic portosystemic shunt; UNOS: United Network for Organ Sharing; VTIRVOT: right ventricular outflow tract velocity time integral

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lung disease (ILD), and other coexisting complications of end-stage liver disease (ESLD) like hepatic hydrothorax (HH). Despite several guidelines from different societies, there are discrepancies among center-based practices for pretransplant pulmonary evaluation. The unique clinical characteristics of patients with ESLD also raises questions about the applicability of available recommendations.[1]

A working group of specialists from the Liver Transplantation Society of India (LTSI) comprising LT anesthesiologists, intensivist, hepatologists, and LT surgeons was constituted to draft a set of consensus guidelines on preoperative pulmonary evaluation of LT recipients. The composition of the working group was approved by the LTSI Governing Council to eliminate any possibility of bias.

All the members of this working group disclosed no conflict of interest. The working group critically reviewed over 100 published articles identified via a MEDLINE search, on pulmonary disorders among CLD patients undergoing liver transplant. Original research articles were preferred but scant data on less common complications like HPS, PoPH, warranted inclusion of case-series, case reports, and expert opinion for drafting these guidelines. The initial draft was discussed and revised in a series of online meetings of the working group between October 2021 and March 2022. The final recommendations were graded based on the strength and quality of the available evidence as outlined below.

This document aims to analyze the existing dilemmas in current practice of pretransplant pulmonary evaluation, conduct a literature review, and present the official recommendations of the Liver Transplantation Society of India (LTSI).

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STRENGTH OF RECOMMENDATION

(1) **Strong.** There is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.
(2) **Weak.** There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment.

Quality of Evidence

Level A: data derived from multiple randomized clinical trials or meta-analyses.
Level B: data derived from a single randomized trial or nonrandomized studies.
Level C: only consensus opinion of experts, case studies, or standard-of-care.

PORTOPULMONARY HYPERTENSION

Introduction

PoPH is the concomitant presence of pulmonary hypertension (PH) and portal hypertension (PoH) in patients with or without cirrhosis. PoPH is in fact a rare condition affecting 2–5% of the population with PoH but having enormous clinical implications.[2–4] The prevalence of PoPH in patients undergoing LT is considered to be higher, with several studies showing prevalence of 8.5–10.5%.[5,6] There is growing recognition of the importance of PoPH as this condition has major clinical implications[1] and significantly increases the mortality rate in LT recipients.[7,8] PoPH in patients with advanced liver disease could also be due to volume overload or hyperdynamic state.[9,10]

The 5-year survival of patients with PoPH, from the time of diagnosis is seen to be worse (40% vs. 64%), in the REVEAL registry than that of patients with idiopathic PH.[1] The 5-year survival of patients with PoPH not receiving PH-targeted therapy, by the Mayo clinic was 14%[11] while the United Kingdom national registry reported a 5-year survival rate of 35%. There was no difference in survival rates between patients with and without cirrhosis.[8]

The 5-year survival in patients with PoPH who were not treated medically or with LT was very poor at 14%, with 54% dying within 1 year of diagnosis. The median survival in patients who received medical therapy for PoPH but did not undergo LT was 46 months and 5-year survival was 45% (P = 0.03), and outcomes were better still in those who underwent LT where the 5-year survival after transplant was 76%.[11]

Pathophysiology

PoPH results when there is obstruction to arterial flow in the pulmonary arterial bed. Obstruction can be due to contributions of vasoconstriction, proliferation of endothelium/smooth muscle, and platelet aggregation. Mediators associated with POPH include increased circulating endothelin-1 and estradiol levels and deficiency of prostacyclin synthase in pulmonary endothelial cells.

Clinical Features

Risk factors associated with increased risk of development of PoPH are female gender and autoimmune hepatitis, while patients with hepatitis C infection had a lower risk.

Dyspnea on exertion is the most common initial symptom of PoPH and fatigue, orthopnea, chest pain, peripheral edema syncope, and dyspnea at rest may develop as the disease progresses.[12–14] Initial symptoms are subtle and nonspecific, and patients may remain asymptomatic at the time of diagnosis despite advanced disease.

Physical examination may show abnormalities like accentuated and split-second heart sound, systolic murmur, right ventricle (RV) heave, right-sided S3 gallop, jugular vein extension, edema, and the signs of overt right-heart failure or nothing at all. Lower leg edema out of proportion to ascites due to portal hypertension may

be suggestive of associated PoPH.[15,16] Arterial blood gasses (ABG) may show hypoxemia and increased alveolar-arterial oxygen gradient (P [A-a]O_2). The decrease in arterial oxygenation was found to be significantly worse in patients with PoPH when compared with a cohort of patients that underwent screening for LT and normal RV systolic pressures (RVSP).[16] Electrocardiograms may show evidence of RV hypertrophy, right atrial enlargement, and right axis deviation. Chest X-ray (CXR) is usually normal but may show enlarged pulmonary arteries. Pulmonary function tests (PFTs) may be normal or may show mild restrictive defects and decreased diffusion capacity.

Diagnosis, Screening, and Grading of Severity

PoPH criteria described in 2004 by the Task Force on pulmonary-hepatic disorders have been maintained in the International Liver Transplant Society practice guidelines for the HPS and PoPH.[7,17] The current diagnostic criteria for PoPH include presence of portal hypertension, mPAP >25 mmHg at rest, PVR >240 dynes.s.cm^{-5} (>3 Wood units), and pulmonary capillary wedge pressure (PCWP) < 15 mmHg[11,18–21] on right-heart catheterization (RHC).[11,18,20] Severity of PoPH is graded as mild (mPAP, 25–35 mm Hg), moderate (mPAP, 36–45 mm Hg), and severe (>45 mm Hg).

The diagnosis of PoPH also requires exclusion of other causes of PH like left-heart failure, obstructive/restrictive lung disease or obstructive sleep apnea or volume overload. Transthoracic echocardiography (TTE) serves as the initial screening test for detection of PoPH in ESLD candidates and is recommended in all patients awaiting LT. According to the guidelines by AASLD, all patients being screened for LT should be evaluated for PoPH by TTE.[19] Presence of RVSP >50 mmHg and/or significant right ventricle (RV) hypertrophy or dysfunction on routine TTE evaluation mandates RHC. The 50 mm Hg cutoff, along with RV function, has been described as the providing the best "diagnostic accuracy" in identifying patients with POPH by Raevens *et al.*[22]

However, RVSP alone might be inaccurate and other signs of PH including pulmonic insufficiency, RV hypertrophy, dilatation and dysfunction, as well as right atrial enlargement should also be looked for.[11] Tricuspid Annular Plane Systolic Excursion (TAPSE) is known as a measuring tool of echocardiography to comment on RV. It is considered among the most reliable tools to measure or estimate the ejection fraction of the RV, cardiac output, and diastolic function. But the value of this tool may get influenced due to the co-occurrence of any other disease such as COPD.[23]

Complete evaluation of the RV systolic function is important as the RV function is the major determinant of morbidity and mortality in the PH population.[8,12] A recent study showed 24-fold higher odds of deaths within 6 months of LT for patients without assessment of RV systolic function.[13] Concurrent RV hypertrophy, dilation, or dysfunction should be investigated with RHC.[14]

Doppler echocardiographic estimate of PVR (ratio of peak tricuspid regurgitant velocity [TRV] to right ventricular outflow tract velocity time integral [VTIRVOT]) is another method to detect POPH before LT. Using a cutoff value of TRV/VTIRVOT >0.12 is another noninvasive method for detection of PVR. Thus, referring all patients with a TRV/VTIRVOT >0.12 for RHC would not miss any cases of significant PoPH, whereas all patients with a TRV/VTIRVOT <0.12 could safely proceed to LT without the need for RHC.[24] These newer ways of assessing the PVR is a good tool in the situation where RHC could not be performed as in the presence of severe TR or TS or PR.

Patients with volume overload would have a PCWP >15 mmHg. In them, a transpulmonary pressure gradient (TPG) > 12 mmHg can be used instead of PCWP.[11] The TPG correlates with the PVR and identifies resistance to pulmonary arterial blood flow.[11] Diuretic therapy is also considered to rule out whether high RSVP is because of volume overload.

Preoperative Optimization and Patient Selection

PoPH alone is not an indication of LT. But it has been found that there is a significant health and economic burden of co-existing PoH and PH.[25] Several studies reported no increase in perioperative mortality if mPAP was <35 mmHg,[1,26] and it is recommended to proceed with LT in mild PoPH with preserved RV function and cardiac output.[20] Moderate and severe PoPH pose a higher risk of prolonged postoperative mechanical ventilation, length of hospital stay, and need for vasodilator therapy.[1] In moderate and severe PoPH, it is advisable to treat with PH medications and reassess. While a mPAP >50 mmHg (>45 mmHg in some centers) remains an absolute contraindication to LT in most centers.[1] Some experts suggest that PoPH should no longer be considered an absolute contraindication unless POPH is severe and associated with RV dysfunction.[27] Further studies are warranted to validate these case reports. Selected patients with severe PoPH and ESLD may be considered for combined lung and liver transplantation.[28]

Recommendations for PAH Associated with POPH

1. Transthoracic echocardiography is recommended for all patients being considered for LT. (1A)
2. Echocardiographic screening should comment on RVSP and assess RV function in all patients with liver disease posted for LT. (1B)
3. It is important to differentiate volume overload from PoPH as a cause of increased RVSP. (2A)

4. Diuretic therapy should be considered in patients with fluid overload. (1B)
5. RHC should be performed in patients with persistently increased RVSP >50 mmHg despite diuretic therapy. (1B)
6. Exclude other causes of pulmonary hypertension in the setting of liver disease. (2A)
7. TRV/TVIRVOT >0.12 on doppler echocardiography can be considered to confirm diagnosis of POPH, when RHC is not feasible or cannot be performed. (1B)
8. PoPH patients with mild PH (mPAP 25–35 mmHg and/or PVR is < 400 dynes.s/cm^5) can be considered for liver transplant in experienced centers. (1B)
9. PoPH patients with moderate PH (mPAP 36–45 mmHg and/or PVR is 400–800 dynes.s/cm^5) should be treated to reduce PA pressures and improve hemodynamics before LT can be considered. (1B)
10. PoPH patients with severe PH (mPAP is > 45 mmHg and/or PVR is > 800 dyn s/cm^5) and poor RV function despite treatment, should not be considered for liver transplant due to high perioperative mortality. (1C)
11. POPH with mPAP >50 mm Hg is an absolute contraindication for LT. (1C)

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HEPATIC HYDROTHORAX

Hepatic hydrothorax is defined as the presence of pleural effusion in ESLD patients in the absence of cardiopulmonary and pleural disease. HH is the most common cause of pleural effusions in cirrhosis. HH is right-sided in 70% of cases, left-sided in 18%, and bilateral in 12%.[29] The pleural cavity is a restricted space and symptoms often develop with smaller volumes of fluid (>500 mL) than what are found in the peritoneal space.

The most important reason behind the development of HH is the presence of diaphragmatic defects leading to passage of ascitic fluid from the peritoneal into the pleural cavity. In addition, negative intrathoracic pressure is believed to contribute to the one-way directional flow of ascitic fluid from the abdominal cavity. HH is mostly right sided and presents with dyspnea, chest pain, or cough. One retrospective series found that 70% of pleural effusions in a cohort of cirrhosis patients were due to uncomplicated HH, 15% were due to infected HH, and 15% were due to causes other than liver disease. In addition, 80% of right-sided pleural effusions were found to be uncomplicated HH, while only 35% of left-sided pleural effusions were uncomplicated HH.[30]

It is important to confirm the etiology of hydrothorax prior to liver transplantation. Diagnostic workup for HH in patients awaiting LT includes imaging like CXR, chest computed tomography (CT) scan (to rule out other causes of pleural effusion), and therapeutic thoracentesis. In the Indian subcontinent, where tuberculosis is a common, pleural fluid analysis is done using cytology, pleural fluid protein, LDH, and ADA to rule it out.

Thoracentesis is required to (1) confirm the diagnosis based on a transudative pleural fluid analysis, (2) detect infection (spontaneous bacterial pleuritis/empyema, polymorphonuclear cell count >500/μL or > 250/μL with positive culture) and (3) relieve symptoms in cases of severe dyspnea or refractory HH.

Massive hydrothorax can sometimes mask underlying lung parenchymal pathology. To evaluate the cause of hypoxia in patients with massive hydrothorax, thoracentesis can be performed to visualize the underlying lung and its expansion post-tapping.[31] The diagnosis of hepatic hydrothorax includes documentation of a pleural effusion and exclusion of alternative causes for the effusion.

Recommendations for HH

1. Diagnostic workup for patients with left-sided pleural effusion should be performed with chest imaging and pleural fluid analysis including TB. (1B)
2. Workup for patients with isolated right-sided and bilateral pleural effusions with chest imaging and pleural fluid analysis can be considered. (2B)
3. In patients with symptomatic hydrothorax, pretransplant therapeutic thoracentesis should be performed. (2B)
4. In massive hydrothorax and in hypoxic patients, thoracentesis can be considered to check post-thoracentesis lung expansion. (2C)

HEPATOPULMONARY SYNDROME (HPS)

HPS is characterized by a triad of arterial hypoxemia, intrapulmonary vascular dilation (IPVD), and ESLD.[32] It is estimated to be present in nearly 5–30% of ESLD candidates evaluated for LT.[33]

Pathogenesis

Hypoxemia in HPS results from ventilation–perfusion mismatch, arteriovenous shunting, and diffusion impairment.[34] Activation of pulmonary macrophages result from increased circulating levels of bile acids, endothelin-1, and bacterial translocation induced endotoxins and tumor necrosis factor alpha (TNF-α). Pulmonary vasodilation factors [nitric oxide (NO) and carbon monoxide (CO)] and mediators of angiogenesis [vascular endothelial growth factor (VEGF)] secreted from activated macrophages and subsequent endothelial dysfunction lead to IPVDs and shunt formation.[32]

Clinical Features

Progressive dyspnea, platypnea, orthodeoxia, digital clubbing, cyanosis, and spider naevi constitute the important clinical findings in ESLD patients with HPS. Platypnea (worsening of dyspnea while shifting from supine to upright position) and orthodeoxia (decrease in PaO_2 by at least 5% or 4 mmHg from supine to upright posture) are pathognomonic for HPS.[35]

Diagnostic Workup

HPS is defined, based on ERS Task Force criteria (2004), as a triad of advanced liver disease, IPVD and abnormal arterial oxygenation (PaO_2 < 80 mm Hg and/or P[A-a] O_2 > 15 mm Hg or > 20 mm Hg in those more than 65 years of age).[7] The severity of HPS is categorized by the degree of hypoxemia. Based on the ERS Task Force, severity is graded as mild ($PaO_2 \geq 80$ mm Hg), moderate (PaO_2 = 60–79 mm Hg), severe (PaO_2 = 50–59 mm Hg), and very severe (PaO_2 < 50 mm Hg).

Pulse oximetry (SpO_2) should be performed as the initial screening test for HPS. ABG analysis should be performed in patients with SpO_2 < 96% while breathing ambient air in the sitting position.[18] However, in a more recent multicenter prospective cohort study, Pulmonary Vascular Complications of Liver Disease 2 (PVCLD2), the cutoff SpO_2 < 96% was found to have unacceptably low sensitivity (28%) to detect HPS and a negative predictive value of 82% implying almost 18% of those with SpO_2 > 96% had HPS.[36] This could be attributed to a relatively preserved PaO_2 with increased A-a gradient in ESLD patients resulting from baseline respiratory alkalosis and lower PCO_2 levels as well as altered hemoglobin dissociation curve. Hence, room air ABG is recommended in all LT candidates to detect HPS allowing suitable prioritization.

ABG should be repeated while breathing 100% oxygen to differentiate between anatomical and functional shunts.[5] PaO_2 < 200 mmHg on 100% oxygen suggests the presence of severe IVPDs, intracardiac shunt or discrete arteriovenous communications. Pulmonary angiography should be reserved for such patients with severe HPS and hypoxemia not responding to 100% oxygen or thoracic CT scan suggesting focal arteriovenous communications potentially curable by embolization.[37]

Contrast-enhanced transthoracic echocardiography (CE-TTE) is the most sensitive test to detect IPVD in patients with suspected HPS.[38,39] Saline contrast is administered through a peripheral vein and appearance of bubbles in the left atrium within 3–6 cardiac cycles after right atrial opacifications on TTE indicate the presence of IPVD. Appearance of bubbles during 1–2 beats denote intracardiac shunt. Transesophageal echocardiography (TEE) can also be done in patients with poor windows for TTE to detect IPVD as well as differentiation from intracardiac shunt by identifying the source of bubbles in left atrium (pulmonary veins or atrial septal defects).

Quantification of the intrapulmonary shunt can be performed using Technetium-99m labeled macroaggregated albumin (MAA) lung perfusion scan involving particles 20–50 microns diameter injected through a peripheral vein. These MAA particles can pass through dilated intrapulmonary vasculature and are trapped by downstream capillary beds (brain, kidneys, etc.). Abnormal brain uptake (>6% uptake of 99m- Tc MAA in brain after lung perfusion) signifies HPS as the more important contributor of hypoxemia in ESLD patients with coexisting pulmonary obstructive or restrictive defects. A recent prospective study by Alipour *et al.* demonstrated higher sensitivity of MAA scan compared to CE-TTE in detecting HPS.[40] Shunt fraction >20% on MAA scan has been associated with higher postoperative mortality and should be utilized for risk-stratification in patients with severe HPS.[41] Coexisting pulmonary causes of hypoxemia should be ruled out in ESLD patients with HPS using PFTs, CXR, and HRCT of the thorax. Currently, LT is the only curative option for HPS with excellent resolution of hypoxemia post-transplant being well-documented. Multicenter data and recent UNOS data suggest that pre-LT PaO_2 less than 45–50 mm Hg is associated with increased risk of post-transplant hypoxemia, morbidity, and mortality.[42] Although some centers have reported good outcomes in select HPS patients with pre-LT PaO_2 less than 50 mm Hg, suggesting center-specific variation.[43]

Standard exception to the MELD scores has been applied in Euro transplant and UNOS registries to severe HPS patients (PaO_2 < 60 mmHg) to prioritize them during organ allocation. Better post-LT survival rates and oxygenation following implementation of the MELD exception policy has recently been demonstrated in a multicenter retrospective European study by Raevens *et al.* (2019) and in a systematic review by Aragon Pinto *et al.* (2020).[44,45]

Recommendations for Evaluation of HPS

1. LT is the only curative treatment modality for HPS. (1B)
2. Active screening for HPS is recommended in all LT candidates, as clinical presentation of HPS may be variable and many patients with HPS may be asymptomatic. (2B)
3. SpO_2 monitoring is a reasonable screening tool to detect HPS in LT candidates, however room air ABG with measurement of A-a gradient is required to make a definitive diagnosis. (1C).
4. Room air ABG (in sitting and lying position) and CE-TTE should be performed in all LT candidates suspected to have HPS. (1B).
5. Other causes of hypoxemia should be ruled out and an HRCT chest can be considered. (1B)

6. Response to 100% oxygen on ABG should be checked in all patients with HPS. (2C)
7. In the absence of other causes of hypoxia and nonresponsiveness to 100% oxygen using nonrebreathing masks (i.e., PaO_2<200 mm Hg) pulmonary angiography can be considered. (2C)
8. Large shunts identified on pulmonary angiography could be considered for coil embolization to improve hypoxemia. (2C)
9. MAA scan is useful for quantification of intrapulmonary shunt. Owing to higher specificity for the detection of IPVDs, it is useful in patients with coexisting cardio-pulmonary disease to understand the contribution of HPS to hypoxia. (1C)
10. Patients with severe HPS and those with poor responsiveness to 100% oxygen can be considered for LT in experienced centers with facilities of NO therapy and ECMO. (2C).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is present during preoperative evaluation in almost 18% of LT candidates based on FEV_1/FVC <70%.[46] Smoking, low body mass index, and elderly age are the common risk factors of COPD in LT candidates. There are conflicting reports of different post-LT survival rates between ESLD patients with or without COPD. Rybak *et al.* (2008) and Kia *et al.* (2016) reported no significant decrease in survival rates post-LT in patients with obstructive lung disease, while it was independently associated with shorter post-LT survival in an analysis by Volk *et al.* (2007).[46–48] In a recent Spanish multicenter observational study which included 14,790 LT recipients over 15 years (2001–15), patients with COPD had lower hospital mortality rates, length of hospital stay, and infectious complications.[49]

Although preoperative PFT parameters do not affect graft and patient survival post-transplant.[50] TLC, DLCO, and residual volume are said to independently predict postoperative pulmonary complications like length of ICU stay and days of mechanical ventilation after LT.[47]

Six-minute walk test less than 250 m is considered a poor prognostic predictor in patients awaiting LT.[50] Preoperative pulmonary rehabilitation programs (dietary interventions, exercise training) during the waiting period might improve exercise capacity and outcomes post-LT.

Recommendations

1. Very severe COPD (FEV1<30%) should be considered contraindications to LT. (1B)
2. Abstinence from smoking for at least 4 weeks prior to surgery is strongly recommended. (1C)
3. Six-minute walk test, when feasible, is a useful test to assess exercise capacity. (1B)
4. PFT should be a part of routine pulmonary evaluation of patients with COPD. (2B)
5. DLCO, TLC and RV are useful adjuncts in predicting postoperative pulmonary complications during preoperative pulmonary evaluation of patients with COPD. (2B)

INTERSTITIAL LUNG DISEASE (ILD)

Interstitial lung disease refers to a spectrum of restrictive lung disorders including idiopathic pulmonary fibrosis and interstitial pneumonia. It is characterized by restrictive patterns on PFT and typical findings on chest HRCT. It is commonly associated with autoimmune liver disease and primary biliary cirrhosis.[51,52] Shen *et al.*, in a prospective study involving 178 primary biliary cirrhosis patients, reported ILD to be present in nearly 15% of the patients and identified presence of Raynaud's phenomenon or concomitant connective tissue disorders (SLE, rheumatoid arthritis, Sjogren's syndrome etc.) as predictors of development of ILD in these patients.[53] Telomeropathies are a group of disorders associated with premature aging, bone marrow failure, cirrhosis, and pulmonary involvement (ILD/HPS).[52] LT has been recently reported as a curative option in these patients including the need for combined liver and lung transplant in those with cirrhosis and ILD.[54] Restrictive lung disease has been associated with increased length of hospital stay and prolonged mechanical ventilation post-LT. However, restrictive PFT patterns in LT candidates might more commonly be due to ascites or hydrothorax.[55] Post-LT outcomes in patients with ILD are not clearly reported so far. ILD is rarely reversible with a median survival of 2–4 years, and the mortality rates have not been favorably affected despite advances in antifibrotic treatment.[56–58] Preoperative home oxygen requirement and increased duration of surgery have been identified as independent predictors of acute respiratory worsening in patients with IPF postoperatively.[59]

Recommendations

1. Active screening for ILD using PFT and HRCT chest should be performed in LT candidates where clinically indicated. (1B).
2. Owing to progressive course and poor prognosis of advanced ILD, LT should not be offered to those with severe ILD. (1C). Where expertise is available a combined liver lung transplantation can be considered. (2B).

Pulmonary Evaluation in Recipients Recovered from COVID

Patients with CLD being evaluated for LT who had developed SARS CoV2 infection earlier should be evaluated carefully for evidence of post COVID pulmonary complications. A detailed history of symptomatology, details of hospitalization and need for oxygen supplementation or other

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therapy at the time of infection and over the next few weeks should be obtained.

Those who developed mild to moderate COVID-19 pneumonia may not be at risk for post-COVID-19 pulmonary fibrosis.[60] However, in the severe forms of lung injury due to COVID-19, the basement membrane is known to get damaged and the repair process ends up with the formation of fibroblastic tissue and scarring, leading to architectural distortion and fibrosis.[61] Long intensive care unit (ICU) stay, use of mechanical ventilation, need for high flow oxygen therapy, smoking, obesity, and chronic alcoholism have also been associated with development of pulmonary fibrosis post COVID-19.

Other respiratory complications that need to be looked for include bronchiectasis, cavitatory lung disease and pneumothorax. Spontaneous pneumothorax has been reported weeks to month after discharge and should be kept in mind during their evaluation for LT.[62]

There is also a risk of pulmonary thromboembolism, which has been reported in 30–40% predominantly segmental and subsegmental levels and therefore needs to be looked for in patients presenting within 4 weeks of COVID-19 infection.[63,64]

In a patient recovering from severe COVID-19 pneumonia, a follow-up CXR and PFT was recommended 4–6 weeks post discharge. Further evaluation with imaging was recommended in those who demonstrated worsening or non-resolution of previous findings.[65] Initial recommendations from transplant societies suggested a gap of at least 4 weeks from COVID positivity before proceeding with transplantation. With the advent of effective vaccination regimens, the incidence of pulmonary involvement, specifically severe pneumonia in the third wave reduced drastically. Hence in the current scenario, evidence of lung involvement should decide on the need for a waiting period for any further recovery.

Recommendations

1. Patients with previous moderate to severe SARS CoV2 infection should be carefully screened for post COVID pulmonary fibrosis, bronchiectasis, pneumothorax and segmental pulmonary thromboembolism. (2B)

Limitations and Future Directions

The working group was unanimous in its opinion that the strength of recommendations put forth in this LTSI Consensus Statement needs to be enhanced significantly. Future research aimed at improving the quality of evidence regarding the severity of pulmonary involvement, preoperative optimization and correlation analysis with relevant outcomes in LT recipients with HPS, PoPH, HH, and COPD is warranted. The lacunae in the existing literature were identified by the experts in the working group and are being presented below in the text-box so as to encourage further research in these topics.

Future Directions

1. Correlation analysis of the severity of HPS/PoPH with post-transplant outcomes.
2. Data on center-specific cutoffs, screening strategies, optimization, and post-LT outcomes in patients with PoPH, HPS, and other respiratory comorbidities.
3. Correlation between PFT findings (DLCO, FVC, FEV1), exercise capacity (6 min walk distance), baseline room-air ABG findings, and post-LT outcomes to identify predictors of post-LT pulmonary complications.

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CONFLICTS OF INTEREST

The authors have none to declare.

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