

# Pulmonary contraindications, indications and MELD exceptions for liver transplantation: A contemporary view and look forward

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## Summary

Pulmonary concerns in liver transplant candidates have intraoperative and outcome implications. Evolving MELD exception policies address transplant priority for problems such as hepatopulmonary syndrome, portopulmonary hypertension, and hemorrhagic hereditary telangiectasia. Other pulmonary issues such as refractory hepatic hydrothorax, advanced chronic obstructive lung disease (including alpha-1 antitrypsin deficiency) and indeterminate pulmonary nodules may affect liver transplant consideration. Herein, we discuss current pulmonary-related contraindications, indications and MELD exception policies for liver transplantation, suggesting future considerations.

Severity and natural history of pulmonary abnormalities may present increased, as well as unacceptable risk for liver transplantation (LT), thus be considered contraindications to LT [1]. However, resolution of certain pulmonary disorders following LT suggests these abnormalities may be appropriate pulmonary indications for LT and should merit higher LT priority to prevent morbidity and mortality [2]. With the inception of the Model of End-Stage Liver Disease (MELD) score in 2002 to prioritize

allocation of deceased donor livers, and the recent (December 13, 2012) standardized MELD exception policy (<http://optn.transplant.hrsa.gov> policy 3.6.4.5), the importance of selected pulmonary issues has been magnified. Therefore, it is instructive to identify the spectrum of pulmonary abnormalities that pose the greatest LT risk and their potential reversibility. The current MELD exception policies (or lack thereof) concerning these pulmonary issues are addressed and future pulmonary considerations are suggested. The major pulmonary concerns that arise in liver transplant candidates discussed in this contemporary view are shown in Table 1.

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## Hepatopulmonary syndrome (HPS)

Documented in 4–32% of patients evaluated for LT, there is no proven medical therapy to cure the arterial hypoxemia that characterizes HPS [3]. A triad defines HPS:

- (1) Portal hypertension with or without cirrhosis;
- (2) Arterial hypoxemia due to;
- (3) Intrapulmonary vascular dilatations (detected by contrast echocardiography or <sup>99m</sup>Tc macroaggregated albumin lung–brain perfusion scanning).

The diagnostic criteria for arterial hypoxemia vary by transplant center and have been summarized by Schenk *et al.* [4] in Table 2. Although initially considered an absolute contraindication to LT if hypoxemia was severe (PaO<sub>2</sub> <50 mmHg), Laberge *et al.* [5] were the first to report resolution of HPS with LT (two children) in 1992 and stated that LT "... may be an actual indication for earlier transplantation even with relatively stable liver disease".

Numerous reports of HPS resolution post LT followed over the ensuing years. Despite these successes, the risk of LT remained significant (15.6% post LT hospitalization mortality in 32 HPS patients as reported from the 10-center liver transplant database) [6]. Mortality was directly related to the pre-LT severity of hypoxemia (PaO<sub>2</sub>: survivors 55 mmHg; non-survivors 37 mmHg). Subsequently, the largest single-center analysis (61 HPS patients)

**Keywords:** Hepatopulmonary syndrome; Portopulmonary hypertension; Hereditary hemorrhagic telangiectasia; Hepatic hydrothorax; Alpha-1 antitrypsin deficiency; Pulmonary nodules.

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**Abbreviations:** LT, liver transplantation; MELD, model for end stage liver disease; HPS, hepatopulmonary syndrome; POPH, portopulmonary hypertension; OPTN, Organ Procurement and Transplant Network; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; REVEAL, registry to evaluate early and long-term pulmonary artery hypertension; SRTR, scientific registry for transplant recipients; HHT, hereditary hemorrhagic telangiectasia; HVM, hepatic vascular malformations; CO, cardiac output; TPG, transpulmonary gradient; RHH, refractory hepatic hydrothorax; HH, hepatic hydrothorax; TIPS, transjugular intrahepatic portosystemic shunt; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in one second; AATD, alpha-1 antitrypsin deficiency; HCC, hepatocellular carcinoma; PET, positron emission tomography; FDG, fluorine-18 fluorodeoxyglucose; CT, computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PBC, primary biliary cirrhosis; TcMAA, technetium macroaggregated albumin; RV, right ventricle.



## Review

**Table 1. Major pulmonary concerns in liver transplant candidates.**

Hepatopulmonary Syndrome (HPS)
Portopulmonary Hypertension (POPH)
Hemorrhagic Hereditary Telangiectasia (HHT)
High output cardiac failure due to intrahepatic vascular malformations
Pulmonary arteriovenous malformations
Refractory Hepatic Hydrothorax (HH)
Advanced Chronic Obstructive Pulmonary Disease (COPD)
Smoking-related emphysema
Alpha-1 Anti-Trypsin Deficiency (AATD)-related emphysema
Pulmonary nodules
Hepatocellular carcinoma metastases
Interstitial Lung Disease (ILD)
Associated with primary biliary cirrhosis, autoimmune liver disease, hepatitis C
Concomitant idiopathic pulmonary fibrosis

**Table 2. Frequency of HPS using various definitions for arterial hypoxemia.\***

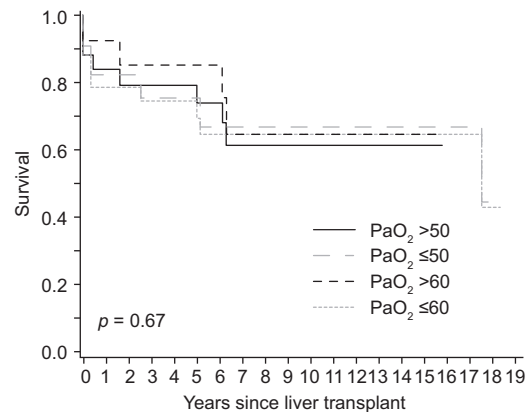
Cut-off value for hypoxemia	N centers (No. of patients screened)	HPS (%)
PaO <sub>2</sub>		
<60 mmHg	1 (98)	12
<70 mmHg	6 (277)	5-18
<80 mmHg	2 (135)	8-19
Alveolar-arterial oxygen gradient		
>15 mmHg	3 (179)	19-32
>age threshold*	8 (356)	4-26

\*Value calculation includes arterial PCO<sub>2</sub> and is adjusted upwards (normal >20 mmHg if age >64 years).

Modified from Schenk *et al.* [4].

documented poor prognosis (5-year survival) in those not transplanted (n = 24; 23%) vs. those transplanted (n = 37; 76%) [7]. No correlation was noted between HPS severity and the degree of hepatic dysfunction (by Child class or MELD score).

Discordance between liver disease severity and degree of hypoxemia, combined with resolution of hypoxemia after LT, resulted in HPS to be considered a standard indication for LT. With the adoption of the MELD allocation system in 2002, patients with HPS were often granted and assigned a priority score which typically allowed them to receive a MELD score exception, though this was done at the level of each individual Organ Procurement and Transplantation Network (OPTN) Regional Review Board. However, HPS diagnostic criteria were not standardized, fostering regional variation in scores, and the need for further discussion [8–10]. To reduce this tremendous variability, MELD exception policy was subsequently formalized (via the MELD exception Study Group Conference in 2006) and revised so that uniform assigned MELD score exception of 22 would be granted across all regions if PaO<sub>2</sub> was less than 60 mmHg (arterial blood gas measured breathing room air, at rest and in the sitting position) [10]. Those patients would have clinical evidence of portal hypertension, demonstrated intrapulmonary vascular dilatation in the absence of underlying primary lung disease that



**Fig. 1. Long-term outcome following liver transplantation in patients with hepatopulmonary syndrome based upon their baseline PaO<sub>2</sub> at the time of diagnosis pre-transplant.** No difference was observed between the PaO<sub>2</sub> cut-offs. Adapted from [12], reprinted with permission.

might account for hypoxemia. Currently, a standard MELD score increase, which is a 10% wait list mortality equivalent, is granted every 3 months if the repeat PaO<sub>2</sub> remains less than 60 mmHg.

Recent HPS reports by Gupta *et al.* [11] (n = 21; no MELD exception) and Iyer *et al.* [12] (n = 28; 21 granted MELD exception) have now clearly demonstrated that LT candidates with severe hypoxemia (PaO<sub>2</sub> <50 mmHg) have minimal waitlist mortality, benefit from improved ICU care, and experience HPS resolution with long-term post LT survival. Eleven of 21 HPS patients in the Gupta report had PaO<sub>2</sub> <50 mmHg and 10 had survived 55–1078 days (median 548) post LT. Iyer noted a 76% 5-year post LT survival in 19/49 HPS patients with baseline PaO<sub>2</sub> <50 mmHg (Fig. 1). Importantly, there have been no reports of intraoperative death due directly to the severity of HPS. There is consensus that the more severe the pre-LT arterial hypoxemia, the longer the post LT recovery in terms of resolving hypoxemia, potential morbidity, and prolonged need for supplemental oxygen [3,13].

Clinical experience has resulted in the expectation that arterial oxygenation due to HPS will normalize following LT, hence the “indication” for LT. OPTN policy states that HPS patients meeting specified criteria receive a standard MELD exception every three months until time of transplant, as long as the patient continues to meet criteria. The decision not to offer LT for those with moderate to severe hypoxemia remains a local transplant center determination based upon co-morbidities and expertise available to manage post LT issues. Living donor LT in the setting of HPS allows flexibility in transplant timing and has been successful in resolving the syndrome. Living donor LT eliminates the need for MELD exception considerations [14].

### Future considerations

With successful LT, severe hypoxemia due to HPS *can* resolve. Current MELD exception guidelines state that no other pulmonary abnormality should co-exist as a reason for hypoxemia. This may be impractical and exclude HPS patients (noting up to 30% may be excluded due some degree of COPD) that would otherwise do well in the long term. Identifying the contribution to hypoxemia from HPS vs. hypoxemia due to COPD, ILD or HH can be accomplished using <sup>99m</sup>TcMAA lung-brain scanning. Individuals with mild to moderate non-HPS pulmonary dysfunction

(with expected 5-year survival >75% associated with those entities) would not be excluded from LT and attain long-term overall survival.

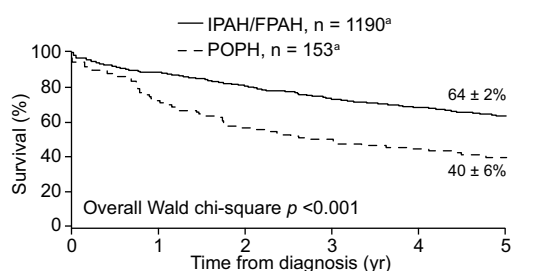
### Portopulmonary hypertension (POPH)

Documented in 4.5–8.5% of liver transplant candidates, the diagnosis of POPH is based upon right heart catheterization [15]:

1. Mean pulmonary artery pressure – MPAP >25 mmHg;
2. Pulmonary capillary wedge pressure – PCWP <15 mmHg;
3. Pulmonary vascular resistance – PVR >240 dynes  $\text{s cm}^{-5}$  (or 3 Wood units).

Not uncommon, POPH comprises up to 10% of all patients referred to the French National Center for pulmonary artery hypertension with outcomes related to the severity of cirrhosis and cardiac function [16]. The controlled trials in idiopathic pulmonary artery hypertension targeting pathways of prostacyclin deficiency, endothelin receptor blockade, and phosphodiesterase inhibition have documented significant success in improving pulmonary hemodynamics (all pathways) and survival (prostacyclin pathway). Using similar approaches in POPH (pathway drugs used alone or in combination during uncontrolled trials), the 5-year POPH survival ( $n = 153$ ) was reported to be 40% from the multicenter REVEAL registry, despite having better hemodynamics than the idiopathic pulmonary artery hypertension subgroup [17] (Fig. 2). Survival in the French study ( $n = 154$ ) was 68% at 5 years and may have reflected a lack of discerning severity and type of hepatic disorders in the REVEAL registry. Without pulmonary vasoactive medications or LT, a single-center 5-year POPH survival has been reported to be 14% [18].

Resolution of severe POPH following LT was first reported by Yoshida *et al.* [19] in 1993 who utilized intravenous prostacyclin pre-LT (MPAP = 45 → 33 mmHg), intraoperatively, and for 3 days post LT. At 22 months post LT, the MPAP as 22 mmHg, prostacyclin discontinued and the authors stated: “Our success . . . suggests that a significant reversible component exists in some cases of portopulmonary hypertension”.



Patients at risk:						
IPAH/FPAH	419	485	527	472	393	311
POPH	56	63	59	55	43	27

**Fig. 2. Five-year survival in patients with portopulmonary hypertension compared to those with idiopathic pulmonary artery hypertension.** Uncontrolled treatments in both groups. None with POPH underwent liver transplant. <sup>a</sup>Only patients enrolled within 5 years of diagnosis were included in the 5-year survival from diagnosis curve. Adapted from [16], reprinted with permission.

Unlike HPS, the outcomes of LT in the setting of POPH have been unpredictable. Intraoperative death due to acute right heart failure has occurred. The multicenter HPS and POPH database ( $n = 36$  POPH patients transplanted) reported pre-LT mean pulmonary artery pressure (MPAP) >35 mmHg and pulmonary vascular resistance (PVR >250 dynes  $\text{s cm}^{-5}$ ) was associated with a 36% mortality (5 intraoperative; 8 transplant hospitalization), all occurring within 18 days of transplant [6]. Subsequent case reports and small series have documented resolution of POPH or improvement with LT if pre-LT therapy with pulmonary vasoactive medications could reduce MPAP to less than 35 mmHg [15,20,21].

Due to the success of LT to resolve POPH, when pre-LT treatments improved pulmonary hemodynamics and hope to reduce pre-LT mortality, MELD exception was allowed for some POPH patients by regional review boards beginning in 2002. A general summary from the Scientific Registry of Transplant Recipients (SRTR) identified outcomes in 155 patients granted POPH MELD exception (2002–2012), but no specific data were available to characterize the severity of POPH or pre-LT pulmonary hemodynamic treatment results. Waitlist death rate was 7.8%; 1 and 3-year survivals were 83% and 76%, respectively (T Leighton, SRTR, personal communication).

Pulmonary hemodynamic criteria for MELD exception were suggested in 2006 and formal criteria established in 2010 to attain review board uniformity in granting standard MELD exception [22]. Currently, if MPAP can be improved to <35 mmHg and PVR reduced to <400 dynes  $\text{s cm}^{-5}$ , then MELD exception is granted, increasing by 10% every three months if repeat RHC demonstrates sustained hemodynamic improvement.

Unlike HPS, the concept of POPH being an “indication for LT” remains controversial due to the variable outcomes of POPH following LT. Limited, but well-documented experience suggests some patients are “cured” of the POPH (normalization of pulmonary hemodynamics) after LT and pulmonary vasoactive medications can be safely discontinued [15,20,21]. Improving pulmonary hemodynamics, to the point of allowing LT, is significant in that approximately 50% of patients with POPH succumb to their hepatic disease (as opposed to right heart failure) if not transplanted [15]. Other POPH patients can successfully complete LT with pulmonary vasoactive medications, but cannot be weaned due to continued abnormal pulmonary hemodynamics. Pre-LT inability to reduce MPAP to less than 35 mmHg with pulmonary vasoactive therapy disqualifies patients for standard MELD exception. Failure to reduce MPAP below 50 mmHg is considered by most centers to be a contraindication to LT or, at the time of operation, grounds to cancel the LT procedure prior to the abdominal incision. Although experience is limited, at this time it seems logical that similar pulmonary hemodynamic guidelines should be followed when living-donor-POPH transplants are considered [23,24].

### Future considerations

With a combination of liver transplantation and pulmonary vasoactive medications, moderate to severe pulmonary artery hypertension is curable in some cases. However, two POPH issues have evolved. First, the MELD exception is not granted under current U.S. policy, even if there is normalization of PVR and right ventricular (RV) function with pre-LT therapy if MPAP remains >35 mmHg. The elevation in MPAP in such patients is a change

## Review

**Table 3. Distinguishing pulmonary hemodynamic patterns.\***

Clinical situation	RVSP	MPAP	PCWP	CO	PVR
Portal hypertension	↑	↑	n	↑	n↓
HPS	n↑	n↑	n	↑	n↓
POPH	↑↑↑	↑↑↑	n↑	↑↓	↑↑↑
HHT (+ hepatic AVM)	↑	↑	n↑	↑↑	n↓
HHT (PAH)	↑↑↑	↑↑↑	n	n↓	↑↑↑
HHT (PAVM)	↑	↑	n	↑	n↓

\*Measurements by right heart catheterization.

PAH, pulmonary artery hypertension; PAVM, pulmonary arteriovenous malformations; n, normal; RVSP, right ventricular systolic pressure by transthoracic echocardiography; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance.

in physiology, the result of pulmonary vasoactive therapy increasing the existing high flow state, and decreasing the pulmonary vascular resistance to flow. Normalization of RV function and PVR is an ultimate, desired goal in treating any form of pulmonary artery hypertension and MELD exception would be granted despite the “abnormal MPAP”. It is hypothesized that for those individuals, cure of POPH after LT can be obtained. However, it does remain unknown whether pulmonary hemodynamic normalization post LT reflects a pathologic pulmonary vascular cure.

Second, with the adoption of the standard MELD exception for POPH, those with exception for this diagnosis can now be tracked in terms of general survival though details regarding specific therapies will not be known. Therefore, the clinical/optimal outcome correlates of POPH post LT long-term survival need to be identified via registry or a multicenter database approach. For example, assessment of acute pulmonary vascular reactivity (by different agents) and effect on PCWP pre-LT (unmasking cardiomyopathy?) may suggest the need for specific pulmonary vasoactive medications [25].

### Hereditary hemorrhagic telangiectasia (HHT)

Although a spectrum of hepatic vascular malformations (HVM) exists in approximately 32–78% of HHT patients, less than 10% are symptomatic [26]. Liver transplantation has been conducted as a means to treat HHT-induced related HVM. These lesions can result in ischemic biliary necrosis, intractable portal hypertension and high output cardiac failure due to increased preload that occurs as a consequence of intrahepatic arteriovenous and arteriportal shunting [26].

Screening transthoracic echocardiography in any patient with HHT may suggest pulmonary hypertension (i.e., right ventricular enlargement and increased tricuspid regurgitant peak velocity). It is important to correctly identify HHT-induced HVM causing increased pulmonary artery pressures which invariably accompanies (and likely predisposes) to high output cardiac failure. Imaging of the liver (Doppler ultrasound or CT scanning) and right heart catheterization are essential in the identification process. Specific pulmonary hemodynamic patterns with normal or reduced PVR would be consistent with that scenario (Table 3). Pulmonary vasoactive medications would not be indicated; LT would be curative of high output cardiac failure based upon experience to date. As a caveat, Trembath *et al.* [27] and Abdalla

*et al.* [28] have described (genetics, hemodynamics and pathology) a form of pulmonary artery hypertension in HHT characterized by very high PVR, similar to what was previously known as primary pulmonary hypertension. Right heart catheterization is key in identifying such patients, noting that HVM were documented in some patients in both series. The role for LT in that entity is unknown and pulmonary vasoactive therapy would seem appropriate.

The co-existence of pulmonary and hepatic AVM does occur, can occur in the setting of high output cardiac failure, but appears to be uncommon (Fig. 3). Unlike successful treatment of pulmonary AVM with coil embolotherapy to treat hypoxemia and prevent paradoxical emboli, embolization of intrahepatic vascular abnormalities is not advised, leading to ischemic biliary necrosis and the need for urgent LT [26]. A recent French HHT experience using the vascular endothelial growth factor inhibitor bevacizumab (biweekly injections for 2.5 months) to ameliorate the high output state due to HVM has been favorable [29]. Six months from the initiation of therapy, mean cardiac index improved (lessened) in 20/24 patients, mean systolic pulmonary pressure decreased (PVR not measured) and a significant reduction in the severity of epistaxis was documented. Subsequent need or outcome of LT was not reported.

The published outcomes of LT in the setting of high output cardiac failures due to HHT-induced HVM are favorable [30]. From the European Liver Transplant Registry, cardiac function improved in 18 (75%) of 24 HHT patients transplanted for such cardiac failure [31]. Dupuis-Girod *et al.* [32] reported 10 HHT patients in a single-center study, transplanted for high output cardiac failure with normalization of hemodynamics (by echo and/or right heart catheterization and significant improvement in epistaxis). In these studies, the 5-year patient survival ranged from 82.5% to 92%. Recurrence of HVM in two patients several years after LT has been reported [33].

There are no formal MELD exception criteria for any pulmonary manifestation of HHT due to the rarity of this condition, but currently, centers may request from their respective RRB, a MELD exception score of 22 to treat high output cardiac failure as per the recommendation of the MELD exception Study Group [34]. Pulmonary hemodynamic patterns that distinguish and characterize HPS, POPH, and HHT patterns are summarized in Table 3.

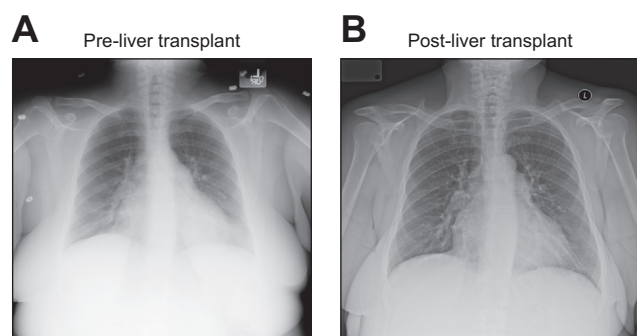
### Future considerations

Pulmonary hypertension-right heart failure due to HHT can be safely accomplished and heart failure reversed. The development of high-output cardiac failure due to hepatic AVM is life-threatening; the relationship between life threatening epistaxis and hepatic involvement in HHT is unknown. The improvement in epistaxis post LT for high output failure now has been documented. The risk/benefit of LT in preventing deadly hemorrhagic complications of HHT warrants further consideration.

### Refractory hepatic hydrothorax (HH)

Occurring in approximately 5–12% of those with advanced liver disease, HH (>500 pleural fluid) is due to the formation of ascitic fluid that is drawn into the hemithorax due to pressure gradient that occurs with inspiration and microscopic passages through the hemidiaphragm [35].





**Fig. 3. Pre and post-transplant CXR in HHT patient with high-output cardiac failure.** (A) Pre-transplant embolization of pulmonary arteriovenous malformation in the left lower lobe was observed. (B) At 24 months post liver transplant, pulmonary venous hypertension and cardiac failure resolved, but cardiomegaly was still present.

Treatment of HH is based upon minimizing ascitic fluid production with salt restriction and diuresis usually accomplished with a combination of furosemide and spironolactone. Failure to control symptomatic HH with sodium restriction (<2 g/day), tolerable amounts of diuretic (160 mg/day furosemide and 400 mg/day spironolactone, or repeated thoracentesis), defines the concept of refractory hepatic hydrothorax (RHH) [35].

Transjugular intrahepatic portosystemic shunting (TIPS) can result in complete, partial or no resolution of RHH. Complications, survival after TIPS, and expectations for subsequent LT are factors to be considered when the decision is made to treat RHH. Dhanasekaran *et al.* [36] reported 73 patients who had undergone TIPS for RHH with varying clinical response at 1 month post-TIPS: complete (59%), partial (21%) and none (21%). Transplant frequency and outcomes were not reported. The 1 and 5-year survivals post-TIPS were 48% and 15%, respectively. Increased pre-TIPS creatinine and MELD >15 had worse survival. Jeffries *et al.* [37] reported 4/12 TIPS patients with RHH who underwent LT. Each required some form of post LT pleural drainage and 3 had favorable long-term post LT outcome (minimal to no pleural effusion at 2 years). One had recurrent ascites and pleural effusion persisting for 3 years post LT.

The outcome of HH (refractory or not) following LT is very favorable. Xiol *et al.* [38] reported 28 HH patients (no definition of fluid amount given) vs. 56 transplanted controls. Five patients were considered refractory; no patient received TIPS or had chest tube drainage. HH persisted in 36% of patients at one month post LT, but had resolved in all patients within 3 months of transplant. Serste *et al.* [39] described no outcome differences in HH (estimated pleural fluid >500 cc by chest radiograph) compared to those with tense ascites and no HH (both groups had  $n = 11$ ). Nine patients were considered to have RHH pre-LT; 73% required pre-LT thoracentesis (55% needed repeat taps) and none had TIPS placed pre-LT.

Pulmonary hypertension is considered a contraindication to TIPS. This concern is based upon increased preload/cardiac output acutely following TIPS that could worsen pre-existing right ventricular dysfunction. However, there are no studies that define at what echo pressures or degree of right ventricular dysfunction may portend hemodynamic collapse following TIPS placement. At our institution, transthoracic echocardiography demonstrating RV systolic pressure >50 mmHg and/or moderate

to severe dilation of the RV would be a contraindication to non-emergent TIPS.

There are no data to suggest an increased mortality on the LT waitlist in the setting of RHH or poor LT outcomes; therefore MELD exception for this entity (regardless of the use or not of TIPS) is not the current OPTN policy.

#### Future considerations

Distinguishing RHH-LT outcomes by the presence or absence of concomitant arterial hypoxemia might be an area of clinical investigation that could impact LT priority.

#### Advanced chronic obstructive pulmonary disease (COPD)

In the largest prospective study to date, smoking history in LT candidates (373 patients at 7 LT centers) was common (~60%) with 27% considered current smokers [40]. Clinically significant COPD ( $FEV_1/FVC < 70\%$  due to bronchitis and/or centrilobular, upper lobe predominance emphysema) was uncommon (67/363; 18%). A previous diagnosis of COPD prior to LT evaluation did not exist in 80% of those patients. Of those listed for LT with pulmonary function testing (204/373), severe COPD (30%  $< FEV_1$  predicted <50%) occurred in 11%. No patient had  $FEV_1 < 30\%$ . LT was conducted in 30% of those listed. Risk of death and outcomes (median follow-up 601 days post LT) were not affected by the existence or severity of COPD [40]. However, no data were presented to describe duration of intubation/mechanical ventilation, length of hospital stay or other morbidities, so post LT morbidities associated with severe COPD remain speculative.

There are no data to justify granting MELD exception for smoking-related COPD, since it is not caused by liver disease or resolved by LT. There are no specific guidelines as to which COPD patients are too advanced to preclude safe LT. Published 5-year survivals for patients, liver disease notwithstanding, with severe COPD ( $FEV_1 < 50\%$  predicted) range from 50–70%, worse (24–30%) in those with  $FEV_1 < 30\%$  predicted and much worse when COPD exacerbation requires non-invasive ventilation (mean  $FEV_1$  37% predicted with 2 and 5-year survivals 52% and 26%, respectively [41,42].

Alpha-1 antitrypsin deficiency (AATD), especially the ZZ genotype, can result in significant pathophysiology due to accumulation/polymerization/abnormal metabolism of the dysfunctional alpha-1 protein in hepatocytes [43]. Unexpected significant liver disease in ZZ-lung patients ( $n = 57$ ; 24 with liver biopsies; 11 had severe fibrosis or cirrhosis) has recently been described [44]. Such accumulation results in circulating serum deficiency, leading to AATD-related emphysema (panlobular, lower lobe predominance), since neutrophil elastase is no longer neutralized and destroys alveolar supporting structures [44]. ZZ patients without clinically obvious hepatic dysfunction can have an accelerated annual decline in  $FEV_1$  and increased mortality compared to controls [43]. In ZZ or SZ LT candidates, the true frequency and degree of abnormal  $FEV_1$  predicted (the most common pulmonary function parameter followed in such patients) are speculative since pre-LT pulmonary function tests are not often accomplished, yet may be surprisingly abnormal [45].

Jain *et al.* [46] reported the effect of LT on pulmonary function ( $n = 7$ ) and 3/7 were considered to be severely deficient pre LT (no alpha-1 genotypes given). The pre LT  $FEV_1$  predicted was

## Review

abnormal in 2 out of three patients (51% and 63%) and had not changed at only 12 and 8 months post LT, respectively. Carey *et al.* [45] have reported longer follow-up in 33 ZZ and 17 SZ LT patients, describing pre-LT FEV<sub>1</sub> in 11/50, with 7/11 experiencing decline in FEV<sub>1</sub> (median of 14%; range 5–29%) at a median of 34 months (range 13–126) post LT. Kemmer *et al.* [47] described 1, 3, and 5 year survivals post LT of 89%, 85%, and 83% for adults (n = 406) from the UNOS database (1995–2004), but it was unclear if data were restricted to ZZ or included MZ and other alpha-1 phenotypes, an important distinction. It is expected and noted that the hepatic allograft (with a normal alpha-1 genotype) will result in normalization of the circulating alpha-1 protein level [45,46]. The long-term pulmonary changes following LT, especially in the pediatric age group, are unknown [48].

For similar reasons stated regarding other causes of COPD in terms of resolution post LT, MELD exception for AATD-related emphysema is not recommended at this time. However, since ZZ and SZ liver disease can directly affect lung function change, additional considerations are suggested below.

### Future considerations

The severe deficiency of circulating AAT protein can resolve, but not necessarily stabilize lung function. Consistent assessment of pulmonary function pre and post LT is needed. In adults and children, an untested hypothesis is whether LT can halt or slow the accelerated lung function decline that exists in ZZ and/or SZ patients. Could progressive pulmonary decline be an indication for earlier LT in adults with severe AAT deficiency? Could LT obviate the need for life-long AAT replacement therapy to prevent further lung injury (weekly or biweekly pooled plasma protein infusions) that now approaches \$100,000 per year?

### Pulmonary nodules

The detection of new pulmonary nodules (solitary or multiple) complicates the decision to proceed to LT in the setting of hepatocellular carcinoma (HCC) [49]. Metastatic pulmonary lesions, biopsy proven, would be a contraindication to LT. Biopsy of suspicious lesions must be obtained since computed tomography (CT) and positron emission tomography-fluorodeoxyglucose (PET-FDG) scanning can lead to images strongly suggestive of malignancy, yet biopsy results may document treatable granulomatous infections such *Cryptococcus*, *Mycobacterium tuberculosis* or *Mycobacterium avium* complex [49,50]. The importance of FDG PET/CT scanning in the setting of HCC does facilitate the identification of multiple lesions, as well as provide a road map for possible endobronchial ultrasound guidance for lymph node needle aspirations. A recent meta-analysis of 239 cases from 3 studies reported a 77% sensitivity and 98% specificity in identifying pulmonary metastases in the presence of newly diagnosed HCC [51].

Multidetector CT scanning remains more sensitive than FDG PET/CT scanning to identify and follow nodules that are less than 8–10 mm [52]. Small nodules (<10 mm) should be followed post LT, especially in the setting of high grade HCC and those tumors exceeding Milan criteria [53]. Despite the best pre-LT efforts to detect pulmonary metastases, if such do arise post LT, surgical excision can be undertaken with resultant long-term survival. Hwang *et al.* [54] reported a 44.7% 5-year post LT, post resection survival in 23 HCC patients.

The occurrence of operable, early lung cancer in the setting of cirrhosis is uncommon (33/876–3.9% in the most recent surgical series), and offers yet another reason to specifically identify the correct etiology of a new pulmonary nodule associated with current or past smoking history [55].

### Future considerations

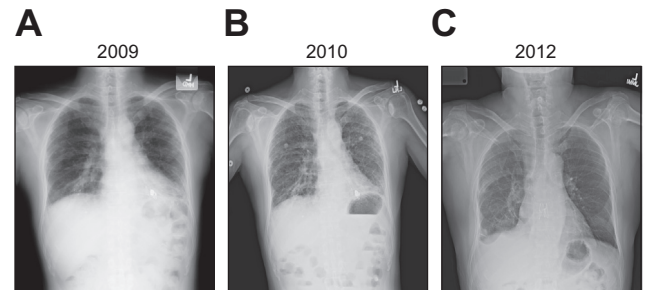
Lung resection for metastatic hepatocellular carcinoma post LT is achievable with acceptable long-term survival and should be considered in highly selected cases.

### Interstitial lung disease (ILD)

Rarely, idiopathic pulmonary fibrosis (IPF) or non-specific interstitial lung disease (ILD) may complicate primary biliary cirrhosis, autoimmune hepatitis or hepatitis C [56]. These entities result in reduced total lung capacity (TLC <80% predicted), reduced FVC and normal expiratory airflow (FEV<sub>1</sub>/FVC >70%). They may contribute to arterial hypoxemia and co-exist with HPS [57]. Herein lies the value of attaining <sup>99m</sup>TcMAA lung-brain perfusion scanning to discern the actual cause of hypoxemia; the brain uptake in any ILD should be normal (<6%) since abnormal ventilation in the setting of normal perfusion is the primary cause of hypoxemia.

With the possible exception of lymphocytic interstitial pneumonitis associated with PBC, ILD is not expected to reverse following LT and may progress despite the use of immunosuppression. Successful single lung transplantation has been accomplished in a patient with severe HPS and mild IPF in which the former resolved and the latter progressed following LT (Fig. 4).

Despite the common occurrence of restrictive lung physiology in advanced liver diseases (usually due to HH or ascites), biopsy proven ILD as a cause of restriction appears uncommon. The reversibility of ILD, especially IPF, is rarely observed and lung transplant is the current treatment of choice. Moderate to severe restriction due to IPF can be considered a contraindication to LT. In the case of IPF, the median survival is 2–4 years and 5-year survival ranges from 20% to 40% without lung transplant [58]. There are no current data to support ILD-related MELD exception when any degree or form of ILD complicates advanced liver disease.



**Fig. 4.** Resolution of severe HPS (standing PaO<sub>2</sub> mmHg: 46 on room air, 106 on 100% inspired oxygen) with liver transplant; followed by progression idiopathic pulmonary fibrosis and subsequent lung single transplant. (A) Pre-liver transplant cxr; (B) 14 month post-liver transplant cxr showing IPF progression (PaO<sub>2</sub>); (C) 20 month post-lung transplant cxr.

**Table 4. Pulmonary contraindications, indications and MELD exception for liver transplant.**

	Contraindication	Indication	Current MELD exception policy (3.6.4.5)
HPS	No; unless co-morbidities	Yes	Yes; PaO <sub>2</sub> <60 mmHg; COPD excluded
POPH	MPAP >50 mmHg*	Yes (?)	Yes; MPAP <35 mmHg and PVR <400 dynes.s.cm <sup>-6</sup>
HHT	If PAH untreated	HAVM	Can petition RRB due to high output failure; no policy
HH (refractory)	No	No supportive data	No policy
COPD	If severe (?); current smokers	No supportive data	No policy (AATD should be studied)
Nodules	If metastatic HCC	No supportive data	MELD exception currently exists for HCC
ILD	If severe	No supportive data	No data to suggest ILD can reverse or be stabilized with LT

HPS, hepatopulmonary syndrome; POPH, portopulmonary hypertension; HHT, hereditary hemorrhagic telangiectasia; HCC, hepatocellular carcinoma; HH, hepatic hydrothorax; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung diseases; PAH, pulmonary artery hypertension.

\*MPAP, mean pulmonary artery hypertension (criteria with or without pulmonary vasoactive therapy); PVR, pulmonary vascular resistance.

HAVM, hepatic arteriovenous malformations; RRB, regional review boards.

### Future considerations

The clinical course of ILD, especially IPF, following LT, warrants further studies. In highly selected cases, sequential liver-then-lung transplant can be successfully accomplished in the setting of progressive IPF post LT.

### Key Points

- Hepatopulmonary syndrome is an indication for liver transplant; severe hypoxemia is reversible post-transplant with support and time
- Severe portopulmonary hypertension is a contraindication to transplant, yet potentially “curable” if medical treatment can significantly improve pulmonary hemodynamics and right heart function pre-transplant
- Hereditary hemorrhagic telangiectasia-related high output heart failure due to intrahepatic arteriovenous malformations can resolve post-transplant
- Refractory hepatic hydrothorax does not impact post-transplant outcome and has yet to merit higher priority for transplant
- Whether development or progression of pulmonary emphysema due to  $\alpha$ -1 antitrypsin deficiency (ZZ or SZ genotypes) may be halted by liver transplant is a valid research question

### Conclusions

Pulmonary priorities for LT, as defined by MELD exception policies, have been evolving over the years and the current policies are summarized in Table 4. Future implications regarding each of these pulmonary-liver transplant issues can be expected to further evolve. To facilitate our understanding of clinical pulmonary-liver transplant advances, the expanded roles of registries and multicenter databases cannot be understated. From such collective experiences, we can hopefully refine and better characterize the current pulmonary contraindications, as well as possibly expand indications for LT.

### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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