Special Considerations for LT Candidates Combined with Serious Non-Hepatic Organ Dysfunction

# LT for patients with moderate to severe portopulmonary hypertension: what is contraindication

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Portopulmonary hypertension (PoPH) is defined as the coexistence of pulmonary arterial hypertension (PAH) and portal hypertension, with or without liver disease, where no other cause of PAH has been identified. Exclusion of secondary causes of PAH is a prerequisite for the diagnosis to be made [1]. It may therefore be defined by a resting mean pulmonary artery pressure (mPAP) >25 mmHg; a pulmonary capillary wedge pressure <15 mmHg; and a pulmonary vascular resistance >240 dynes/s/cm$^{-5}$ [2].

PoPH is a relatively rare condition. Although most commonly observed in patients with end-stage liver disease, PoPH has also been identified in the context of non-cirrhotic portal hypertension. An autopsy study showed that less than 1% of patients with liver cirrhosis had PoPH [3]. Prospective studies estimate the prevalence at 2-6% [4-6].

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 [7]. The severity of POPH is based on mean pulmonary artery (PA) pressures (in the setting of increased pulmonary vascular resistance (PVR)) determined via right heart catheterization (RHC) data at rest. Based on the European Respiratory Society (ERS) Task Force, it is graded as mild (25 ≤ mPAP < 35 mm Hg), moderate (35 ≤ mPAP < 45 mm Hg), and severe (mPAP ≥ 45 mm Hg) [1].

Since PoPH may be asymptomatic at presentation or only accompanied by non-specific symptoms, patients with portal hypertension undergoing pre-LT evaluation as well as those who develop dyspnea suspected of having PoPH require a thorough cardiopulmonary evaluation. Trans-thoracic

Echocardiography (TTE) is regarded as the most practical screening tool in evaluating patients for the presence of PoPH. It is important to recognize, however, that pulmonary artery systolic pressure (PASP) estimation by echocardiography is an inexact science, as it is highly operator-dependent and may underestimate pulmonary pressures in the context of impaired right ventricular function. Suspected PoPH is confirmed in patients who meet diagnostic criteria at RHC. All patients with TTE findings suggestive of pulmonary hypertension must undergo a hemodynamic assessment by RHC, which is required for the definitive diagnosis of PoPH.

Without liver transplantation and medical therapy, cirrhotic patients with PoPHT have very poor prognosis. Before the availability of PAH-specific therapies, the survival of patients with PoPHT is very poor. Old data from the Multicenter Liver Transplant Database demonstrated a mortality rate of 36% in patients with PoPHT undergoing liver Transplantation (LT) [8]. PoPH is a subtype of the broader group of conditions causing PAH, which share pathophysiology and have been treated in similar ways. Prostacyclin analogues, phosphodiesterase inhibitor subtype 5 inhibitors, and endothelin receptor antagonists are commonly used drugs for PoPH treatment. With PAH-specific therapies, recent post-LT survival data for POPH MELD exception patients have been reported since 2002. Waitlist mortality ranged from 7.0% to 10.3%; 1- and 3-year post-LT survivals ranging from 86.4% to 64.0% [9-11].

POPH with mPAP of 35 to 50 mm Hg or greater poses higher risk for LT, longer post-LT ventilation and length of hospital stay [11]. Regardless of therapy, mPAP greater than 50 mm Hg (≥45 mm Hg in some centers) remains an absolute contraindication to LT in most centers. Rarely, patients with mPAP greater than 50 mm Hg can survive LT without pulmonary targeted therapy, as long as cardiac index is preserved [2, 7, 11].

No controlled, prospective trials have addressed long-term, post-LT outcomes in the setting of POPH. It is necessary to develop prognostic risk scores for HPS and POPH based on multiple peri-operative factors including hepatic dysfunction severity, coexistent lung conditions, oxygenation, and hemodynamics in the future.

References

[1] Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB, Committee ERSTFP-HVDS. Pulmonary-Hepatic vascular Disorders (PHD). Eur Respir J 2004;24:861-880.

[2] Houlihan DD, Holt A, Elliot C, Ferguson JW. Review article: liver transplantation for the pulmonary disorders of portal hypertension. Aliment Pharmacol Ther 2013;37:183-194.

[3] McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis 1983;127:437-441.

[4] Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100:520-528.

[5] Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology 2003;37:401-409.

[6] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023-1030.

[7] Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, et al. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. Transplantation 2016;100:1440-1452.

[8] Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. Liver Transpl 2004;10:174-182.

[9] DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, Salgia RJ, et al. Predictors of Waitlist Mortality in Portopulmonary Hypertension. Transplantation 2017.

[10] Goldberg DS, Batra S, Sahay S, Kawut SM, Fallon MB. MELD exceptions for portopulmonary hypertension: current policy and future implementation. Am J Transplant 2014;14:2081-2087.

[11] Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol 2013;59:367-374.