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MELD exception for liver transplantation in portopulmonary hypertension: current implementation and future considerations

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Portopulmonary hypertension (PoPH) is a serious lung vascular complication of portal hypertension. Current definition criteria for PoPH include the following:

- Presence of portal hypertension with or without cirrhosis.
- Presence of pulmonary arterial hypertension (PAH) diagnosed by right heart catheterization (RHC); and absence of an alternative cause for PAH. Hemodynamic criteria for PAH, as based on RHC, must include a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, and pulmonary vascular resistance (PVR) > 240 dynes/sec/cm^{-5} [PVR = mPAP - PAOP/cardiac output (CO) x 80] or > 3 Wood units (Wood units= mPAP – PAOP/CO).[1,2] Ideally, pulmonary arterial occlusion pressure (PAOP) should be ≤ 15 mmHg, and whenever this criterion is not met, the transpulmonary gradient (TPG) must be > 12 mmHg, reflecting the presence of true PAH in association with venous hypertension.

Although PoPH is not a common condition, it is identified in 6-9% of patients evaluated for liver transplantation (LT).[2] In the recent United States (US) REVEAL (Registry to EValuate Early And Long-term pulmonary arterial hypertension) study, analyzing more than 3,500 patients with diverse forms of pulmonary vascular disease, 5% were reported to have PoPH.[3] Prognostication of LT outcomes in the setting of PoPH is flawed with uncertainty given the paucity of prospective data, variations in screening protocols, and small number of patients included in most reported series. However, moderate to severe PoPH confers high morbidity and mortality, particularly from right ventricular (RV) failure in the perioperative LT period.[1,2] The time of liver reperfusion is particularly crucial during the LT as it represents a critical time when preload increases, cytokines are released, and/or thrombi migrate into the pulmonary vasculature, therefore abruptly increasing the chances of intraoperative death from acute RV failure. Carefully selected patients with milder forms of PoPH (mPAP 25 to 35 mmHg) can be safely managed through the acute peri-LT period, with excellent long-term outcomes, with 1-year and 5-year post LT survival of 91 and 67%, respectively.[3,4] In contrast it has been shown that mPAP > 35 mmHg and/or PVR > 400 dynes/sec/cm^{-5} are associated with peri-LT mortality of 50%, and more severe PoPH, with a mPAP > 45 mmHg, is considered an absolute contraindication for LT, with reported mortality > 65% in relation to fulminant RV failure.[1]

The impact of PAH-specific therapies in achieving improvement in the post-LT outcomes is still evolving, although these have been proven to be useful in safely bridging patients towards LT in selected cases. Contemporary LT outcomes in PoPH with the advent of PAH-specific therapies, increased awareness, earlier detection, and better risk assessment are encouraging.

Unlike hepatopulmonary syndrome, the effect of LT on PoPH is unpredictable and PoPH itself is not an indication for LT. Nonetheless, a few series have reported resolution of PoPH post-LT. Given the higher waiting list mortality observed in patients with PoPH, LT programs in the US can request higher priority (MELD exception points) for liver al-

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location to selected PoPH cases exhibiting a favorable cardiopulmonary hemodynamic profile.[5] Since 2006, the United Network for Organ Sharing (UNOS) has accepted the following treatment goals as adequate for MELD exception in the US:

a) Moderate to severe PoPH diagnosis by RHC:

- mPAP ≥ 35 mmHg, and
- PVR > 240 dynes/sec/cm^{-5}

b) Improvement with PAH-specific therapies by:

- mPAP < 35 mmHg, and
- PVR < 400 dynes/sec/cm^{-5} (< 5 Wood units) regardless of mPAP, and
- Satisfactory RV function (center-specific testing)

c) MELD exception updated (additional 10% MELD points) every three months.

Importantly, there are no proposed criteria to define "satisfactory RV function", even though from a global perspective, this is one of the most relevant endpoints in PoPH treatment. Another flaw of current policy is that MELD exception is generally not granted under current UNOS policy if the mPAP remains > 35 mmHg despite normalization of PVR and RV function with pre-LT therapies. In such patients, the elevation in mPAP is no longer derived from true PAH, but is the result of vasoactive therapies increasing the existing high flow state while decreasing the PVR. It is hypothesized that these individuals would have a favorable prognosis after LT, and therefore should not be excluded from LT.

Current evidence has not allowed defining the subgroup of patients that will experience reversal of PoPH after LT, and in whom vasoactive therapy can be safely stopped. Thus, periodic RHC should be considered to allow adjustment of PAH-specific therapies aiming to identify patients who may be weaned off these medications.

Recently, Goldberg, *et al.*[6] evaluated the current PoPH MELD exception policy and its implementation by analyzing data from the Organ Procurement and Transplantation Network (OPTN)/UNOS between 2006 and 2012. Interestingly, out of 155 LT waitlist candidates approved for PoPH MELD exception points, 55 (36%) did not have consistent hemodynamic criteria to establish the diagnosis of PoPH, or had a fluid overload/overflow state, and among the 100 patients with consistent hemodynamic criteria, 27 (17%) did not fulfill the vasoactive "response criteria" requested for listing. In the end, only 47% of the total number of patients transplanted with MELD exception points for PoPH had accurate data to proceed with LT. Patients with PoPH had a significantly higher chance to achieve LT (80% in the group with nonconsistent PoPH criteria, 63% in the group with consistent PoPH criteria) when compared to the nonexception waitlist cohort (38%; n = 34,180), with increased waiting list mortality only noted in the patients with consistent PoPH hemodynamic criteria. Of note, the corresponding overall unadjusted survival for these groups was 77, 64, and 70% (p = 0.08), and multivariate multistate survival analysis accounting for all survival time from listing showed that both cohorts of patients with PoPH MELD exception points had greater mortality as compared to all nonexception waitlist candidates (HR: 1.60, 95% CI: 1.04-2.47, for nonconsistent PoPH criteria group; and HR: 2.46, 95% CI: 1.73-3.52, for consistent PoPH criteria group). There were 18 deaths (17%) among LT recipients in the PoPH groups, majority occurring in the first month post-LT, and likely associated with cardiac causes.

Results from this study revealed some valid concerns with current implementation of MELD exception policy for PoPH: LT centers are not providing appropriate and/or complete hemodynamic information, Organ Procurement Organizations (OPO) are not strictly following the recommended guidelines for MELD exception points, inaccuracies in diagnosis of PoPH might have resulted in an unfair organ allocation not prioritizing "sickest first" LT, and the mortality in peri- to immediate post-LT period noted in the PoPH groups was unacceptably high.

The reported limitations on the implementation of OPTN/UNOS policy on PoPH MELD exception points should stimulate reflection among LT health care providers, policymakers, and implementing agencies. From the health care provider perspective, although it is clear that there are more questions to be answered than evidence regarding the ideal criteria for a fair LT prioritization in PoPH, there are some opportunities for improved implementation of current policies. First, RHC hemodynamic criteria should be reported in its completeness to the OPO (mPAP, PVR, CO, PAOP) to allow calculation of secondary criteria such as the TPG, which has been associated with post-LT mortality (> 15 mmHg), as it facilitates identification of real vasoconstrictive

and vasobliterative arteriopathic changes within the pulmonary vasculature, as well as pulmonary vascular remodeling.[2,5,7] Second, the time elapsed between the start of vasoactive therapy and repeat RHC for confirmation of favorable response to drug intervention needs to be not only standardized (i.e. 12 weeks), but made mandatory across LT centers. Third, the method(s) and criterion(a) utilized to define satisfactory RV function should not be left open to the best judgment of each center, but defined on the basis of best available evidence (RV dilation or other RV parameters such as strain imaging, etc.). This would allow a more accurate risk-stratification of waitlist candidates with PoPH. Fourth, as previously mentioned, the need to accomplish mPAP < 35 mmHg for facilitated allocation might need to be revised, particularly in the setting of greatly improved echocardiographic parameters. Fifth, post-LT follow up with echocardiogram, biomarkers of RV strain, and RHC should be protocolized in order to prevent deterioration of cardiac function among patients that will not show spontaneous improvement in PoPH after LT.

Future research is needed to more accurately categorize and risk stratify PoPH patients. These goals can be only achieved with improvement in prospective data collection. Given the low frequency of PoPH and the scarcity of data regarding post-LT outcomes, we believe that a multicenter cohort data registry should be sought as to facilitate expansion of knowledge. Such a registry would allow identification of PAH-specific therapies commonly used for treating PoPH patients during the pre- and peri-LT period, an accurate characterization of methods used to define response to vasoactive drugs, and reporting of long-term outcomes, with accurate causes of death data. Eventually, this information could be used to develop clinical studies on novel diagnostic methods (i.e. diastolic pulmonary vascular pressure gradient[7]), clinical trials to improve PoPH treatment with novel vasoactive drugs, as well as better LT selection criteria.

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