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# Hepatopulmonary syndrome: Is it time to redefine the MELD exception score for better organ allocation and outcomes?

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## Article commented

Goldberg DS, Krok K, Batra S, Trotter JF, Kawut SM, Fallon MB. Impact of the hepatopulmonary syndrome MELD exception policy on outcomes of patients after liver transplantation: An analysis of the UNOS database. *Gastroenterology* 2014; 146: 1256-65.

## Comment

Hepatopulmonary syndrome (HPS) represents a serious lung vascular disorder, resulting in significant morbidity and mortality, especially when liver transplantation (LT) is being considered, influencing the pre, trans, and post-LT outcomes. HPS is best characterized by the documentation of impaired oxygenation (widened alveolar-arterial oxygen pressure gradient [PA-$aO_2$] > 15 or > 20 mmHg in patients older than 64 years, with or without concomitant hypoxemia at room air) in the setting of intrapulmonary vascular dilatations (IPVD) confirmed by contrast-enhanced echocardiography or lung perfusion scanning (shunt fraction > 6%) and liver disease or portal hypertension.[1-4] HPS can occur in the setting of any degree of liver disease, from well-compensated liver cirrhosis with portal hypertension to acute liver failure.[1-3] The prevalence of HPS ranges from 1-4% in non-LT referral community hospitals up to 32% in patients being evaluated for LT.[4] Perhaps such a differing prevalence can be attributed to the wide heterogeneity of the applied diagnostic criteria.

LT represents the only definitive therapeutic option that can improve oxygenation and survival in patients with HPS. Because HPS is progressive, being associated with higher pre-LT mortality, patients with severe hypoxemia (partial arterial pressure of oxygen [$PaO_2$] < 60 mmHg) are eligible for Model of End-stage Liver Disease (MELD) exception points assigned by the Organ Procurement Transplant Network (OPTN)/United Network of Organ Sharing (UNOS) in the United Stated (US) in order to expedite LT.[5-6] Interestingly, some reports raised the concern that mortality was higher among HPS patients with severe hypoxemia pre-LT, however other studies did not support this relationship.[3] The largest of these studies was a retrospective single center study performed at Mayo Clinic where they demonstrated a 5-year post-transplant survival of 76% as compared to a 26% survival of matched HPS patients with equivalent degree of hypoxemia and liver disease who were not transplanted. They concluded that outcomes have improved in HPS as a result of MELD exception policy and that the severity of hypoxemia did not predict early post-LT mortality, supporting the existing MELD exception policy.[7]

Goldberg, *et al.*[8] in the May 2014 issue of Gastroenterology performed a retrospective cohort study analyzing data from OPTN/UNOS database with the main objective to assess the potential association between room air oxygenation ($PaO_2$) and pre-LT and post-LT outcomes in the largest cohort of HPS patients reported to date. From February 27, 2002 to December 14, 2012, 973 patients with HPS had at least one MELD exception application approved and were included in the HPS cohort, and 868 (89%) of them had $PaO_2$ values available. They compared

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this group with close to 60,000 patients without HPS, and assessed pre-LT and post-LT patient survival. There were significant differences in certain demographic and clinical variables between these 2 groups with HPS MELD exception patients more likely to be white and female and not unexpectedly, to have lower laboratory MELD scores at the time of listing. There was an 18% decreased risk of dying on the waitlist in patient with HPS compared to the non-HPS group (HR=0.82; 95% CI: 0.70-0.96), which was even more pronounced when the analysis was restricted to the non-HPS cohort with a listing MELD of 21-23 points (HR = 0.53; 95% CI: 0.44-0.65); suggesting that the current MELD exception policy overprioritizes waitlisted patients with HPS. However, there was no significant difference in the 1-,3-, and 5-year survival between the HPS and non-HPS cohorts overall. The authors determined optimal $PaO_2$ cut-off points to predict post-transplantation mortality to refine the current oxygenation standard categories ($PaO_2$ < 50 mmHg; 50-59 mmHg and 60-69 mmHg) used to approve MELD exception points. Using cubic splines, an elegant statistical method to evaluate for thresholds (inflection points or knots) in the relationship between an exposure (arterial oxygenation) and outcome (death) they identified room-air oxygenation thresholds that correlated better with pre- and post-LT outcomes. This is a superior method for modeling the relationship between a continuous exposure and an outcome that does not follow a simple linear relationship. They identified 4 categories of room-air $PaO_2$: ≤ 44 mmHg; 44.1-54 mmHg; 54.1-61 mmHg > 61.1 mmHg in the cohort with HPS. There was no association between oxygenation status and pre-LT waitlist mortality. However, in multivariable Cox models, there was a significant association between room-air oxygenation and post-LT patient survival. This association was particularly evident among HPS recipients with $PaO_2$ ≤ 44 mmHg compared to recipients with $PaO_2$ 44.1-54 mmHg (HR=1.58; 95% CI, 1.15-2.18); refuting previously published evidence that suggested even severe hypoxemia did not have a negative impact on post-LT outcomes.[7-9] Of note though, there were only 66 patients with such severe hypoxemia, representing 11% of the HPS cohort. Although their 5-year post-LT survival was only 59%, compared to 76% among all HPS recipients, it was still above the threshold of 50% 5-year survival, commonly considered the point of transplantation futility. This finding suggests that worsening hypoxemia can be a marker of poor post-LT outcomes in HPS.

The study by Goldberg, *et al.*[8] provides the following strengths over previous reports:

- It represents the largest study to evaluate the relationship between room-air $PaO_2$ and post-LT outcomes in patients with HPS.
- They assessed data from a comprehensive national database of all LTs performed in the US with a sample size nearly four times larger than that analyzed in an earlier report from OPTN/UNOS database that evaluated HPS patient data from February 2002 to March 2007.[10]
- They provide evidence that LT is feasible in patients with HPS and results in similar post-LT survival compared to non-HPS recipients, but that a sub-group of patients with HPS and very severe hypoxemia defined as room-air $PaO_2$ ≤ 44 mmHg have an almost 60% increased risk of post-LT death compared to HPS patients with $PaO_2$ 44.1-54 mmHg (with 3-year and 5-year survival of 68 and 59% compared to 84 and 78%, respectively).

Severe hypoxemia in the early post-LT period in patients suffering from HPS has been reported as a common major complication, often leading to death in HPS, however it has been poorly characterized. Recently, Nayyar, *et al.,* proposed an objective definition of this complication, describing its prevalence, risk factors, and outcomes.[11] They performed a systematic literature review and reviewed their single-center experience, defining severe post-LT hypoxemia as hypoxemia requiring 100% fraction of inhaled oxygen to maintain saturation > 85% and out of proportion to any primary concurrent pulmonary process (e.g. significant chronic obstructive lung disease or interstitial lung disease). There was a trend toward an increased risk of developing this complication in patients with very severe hypoxemia, defined as $PaO_2$ ≤ 50 mmHg and anatomic intrapulmonary shunting > 20% quantified by lung perfusion scan, concluding that preoperative awareness of this common complication is required among high-risk patients.

Goldberg, *et al*. also found that despite estimates that 5-15% of candidates on the waitlist have HPS meriting automatic MELD exceptions by current criteria ($PaO_2$ < 60 mmHg), and that up to 30% have HPS based on the alveolar-arterial gradient, less than 2% of waitlist candidates actually applied for an HPS exception. This observation would suggest that even in LT centers, HPS remains an under-recognized lung vascular complication of liver disease, despite its impact on patient survival.

It is of paramount importance for the LT community to actively screen patients for HPS, not only during the LT evaluation, but also periodically during the candidate's time on the waitlist. Clinicians should be able to accurately identify and characterize the severity of HPS, with special emphasis on recognizing those with more severe disease ($PaO_2 \leq$ 44 mmHg, lung perfusion scan shunt fraction > 20%), as these patients are at increased risk of dying after LT. Changes in the prioritization process of waitlist candidates with HPS might be implemented in the future to optimize post-LT outcomes in these patients, without disadvantaging the broader transplant population.

We encourage clinicians and researchers to take advantage of the valuable information provided by Goldberg, *et al*.[8] by appropriately screening and diagnosing HPS, potentially adopting this new categorization of severity of hypoxemia and exploring changes in the prioritization of MELD exceptions in candidates with HPS that provide a fair balance between waitlist mortality and post-LT survival.

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