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Excellent outcomes with liver transplantation in hepatopulmonary syndrome across pre-transplant PaO_2 spectrum

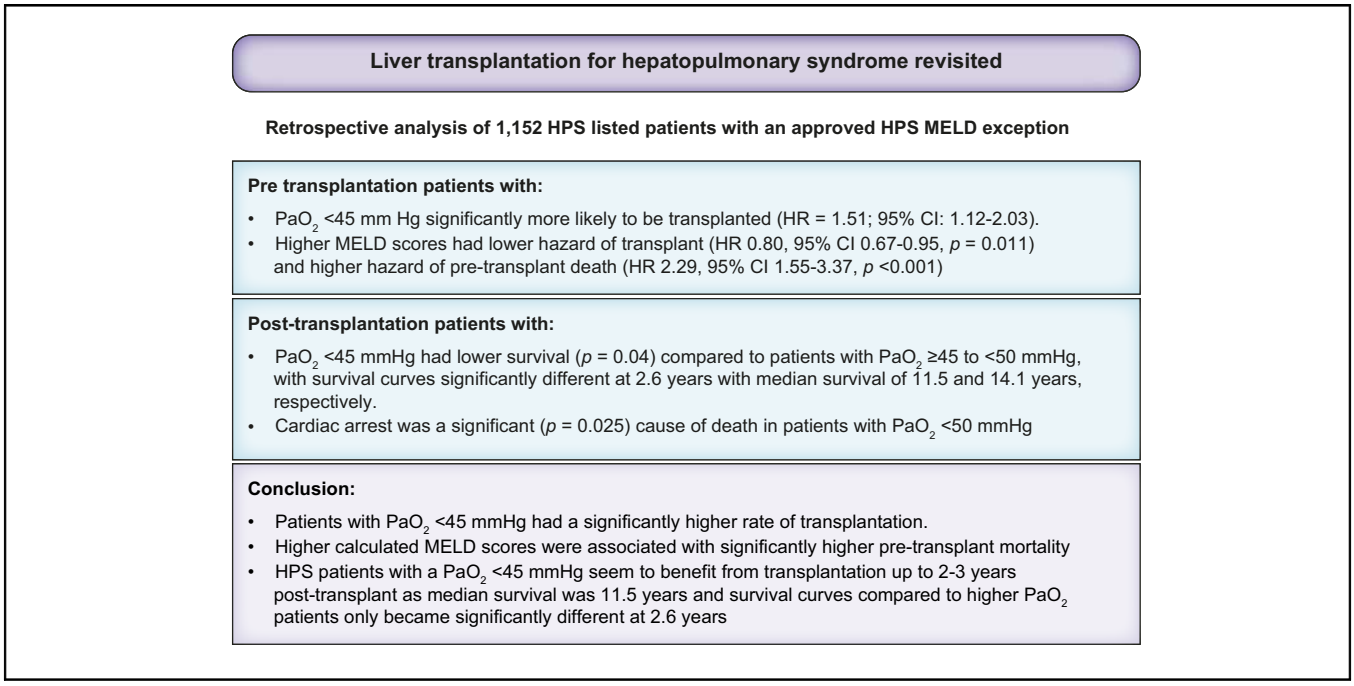
Authors

Zakiyah Kadry, Eric Schaefer, Karen Krok, Alison Faust, Jonathan Gibson Stine, Ian Roy Schreibman, Dmitri Bezinover, Thomas Roberts Riley

Correspondence

zkadry@pennstatehealth.psu.edu (Z. Kadry).

Graphical abstract



Highlights

- A retrospective analysis of 1,152 patients with hepatopulmonary syndrome and an approved MELD exception was performed.
- Patients with a PaO2 <45 mmHg had a significantly higher rate of transplantation (HR 1.51, 95% CI 1.12–2.03).
- Higher calculated MELD scores were associated with significantly higher pre-transplant mortality (HR 2.29, 95% CI 1.55–3.37, p <0.001).
- Although post-transplant survival was lower in patients with a PaO2 <45 mmHg, the median survival was 11.5 years and survival curves only became significantly different at 2.6 years.

Lay summary

A total of 1,152 patients with hepatopulmonary syndrome listed for liver transplant were analysed. Patients with a low PaO_2 <45 mmHg had a high likelihood of transplantation. If associated with advanced liver disease, the mortality risk was higher for patients with hepatopulmonary syndrome on the wait list. After liver transplantation, patients with a PaO_2 <45 mmHg had a lower survival, but this only became significant after 2.6 years, and the median survival was 11.5 years. This suggests that patients with hepatopulmonary syndrome do benefit from transplantation.

https://doi.org/10.1016/j.jhepr.2021.100351

Research article

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Excellent outcomes with liver transplantation in hepatopulmonary syndrome across pre-transplant PaO_2 spectrum

Zakiyah Kadry,[1,*] Eric Schaefer,[2] Karen Krok,[3] Alison Faust,[3] Jonathan Gibson Stine,[3] Ian Roy Schreibman,[3] Dmitri Bezinover,[4] Thomas Roberts Riley III[3]

[1]Division of Transplantation, Department of Surgery, Penn State College of Medicine, Hershey, PA, USA; [2]Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA; [3]Division of Gastroenterology and Hepatology, Department of Medicine, Penn State College of Medicine, Hershey, PA, USA; [4]Department of Anesthesiology, Penn State College of Medicine, Hershey, PA, USA

JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2021.100351

Background & Aims: Significantly worse survival has been reported in patients with hepatopulmonary syndrome (HPS) and partial pressure of arterial oxygen (PaO_2) <45 mmHg undergoing liver transplantation. Long-term pre- and post-transplant outcomes based on degree of hypoxaemia were re-examined.
Methods: A retrospective analysis of 1,152 HPS candidates listed with an approved HPS model for end-stage liver disease (MELD) exception was performed. A Fine and Gray competing risks model was utilised to evaluate pre-transplant outcomes for PaO_2 thresholds of <45, 45 to <60, and ≥60 mmHg. Post-transplant survival was analysed using the Kaplan–Meier method.
Results: Patients with a PaO_2 <45 mmHg were significantly more likely to undergo transplantation (hazard ratio [HR] 1.51; 95% CI 1.12–2.03), whereas patients with higher MELD scores had lower hazard of transplant (HR 0.80, 95% CI 0.67–0.95, p = 0.011) and higher hazard of pre-transplant death (HR 2.29, 95% CI 1.55–3.37, p <0.001). Post-transplantation, patients with a PaO_2 <45 mmHg had lower survival (p = 0.04) compared with patients with a PaO_2 ≥45 to <50 mmHg, with survival curves significantly different at 2.6 years (75% survival compared with 86%) and median survival of 11.5 and 14.1 years, respectively. Cardiac arrest was a more likely (p = 0.025) cause of death for these patients. Cardiac arrest incidence in patients who died with a PaO_2 >50 mmHg was 6.2%.
Conclusions: Patients with a PaO_2 <45 mmHg had a significantly higher rate of transplantation, and higher calculated MELD scores were associated with significantly higher pre-transplant mortality. Although post-transplant survival was lower in patients with a PaO_2 <45 mmHg, the median survival was 11.5 years, and survival curves only became significantly different at 2.6 years. This suggests that patients with HPS do benefit from transplantation up to 2–3 years post-transplant regardless of the severity of pre-transplant hypoxaemia.
Lay summary: A total of 1,152 patients with hepatopulmonary syndrome listed for liver transplant were analysed. Patients with a low PaO_2 <45 mmHg had a high likelihood of transplantation. If associated with advanced liver disease, the mortality risk was higher for patients with hepatopulmonary syndrome on the wait list. After liver transplantation, patients with a PaO_2 <45 mmHg had a lower survival, but this only became significant after 2.6 years, and the median survival was 11.5 years. This suggests that patients with hepatopulmonary syndrome do benefit from transplantation.

Introduction

Hepatopulmonary syndrome (HPS) is a complication of end-stage liver disease characterised by intrapulmonary vascular dilatations and shunting, thereby resulting in abnormalities in arterial oxygenation that can range from mild to severe and may be associated with significant symptoms and impaired quality of life.[1–3] Up to 32% of patients with cirrhosis have some degree of HPS,[4–6] and liver transplantation is currently the only curative treatment.[1,7,8] Liver allocation for HPS based on model for end-stage liver disease (MELD) exceptions has generated considerable debate. Several studies have shown that patients with HPS have superior waiting list survival compared with patients with liver disease but without HPS. There has also been discussion on the determination of the degree of hypoxaemia at which patients with HPS benefit from transplantation without compromising their post-transplantation outcomes.[9–11] In 2014, a retrospective analysis, examining 973 patients with HPS listed for transplantation, showed no association between pre-transplantation oxygenation and wait-list survival in patients with HPS, whereas post-transplant survival was significantly worse in patients with room air partial pressure of arterial oxygen (PaO_2) ≤44.0 mmHg.[9] Our study looks at a larger cohort for analysis with a longer period of follow-up. We examined both wait-list

Keywords: Hepatopulmonary syndrome; Hypoxia; Liver transplantation.
Received 23 June 2021; received in revised form 2 August 2021; accepted 3 August 2021; available online 12 August 2021
* Corresponding author. Address: Division of Transplantation, The Pennsylvania State University, College of Medicine, 500 University Drive, H062, Hershey, PA 17033-0850, USA. Tel.: 717-531-5921; Fax: 717-531-5851.
E-mail address: zkadry@pennstatehealth.psu.edu (Z. Kadry).

and post-transplantation outcomes in patients with MELD exception points for HPS.

Patients and methods

Data were provided through the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) file from the Organ Procurement and Transplant Network (OPTN). The file contained de-identified patient data from 27 February 2002, when the MELD allocation system began in the USA, to 30 June 2019. Institutional review board approval was obtained for the study.

To ensure that only candidates listed after the implementation of the MELD-based allocation were included in the analysis, the study period began on 1 January 2003 and extended until 30 June 2019. Only adult patients ≥18 years of age with an approved HPS MELD exception and who had PaO_2 values for their MELD exception at listing were included in the study. To gather the relevant PaO_2 data from the UNOS STAR file, all HPS narratives were processed using an automated computer program that searched for the specific phrases 'PaO_2 < 60 mm Hg on room air at rest', 'PaO_2, or 'PO_2' (in order, and without regard to capitalisation or spacing) and extracted the first number found after those phrases. Records in which the resulting number was clearly spurious (*e.g.* a value of 1 or 1,000) were manually reviewed and the correct number extracted (if available). To maximise capture of data among the narratives with these phrases, 93% had an extracted PaO_2 value within the range between 24 and 98 mmHg; 7% were manually reviewed. The final study sample analysed was limited to patients with HPS and a PaO_2 range from 31 to 96 mmHg.

Statistical analysis

The primary outcome was the time from first HPS diagnosis (date of exception record) to transplant, pre-transplantation death, or removal from the waiting list as a result of condition deteriorating, whichever occurred first. Pre-transplantation death on the waiting list included patients removed from the waiting list who were coded in the UNOS file as 'too sick to transplant' or 'other' who died within 90 days of delisting, confirmed by OPTN and the Social Security Death Master File. The rationale behind the decision to include patients who died at a short time frame of 90 days from delisting was based on its reflecting severity of disease and because transplant centres may delist severely decompensated patients shortly before their death, resulting in an underestimation of the true number of deaths on the waiting list. All other removal codes were considered censored at the time of removal. Patients were censored at the last known follow-up time if they were still alive, had not yet underwent transplantation, and had not yet been removed from the waiting list for a deteriorating condition.

We used methods appropriate for competing risks in the analysis. To estimate the crude incidence of each event as a function of time, the cumulative incidence function (CIF) was calculated. The CIF, and the test of Gray, was also used with respect to examining incidence by PaO_2 at the initial exception request as a categorical variable.[12]

We used the model of Fine and Gray to analyse PaO_2 at the initial exception request as a continuous variable.[13] We used a restricted cubic spline with 3 degrees of freedom to allow for non-linear associations with outcomes.[14] Based on the non-linear association, the following groups of room air PaO_2 were deemed reasonable and used in the analysis: <45, 45 to <60, and ≥60 mmHg. We also used the Fine and Gray model to examine associations between PaO_2 and outcomes after adjusting for age at exception listing, MELD at exception listing, year of request, sex, and aetiology group. Age was modelled linearly, which was appropriate based on spline fits and other graphical methods. MELD and year were modelled non-linearly using restricted cubic splines. The other variables in the model were categorical and used reference coding. Hazard ratios (HRs) and corresponding 95% CIs were reported for these models. For non-linear terms of MELD and year of request, HRs were reported for the 75th *vs.* 25th percentiles.

For the subgroup of patients who underwent transplantation, we examined survival by room air PaO_2 groups using the method of Kaplan and Meier.[15] Patients who were still alive at the last follow-up were censored at that time. The log-rank test was used to test for differences among PaO_2 groups.[16] The method of Klein was used to determine the time point in which survival curves first differed statistically.[17] Causes of death were compared between groups using Chi-square tests with a continuity correction for small samples.[18]

Results

The study included 1,152 candidates who were diagnosed with HPS, had an approved HPS MELD exception, and had a PO_2 value available and extracted from the HPS exception narrative. Table 1 shows the patient characteristics at the time of listing. The median age at listing was 55 years (range 18–75 years). Median MELD score at listing was 13 (range 6–38). Sex was equally divided (female 50.3%; male 49.7%). A primary diagnosis of viral aetiology was most common (34.7%), followed by alcohol-related cirrhosis (20.4%), non-alcoholic steatohepatitis (NASH; 16.4%), autoimmune (7.1%), and other diagnoses (21.4%).

The initial exception request in which room air PaO_2 was extracted occurred at a median of 10 days after listing (IQR 3–128 days). The median PaO_2 value at the initial exception request was 55 (IQR 50–59) with a range of 31–96. Fig. 1A shows a histogram of PaO_2 values at the time of HPS MELD exception request. Most patients received an HPS MELD exception approval at a PaO_2 of 60 mmHg or less as required by UNOS rules. Fig. 1B shows a scatter plot of PaO_2 values by year of exception request, which

Table 1. Patient characteristics at listing and at transplant for the subgroup of patients who underwent transplantation.

	Listing (n = 1,152)	Transplant (n = 838)
Age at listing/transplant		
Median (IQR)	55 (49–60)	55 (50–60)
Range	18–75	18–75
Sex		
Female	579 (50.3%)	418 (49.9%)
Male	573 (49.7%)	420 (50.1%)
MELD at listing/transplant		
Median (IQR)	13 (11–16)	14 (12–17)
Range	6–38	6–44
Aetiology at diagnosis		
Viral	400 (34.7%)	300 (35.8%)
Autoimmune	82 (7.1%)	51 (6.1%)
Alcohol	235 (20.4%)	167 (19.9%)
NASH	189 (16.4%)	133 (15.9%)
Other	246 (21.4%)	187 (22.3%)

MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis

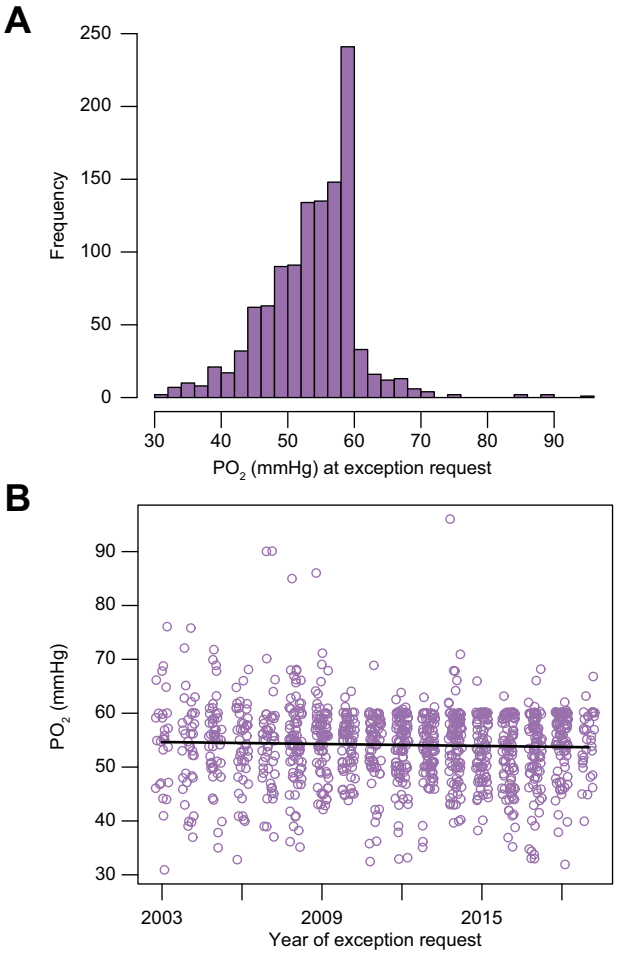

Fig. 1. PO_2 values. (A) Histogram of PO_2 (mmHg) at exception request. Histogram bars show frequency by PO_2 value at time of MELD exception request. (B) Scatter plot of PO_2 (mmHg) by year of exception request. Within the scatter plot, the mean estimate (solid black line) from linear regression model is overlaid.

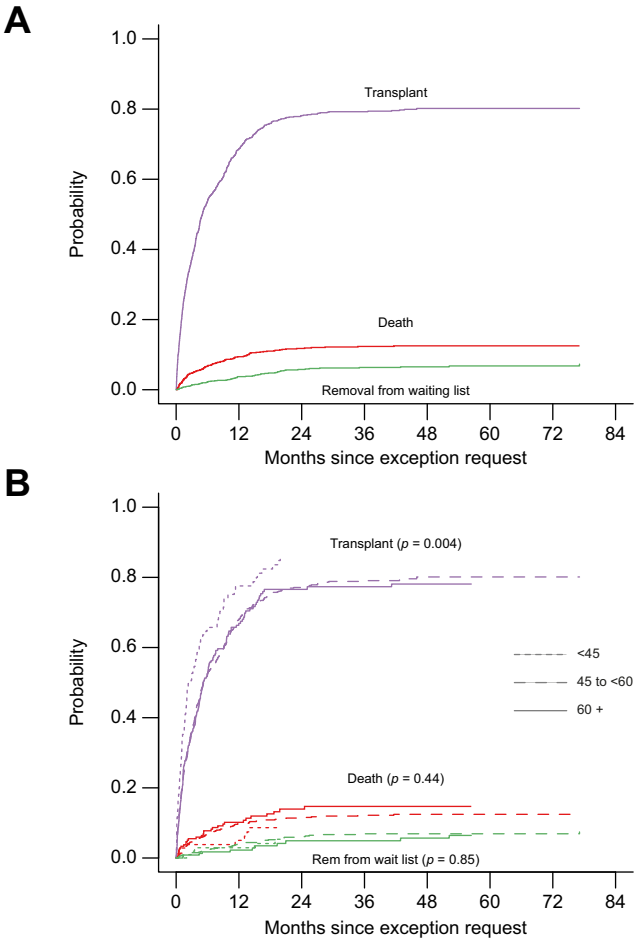

Fig. 2. Cumulative incidence curves. (A) The cumulative incidence curves for transplant, death on the waiting list, and removal from waiting list for the entire hepatopulmonary syndrome cohort shown over time in months from MELD exception request. (B) Cumulative incidence curves of transplant (purple line), death on the waiting list (red line), and removal from the waiting list (green line) stratified by PO_2 groups (<45 mmHg dotted line, ≥45 to <60 mmHg interrupted bars, and ≥60 mmHg continuous line) for the same cohort. Values of p for PO_2 groups are $p = 0.004$ for transplant; $p = 0.44$ for death; and $p = 0.85$ for removal from the waiting list.

demonstrated that most HPS MELD exceptions at a PaO_2 >60 mmHg occurred in earlier years, and there was little change over time with regard to mean PO_2 values.

For the duration of the study, 838 patients (72.7%) underwent transplantation, 126 patients (10.9%) died on the waiting list, 63 patients (5.5%) were removed from the waiting list, and 125 patients were censored (still at risk for any outcome at the time of study analysis). Fig. 2A shows a cumulative incidence curve for transplant, death on the waiting list, and removal from the waiting list. The most striking feature of these cumulative incidence curves is the transplant curve, which showed that most patients underwent transplantation within 12 months. At 12 months, the cumulative incidence curve indicated that 69% of patients had undergone transplantation, 9% had died, and 4% were removed from the waiting list, with the remaining 18% of patients still at risk for 1 of these outcomes.

Outcomes based on room air PaO_2 values

To further examine waiting-list outcomes, oxygenation based on PaO_2 as a non-linear continuous variable was examined by utilising a Fine and Gray model for competing risks with PaO_2 as the only predictor in the model. The non-linear relationship was significant for transplant ($p = 0.007$) but non-significant for death ($p = 0.33$) and removal from the waiting list ($p = 0.42$). Based on the shape of the significant curve for transplant, the following groups of PaO_2 were deemed reasonable: <45, 45 to <60, and ≥60 mmHg. Respective sample sizes for these groups were 105, 807, and 240. There were 91 cases with a PaO_2 >60 mmHg from the cohort of 240 patients on the waiting list with a PaO_2 ≥60 mmHg. Patients with a PaO_2 >60 mmHg had a significantly lower median age (52.4 *vs.* 54.2 years; $p = 0.045$) and a higher percent incidence of viral hepatitis as the primary cause of their liver disease (40.7% *vs.* 34.2%; $p = 0.017$) compared with patients with a PaO_2 <60 mmHg. Sex was equally distributed, and there was no significant difference between the 2 groups ($p = 0.954$). Median MELD score was also not significantly different between the 2 groups (13.0 *vs.* 14.0 for patients listed with a PaO_2 <60 mmHg; $p = 0.447$).

Table 2. HRs estimated from the Fine and Gray competing risks model.

Variable	Transplant		Death prior to transplant		Removed from wait list	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PO_2 (mmHg) group						
<45	1.51 (1.12–2.03)	0.007	0.65 (0.29–1.45)	0.29	1.10 (0.37–3.24)	0.87
45 to <60	1.12 (0.93–1.36)	0.22	0.76 (0.50–1.16)	0.20	1.25 (0.64–2.42)	0.51
≥60 (ref)	1		1		1	
Age, 5-year increase	1.03 (0.99–1.07)	0.18	1.06 (0.95–1.18)	0.32	1.10 (0.93–1.29)	0.27
MELD, 17 *vs.* 11*	0.80 (0.67–0.95)	0.011	2.29 (1.55–3.37)	<0.001	1.36 (0.76–2.45)	0.30
Year of request, 2016 *vs.* 2009*	0.54 (0.44–0.67)	<0.001	0.91 (0.56–1.48)	0.07	3.27 (1.42–7.53)	0.005
Sex, M *vs.* F	1.07 (0.93–1.24)	0.35	1.19 (0.82–1.72)	0.37	1.44 (0.84–2.45)	0.19
Aetiology group						
Viral (ref)	1		1		1	
Autoimmune	0.92 (0.65–1.31)	0.66	2.02 (1.10–3.69)	0.023	0.89 (0.34–2.33)	0.80
Alcohol	1.11 (0.91–1.36)	0.32	0.95 (0.56–1.58)	0.83	0.63 (0.31–1.26)	0.19
NASH	1.21 (0.98–1.50)	0.08	1.39 (0.84–2.30)	0.20	0.44 (0.19–1.02)	0.06
Other	1.13 (0.94–1.37)	0.20	0.92 (0.55–1.56)	0.76	0.75 (0.38–1.47)	0.40

HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.
* HR reported for the 75th *vs.* 25th percentile because the variable was modelled non-linearly.

Fig. 2B shows the cumulative incidence curves by these PaO_2 groups. Differences between PaO_2 groups were significant for transplant (p = 0.004) but not for death (p = 0.44) or removal from the wait list (p = 0.85). The significant results for transplant were primarily as a result of patients with a PaO_2 <45 mmHg having a higher likelihood of transplant relative to the other groups.

Table 2 shows HRs estimated from the Fine and Gray competing risks model adjusted for age, year of exception request, aetiology group at diagnosis, and sex at exception listing. The model showed that patients with a PaO_2 <45 mmHg had a significantly higher likelihood of receiving a liver transplant relative to patients with a PaO_2 ≥60 mmHg (HR 1.51, 95% CI 1.12–2.03, p = 0.007). No other HRs for transplant, death, or removal from the waiting list were significant with respect to PaO_2.

Mortality on the waiting list

A total of N = 126 patients died on the waiting list. Table 3 describes the PaO_2 values and native MELD values of this group. Table 2 shows that patients with higher MELD scores (17 *vs.* 11) had a lower hazard of transplant (HR 0.80, 95% CI 0.67–0.95, p = 0.011) with a significantly higher hazard of death on the waiting list (HR 2.29, 95% CI 1.55–3.37, p <0.001). Also, when comparing 2 time periods, 2016 *vs.* 2009, Table 2 shows that in later years, listed patients with HPS (2016 *vs.* 2009) had a significantly lower hazard of transplant (HR 0.54, 95% CI 0.44–0.67, p <0.001), had a significantly higher hazard of removal from the waiting list (HR 3.27, 95% CI 1.42–7.53, p = 0.005), and trended toward higher mortality hazard on the waiting list (HR 0.91, 95% CI 0.56–1.48, p = 0.07). A primary diagnosis of autoimmune-related liver disease was associated with a significantly higher hazard of death on the waiting list relative to those with viral diagnoses (HR 2.02, 95% CI 1.10–3.69, p = 0.023), whereas the hazard of transplant was not significantly different (HR 0.92, 95% CI 0.65–1.31, p = 0.66).

Table 3. Variables from exception request: patients who died on the waiting list.

	Total (n = 126)
PO_2 at exception request	
N	126
Mean (SD)	54.4 (6.46)
Median	55.0
Interquartile range	51.0, 59.3
Range	(33.0–69.0)
MELD at exception request	
N	126
Mean (SD)	16.4 (5.23)
Median	16.0
Interquartile range	13.0, 19.0
Range	(7.0–39.0)

MELD, model for end-stage liver disease.

Post-transplant patient outcomes

A total of 838 patients underwent transplantation. Table 1 shows that patient demographics were generally similar to those at the time of listing.

Fig. 3A shows a Kaplan–Meier curve of survival based on room air PaO_2 defined as <45, 45–<60 and ≥60 mmHg, whereas Fig. 3B specifically compares outcomes at lower PaO_2 values of <45 and 45 to <50 mmHg. Respective sample sizes in Fig. 3A were 85, 584, and 169 with median survival times of 11.5 years (PaO_2 <45), of 13.3 years (PaO_2 45 to <60), and not yet reached (PaO_2 ≥60). Overall survival was not significantly different among the 3 groups (p = 0.10). In Fig. 3B, the respective sample sizes for the 2 groups were 85 and 125 with median survival times of 11.5 years for PaO_2 <45 mmHg and 14.1 years for patients with a PaO_2 of 45 to <50 mmHg. Patients with a PaO_2 value <45 mmHg had a significantly lower survival (p = 0.04); however, the time point at which the survival curves became significantly different, based on the method of Klein, was 2.6 years. At that time point, the estimated proportions of patients being alive were 0.75 for PaO_2 <45 mmHg and 0.86 for PaO_2 ≥45 to <50 mmHg.

Post-transplant mortality

For the subgroup of patients who underwent transplantation with a pre-transplant PaO_2 <50 mmHg, a total of 57 patients died post-transplant, with 29 deaths for PaO_2 <45 mmHg and 28 deaths for PaO_2 ≥45 to <50 mmHg. Cardiac arrest occurred in 8 patients with a PaO_2 ≥45 to <50 and 1 patient with a PaO_2 <45 (29% *vs.* 3%, respectively, p = 0.025). Differences with respect to respiratory failure (PaO_2 <45 mmHg, n = 5, 17% *vs.* PaO_2 ≥45 to <50 mmHg, n = 1, 3.6%; p = 0.21) were not statistically significant.

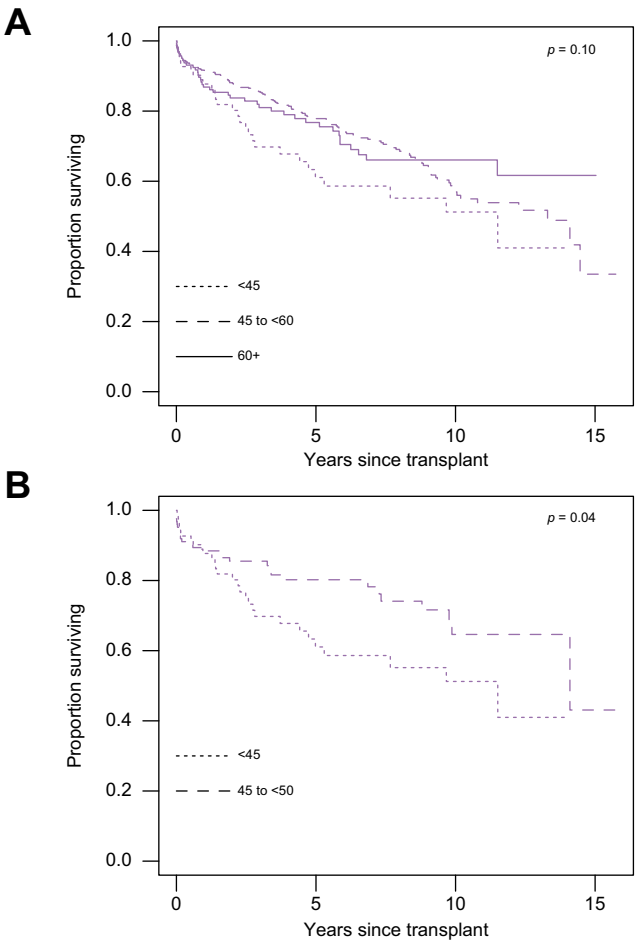

Fig. 3. Kaplan–Meier survival curves. (A) Kaplan–Meier curve of overall survival after transplant stratified by PO_2 groups (<45 mmHg: dotted line; ≥45 to <60 mmHg: interrupted bar line; and ≥60 mmHg: continuous line) with a log-rank *p* value, *p* = 0.1, for difference among curves. (B) Kaplan–Meier curve of overall survival for the subgroup of patients with PO_2 <50 mmHg after transplant, stratified by PO_2 group (<45 mmHg: dotted line; ≥45 to <50 mmHg: thick bar line) with a log-rank *p* value = 0.04, for differences among curves.

Miscellaneous other causes of death included graft failure from hepatitis recurrence (PaO_2 ≥45 to <50: n = 1), graft failure from rejection (PaO_2 ≥45 to <50: n = 1), graft failure with cause not specified (PaO_2 ≥45 to <50: n = 1); unknown (PaO_2 ≥45 to <50: n = 5; PaO_2 <45: n = 10), cardiac not related to cardiac arrest (PaO_2 ≥45 to <50: n = 1; PaO_2 <45: n = 1), cerebrovascular embolic stroke (PaO_2 ≥45 to <50: n = 1), cerebrovascular haemorrhagic stroke (PaO_2 ≥45 to <50: n = 2), multiple organ system failure (PaO_2 ≥45 to <50: n = 1; PaO_2 <45: n = 3), infection/sepsis (PaO_2 ≥45 to <50: n = 4; PaO_2 <45: n = 7), and malignancy (PaO_2 ≥45 to <50: n = 3; PaO_2 <45: n = 1). In the subgroup of patients who died with a PaO_2 >50 mmHg (n = 162), the incidence of cardiac arrest was only 6.2% (n = 10).

Discussion

Liver allocation for HPS based on MELD exceptions has evolved over time with earlier reports describing a significant increase in risk of death as well as worse functional status and quality of life in candidates for liver transplant,[4,19,20] whereas later publications reported superior waiting list survival compared with patients with liver disease but without HPS.[9–11] Furthermore, the determination of the degree of hypoxaemia at which patients with HPS may benefit from transplantation without compromising their post-transplantation outcomes has come under scrutiny.[9] In 2014, Goldberg *et al.*[9] reported their retrospective analysis of one of the largest cohorts of patients with HPS (n = 973) listed for liver transplantation in the USA and concluded that although there was no association between pre-transplantation oxygenation and waiting list survival, there was a significantly increased post-transplantation mortality in patients with HPS with a pre-transplant room air PaO_2 ≤44 mmHg when compared with patients with a PaO_2 of 44.1–54.0 mm Hg (HR 1.58; 95% CI 1.15–2.18). For our study, we aimed to re-evaluate these findings and expand the data set to include a larger cohort of patients (n = 1,152) with a longer 15-year follow-up, looking into the impact of the severity of HPS on the wait list and post-transplantation outcomes.

To qualify for a MELD exception for HPS in the USA, patients must have a PaO_2 of ≤60 mmHg, associated with either an echocardiogram or a lung scan showing the presence of an intrapulmonary shunt, evidence of portal hypertension, and no other underlying pulmonary disease.[10,21] For the early years of MELD allocation, approval for HPS MELD exceptions were less stringent,[10,22] but the rules were applied more strictly over time, especially after the creation of a National Liver Review Board in May 2019. This was clearly reflected in our study in Fig. 1B, where a scatter plot of PaO_2 values by year of exception request showed that listing approvals of most HPS MELD exceptions at a PaO_2 >60 mmHg occurred in earlier years. Further analysis of the characteristics of patients with a PaO_2 >60 mmHg showed that they were significantly younger (*p* = 0.045) with a higher percent incidence of viral hepatitis as the primary cause of their liver disease (*p* = 0.017) compared with patients with a PaO_2 ≤60 mmHg, but there was no significant difference in the degree of illness based on calculated MELD score to warrant earlier listing (*p* = 0.447). The histogram in Fig. 1A confirmed that the great majority of MELD exception approvals had a PaO_2 ≤60 mmHg with very few above that cut-off. However, in spite of the limited number of patients with a pre-transplant PaO_2 >60 mmHg in our study, the median PaO_2 value at the initial exception request remained 55 (IQR 50–59) for our analysis.

Our study showed that the great majority of patients with HPS on the waiting list underwent transplantation within 12 months of listing (Fig. 2). Additionally, differences between PaO_2 groups were significant for transplant (*p* = 0.004) but not for pre-transplant death (*p* = 0.44) or removal from waiting list (*p* = 0.85). Finally, in spite of reports outlining worse post-transplant outcomes at significant hypoxaemia <45 to 50 mmHg,[9,18,20] we found in our analysis that patients with a pre-transplant room air PaO_2 <45 mmHg had a significantly higher likelihood of receiving a liver transplant (HR 1.51, 95% CI 1.12–2.03, *p* = 0.007; Table 2). No other HRs for transplant, death, or removal from waiting list were significant with respect to PaO_2 (Table 2). This finding suggests that transplant centres prioritised transplantation of patients with advanced HPS and with a low room air PaO_2 <45 mmHg to avoid further decompensation and worsening hypoxaemia, which could require delisting of these patients on 3 monthly MELD exception UNOS submission updates.

Table 2, which uses a Fine and Gray competing risks model, also shows that patients with higher MELD scores (17 *vs.* 11)

had a lower rate of transplant (HR 0.80, 95% CI 0.67–0.95, p = 0.011) with a significantly higher risk of death on the waiting list (HR 2.29, 95% CI 1.55–3.37, p <0.001), suggesting that additional comorbid factors associated with more advanced cirrhosis in the setting of hypoxaemia tended to result in worse waiting list outcomes with higher pre-transplant death rates. This finding may need to be examined further with the development of future allocation policies for HPS, which currently cap access to transplantation of MELD exception categories including HPS.

Patients with HPS listed in later years (2016 *vs*. 2009) had a significantly lower rate of transplant (HR 0.54, 95% CI 0.44–0.67, p <0.001), a higher rate of removal from the waiting list (HR 3.27, 95% CI 1.42–7.53, p = 0.005), and a trend for higher mortality on the waiting list (HR 0.91, 95% CI 0.56–1.48, p = 0.07). It is unclear why patients in the later study period had significantly lower rates of transplantation. This may be related to the broader regional sharing and implementation of Share 35 from June 2013 onwards, which may have reduced the ease with which patients with MELD exception could access liver organs at lower MELD scores compared with that before 2013.[23] The MELD exception cap cannot explain lower transplantation rates in later years as the UNOS MELD exception policy cap implemented in 2015 was limited only to patients with hepatocellular cancer.[24]

In terms of post-transplant outcomes, our study showed a finding similar to that of Goldberg *et al.*[9] of significant lower post-transplant survival in patients with a pre-transplant PaO_2 value <45 mmHg (HR 1.74, 95% CI 1.03–2.94, p = 0.039). However, we found that the outcomes were still good given that the median survival in patients with a pre-transplant PaO_2 <45 mmHg was 11.5 years and mortality only became significantly higher at 2.6 years post-transplant compared with the other cohorts of patients with a higher PaO_2. This appears to support considering liver transplantation as a treatment option, and providing MELD exception points, for patients with HPS with a lower PaO_2 value. The early positive outcomes in the first 2 years post-transplantation in patients with low PaO_2 values <50 mmHg may be related to advances in clinical management of severe hypoxaemia in the intensive care setting. Severe postoperative hypoxaemia in patients with HPS tends to occur early in the first 24 h after liver transplantation and is a known significant contributor to the majority of reported deaths in this setting.[25–27] However, treatment algorithms have been developed for the treatment of refractory hypoxaemia in HPS, which include approaches such as Trendelenburg or prone patient positioning, inhalational nitric oxide or epoprostenol, intravenous methylene blue, ventilatory modifications, embolisation of lower lobe pulmonary vessels, and, in some cases, extracorporeal membrane oxygenation (ECMO).[25,28–32] There have been several case reports involving the use of ECMO in severe refractory hypoxaemia associated with both pre- and post-transplant HPS cases.[28–32] Veno-venous ECMO has been mainly utilised in patients with HPS and profound hypoxaemia unresponsive to other therapies where heart function is considered adequate. There have been rare reports of venous-arterial ECMO in patients with severe hypoxaemia associated with cardiac failure and haemodynamic instability.[33,34] Improvement of HPS-associated hypoxaemia after liver transplantation is highly variable and difficult to predict with reports of ECMO support ranging from a few days to several weeks. Early consideration for the implementation of ECMO is recommended in persistent HPS-associated refractory hypoxaemia post-transplant, but it is still advised as a 'last resort' approach given the associated high risk of complications such as bleeding, infections, and cannula malposition.[25] ECMO also requires specialised intensive medical and nursing care preferably through an established ECMO service.[31]

Our study findings are particularly interesting as most prior studies focused mainly on the higher early <1-year post-transplant mortality in patients with HPS, described as 14% in the first year for severe HPS (PaO_2 ≤50 mmHg) by Gupta *et al.*[35] in 2010, as 29% deaths within 10 weeks of transplantation for PaO_2 <50 mmHg by Arguedas *et al.*[5] in 2003, and, in France, as 1-year 26% mortality post-transplant by Taille *et al.*[36] Goldberg *et al.*[9] reported an improved overall 1-year post-liver transplant survival of 91% (95% CI 88–93%) and a 3-year survival of 81% (95% CI 78–84%) for all patients with HPS. However, although post-transplant survival follow-up in the latter study was only 5 years, there appeared to be an important decline at 3 years, with the cohort of patients with a PaO_2 <50 mmHg showing a 1-year post-transplant survival of 87.2% (95% CI 81.1–91.5) and 75.0% (95% CI 66.6–81.5) at 3 years,[9] which is consistent with our finding of a decline in post-transplant survival at the 2- to 3-year mark.

To evaluate the survival differences between patients with a PaO_2 <45 mmHg and those with a PaO_2 45–50 mmHg, we looked at the cause of death and were intrigued to find that deaths were cardiovascular rather than respiratory. Cardiac arrest was a statistically significant (p = 0.025) cause of death, particularly for patients with a PaO_2 <50 mmHg. This seems to imply that prolonged pre-transplant hypoxaemia at <50 mmHg may ultimately impact heart function over time. Pre- and post-transplant myocardial dysfunction associated with HPS has been recognised as an entity that requires more investigation in the future.[37] Current literature does not support an association between HPS and cirrhotic cardiomyopathy,[37,38] a disorder characterised by attenuated contractile responsiveness to stress, diastolic dysfunction and impaired ventricular relaxation and filling, and/or electrical conductance abnormalities, which in turn may be exacerbated by the increase in venous return after liver transplantation.[37,38] Intrapulmonary vasodilatation and shunting associated with HPS has been described as being associated with an intense hyperdynamic circulation leading to higher cardiac output and long-term left ventricular dysfunction.[37] Additionally, although HPS and portopulmonary hypertension (POPH) are seen as 2 separate pulmonary complications of cirrhosis, there have been reports in the literature of an overlap suggesting a continuum of these 2 entities.[39] Right ventricular diastolic dysfunction with increased right ventricular and right atrial diameters and right ventricular wall thickness, as noted by Doppler echocardiography, has been reported in HPS.[37,39,40] Animal studies have also shown similar mediators and histologic features in HPS and POPH.[39] The findings in our study of significantly increased cardiac-related mortality post-transplant in patients with severe pre-transplant hypoxaemia of <50 mmHg, and the current literature suggesting a possible HPS-related long-term myocardial dysfunction[37,39] may need to be examined in more detail in the future with prospective data collection. It is also important to note that our study, including other past publications on the topic of liver transplantation for HPS, have only focused on patients who actually received an HPS MELD exception. There are an unknown number of patients suffering from HPS who underwent transplantation without an HPS MELD exception and whose outcomes are unknown but would be of interest.

In summary, our study, examining pre- and post-liver transplant outcomes in 1,152 patients with HPS on the US liver transplant waiting list over a 15-year period, demonstrated a high rate of transplantation in the first 12 months of listing, especially in patients with a PaO_2 <45 mmHg, with pre-transplant mortality significantly higher in patients with more advanced calculated MELD scores. Although post-transplant survival was significantly lower in the cohort of patients with HPS and a PaO_2 <45 mmHg, the median survival was 11.5 years for the latter group, with the separation from the other higher PaO_2 groups occurring at 2.6 years. This suggests that patients with HPS do benefit from transplantation up to 2–3 years post-transplant regardless of the severity of pre-transplant hypoxaemia, with a survival of 75% compared with 86% in those with higher PaO_2. After 3 years, however, the survival curves separate, and cardiac arrest is a significant long-term cause of death in patients with severe hypoxaemia at a PaO_2 <50 mmHg. However, given that a survival benefit was still seen in the first 2.6 years after liver transplantation, associated with a long-term median survival of 11.5 years in patients with an extremely low PaO_2 of <45 mmHg, our results suggest that the latter group should be considered for liver transplantation by the transplant community.

Abbreviations

CIF, cumulative incidence function; ECMO, extracorporeal membrane oxygenation; HPS, hepatopulmonary syndrome; HR, hazard ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OPTN, Organ Procurement and Transplant Network; PaO_2, partial pressure of arterial oxygen; POPH, portopulmonary hypertension; STAR, Standard Transplant Analysis and Research; UNOS, United Network for Organ Sharing.

Financial support

No funding was provided for the conduct of this research. The raw data for this study are available from the United Network for Organ Sharing. This service is supported in part by Health Resources and Services Administration contract HHSH250-2019-00001C. The content of the manuscript is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organisations imply endorsement by the US Government.

Conflicts of interest

The authors have no conflicts of interest or financial disclosures to make.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Research design: ZK, TRRIII. Obtained the database: ZK. Performed the research: ZK, TRRIII. Performed data analysis: ES, ZK, TTRRIII, KK, AF, JS, IRS, DB. Performed statistical analysis: ES. Participated in research design: KK, AF, JS, IRS, DB. Wrote the manuscript: ZK. Contributed input to the manuscript: TRRIII. Provided input to the manuscript: KK, AF, JS, IRS, DB.

Data availability statement

The raw data for this study are available from OPTN.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100351.

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Author names in bold designate shared co-first authorship

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