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ORIGINAL ARTICLE

Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease exception policy and outcomes in pediatric patients with hepatopulmonary syndrome requiring liver transplantation

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Abstract

Hepatopulmonary syndrome (HPS) is associated with increased waitlist mortality in liver transplantation (LT) candidates. Children with HPS are granted Model for End-Stage Liver Disease (MELD)/Pediatric End-Stage Liver Disease (PELD) exception points for waitlist prioritization in the United States based on criterion developed for adults. In this study, the impact of this MELD/PELD exception policy on post-LT survival in children was examined. A retrospective cohort of patients aged younger than 18 years with a MELD/PELD exception request who underwent LT between 2007 and 2018 were identified in the Scientific Registry of Transplant Recipients. Patients were stratified by waitlist partial pressure of arterial oxygen (PaO_2) to assess risk factors for waitlist mortality and post-LT survival. Among 3082 pediatric LT recipients included in the study, 124 patients (4%) received MELD/PELD exception points for HPS. Patients with HPS were a median age of 9 years (interquartile range: 6, 12 years), 54.8% were girls, and 54% were White. Most patients (87.9%) were listed with laboratory MELD/PELD scores <15. Waitlist mortality for patients with HPS exception points was rare and not different from patients without HPS. When stratified by pre-LT PaO_2, hypoxemia severity was not associated with differences in 1-, 3-, or 5-year survival rates after LT ($p = 0.13$). However, patients with HPS showed a slightly lower survival rate at 5 years compared with patients without HPS

Abbreviations: CI, confidence interval; HPS, hepatopulmonary syndrome; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; PaO_2, partial pressure of arterial oxygen; PELD, Pediatric End-Stage Liver Disease; SD, standard deviation; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

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(88.7% vs. 93.4%; $p = 0.04$). MELD/PELD exceptions for children with HPS mitigated waitlist mortality, and recipients with HPS experienced excellent 5-year survival after LT, although slightly lower than in patients without HPS. Unlike adults with HPS, the severity of pre-LT hypoxemia in children does not impact post-LT survival. These data suggest that adult criteria for granting MELD/PELD exception points may not appropriately capture HPS severity in pediatric patients. Further prospective multicenter studies to examine the risk factors predicting negative survival outcomes in children with HPS are warranted.

INTRODUCTION

Hepatopulmonary syndrome (HPS) is a pulmonary vascular disease that develops in a subset of patients with chronic liver failure and portal hypertension and is characterized by intrapulmonary vascular dilations with resultant arterial hypoxemia.[1–3] Although there is significant variation in the reported prevalence of HPS secondary to differences in diagnostic criteria and heterogeneity of underlying liver disease, its prevalence among candidates for liver transplantation (LT) has been reported at up to 32% for adults[4,5] and up to 20% in the pediatric population.[6–8] Simultaneously, HPS is associated with a decreased quality of life and an increase in the risk of death among both adult and pediatric LT candidates.[3,5,9,10] Although there are currently no effective medical treatments for HPS as measured by sustained improvement in oxygenation or reduction in mortality, LT has been demonstrated to reverse the syndrome and improve survival rates.[1,3,11–18]

The Model for End-Stage Liver Disease (MELD) scoring system, first adopted in 2002 as the standard method of determining LT waitlist priority, is based on objective data and has been validated as an accurate predictor of 3-month mortality.[19] The Pediatric End-Stage Liver Disease (PELD) scoring system was developed around the same time and with the same set of principles in mind but with the intent of addressing characteristics unique to children with chronic liver disease.[19–21] By aiming to reflect the severity of a patient's disease based on an estimated 3-month mortality without transplant, implementation of the MELD/PELD system has resulted in a decrease in the proportion of children dying while on the waiting list.[22] Importantly, however, the PELD system has been shown to underestimate pretransplantation mortality for children, which may be placing them at a systemic disadvantage in organ allocation relative to adults.[23]

The MELD system ranks candidates aged 12 years or older for LT, whereas the PELD system is used for younger patients. Given that HPS prognosis is thought to be worse than predicted by MELD/PELD alone, patients with HPS can be granted exception points to compensate for increased mortality risk under United Network for Organ Sharing (UNOS) policy in the United States.[24–28] As degree of hypoxemia dictates disease severity,[29] in 2007 UNOS first recommended assigning a MELD score of 22/PELD score of 28 for the initial application of patients with severe HPS (partial pressure of arterial oxygen [PaO_2] < 60 mm Hg).[30] Further increases every 3 months were also recommended to balance pre- and post-LT outcomes between candidates with and without HPS. Thus, children with HPS have been granted MELD/PELD exception points for LT prioritization in the United States based on similar criterion developed for adults (Organ Procurement and Transplantation Network [OPTN] Policy 9.5.E).[28] These criteria consist of (1) ascites, varices, splenomegaly, or thrombocytopenia; (2) shunting shown by either contrast echocardiogram or lung scan; (3) $PaO_2 < 60$ mmHg on room air; and (4) no clinically significant underlying primary pulmonary disease.

There is a paucity of literature correlating outcomes between pediatric and adult patients with HPS. For instance, at higher MELD/PELD scores, the probability of death for patients on the waiting list is significantly higher in adults than children, so children may receive organs at a relatively less severe stage in their disease.[16] Therefore, adult criteria may not be reliable in predicting and capturing outcomes in the pediatric HPS population. There has been further debate surrounding the association between pretransplantation oxygenation and posttransplantation outcomes in patients with HPS.[25] As a result, the suitability of current criteria for MELD and PELD exception point granting in the pediatric HPS population must be assessed.

The purpose of our study was to determine the impact of the MELD/PELD HPS exception policy on outcomes in pediatric patients receiving LT in the United States. We investigated the relationship between pretransplantation oxygenation levels and posttransplantation survival in pediatric patients with and without

HPS while assessing clinical and demographic variables that may have value in predicting post-LT outcomes. The cohort examined in this study represents the largest published examination of the pediatric HPS population to our knowledge.

PATIENTS AND METHODS

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlist candidates, and transplant recipients in the United States submitted by the members of the OPTN. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US government.

Data extraction and outcome measures

Pediatric patients (younger than 18 years of age at listing) placed on the LT waiting list between January 2007 and December 2018 with an approved MELD/PELD exception request for HPS were extracted and compared with a reference group of patients who did not receive a MELD/PELD exception for any other reason. Patients who underwent retransplant or multi-organ transplant were excluded. Features of HPS noted in approved HPS MELD/PELD exception application narratives, including PaO_2 values, evidence of shunting, history of underlying pulmonary disease, clubbing, supplemental oxygen requirement, portal hypertension, splenomegaly, thrombocytopenia, varices, ascites, or history of gastrointestinal bleeding were extracted from the database for each patient. Patients with HPS were categorized using the standard diagnostic criteria: an alveolar-arterial gradient ≥ 15 mmHg, evidence of intrapulmonary shunting, and the absence of severe restrictive or obstructive pulmonary disease.[25] If an alveolar-arterial gradient was not available, we defined hypoxemia as $PaO_2 < 70$ mmHg on room air or pulse oximetry $\leq 96\%$ on room air or supplemental oxygen. When no discrete PaO_2 values were included in the exception narrative, we included these patients as their exception had been approved based on a statement made by the transplant center indicating that HPS diagnostic criteria were met; however, PaO_2 values were categorized as "unknown" for this subset of patients. Demographic data as well as variables related to HPS status and liver failure were evaluated and categorized. SRTR primary diagnosis codes were grouped into categories (acute failure, chronic cholestatic, hepatitis, hepatocellular, malignancy, other) as shown in Table S1. Each narrative was coded by a trained member of the research team and subsequently reviewed by a secondary investigator.

The primary study outcome was 5-year patient survival after LT. Follow-up time for pediatric waitlist candidates with HPS began on the date of the first approved MELD/PELD exception. Survival was analyzed in relation to pre-transplantation PaO_2 levels, which were categorized as: <50 mm Hg; 50-59 mm Hg; 60-69 mm Hg; and "unknown" for patients who were granted an HPS MELD/PELD exception without a listed PaO_2 level: <50 mm Hg, 50–59 mm Hg, and 60–69 mm Hg. Patients with HPS with unknown pre-LT PaO_2 values were excluded from this aspect of survival analysis. Unadjusted posttransplantation survival rates were evaluated by HPS versus non-HPS status. For patients with HPS, unadjusted posttransplant survival rates were also analyzed in relation to PaO_2 level, with categories as listed previously.

Statistical analysis

Transplant recipients with and without HPS were compared across several a priori selected variables. Mean and standard deviation (SD) are reported for most continuous variables, and frequencies and percentages are reported for categorical variables; variables displaying a skew in distribution were reported with the median and interquartile range (IQR). A two sample t-test was used where mean and SD are reported, a chi-square test when the number and percentage are reported, and a Wilcoxon test when median and IQR are reported.

Survival rates were calculated at 1-,3-, and 5-year intervals across PaO_2 categories and HPS status along with 95% confidence intervals (CIs). In addition, 5-year post-LT survival was assessed across PaO_2 categories for patients with HPS using Kaplan–Meier curves and log-rank tests. Similarly, waitlist mortality/removal was assessed for a wider cohort of all listed patients using cumulative incidence curves comparing patients with and without HPS using log-rank tests.

Additional survival analysis was performed to identify predictors of overall survival using a Cox proportional hazards model. We identified variables from Tables 1 and 2 that showed a significant difference overall or within a subcategory of a categorical variable when controlling for HPS status. Selected variables were modeled together and displayed with adjusted hazard ratios (HRs), 95% CIs, and log-rank test p values.

A p value < 0.05 was considered significant. All statistics were performed in R Version 4.0 (R Foundation for Statistical Computing).

RESULTS

Patient characteristics

A total of 3082 pediatric LT recipients were included in the study, and clinical and demographic characteristics are listed in Table 1. Based on the HPS diagnostic criteria, 124 patients (4%) received MELD/PELD exception points for HPS. Patients with HPS were a median age of 9 years (IQR: 6, 12 years), 54.8% were girls, and 54.0% were White. Most patients (87.9%) were listed with a laboratory MELD/PELD score <15. There were no differences in sex, race, or blood type between patients with and without HPS. When compared with patients without HPS, children with HPS were more likely to have a primary diagnosis of hepatocellular liver disease ($p < 0.01$), a lower laboratory PELD score at listing ($p < 0.01$), less likely to have a history of ascites at listing ($p = 0.02$), and less likely to be hospitalized at the time of transplant ($p = 0.05$).

Variables associated with HPS status and end-stage liver disease noted in MELD/PELD exception application narratives were evaluated and categorized as summarized in Table 2. These include shunting, portal hypertension, splenomegaly, thrombocytopenia, varices, home O_2 use, ascites, prior gastrointestinal bleeding, clubbing, and underlying pulmonary disease. To improve sample size for further analysis, we combined HPS criteria from Table 2 into categories for "portal hypertension related" (portal hypertension, splenomegaly, thrombocytopenia, varices, prior gastrointestinal bleeding, and ascites) and "pulmonary symptoms" (shunting, supplemental O_2, clubbing, underlying pulmonary disease). Portal hypertension–related pretransplant variables did not impact the 5-year overall survival rates (HR = 0.80 [95% CI: 0.22, 2.88]; $p = 0.74$). Similarly, pulmonary symptoms were not associated with inferior survival at 5 years after transplant (HR = 0.39 [95% CI: 0.09, 1.77]; $p = 0.22$).

Posttransplant survival

First, posttransplantation survival was compared between patients with HPS and patients without HPS (Table 3). The 1-, 3-, and 5-year posttransplantation survival rates for patients with HPS ($n = 124$) were 93.5%, 88.7%, and 88.7%, respectively. The 1-, 3-, and 5-year posttransplantation survival rates for patients without HPS ($n = 2958$) were 95.7%, 94.4%, and 93.7%, respectively. Patients with HPS showed a slightly lower overall survival at 5 years compared with patients without HPS (88.7% vs. 93.7%; $p = 0.04$).

To evaluate for any potential relationship between pretransplantation PaO_2 level and posttransplantation survival in patients with HPS, unadjusted post-LT survival rates were calculated for each pretransplantation PaO_2 level category, as depicted in Table 3. For patients with a PaO_2 <50 mm Hg ($n = 47$), the 1-, 3-, and 5-year posttransplantation survival rates were 93.6%, 89.4%,

TABLE 1 Clinical and demographic characteristics for pediatric LT recipients with and without HPS between 2007 and 2018

Variable	No HPS, $n = 2958$	HPS, $n = 124$	p value
Age at listing, years	1 (0, 8)	9 (6, 12)	<0.01
Female sex	1509 (51)	68 (54.8)	0.40
Race/ethnicity			
White	1630 (55.1)	67 (54)	0.78
Black	410 (13.9)	14 (11.3)	
Hispanic	652 (22)	32 (25.8)	
Asian	193 (6.5)	7 (5.6)	
Other	73 (2.5)	4 (3.2)	
Primary diagnosis[a]			
Acute failure	51 (1.7)	5 (4)	<0.01
Hepatitis	5 (0.2)	1 (0.8)	
Hepatocellular	144 (4.9)	24 (19.4)	
Chronic cholestatic	1487 (50.3)	57 (46)	
Malignancy	266 (9)	0 (0)	
Other	1005 (34)	37 (29.8)	
Listing laboratory MELD/PELD score			
PELD score	5 (−3, 15)	-2 (−5, 3)	<0.01
MELD score	11 (7, 16)	10 (8, 14)	0.99
Listing laboratory MELD/PELD score category			
<15	2125 (71.8)	109 (87.9)	<0.01
15–20	463 (15.7)	10 (8.1)	
>20	370 (12.5)	5 (4)	
Days on waiting list	91 (42, 202)	70 (32, 173)	0.04
History of ascites before listing	1013 (34.2)	30 (24.2)	0.02
Blood type			
A	935 (31.6)	39 (31.5)	0.46
AB	106 (3.6)	2 (1.6)	
B	444 (15)	15 (12.1)	
O	1473 (49.8)	68 (54.8)	
Medical condition at transplant			
ICU	242 (8.2)	14 (11.3)	0.05
Hospital, not ICU	543 (18.4)	13 (10.5)	
Home	2173 (73.5)	97 (78.2)	

Note: Data are provided as median (IQR) or *n* (%).
Abbreviations: HPS, hepatopulmonary syndrome; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.
[a]Diagnosis groupings are outlined in Table S1.

TABLE 2 Pretransplant clinical presentations documented in MELD/PELD exception narratives for pediatric LT recipients with HPS between 2007 and 2018

Variable	Patients	Alive at 5 years after LT, $n = 107$	Death within 5 years after LT, $n = 14$	p value
PaO_2 categories				
PaO_2 <50 mm Hg	44 (36.4)	39 (36.4)	5 (35.7)	0.45
PaO_2 50–59 mm Hg	40 (33.1)	37 (34.6)	3 (21.4)	
PaO_2 60–69 mm Hg	18 (14.9)	14 (13.1)	4 (28.6)	
PaO_2 not reported	19 (15.7)	17 (15.9)	2 (14.3)	
Portal hypertension related	100 (82.6)	89 (83.2)	11 (78.6)	0.67
Portal hypertension	72 (59.5)	66 (61.7)	6 (42.9)	0.18
Splenomegaly	67 (55.4)	61 (57)	6 (42.9)	0.32
Thrombocytopenia	55 (45.5)	48 (44.9)	7 (50)	0.72
Varices	54 (44.6)	46 (43)	8 (57.1)	0.32
Gastrointestinal bleeding	9 (7.4)	9 (8.4)	0 (0)	0.26
Ascites	23 (19)	21 (19.6)	2 (14.3)	0.63
Pulmonary symptoms	112 (92.6)	100 (93.5)	12 (85.7)	0.30
Supplemental O_2	29 (24)	26 (24.3)	3 (21.4)	0.81
Evidence of shunting	107 (88.4)	95 (88.8)	12 (85.7)	0.74
Clubbing	8 (6.6)	7 (6.5)	1 (7.1)	0.93
Underlying pulmonary disease	4 (3.3)	2 (1.9)	2 (14.3)	0.01

Note: Data are presented as *n* (%) unless otherwise indicated.
Abbreviations: HPS, hepatopulmonary syndrome; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PaO_2, partial pressure of arterial oxygen; PELD, Pediatric End-Stage Liver Disease.

and 89.4%, respectively. For patients with a PaO_2 50–59 mm Hg ($n = 38$), the 1-, 3-, and 5-year posttransplantation survival rates were 97.4%, 92.1%, and 92.1%, respectively. For patients with a PaO_2 60–69 mm Hg ($n = 17$), the 1-, 3-, and 5-year posttransplantation survival rates were 82.4%, 76.5%, and 76.5%, respectively. Kaplan–Meier survival curves with log-rank tests were also generated to evaluate the overall posttransplantation survival relative to pretransplantation PaO_2 level (Figure 1). Patient survival was calculated for up to 5 years after LT for patients with PaO_2 levels <50 mm Hg ($n = 47$), 50–59 mm Hg ($n = 38$), and 60–69 mm Hg ($n = 17$). The differences in posttransplantation survival up to 5 years based on patients' pre-LT PaO_2 levels were not significant ($p = 0.13$).

Next, a Cox proportional hazards model was constructed to identify risk factors for survival after LT (Figure 2). When controlling for race/ethnicity, children with HPS demonstrated a higher risk of death when compared with patients without HPS (adjusted HR = 1.75 [95% CI: 1.0–3.0]; $p = 0.043$). In addition, when controlling for HPS status, Hispanic/Latino children experienced a higher risk of death when compared with White children (adjusted HR = 1.58 [95% CI: 1.15–2.2], $p = 0.005$).

Impact of HPS on pediatric waitlist mortality

To evaluate for potential differences in survival between patients with and without HPS, SRTR data for all waitlist

TABLE 3 Unadjusted 1-, 3-, and 5-year posttransplantation patient survival outcomes

	1-Year survival	3-Year survival	5-Year survival
Stratified by HPS status			
HPS	93.5 (87.7, 97.2)	88.7 (81.8, 93.7)	88.7 (81.8, 93.7)
No HPS	95.7 (94.9, 96.4)	94.4 (93.5, 95.2)	93.7 (92.8, 94.6)
Patients with HPS, stratified by PaO_2			
<50 mm Hg	93.6 (82.5, 98.7)	89.4 (76.9, 96.5)	89.4 (76.9, 96.5)
50–59 mm Hg	97.4 (86.2, 99.9)	92.1 (78.6, 98.3)	92.1 (78.6, 98.3)
60–69 mm Hg	82.4 (56.6, 96.2)	76.5 (50.1, 93.2)	76.5 (50.1, 93.2)

Note: Data are presented as percentage survival (95% CI).
Abbreviations: HPS, hepatopulmonary syndrome; PaO_2, partial pressure of arterial oxygen.

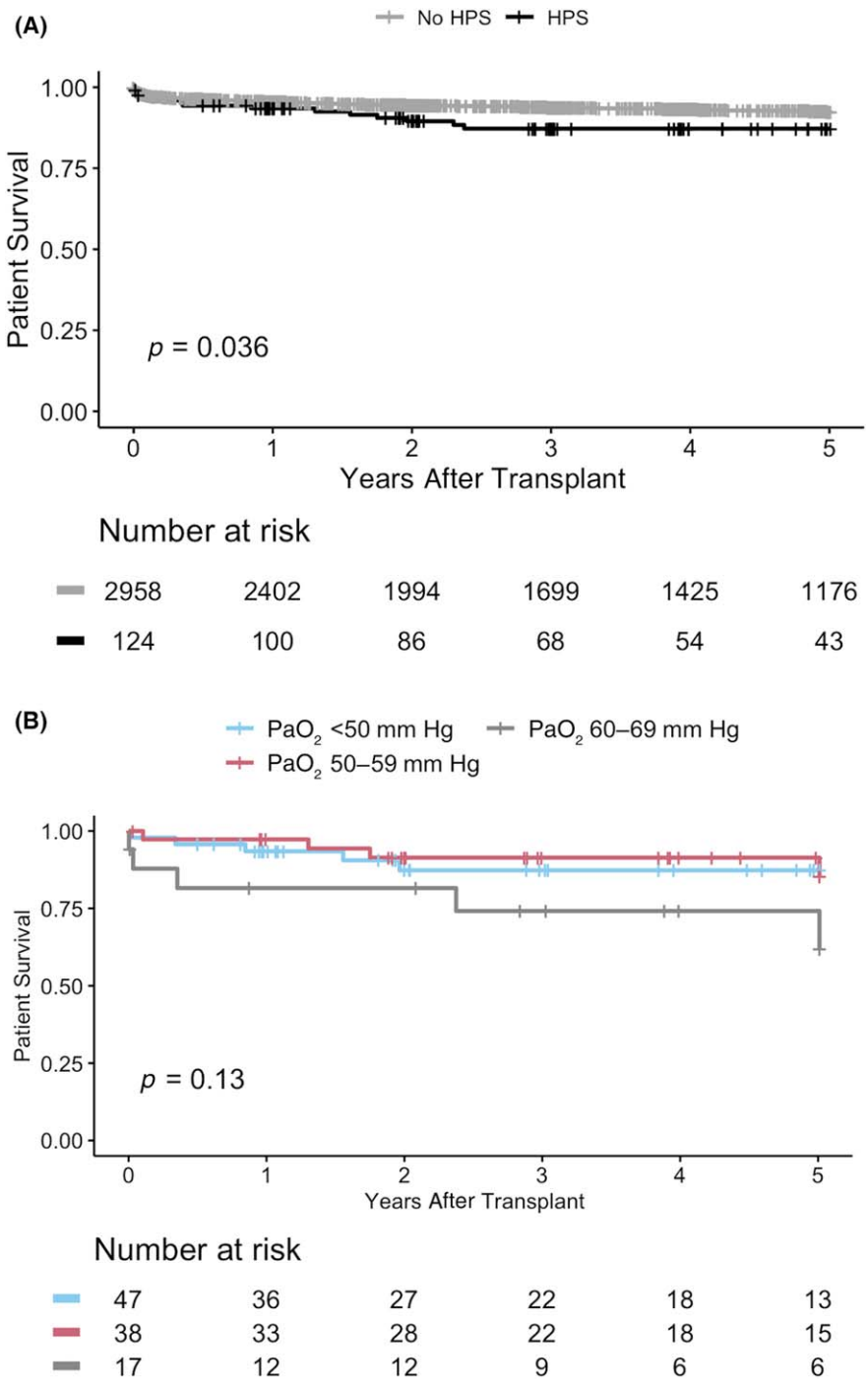

FIGURE 1 Overall survival by HPS status and PaO_2 levels. (A) Overall survival by HPS status. HPS had slightly lower survival rates compared with patients without HPS (log-rank $p = 0.036$). (B) Survival of patients with HPS only by PaO_2 level categories. There was no statistical difference observed between PaO_2 subgroups (log-rank $p = 0.13$).

candidates were also studied (Table 4). The cumulative incidence of death on the waiting list or within 90 days of removal from the waiting list was calculated for each. For patients with HPS ($n = 148$), the cumulative incidence of death at 250, 500, 750, and 1000 days was not different compared with patients without HPS ($n = 3776$) (Figure 3; $p = 0.69$).

DISCUSSION

In this study, we present the largest national analysis of waitlist and post-LT survival outcomes for children with HPS. Our findings confirm that waitlist mortality in children with HPS is mitigated by the MELD/PELD exception system, and recipients with HPS can

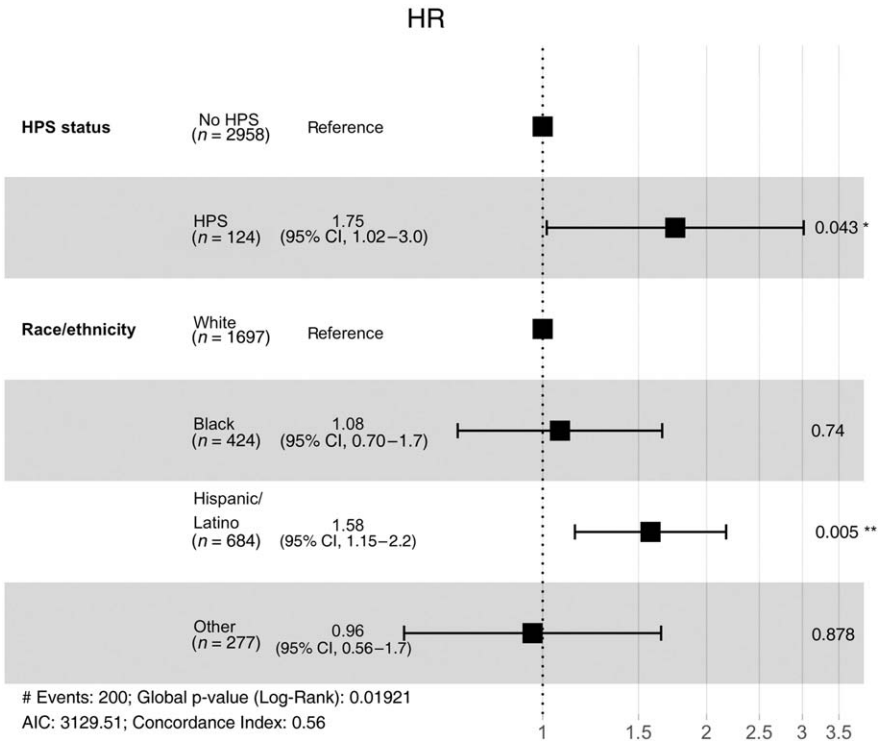

FIGURE 2 Impact of HPS status and race/ethnicity on survival outcomes in children who underwent LT with a MELD/PELD exception for HPS. Results from Cox proportional hazards model for 5-year survival after transplant. When controlling for race/ethnicity, children with HPS demonstrated an increased risk of death after LT. In addition, Hispanic/Latino ethnicity was associated with an increased risk of death after LT compared with White when controlling for HPS status. Akaike information criterion = 3129.51; concordance index = 0.56. Global *p* value (log-rank test) = 0.01921 (200 total events). *$p < 0.05$ and **$p < 0.01$.

experience excellent 5-year survival after LT, although slightly lower than patients without HPS. Granting exception points to HPS candidates meeting established criteria is having its intended effect. However, our finding that severity of pre-LT hypoxemia does not impact post-LT survival in the pediatric population contradicts current policy that factors into consideration the degree of pretransplant hypoxemia prior to granting exception points for LT prioritization.[28] Although these data need to be validated by future cohort studies, they suggest that increasing hypoxemia, unlike in adults, should not be interpreted as a marker of worsened post-LT outcomes in pediatric transplant recipients with HPS. Furthermore, given that pediatric candidates with HPS exception points experience slightly lower 5-year post-LT survival than patients without HPS, current exception policy may be overprioritizing hypoxemia at the expense of other clinical sequelae more predictive of negative outcomes. These data can be used to potentially modify exception policies for pediatric waitlist candidates with HPS to better reflect disease severity and ultimate prognosis.

A limited number of case series studying HPS in children with chronic liver disease requiring LT have been published.[7,10,13,14,31–36] A more recent meta-analysis of both adults and children with HPS reports similar survival outcomes to our study.[37] Although there are robust data to support an association between room air oxygenation and posttransplantation survival in adult HPS patients, the largest studies on this topic in children were just recently published and derived from retrospective cohorts of less than 25 patients each.[38,39] The authors observed that although children with very severe HPS (PaO_2 < 50 mm Hg) required longer durations of mechanical ventilation, longer intensive care unit (ICU) and hospital stays, and longer O_2 weaning time than those with mild, moderate, or severe HPS (PaO_2 > 50 mm Hg), there was no difference in mortality across subgroups. Although our findings also indicate that severity of HPS does not impact post-LT survival in children, our analysis expands on the size and depth of this work. First, our data are derived from a national database reflective of the entire pediatric HPS population on the waiting list and after LT in the United States. Second, we were able to stratify the degree of pre-LT hypoxemia in these patients with more granularity in oxygenation cutoffs. Third, our sample size was nearly sixfold larger and represented experience across multiple transplant centers.

Although the data presented here demonstrate that current exception policy provides children with HPS adequate access to LT with excellent post-LT outcomes, it also raises several questions. Given the paucity of pediatric-specific research in this area,

TABLE 4 Clinical and demographic characteristics for patients with and without HPS on pediatric LT waiting list

Variable	No HPS, $n = 3776$	HPS, $n = 148$	p value
Age at listing, years	2 (0, 9)	9.5 (6, 13)	< 0.01
Female sex	1644 (50.8)	71 (55)	0.34
Race/ethnicity			
White	1789 (55.3)	72 (55.8)	0.79
Black	449 (13.9)	14 (10.9)	
Hispanic	715 (22.1)	32 (24.8)	
Asian	208 (6.4)	7 (5.4)	
Other	615 (16.6)	23 (15.9)	
Listing laboratory MELD/PELD score			
PELD score	4 (−3, 15)	−2 (−5, 4)	< 0.01
MELD score	12 (8, 17)	11 (9, 16)	0.83
Listing laboratory MELD/PELD category			
< 15	2706 (71.7)	126 (85.1)	< 0.01
15–20	588 (15.6)	13 (8.8)	
> 20	482 (12.8)	9 (6.1)	
History of ascites before listing	1073 (28.4)	22 (14.9)	< 0.01
Blood type			
A	1019 (31.5)	41 (31.8)	0.41
AB	115 (3.6)	2 (1.6)	
B	481 (14.9)	15 (11.6)	
O	1622 (50.1)	71 (55)	
Missing	539 (14.3)	19 (12.8)	

Note: Data are provided as median (IQR) or *n* (%).
Abbreviations: HPS, hepatopulmonary syndrome; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.

current OPTN policy requiring PaO_2 < 60 mm Hg[28] to grant MELD/PELD standardized exceptions to pediatric patients with HPS has been guided by findings in adults.[25,40] Our finding that the degree of hypoxemia does not impact post-LT survival ($p = 0.13$) contradicts these assumptions and is consequential for several reasons. First, it merits a reassessment of the relevance that PaO_2 criteria hold for MELD/PELD exception points to be granted to pediatric patients with HPS. This can take heightened importance as it relates to equitable patient outcomes. In our study, patients with PaO_2 levels between 60 and 69 mmHg—those who would not be granted exception points per existing policy—appear paradoxically to have worse outcomes (although not statistically significant) than patients with lower PaO_2 values, typically representative of more severe HPS. Thus, there may be children awaiting LT who suffer from the increased mortality risk associated with HPS who are not adequately prioritized because of an inability to meet the criteria for standardized exceptions based on pre-LT PaO_2. Furthermore, requiring measurement of hypoxemia may pose an undue obstacle to LT for these patients given the widely reported procedural difficulties and subsequent risks of obtaining arterial oxygenation levels in the pediatric population.[41] The transplant community must ultimately reassess the degree to which hypoxemia should merit LT prioritization in pediatric patients with HPS to balance waitlist mortality with post-LT outcomes.

Given these findings, we are left to wonder which factors, if any, may be predictive of survival outcomes for pediatric patients with HPS. Although the research is limited for this specific population, prior studies have revealed predictive factors that could be used to stratify risk in pediatric LT candidates, including those with HPS. First, sarcopenia, as measured by psoas muscle surface area, is prominent in children with end-stage liver disease and has been reported as a useful, objective biomarker for nutritional status.[42] It is associated with adverse outcomes for pediatric LT candidates and has been shown to significantly increase risk of death.[43,44] Second, estimated glomerular filtration rate, dialysis status, and serum sodium levels have also been shown to be predictive of 90-day mortality in pediatric LT candidates.[44] A PELD score that incorporates sodium and creatinine levels has been demonstrated to more accurately reflect medical urgency and could better prioritize children with the knowledge that traditional PELD scores significantly underestimate waitlist mortality, especially compared with adult MELD scores.[45] Thus, further examination of these clinical variables and their relationship to HPS in children may provide insight into more appropriate predictors of morbidity in this population. Lastly, our study is the first to demonstrate a discrepancy in outcomes for patients with HPS based on ethnicity, with Hispanic/Latino patients at an increased risk of death after LT compared with White patients ($p = 0.005$). Thus, we may also need to consider ethnicity as a predictive factor in the HPS population. Ultimately, further prospective multicenter studies are required to assess the relationship between these variables in the context of pediatric HPS to better guide LT prioritization policy.

There are several limitations to our findings as presented. First, similar to adult studies on the topic using a national database, we were unable to apply the stringent criteria to define HPS as used in prospective, multicenter studies.[9,25] Nevertheless, we are confident that most, if not all, patients in our study did indeed have an accurate diagnosis of HPS given that virtually all patients were hypoxemic at transplant and nearly 90% were noted to have evidence of shunting. Second, although we report post-LT outcomes derived from a national database (SRTR) for the largest sample of pediatric patients with HPS studied to date, we cannot match the granularity of data reported in center-specific studies. Lastly, our reliance on data extracted from

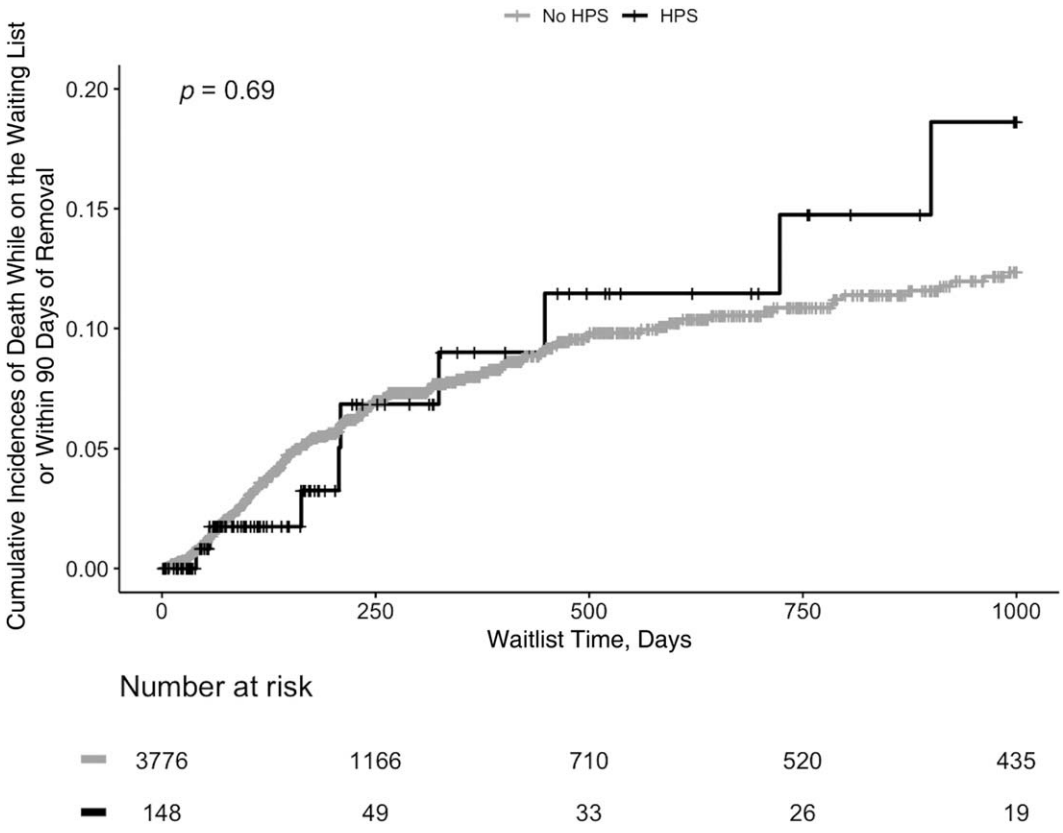

FIGURE 3 Cumulative incidence of death while on the waiting list or within 90 days of removal, stratified by HPS status. There was no difference in waitlist mortality between children with and without HPS.

MELD/PELD exception application narratives leaves us vulnerable to bias resulting from missing data. The HPS features in Table 2 reflect what was reported by each center, and some patients may have exhibited more features than were described in the exception narrative. Given that HPS prevalence is estimated at up to 20% in the pediatric population,[6–8] it is probable that this limitation is further exacerbated by an underreporting of pediatric HPS overall. Indeed, only 4% of pediatric patients with HPS receiving MELD/PELD exceptions points underwent LT, with an even smaller proportion (3.8%) comprising the total pediatric LT waiting list. This further highlights the importance of revisiting current MELD/PELD exception policy for pediatric HPS given the burdens that documenting pre-LT hypoxemia may impose.

In conclusion, we find that the pediatric HPS MELD/PELD exception policy has been successful to the extent that waitlist mortality and post-LT survival outcomes are excellent for pediatric patients with HPS and only marginally worse compared with children without HPS. We also find, however, that the pre-LT arterial oxygenation levels embedded in the current exception policy criteria are not related to post-LT survival in the pediatric population. This finding runs contrary to findings in adults and indicates that the degree of hypoxemia should not be used as a predictive factor for post-LT survival in pediatric patients with HPS in the way that it is currently being used for adults. Our study suggests that current criteria are leading to waitlist prioritization based on an arbitrary factor, potentially resulting in inequitable outcomes that could be mediated with the modification of current policy. We hope that these findings will be considered as policies continue to evolve to better reflect true risk factors and prognoses, especially considering a pattern of research highlighting systemic disadvantages children face compared with adults on the LT waiting list.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

Kambiz Etesami owns stock in Johnson & Johnson and Pfizer.

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