Temporal Trends in Portopulmonary Hypertension Model for End-stage Liver Disease Exceptions and Outcomes

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INTRODUCTION

Portopulmonary hypertension (POPH) describes pulmonary arterial hypertension (PAH) that develops within the setting of cirrhotic or noncirrhotic portal hypertension and is recognized as a subset of group 1 PAH. Like other forms of PAH, it has been classically defined by precapillary pulmonary hypertension, defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg and pulmonary vascular resistance (PVR) >3 wood units (WU) with a normal pulmonary arterial wedge pressure ≤15 mmHg. Of note, recently1 there has been a proposed change to decrease the mPAP threshold to >20 mmHg to facilitate earlier diagnosis.1 A diagnosis of POPH also requires that alternative causes of PAH be excluded. POPH affects an estimated 5% to 6% of patients with advanced liver disease2–4 and is associated with worse outcomes, including increased mortality. Without PAH-directed therapy or liver transplant (LT), 5-y survival is poor (14%).5

POPH patients also have increased peri- and postoperative risk when undergoing LT.6,7 However, the model for end-stage liver disease (MELD) laboratory score, which plays a key role in determining LT waitlist priority, does not take such additional risk into account. Therefore, since 2006, these patients have been eligible for MELD exception points, with the goal of appropriately prioritizing patients for LT before possible POPH disease progression and eventual right heart failure. Per the Organ Procurement and Transplantation Network (OPTN) guidelines, the original criteria for POPH MELD exception

Background. Model for end-stage liver disease (MELD) exception criteria for portopulmonary hypertension (POPH) were created to prioritize patients for liver transplant before POPH progression. Little is known about trends in POPH exception frequency, disease severity, pulmonary hypertension treatment patterns, or outcomes since the POPH MELD exception began. Methods. Using data from the Organ Procurement and Transplantation Network database, we describe the frequency of POPH MELD exceptions between 2006 and 2019, compare baseline patient characteristics, and characterize trends in liver disease and POPH severity, as well as POPH treatment and outcomes, over time. To facilitate comparison, we divided this 14-y period into 3 “eras” (2006–2010, 2011–2015, and 2016–2019). Results. Between 2006 and 2019, 504 unique POPH MELD exceptions were granted. Both liver disease severity and patient age have increased over time (P=0.04 and P=0.006, respectively). Posttreatment hemodynamic values (mean pulmonary arterial pressure and pulmonary vascular resistance) have significantly improved (P<0.001 and P=0.008, respectively). Treatment with endothelin receptor antagonists has become more prevalent, whereas use of parenteral therapy and monotherapy regimens has decreased (P<0.001). Neither waitlist nor liver transplant mortality outcomes have significantly changed over the eras analyzed. Conclusions. In conclusion, 504 patients have received POPH MELD exceptions between 2006 and 2019. Since 2010, nearly all patients granted POPH MELD exceptions have met hemodynamic criteria for POPH. Over time, there has been a trend toward older age and higher MELD scores with significant changes in pulmonary arterial hypertension treatment patterns and an improvement in posttreatment hemodynamics without major change in outcomes. (Transplantation Direct 2022;8: e1410; doi: 10.1097/TXD.0000000000001410).
points included the following: (1) diagnosis of POPH via right heart catheterization (RHC) demonstrating mPAP >35 mmHg, (2) concurrent portal hypertension, (3) documented treatment with US Food and Drug Administration–approved PAH therapy, and (4) posttreatment RHC confirming mPAP <35 mmHg and PVR <400 dynes*sec/cm$^5$ or <5 WU. Of note, POPH MELD exception criteria were recently revised in 2021 to reflect newer evidence regarding POPH patients’ peri- and post-LT outcomes, as well as advancements in treatment of POPH patients with PAH therapies. Specifically, the updated criteria allow for exception points to be granted to patients with either of the following posttreatment hemodynamic profiles: mPAP <35 mmHg and posttreatment PVR <400 dynes*sec/cm$^5$ (or <5 WU) or mPAP ≥35 mmHg and <45 mmHg and posttreatment PVR <240 dynes*sec/cm$^5$ (or <3 WU).

Since the POPH MELD exception began in 2006, little is known about whether there have been significant changes in frequency of approved exceptions, POPH or liver disease severity, PAH-targeted treatment patterns, or posttransplant outcomes over time. Using data from the OPTN database, we sought to describe the frequency of approved POPH MELD exceptions in the United States between 2006 and 2020 and to characterize trends in liver disease and pulmonary hypertension (PH) severity, as well as treatment and posttransplant outcomes. Our goal was to provide insight into both patient characteristics and POPH treatment trends to help inform future practice recommendations and policies. Given the advances in PAH therapeutic options over the past several years, we hypothesized that POPH MELD exception frequency has decreased over time and that waitlist and posttransplant survival have improved.

**MATERIALS AND METHODS**

**Study Design**

We performed a retrospective cohort study from the OPTN database.

**Subjects**

All patients in the OPTN database that applied for an initial or extension POPH MELD exception by regional LT review boards were eligible for the study. We included patients ≥18 y old who were approved for an initial POPH MELD exception between January 1, 2006, and December 31, 2019. Duplicate listings of candidates (eg, at multiple centers), those whose exception applications were not approved or withdrawn, and exceptions with missing approval dates were excluded. Demographic and additional patient characteristics (eg, MELD score) were provided by OPTN. We reviewed exception narratives to extract hemodynamic data and PH-targeted treatment information. We divided this 14-y period into 3 “eras” (era 1: 2006–2010, era 2: 2011–2015, era 3: 2016–2019) to assess changes over time and facilitate identification of patterns. These were chosen with the aim of being roughly equivalent in length, although era 3 is shorter by 1 y given the 14-y time period. Additionally, in 2010, the POPH MELD exception criteria were formalized within a standardized application format, and there have been no newly approved PAH therapies since 2015.

**Hemodynamic and Laboratory Values**

As stated earlier, MELD exception narratives were reviewed, and hemodynamic values were extracted. Initial hemodynamic values (mPAP, PVR, etc.) refer to measurements taken during earliest reported (diagnostic) RHC. “Posttreatment” hemodynamic values refer to data collected during the first RHC performed after initiation of PAH therapy. When PVR values were given in WU, they were multiplied by 80 to convert to dynes/cm$^5$. Throughout our analysis, MELD score indicates native MELD laboratory score reported at time of initial listing for LT.

**PAH Therapy**

PAH therapy was determined from MELD exception narratives. Patients in the monotherapy group received monotherapy for the entire duration of their waitlist course. The remainder received combination therapy with >1 therapeutic class. Patients treated with an individual class of therapy, such as phosphodiesterase 5 inhibitors, at any point during their waitlist course were included within that therapeutic class category.

**Outcomes**

We defined waitlist mortality as waitlist removal for death or clinical deterioration. This included OPTN codes “died,” “too sick for transplant,” and “medically unsuitable” because prior studies have shown that removal from the waitlist for clinical deterioration is equivalent to death.9,10 Waitlist candidates who were removed for transplantation or other reasons were censored at the time of waitlist removal. We also compared likelihood of LT among patients in each era by comparing time from exception approval to LT as detailed later. We also examined post-LT mortality. Only patients who underwent LT were included in this analysis. Posttransplant mortality was defined by death following LT. Patients who were listed as alive were censored at the time of last follow-up.

**Statistical Methods**

Data were summarized using mean ± standard deviation (SD) or n (%). We compared baseline patient characteristics, liver disease severity (as determined by MELD score), and POPH severity (as determined by hemodynamic data obtained via RHC) across eras using the 1-way analysis of variance, chi-square, or Fisher exact test as appropriate. For our survival analysis, we used a Cox proportional hazards model, adjusting for a priori determined variables of age and initial MELD score. We also performed a sensitivity analysis in which only patients who met initial hemodynamic criteria for POPH were included. Kaplan-Meier survival curves were generated and the log-rank test was used to compare unadjusted survival over time among eras. To compare time to transplantation, we used the Fine and Gray competing risk method to compare the subdistribution hazard of LT when accounting for the competing risk of waitlist death or clinical deterioration.11 Significance was defined as a P value <0.05. All data were analyzed in SAS, version 9.4 (SAS Institute, Cary, NC). The study was approved by the institutional review board (Mayo Clinic, IRB 20-004326), OPTN, and the Health Resources and Services Administration.

**RESULTS**

**Number of POPH MELD Exceptions and Patient Demographics**

A total of 504 POPH initial MELD exceptions were approved between 2006 and 2020 and were included in
our final analysis. The flow diagram of patients included and excluded is shown in Figure 1. Forty-one patients were excluded: 17 denials, 3 withdrawn, 13 with no approval date, and the remainder with approval dates before 2006 or later than December 31, 2019. The number of exceptions approved per year is depicted in Figure 2A. Following 2006 to 2008, there was an increase in the total number of exceptions approved that has remained relatively stable over time with some fluctuations from year to year and a recent decrease in 2019. The number of patients granted POPH MELD exceptions as a percentage of total annual waitlist additions has followed a similar pattern (Figure 2B). Over time, the average age of patients granted exceptions increased, whereas there were no significant differences in sex distribution or body mass index (Table 1). Primary etiologies of liver disease have varied significantly over time, with the frequency of hepatitis C (HCV) decreasing and nonalcoholic steatohepatitis (NASH) increasing. Overall waitlist time has not significantly changed. Additional patient characteristics are fully detailed in Table 1.

Liver Disease Severity and LT

Over time, POPH MELD exception patients had worsening liver disease severity at the time of listing, as indicated by the MELD score gradually increasing in more recent eras: 12.9 ± 4.5 in era 1, 13.4 ± 4.8 in era 2, and 14.4 ± 5.4 in era 3 (P = 0.04). Compared with era 1, MELD exception patients in era 2 (subdistribution HR 0.68; 95% CI, 0.52-0.91; P = 0.008) and era 3 (subdistribution HR 0.72; 95% CI, 0.54-0.96; P = 0.03) were less likely to get transplanted, but there was no significant difference between eras 2 and 3 (subdistribution HR 1.06; 95% CI, 0.83-1.34). Results were similar with significant differences between eras 2 and 3 compared with era 1 when models were adjusted for age and initial MELD score. Among patients who ultimately underwent LT, the transplant hospitalization length of stay did not change significantly over time (Table 1).

Pulmonary Hemodynamics

Initial POPH disease severity at the time of diagnosis, as measured by RHC hemodynamic parameters (mPAP, PVR), was overall similar between the 3 eras (Table 2). Given how many patient entries were missing data on cardiac output (CO), we did not include it in our final analysis. Notably, the proportion of patients that met specific hemodynamic criteria for POPH (defined as mPAP ≥25 mmHg AND PVR >3 WU) documented on initial RHC increased significantly in later eras. Before 2010, only 53.9% (56/104) of patients granted exceptions met hemodynamic (mPAP, PVR) criteria, but since then, nearly all (≥95%) have met hemodynamic criteria for POPH (Table 2).

In contrast to POPH severity at the time of diagnosis (per initial RHC hemodynamics), pre-LT, posttreatment mPAP, and PVR were lower in later eras (P < 0.001 and 0.008, respectively) (Table 2). The proportion of patients with posttreatment mPAP <35 mmHg also increased over time: 71.2% in era 1, 90.7% in era 2, and 90.2% in era 3 (P < 0.0001). Similarly, the proportion of those with posttreatment PVR <3 WU also increased in later eras (Table 2).

Pre-LT PH Treatment Patterns

There were several changes in PH-targeted therapy use (Table 3; Figure 3). Over time, the frequency of parenteral prostacyclin therapy has declined, used in 57.4% of patients granted exceptions in era 1 compared with 34.7% in era 2 and 27.2% in era 3. Conversely, there has been an increase in the use of oral agents, including both phosphodiesterase 5 inhibitors, such as sildenafil and tadalafil (61.4% in era 1 versus 77.2% in era 3) and endothelin receptor antagonists (ERA) (15.8% in era 1 versus 57.6% in era 3) (Table 3; Figure 3). Use of monotherapy has fluctuated over time with a decrease in the most recent era.

Survival

Among all patients, there was no difference in unadjusted waitlist survival over time (log-rank P = 0.38) (Figure 4). Among all patients who underwent LT, there was no difference in unadjusted posttransplant survival over time (log-rank P = 0.46) (Figure 5). In a sensitivity analysis of only patients meeting initial hemodynamic criteria for POPH, results were similar (log-rank P = 0.51 and log-rank P = 0.41, respectively). In multivariate analysis adjusting for initial age and MELD score, approval era was not significantly associated with waitlist mortality (era 2 compared with era 1 as a reference: HR 1.11; 95% CI, 0.64-1.93; P = 0.70; era 3 compared with era 1 as a reference: HR 0.75; 95% CI, 0.42-1.34; P = 0.33) or posttransplant mortality (era 2 compared with era 1 as a reference: HR 0.94; 95% CI, 0.52-1.70; P = 0.84; era 3 compared with era 1 as a reference: HR 1.29; 95% CI 0.65-2.57; P = 0.46).

DISCUSSION

In our retrospective analysis of 504 POPH MELD exceptions approved between 2006 and 2020, we identified several significant trends in disease severity and treatment patterns. Over time, there has been an increase in the average age of patients with approved POPH MELD exceptions, as well as an increase in MELD score, indicative of more advanced liver disease. Similar to trends in liver disease etiology among all LT candidates, we also noted a decline in HCV and an increase in NASH as primary diagnoses among patients with POPH MELD exceptions over time. Initial POPH disease severity has not changed over time, but posttreatment pulmonary hemodynamics (mPAP

FIGURE 1. Flow diagram of patients included and excluded in final analysis. MELD, model for end-stage liver disease; POPH, portopulmonary hypertension.
and PVR) have improved in more recent eras. There has also been an overall decline in the use of parenteral therapy and an increase in the use of oral PAH-targeted therapy. Although other analyses of POPH MELD exception LT candidates have been previously published, our study is novel because it is the first to provide important insights into the temporal trends of liver disease etiology and severity and POPH severity and treatment over time. As most individual POPH studies are small and often span a long period of time, these insights help to provide context for critical analysis and interpretation of the literature.

Since the inception of the POPH MELD exception in 2006, there has been variability in the number of POPH MELD exceptions approved per year, both in the use of parenteral therapy and an increase in the use of oral PAH-targeted therapy. Although other analyses of POPH MELD exception LT candidates have been previously published, our study is novel because it is the first to provide important insights into the temporal trends of liver disease etiology and severity and POPH severity and treatment over time. As most individual POPH studies are small and often span a long period of time, these insights help to provide context for critical analysis and interpretation of the literature.

Since the inception of the POPH MELD exception in 2006, there has been variability in the number of POPH MELD exceptions approved per year, both in the use of parenteral therapy and a proportion of annual LT waitlist additions. In 2006 to 2008, there were notably <20 exceptions per year with a greater number of exceptions in later years, peaking at 56 and 66 in 2017 and 2018, respectively. Interestingly, there was a significant decline in the number of exceptions approved in 2019. This could potentially be the result of delayed data capture from 2019. The exact reasons for the overall variability cannot be determined, but the general increase in later years could be due to increased awareness of the POPH MELD exception over time and/or an increase in therapeutic options for POPH, allowing more patients to meet the MELD exception posttreatment hemodynamic criteria. It is possible that awareness of the POPH MELD exception has grown and that transplant teams have become more comfortable with the criteria and overall application process. Furthermore, over the past 15 y, there has been increased appreciation for the complex relationship between POPH and LT among hepatologists and PH specialists, as well as increased understanding of the role and potential benefit of LT in the management of POPH. Additionally, the general increase in exception frequency over time may be related to the shifting epidemiology in etiology of cirrhosis seen in this cohort, specifically the decline

FIGURE 2. Approved portopulmonary hypertension MELD exceptions per year. A, Number of POPH MELD approved exceptions per year. B, Number of POPH MELD exceptions approved as percentage of total liver transplant waitlist additions in candidates 18+ (source of total waitlist additions: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#). MELD, model for end-stage liver disease; POPH, portopulmonary hypertension.
in HCV, which is associated with a decreased risk of POPH, and increase in other causes, including NASH.16 In a prior analysis of approved POPH MELD exceptions between 2006 and 2012, Goldberg et al found that only 47% of patients met formal OPTN exception criteria for POPH and that one third either did not fulfill hemodynamic criteria for POPH or had missing data.17 Reassuringly, we have found that there has been a significant improvement over time in the proportion of patients granted POPH MELD exceptions who met hemodynamic criteria for POPH. After 2010, nearly all (≥ 95%) met hemodynamic criteria, compared with roughly half (54%) of patients approved from 2006 to 2010.

### TABLE 1.

| Characteristic                | Era 1 2006–2010 (n = 104) | Era 2 2011–2015 (n = 216) | Era 3 2016–2019 (n = 184) | P     |
|------------------------------|----------------------------|----------------------------|----------------------------|-------|
| Initial age, y               | 51.2 ± 7.7                 | 52.9 ± 9.4                 | 54.8 ± 9.6                 | 0.006 |
| Male sex                     | 58/104 (56.8%)             | 116/216 (53.7%)            | 85/184 (46.2%)             | 0.20  |
| Body mass index, kg/m²       | 28.4 ± 5.1                 | 28.5 ± 5.9                 | 28.8 ± 5.4                 | 0.83  |
| Initial MELD laboratory score| 12.9 ± 4.5                 | 13.4 ± 4.8                 | 14.4 ± 5.4                 | 0.04  |
| Initial bilirubin, mg/dL     | 2.2 ± 1.7                  | 2.3 ± 3.0                  | 2.2 ± 1.6                  | 0.82  |
| Initial albumin, g/dL        | 3.2 ± 0.7                  | 3.3 ± 0.7                  | 3.4 ± 0.7                  | 0.04  |
| Initial INR                  | 1.3 ± 0.2                  | 1.4 ± 0.3                  | 1.3 ± 0.3                  | 0.41  |
| Initial sodium, mEq/L        | 136.3 ± 4.4 (n = 90)       | 137.3 ± 4.0 (n = 212)     | 137.2 ± 4.0 (n = 184)     | 0.10  |
| Initial creatinine, mg/dL    | 1.1 ± 1.0 (n = 100)        | 1.2 ± 1.2 (n = 214)       | 1.3 ± 1.5 (n = 184)       | 0.48  |

**Etiology of liver disease**

| Etiology of liver disease | Era 1 2006–2010 (n = 104) | Era 2 2011–2015 (n = 216) | Era 3 2016–2019 (n = 184) | P     |
|---------------------------|----------------------------|----------------------------|----------------------------|-------|
| HCV                       | 41/104 (39.4%)             | 70/216 (32.4%)             | 32/184 (17.4%)             | <0.001|
| Autoimmune                | 4/104 (3.8%)               | 16/216 (7.4%)              | 7/184 (3.8%)               |       |
| Cryptogenic               | 8/104 (7.7%)               | 11/216 (5.1%)              | 14/184 (7.6%)              |       |
| NASH                      | 3/104 (2.9%)               | 19/216 (8.8%)              | 34/184 (18.5%)             |       |
| ETIH                      | 19/104 (18.3%)             | 37/216 (17.1%)             | 45/184 (24.5%)             |       |
| ETIH + HCV                | 9/104 (8.6%)               | 11/216 (5.1%)              | 7/184 (3.8%)               |       |
| PBC                       | 2/104 (1.9%)               | 14/216 (6.5%)              | 11/184 (6.0%)              |       |
| Other                     | 13/104 (12.5%)             | 24/216 (12.5%)             | 23/184 (12.5%)             |       |
| HCC                       | 5/104 (4.8%)               | 14/216 (6.5%)              | 11/184 (6.0%)              |       |
| Waitlist time, y          | 1.9 ± 2.6                  | 2.0 ± 2.6                  | 1.7 ± 2.1                  | 0.52  |
| Liver transplant hospitalization length of stay, d | 16.1 ± 18.3 | 13.3 ± 14.8 | 15.3 ± 13.4 | 0.39 |

Bold indicates it meets criteria for statistical significance (P < 0.05).

### TABLE 2.

**Pulmonary hemodynamics per RHC**

| Characteristic                | Era 1 2006–2010 | Era 2 2011–2015 | Era 3 2016–2019 | P     |
|------------------------------|-----------------|-----------------|-----------------|-------|
| POHP (defined as initial mPAP ≥25 mmHg and PVR >3 WU)* | 56/104 (53.9%) | 210/216 (97.2%) | 175/184 (95.1%) | <0.001|
| Initial mPAP (mmHg)          | 48.2 ± 9.0      | 45.8 ± 10.0     | 46.2 ± 9.4      | 0.13  |
| Initial PVR (dynes/s/cm²)    | 512.7 ± 315.1   | 489.8 ± 286.5   | 532.8 ± 335.4   | 0.40  |
| Posttreatment mPAP (mmHg)    | 32.1 ± 6.7      | 29.1 ± 5.3      | 28.3 ± 6.2      | <0.001|
| Posttreatment PVR (dynes/s/cm²) | 230.1 ± 120.4 | 195.2 ± 87.3 | 187.0 ± 98.5 | 0.008 |
| Posttreatment POHP <35 mmHg  | 67/94 (71.2%)   | 196/216 (90.7%) | 165/183 (90.2%) | <0.0001|
| Posttreatment POHP <240 dynes/s/cm² (3 WU) | 45/67 (67.2%) | 157/210 (74.8%) | 141/178 (79.2%) | 0.002 |

Bold indicates it meets criteria for statistical significance (P < 0.05).

mPAP, mean pulmonary arterial pressure; POHP, POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, wood units.
are multiple plausible explanations for this. First, although POPH exception criteria were suggested and began being implemented by regional review boards in 2006, they were formally and uniformly standardized in 2010. This policy change also included a mechanism for entering the required hemodynamic data into the exception request in a standardized way. Interestingly, with greater adherence to hemodynamic criteria in later eras, we also observed that patients in eras 2 and 3 were less likely to undergo LT than patients in era 1, which may be due to the rise in median MELD at transplant over time in addition to the recognition that POPH alone should not be an indication for LT, so centers may have opted to defer some patients for LT in the alter eras based on their clinical course. Finally, there was more missing initial hemodynamic data in era 1 than eras 2 and 3 (Table 2). Therefore, although our analysis had less missing

| Treatment                                        | Era 1 2006–2010 | Era 2 2011–2015 | Era 3 2016–2019 | P    |
|--------------------------------------------------|-----------------|-----------------|-----------------|------|
| PDE5i therapy                                    | 62/101 (61.4%)  | 168/216 (77.8%) | 142/184 (77.2%) | 0.004|
| ERA therapy                                      | 16/101 (15.8%)  | 83/216 (38.4%)  | 106/184 (57.6%) | <0.001|
| Parenteral therapy                               | 58/101 (57.4%)  | 75/216 (34.7%)  | 50/184 (27.2%)  | <0.001|
| Monotherapy                                      | 28/101 (27.2%)  | 90/216 (41.7%)  | 61/184 (33.2%)  | 0.04 |
| Inhaled prostacyclin therapy                     | 9/101 (8.9%)    | 28/216 (13.0%)  | 17/184 (9.2%)   | 0.42 |
| Soluble guanylate cyclase stimulator therapy     | 0               | 0               | 0/184           | N/A  |

Bold indicates it meets criteria for statistical significance (P < 0.05).

ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension.

**FIGURE 3.** PH treatment trends. PH, pulmonary hypertension.

**FIGURE 4.** Waitlist survival by era.
data in earlier years than prior studies, conclusions about hemodynamics in era 1 (2006-2010) should still be interpreted with caution.

Over time, there was a trend toward older age and more advanced liver disease at the time of listing. One potential explanation for the temporal increase in age may be the increase in proportion of patients with liver disease secondary to NASH as discussed earlier because NASH has been shown to be associated with older age in LT registrants compared with HCV and other forms of liver failure. Nonetheless, although the reason for older age is largely speculative (other possible explanations: delay in POPH diagnoses, expanding the age of the transplant candidate pool, etc.), there are possible reasons for the trend in higher MELD scores over time. First, there has been increasing evidence, as well as guideline recommendations, that POPH should not be considered an indication for LT by itself in the absence of decompensated liver disease. Initial case series, subject to publication bias, reported improvement in POPH following LT, but more recent, larger studies have demonstrated that only half of patients are able to be weaned off PAH therapy post-LT. Therefore, providers may be delaying exception applications or delaying LT for those with exceptions until patients have more advanced liver disease given current guidelines and this recent evidence. Prior analyses of the OPTN database by our group also found that patients with a low MELD score, particularly those with less severe PH, had excellent waitlist survival and may not be appropriate candidates for POPH MELD exception because there is no guarantee of improvement in POPH following LT. Notably, a retrospective analysis of LT recipients with alcoholic hepatitis using OPTN data revealed a recent trend toward younger age and did not show significant differences in baseline MELD score between 2014 and 2019. Thus, our findings may be unique to the POPH MELD exception cohort.

Initial PH disease severity was unchanged over time, suggesting that screening recommendations may need revision in terms of which patients should undergo RHC to confirm the diagnosis of POPH. Current American Association of the Study of Liver Disease (AASLD) and International Liver Transplant Society (ILTS) guidelines recommend that potential LT candidates be referred for RHC if screening transthoracic echocardiogram reveals right ventricular systolic pressure above 45 mmHg. However, given that the average initial mPAP was above 45 throughout all 3 eras, our data support the potential consideration of lowering this screening threshold to promote earlier diagnosis and treatment of POPH. Having said that, our analysis also demonstrated a significant improvement in posttreatment mPAP and PVR in later years, suggesting that treatment regimens have become more robust and effective given that initial hemodynamics remain the same. This is consistent with numerous studies demonstrating efficacy of PAH treatment in POPH patients. PAH therapies in POPH have been associated with improvements in hemodynamics, LT risk stratification, and functional outcomes such as 6-min walk distance. Within our study cohort, it is somewhat surprising that there has been an improvement in posttreatment hemodynamics over time in the setting of a decline in use of parenteral therapy, but this may be related to more judicious use of parenteral therapy in patients with moderate to severe POPH and an increase in availability of oral PAH treatment options, often used in combination therapy. There was an increase in the use of oral agents over time, particularly ERAs, and a decline in the use of monotherapy in the most recent era. This reflects treatment advances in PAH seen not only in POPH but also idiopathic and other forms of group 1 PH. These observations provide insight into the changing patterns of POPH treatment over time and, to our knowledge, summarize treatment in the largest cohort of LT candidates with POPH to date.

Neither transplant hospitalization length of stay, waitlist survival, nor post-LT survival changed significantly over time, although we may have been underpowered to detect differences in survival between eras. Notably, outcomes did not change in later years despite improved posttreatment hemodynamics and an increase in PAH therapeutic options, suggesting that there are multiple factors that play a role in determining outcomes in LT candidates with POPH. Although there was no significant change in survival, waitlisted patients in later eras were less likely to undergo LT than patients who received POPH MELD exceptions in era 1. Finally, survival in this cohort was notably better than the overall 5-y survival among POPH patients in the REVEAL registry (40%).

**FIGURE 5.** Post-LT survival by era. LT, liver transplant.
although direct comparisons between studies are biased because comorbidities or inadequate hemodynamic response to PAH therapy may have precluded some patients from LT consideration/eligibility for MELD exceptions.

Our study had several limitations. These include missing data and frequent nonstandardization of information in the MELD exception narratives (especially before 2010), lack of a control group for comparison, the retrospective nature of the study, and lack of availability of other variables that may affect outcomes such as cardiac index, right ventricular function, and other comorbidities. We also chose to include only initial posttreatment RHC values, so subsequent pre- LT hemodynamics may have demonstrated further improvement. As mentioned above, we suspect there may have been a delay in data capture from 2019, resulting in notably fewer approved exceptions. Despite these limitations, this analysis is the only study to date to evaluate trends in disease severity, treatment, and outcomes among all patients granted POPH MELD exceptions since their inception in 2006 through 2019.

There are several evolving developments in this field that will likely influence future trends in this patient cohort. First, given the recent modification to the POPH MELD exception criteria in 2021, future studies to determine the impact of these changes on outcomes will be important. Additionally, starting in May of 2019, the regional review board system changed to a national system, with a computer-based automated review system and assigned scores based on the median MELD at transplant –3 for the area of organ distribution where the patient is listed, as opposed to a score which started at 22 and increased every 3 mo until transplant. Moreover, improved screening to facilitate earlier diagnosis of POPH is needed in addition to reconsideration of the MELD exception hemodynamic thresholds used to define POPH given recent modifications to the definition of precapillary PH (including POPH). Finally, prospective studies aimed at assessing differences in hemodynamic response, RV function, and LT outcomes using different PAH therapy regimens would also be useful to help guide treatment recommendations for these patients.

In conclusion, 504 patients have received POPH MELD exceptions between 2006 and 2019. Since 2010, nearly all patients granted POM MELD exceptions have met hemodynamic criteria for POPH. Over time, there has been a trend toward older age and higher MELD scores with significant changes in PAH treatment patterns and an improvement in posttreatment hemodynamics.

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The data reported here have been supplied by UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government. We thank the OPTN for providing us with these data and allowing us to use them for analysis.

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