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# The Clinical Course of Portopulmonary Hypertension and Outcomes With Endothelin Receptor Antagonist Treatment: Observational Study of Data From the US Organ Procurement and Transplantation Network

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**Background.** Portopulmonary hypertension (PoPH) occurs in patients with advanced liver disease and can be a contraindication to liver transplant (LT). Improvement of hemodynamic parameters with pulmonary arterial hypertension (PAH) therapies (including endothelin receptor antagonists [ERAs]) may help some patients to become eligible for LT. **Methods.** We conducted a retrospective secondary data analysis to describe the clinical course and management of PoPH in patients on a US registry LT waitlist and outcomes in patients receiving an ERA. **Results.** At the time of LT waitlist entry (1996–2019), patient characteristics and disease severity were similar in the 685 patients with PoPH enrolled overall (LT waitlist data set) and the 420 of them who underwent LT (LT data set). Most patients (92.0%) had a model for end-stage liver disease exception granted before entering the LT waitlist. Patients spent a median of 8.9 mo (interquartile range, 3.7–19.7) on the LT waitlist before undergoing LT. Overall, 77.1% of patients received PAH treatment at LT waitlist entry (ERAs, 30.1%). Hemodynamic parameters improved in ≥95% of patients between the first assessment versus the second (median interval, 9 mo) and last assessments (median interval, 14 mo). At the first assessment, 49.6% of patients had mean pulmonary arterial pressure ≥45 mm Hg versus 2.6% and 1.8% of patients at the second and last assessments, respectively; 47.5% of patients had pulmonary vascular resistance >450 dynes·s/cm$^5$ versus 0.9% and 0.2% of patients at the second and last assessments. One-year survival was 90.6% (95% confidence interval [CI], 87.6-92.9) following LT waitlist entry and was 86.4% (95% CI, 82.6-89.5) after LT; 5-y survival was 67.4% (95% CI, 60.0-73.8) while on the LT waitlist (before LT) and was 75.6% (95% CI, 70.4-80.0) following LT. **Conclusions.** This large US study of patients with PoPH on an LT waitlist confirms that effective PAH treatments can help patients achieve acceptable hemodynamics, providing the opportunity to undergo LT.

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Portopulmonary hypertension (PoPH) is a form of pulmonary arterial hypertension (PAH), which develops in patients with portal hypertension and is characterized by elevated pulmonary vascular resistance (PVR) that can lead to right heart failure and death.[1,2] PAH registries indicate that 5% to 18% of patients with PAH have PoPH.[3-5] In a prospective US study, ~5% of patients with advanced liver disease evaluated for a liver transplant (LT) met hemodynamic criteria for

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PoPH: mean pulmonary arterial pressure (mPAP) >25 mm Hg, PVR >3 Wood units (WU), and pulmonary arterial wedge pressure <15 mm Hg.[1,6] PoPH has a poor prognosis when left untreated (1-y survival rate <50%), largely due to advanced liver disease combined with PAH-induced right heart failure.[7,8] Moderate PoPH (mPAP ≥35 mm Hg and elevated PVR >240 dynes·s/cm$^5$ [>3 WU]) and severe PoPH (mPAP >45 mm Hg) are contraindications to LT because of increased risk of cardiovascular mortality and intraoperative death.[1,2,9] Pulmonary hemodynamics can be stabilized or improved through a combination of PAH-targeted therapy and LT.[10,11]

Hemodynamic disease severity predicts survival following LT.[12] It is recommended that patients with PoPH receive PAH therapy to decrease hemodynamic disease severity (mPAP and PVR), improve symptoms and survival, and allow some patients to become eligible for LT.[13,14] The only randomized controlled trial of PAH-targeted therapy in PoPH is PORTICO, in which the endothelin receptor antagonist (ERA) macitentan significantly reduced PVR by 35% versus placebo.[15] A post hoc analysis of the PORTICO study demonstrated that macitentan also improved patients' risk categories for LT waitlist and perioperative mortality.[16] Furthermore, PORTICO raised no hepatic safety concerns with macitentan.[15]

In patients with severe liver disease requiring LT, the model for end-stage liver disease (MELD) score is used to rank LT waitlist candidates according to their needs and the urgency for LT.[2] The United Network for Organ Sharing (UNOS) manages the US Organ Procurement and Transplantation Network (OPTN), which has a system of exception points for prioritizing patients whose illness severity or risk of complications are not captured by the MELD score. Patients with PoPH are eligible for MELD exception points in recognition of their additional cardiovascular and overall mortality risk; this makes it possible for them to undergo LT before progression to severe pulmonary hypertension and right ventricular (RV) failure.[2] MELD exception criteria were defined in 2006 for patients with PoPH and mPAP >35 mm Hg, who achieved hemodynamic improvement (mPAP <35 mm Hg, PVR <400 dynes·s/cm$^5$ [<5 WU], and satisfactory RV function) following treatment with an approved PAH therapy.[2,17] These criteria were revised to allow either of the following post-PAH treatment, pre-LT hemodynamic profiles: mPAP <35 mm Hg and posttreatment PVR <400 dynes·s/cm$^5$ (<5 WU) or mPAP ≥35 mm Hg and <45 mm Hg and posttreatment PVR <240 dynes·s/cm$^5$ (<3 WU).[2]

Real-world data from observational studies have provided insights into clinical management and outcomes in patients with PoPH.[12,18-20] US surveys showed marked variability in screening for PoPH in LT candidates, heterogeneity in PoPH management following LT, and lack of guideline concordance when managing elevated mPAP and PVR to achieve LT eligibility.[12,18] Analysis of patients with idiopathic PAH or PoPH in the US Pulmonary Hypertension Association Registry revealed that patients with PoPH were less likely to receive upfront combination PAH treatment and ERAs.[20]

We conducted a retrospective, longitudinal, descriptive analysis of real-world data from US patients with PoPH on the LT waitlist in the UNOS-OPTN Registry. We evaluated patient characteristics, use of PAH treatment with a specific focus on ERA treatment patterns, changes in hemodynamic parameters, and clinical outcomes with and without LT. We also analyzed outcomes specifically among ERA-treated patients. The rationale is that ERA is the only class of PAH-targeted therapy evaluated in a randomized, controlled trial (PORTICO) in patients with PoPH. In PORTICO, the ERA, macitentan, significantly reduced PVR versus placebo.[15] Despite this evidence, ERAs are underused in patients with PoPH.[20] To build on this evidence and to examine long-term outcomes among patients with PoPH treated with ERAs, the current analysis evaluated the impact of ERAs in a population of patients with PoPH eligible for LT.

## MATERIALS AND METHODS

### Study Design

This analysis used data from the US UNOS-OPTN Registry (Figure 1). The main objective was to describe the clinical course of PoPH in patients on the OPTN-UNOS LT waitlist, including patient characteristics, PAH severity, PAH treatments, hemodynamics at LT waitlist registration and at LT, time on the LT waitlist, and LT waitlist and post-LT survival.

Data analysis was conducted under Janssen Research and Development protocol number NOPRODPAH4009 and approved by an independent, accredited institutional review board (WCG IRB; protocol number 20192714). The use of UNOS-OPTN data for this study was approved by the US Health Resources and Services Administration. No additional approval was required for secondary analysis of existing data, and confidentiality of patient records was maintained.

### Data Source

The data source was a modified UNOS-OPTN data set meeting predefined criteria: data were already collected, cleaned, and ready for analysis; the data source included incident and/or prevalent patients with PoPH, with any PAH treatment, irrespective of PAH and liver disease severity; and follow-up information was provided for at least 1 time point, including LT eligibility and/or post-LT outcomes. Anonymized, patient-level data were provided to the study sponsor through a data-sharing agreement.

LT waitlist candidates with PoPH were identified from the registry (data cut September 30, 2019) per the treating physician's assessment. For patients with PoPH, MELD exception was granted in cases of improved PAH, with mPAP ≤35 mm Hg, PVR <400 dynes·s/cm$^5$ (<5 WU), and satisfactory RV function. This first assessment corresponded with the first report by the treating physician to request a MELD exception; therefore, the MELD exception request could have occurred later than the LT waitlist registration date. MELD exception score and MELD exception granted were separate variables.

### Data Variables and Statistical Analyses

All analyses are descriptive. The schedule of assessments (including right heart catheterization [RHC]) was at the treating physician's discretion. Variables described for the LT waitlist data set and LT data set (patients with PoPH on the LT waitlist who received LT) at registry entry, or at the time of LT, or after LT waitlist registration follow-up, included demographics (age, sex, body mass index, and race/ethnicity), liver disease severity (MELD score), PAH disease history (age at diagnosis, time since diagnosis), hemodynamic parameters (PVR, mPAP), PAH treatment (none, monotherapy, double therapy, or triple therapy, and by treatment class; assignment of treatment as monotherapy or combination was based on

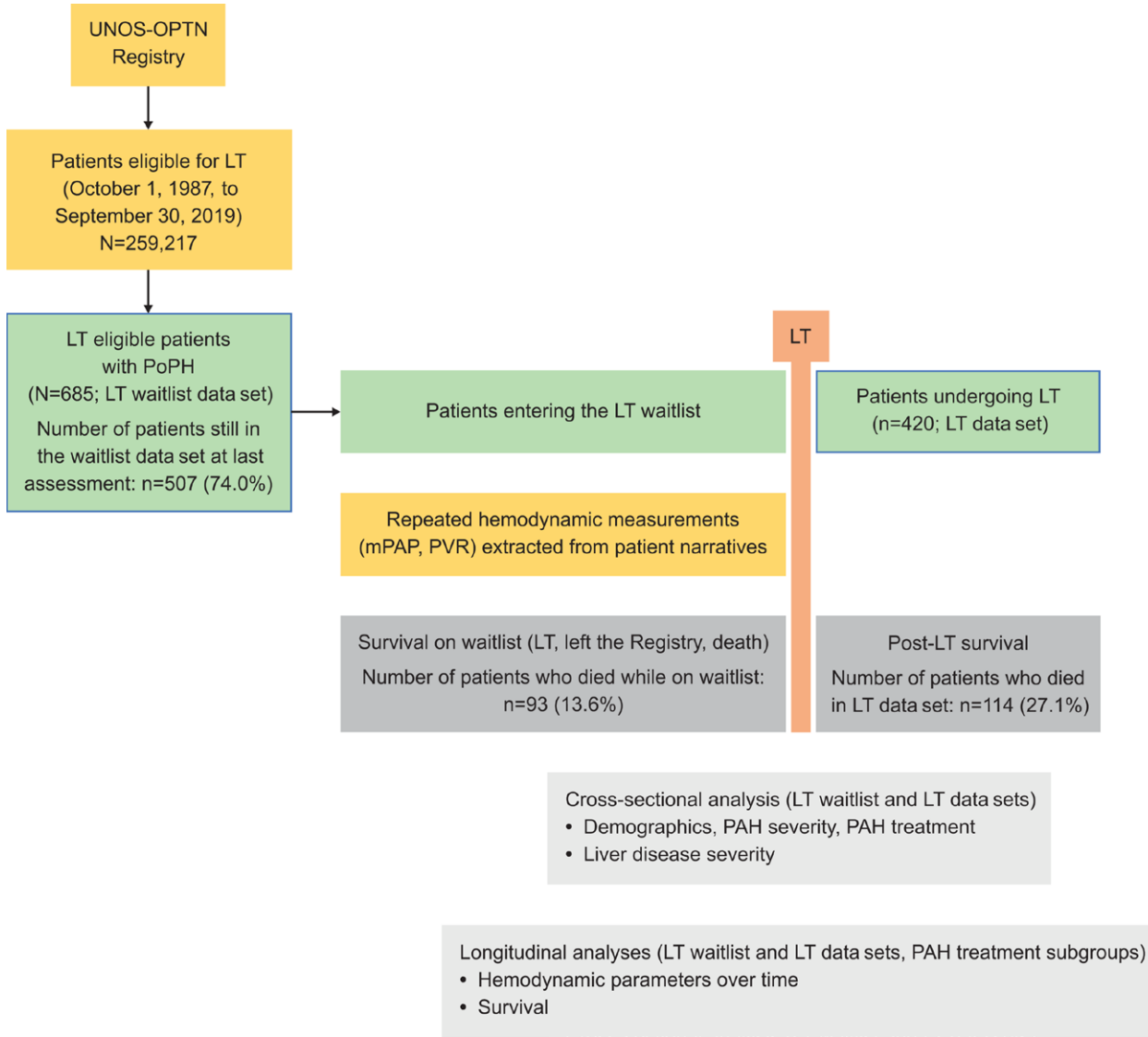


**FIGURE 1.** Design of the observational cohort study using data from patients with PoPH registered on the LT waitlist in the US UNOS-OPTN Registry. Note, the first patient with PoPH included in this analysis was registered on the LT waitlist in 1996. LT, liver transplant; mPAP, mean pulmonary arterial pressure; OPTN, Organ Procurement and Transplantation Network; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; UNOS, United Network for Organ Sharing.

the number of different classes of PAH treatment administered concomitantly), comorbidities, and non-PAH comedications.

First, second, and last RHC (before LT) were selected as reporting time points. The rate of missing data was >95% for cardiac output; this parameter is not a mandatory criterion per UNOS-OPTN assessment and was not analyzed. Where no MELD exception was stated, data relating to MELD exception criteria (mPAP, PVR, and satisfactory RV function) were manually extracted from patient narratives and transformed into the structured database for the PoPH cohort. Hemodynamic parameters, mPAP and PVR, were reported as median (interquartile range [IQR]) and number (%) patients in prespecified mPAP and PVR categories. The threshold for PVR of >450 or ≤450 dynes·s/cm$^5$ was validated in previous studies.[16,21]

Subgroup analyses according to ERA treatment at LT waitlist registration were prespecified in the analysis plan. Longitudinal variables included time on the LT waitlist before LT and overall survival from the time of LT waitlist registration or from the time of LT.

Descriptive data were expressed as median (IQR) for continuous variables and frequency (percentage) for categorical variables. Survival was estimated, up to the date of LT, death, removal from the LT waitlist, or last information available, using the Kaplan-Meier (KM) method.

## RESULTS

### Patient Demographics and Disease Characteristics

The LT waitlist data set (overall cohort) comprised data from 685 patients with PoPH, including 420 who underwent LT (LT data set; Figure 1). At LT waitlist registration, 92.0% of patients had a MELD exception granted before joining (Table 1). In the LT waitlist data set, half of the patients were men (52.3%), and the median age was 54 y (IQR, 48–59 y). Patients were enrolled between 1996 and 2019. The median year of LT waitlist registration was 2012 (IQR, 2008–2016). Most patients were awaiting LT for the first time (98.1%). Patient characteristics were similar in the LT waitlist and LT data sets (Table 1).

**TABLE 1.**

**Patient demographics and disease characteristics at the time of LT waitlist entry**

| Characteristic | LT waitlist data set (N = 685) | LT data set (N = 420) |
|---|---|---|
| Male, n (%) | 360 (52.3) | 221 (52.6) |
| Female, n (%) | 325 (47.5) | 199 (47.4) |
| Age, y, median (IQR) | 54.0 (48–59) | 53.5 (48–59) |
| Race/ethnicity, n (%) | | |
| White | 503 (73.4) | 316 (75.2) |
| Black | 35 (5.1) | 25 (6.0) |
| Hispanic | 109 (15.9) | 57 (13.6) |
| Asian | 20 (2.9) | 12 (3.0) |
| American Indian/Alaska Native | 7 (1.0) | 5 (1.2) |
| Native Hawaii/Other Pacific | 1 (0.2) | 0 |
| Multiracial | 10 (1.5) | 5 (1.2) |
| Weight, kg, median (IQR) | 81.9 (68.5–96.0) | 82.8 (68.9–96.8) |
| Body mass index, kg/m², median (IQR) | 27.9 (24.5–32.3) | 27.8 (24.4–32.3) |
| Year of registration/transplantation, y | | |
| Median (IQR) | 2012 (2008–2016) | 2011 (2007–2015) |
| Min, max | 1996, 2019 | 1996, 2019 |
| Missing,[a] n (%) | 0 | 0 |
| Previous organ transplantation, n (%) | 13 (1.9) | 6 (1.4) |
| Diabetes reported, n (%) | 171 (25.2) | 105 (25.1) |
| Missing[a] | 7 (1.0) | 2 (0.5) |
| Ascites, n (%) | | |
| No | 185 (27.6) | 104 (25.5) |
| Slight | 378 (56.4) | 235 (57.6) |
| Moderate | 107 (16.0) | 69 (16.9) |
| Missing[a] | 15 (2.2) | 12 (2.9) |
| Encephalopathy, n (%) | | |
| No | 300 (44.8) | 165 (40.4) |
| Grade 1–2 | 350 (52.4) | 230 (56.4) |
| Grade 3–4 | 20 (3.0) | 13 (3.2) |
| Missing[a] | 15 (2.2) | 12 (2.9) |
| Bilirubin level, IU/L, median (IQR) | 1.7 (1.1–2.7) | 1.7 (1.0–2.7) |
| Missing,[a] n (%) | 15 (2.2) | 12 (2.9) |
| MELD score, median (IQR) | 13 (10–17) | 13 (10–16) |
| MELD exception granted,[b] n (%) | 630 (92.0) | 389 (92.6) |

[a]Proportion of missing data is based on total number of patients in the LT waitlist and LT data sets. Percentages for the different demographic and disease characteristics are based on the number of patients with nonmissing data.

[b]For some patients with a diagnosis of PoPH confirmed by their treating physician, a MELD exception was not requested/granted at the time of LT waitlist entry (but was requested/granted at a later date).

IQR, interquartile range; IU, international unit; LT, liver transplant; MELD, model for end-stage liver disease; PoPH, portopulmonary hypertension.

## PAH Medications at LT Waitlist Registration

At waitlist registration, 528 of 685 patients (77.1%) in the LT waitlist data set were receiving PAH treatment (Table 2), including 206 (30.1%) receiving an ERA. In the overall LT waitlist data set and the subgroup receiving an ERA, 37.1% and 23.3% of patients, respectively, received monotherapy, 33.4% and 57.8% of patients received dual therapy, and 5.7% and 18.9% of patients received triple therapy.

At LT waitlist registration, the ERA subgroup included a higher proportion of women, a higher median age, and fewer patients with ascites and encephalopathy versus the overall LT waitlist data set (**Figure S1, SDC,** http://links.lww.com/TXD/A616). MELD scores were similar between the groups.

## Patient Characteristics at the Time of LT

Patients in the LT data set spent a median of 8.9 mo (IQR, 3.7–19.7) on the LT waitlist before LT. Patients receiving an ERA who underwent LT were on the LT waitlist for a median of 12.3 mo (IQR, 5.4–25.9). At LT waitlist registration, liver disease severity was similar in the LT waitlist and LT data sets: ascites were present in 72.4% and 74.5% of patients, respectively, encephalopathy was present in 55.2% and 59.6% of patients, respectively; and the median MELD score was 13 (IQR, 10–17) and 13 (IQR, 10–16), respectively.

In the subgroup receiving an ERA at waitlist registration, the median MELD score was the same in the LT waitlist and LT data sets (12 [IQR, 9–14]); the LT data set had a lower proportion of patients with ascites (67.5%) and encephalopathy (51.2%).

## Hemodynamic Characteristics Over Time in LT Waitlist Patients With PoPH

Data were analyzed from 3 RHC assessments of patients in the overall LT waitlist data set (N = 685). The median time from the first (baseline) to the second assessment was 9 mo and from the first to the last assessment was 14 mo. Hemodynamics improved over time (Table 3). Overall, mPAP decreased in 469

**TABLE 2.**

**PAH medications received at the time of LT waitlist entry**

| PAH medication | LT waitlist data set (N = 685) | ERA subgroup from LT waitlist data set (N = 206) |
|---|---|---|
| No PAH treatment reported | 157 (22.9) | NA |
| PAH treatment | 528 (77.1) | 206 (100) |
| Monotherapy | 254 (37.1) | 48 (23.3) |
| PDE5i | 125 (18.2) | NA |
| ERA | 48 (7.0)[a] | 48 (23.3) |
| Macitentan | 11 (1.6) | 11 (5.3) |
| Ambrisentan | 30 (4.4) | 30 (14.6) |
| Bosentan | 8 (1.2) | 8 (3.9) |
| Prostanoids | 81 (11.8) | NA |
| Riociguat | 0 | NA |
| Dual therapy | 229 (33.4) | 119 (57.8) |
| ERA-PDE5i | 98 (14.3) | 98 (47.6) |
| Macitentan-PDE5i | 32 (4.7) | 32 (15.5) |
| ERA-prostanoids | 19 (2.8) | 19 (9.2) |
| Macitentan-prostanoids | 6 (0.9) | 19 (9.2) |
| PDE5i-prostanoids | 109 (15.9) | NA |
| ERA-riociguat | 2 (0.3) | 2 (1.0) |
| Macitentan-riociguat | 2 (0.3) | 2 (1.0) |
| Prostanoids-riociguat | 0 | NA |
| Triple therapy | 39 (5.7) | 39 (18.9) |
| ERA-PDE5i-prostanoids | 39 (5.7) | 39 (18.9) |
| Macitentan-PDE5i-prostanoids | 13 (1.9) | 13 (6.3) |
| Any prostanoid therapy | 248 (36.2) | 58 (28.2) |
| Unspecified | 6 (0.9) | 0 |

Data are presented as n (%) of patients.
[a]One patient received macitentan and ambrisentan.
ERA, endothelin receptor antagonist (macitentan, ambrisentan, and bosentan); LT, liver transplant; NA, not applicable; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor.

of 494 patients (94.9%) with available data between the first and second assessments, and in 468 of 492 patients (95.1%) with available data between the first and last assessments. The proportion of patients with mPAP ≥45 mm Hg decreased from 49.6% (257/518 with available data) at the first assessment to 2.6% (13/506 with available data) and 1.8% (9/507 with available data) at the second and last assessment, respectively.

Similarly, the median PVR (quartile 1; quartile 3) decreased from 440 (304; 600) dynes·s/cm$^5$ (5.5 WU) at the first assessment to 187.2 (128; 239) dynes·s/cm$^5$ (2.3 WU) at the second and 180 (128; 234) dynes·s/cm$^5$ (2.25 WU) at the last assessment. Among 408 patients with available data, PVR decreased in 391 patients (95.8%) between the first and second assessments and in 399 of 416 patients (95.9%) between the first and last assessments. The proportion of patients with PVR >450 dynes·s/cm$^5$ (>5.6 WU) decreased from 208 of 438 (47.5%) at the first assessment to 4 of 446 (0.9%) and 1 of 440 (0.2%) at the second and last assessment, respectively, among patients with available data.

Improvement in hemodynamics was also reflected by shifts in mPAP distribution (Figure 2A; **Table S1, SDC,** http://links.lww.com/TXD/A616) and PVR (**Table S2, SDC,** http://links.lww.com/TXD/A616) categories between assessments. Between the first and second assessments (494/685 [72.1%] patients with available data; missing data in 191/685 [27.9%] patients), the majority of patients with available data shifted to a lower mPAP category (436 [88.3%]; Figure 2) or remained stable (49 [9.9%]; **Table S1, SDC,** http://links.lww.com/TXD/A616). Nine patients (1.8%) experienced worsening mPAP from the first to the second assessment. Similarly, between the first and last assessments, 439 patients (89.2%) shifted to a lower mPAP category, 45 (9.1%) remained stable, and 8 (1.6%) had higher mPAP (**Table S1, SDC,** http://links.lww.com/TXD/A616).

For PVR from the first to the second assessments (420 patients with data available), nearly all patients shifted to the lower category of PVR ≤450 dynes·s/cm$^5$ (≤5.6 WU) or remained stable (197 [46.9%] and 222 [52.9%], respectively); only 1 patient (0.2%) showed worsened PVR (with missing data in 265/685 [38.7%]; **Table S2, SDC,** http://links.lww.com/TXD/A616). The rate of stabilization and improvement in PVR category at the last assessment while on the LT waitlist was similar to the comparison between the first and second assessments. Among patients with PVR data at the first and second LT waitlist assessment, 273 of 367 patients (65.0%) with abnormal PVR >240 dynes·s/cm$^5$ (>3.0 WU) experienced PVR normalization to ≤240 dynes·s/cm$^5$ (≤3.0 WU) at the second waitlist assessment (**Table S2, SDC,** http://links.lww.com/TXD/A616). Similarly, with PVR data at the first and last LT waitlist assessments, 272 of 363 patients (65.4%) with abnormal PVR >240 dynes·s/cm$^5$ (>3.0 WU) experienced PVR normalization to ≤240 dynes·s/cm$^5$ (≤3.0 WU) at the last waitlist assessment (**Table S2, SDC,** http://links.lww.com/TXD/A616).

## Hemodynamic Characteristics Over Time in ERA-treated LT Waitlist Patients

Median mPAP and PVR improved over time in patients receiving an ERA at LT waitlist registration (n = 206; **Table**

**TABLE 3.**

**Hemodynamic parameters over time in the overall LT waitlist data set**

| Parameter | First LT waitlist assessment (N = 685) | Second LT waitlist assessment (N = 685) | Last LT waitlist assessment (N = 685) | Difference from first to second assessment | Difference from first to last assessment |
|---|---|---|---|---|---|
| mPAP, mm Hg, median (IQR) | n = 518<br>44 (39–52) | n = 506<br>30 (25–33) | n = 507<br>30 (26–33) | −16 (−23 to −10) | −16 (−23 to −10) |
| Missing,[a] n (%) | 167 (24.4) | 179 (26.1) | 178 (26.0) | 191 (27.9) | 193 (28.2) |
| mPAP improvement, n (%) | NA | NA | NA | 469 (94.9) | 468 (95.1) |
| Missing[a] | NA | NA | NA | 191 (27.9) | 193 (28.2) |
| mPAP categories, n (%) | n = 518 | n = 506 | n = 507 | | |
| <25 mm Hg | 3 (0.6) | 107 (21.1) | 104 (20.5) | NA | NA |
| ≥25–<35 mm Hg | 47 (9.1) | 322 (63.6) | 331 (65.3) | NA | NA |
| ≥35–<45 mm Hg | 211 (40.7) | 64 (12.6) | 63 (12.4) | NA | NA |
| ≥45 mm Hg | 257 (49.6) | 13 (2.6) | 9 (1.8) | NA | NA |
| Missing[a] | 167 (24.4) | 179 (26.1) | 178 (26.0) | NA | NA |
| PVR, dynes·s/cm$^5$,[b] median (IQR) | n = 438<br>440 (304–600) | n = 446<br>187.2 (128–239) | n = 440<br>180 (128–234) | −241.8<br>(−396.3 to −112.0) | −255.6<br>(−409.5 to −127.5) |
| Median, WU | 5.5 | 2.3 | 2.2 | −3.0 | −3.2 |
| Missing,[a] n (%) | 247 (36.1) | 239 (34.9) | 245 (35.8) | 277 (40.4) | 269 (39.3) |
| PVR improvement, n (%) | NA | NA | NA | 391 (95.8) | 399 (95.9) |
| Missing[a] | NA | NA | NA | 277 (40.4) | 269 (39.3) |
| PVR, categories 1, n (%) | n = 438 | n = 446 | n = 440 | | |
| ≤240 dynes·s/cm$^5$ (≤3 WU) | 56 (12.8) | 342 (76.7) | 343 (78.0) | NA | NA |
| >240 dynes·s/cm$^5$ (>3 WU) | 382 (87.2) | 104 (23.3) | 97 (22.0) | NA | NA |
| Missing[a] | 247 (36.1) | 239 (34.9) | 245 (35.8) | NA | NA |
| PVR, categories 2, n (%) | n = 438 | n = 446 | n = 440 | | |
| ≤450 dynes·s/cm$^5$ (≤5.6 WU) | 230 (52.5) | 442 (99.1) | 439 (99.8) | NA | NA |
| >450 dynes·s/cm$^5$ (>5.6 WU) | 208 (47.5) | 4 (0.9) | 1 (0.2) | NA | NA |
| Missing[a] | 247 (36.1) | 239 (34.9) | 245 (35.8) | NA | NA |

[a]Proportion of missing data is based on the total number of patients in the LT waitlist data set. The first PVR/mPAP assessments were at baseline (LT waitlist registration). Percentages for the different demographic and disease characteristics are based on the number of patients with nonmissing data.
[b]80 dynes·s/cm$^5$ = 1 WU.
IQR, interquartile range; LT, liver transplant; mPAP, mean pulmonary arterial pressure; NA, not applicable; PVR, pulmonary vascular resistance; WU, Wood units.

**S3, SDC,** http://links.lww.com/TXD/A616; Figure 2B). Between the first and subsequent assessments, mPAP decreased in 96.0% (191/200 and 199 patients with available data for the first and second assessments and last assessment, respectively). PVR also decreased between the first and second assessments in 172 of 178 patients (96.6%) with available data and between the first and last assessments in 174 of 182 patients (95.6%). Most patients with available data who received an ERA (182/200 [91.0%]) either shifted to a lower mPAP category or remained stable across assessments (**Table S4, SDC,** http://links.lww.com/TXD/A616). Between the first and second assessments, only 5 patients (2.5%) demonstrated increased mPAP; 3 patients (1.5%) had increased mPAP between the first and last assessments. This trend was also seen in PVR, where almost all patients with available data shifted to a lower PVR category or remained stable between assessments (**Table S5, SDC,** http://links.lww.com/TXD/A616).

## Survival in Patients With PoPH

In the LT waitlist data set (N = 685), 93 (13.6%) deaths were reported up to the last available follow-up, whereas in the LT data set (n = 420), 114 (27.1%) deaths were reported (including 8 [1.9%] on the day of LT). For the LT waitlist data set, survival time was calculated through to the time of LT, death, removal from the LT waitlist, or last follow-up; for the LT data set, it was calculated from LT to death or last follow-up.

The KM curve for the overall survival of patients on the LT waitlist is shown in Figure 3A (calculated from the time of LT waitlist registration through to LT or death, or removal from LT waitlist or last information available). Figure 3B shows the KM curve for survival of patients following LT (calculated from LT through to death or last follow-up information). Landmark survival estimates are given in Table 4. The estimated 1-y survival was 90.6% (95% confidence interval [CI], 87.6-92.9) for the LT waitlist data set and 86.4% (95% CI, 82.6-89.5) for the LT data set. At 5 y, estimated survival was 67.4% (95% CI, 60.0-73.8) and 75.6% (95% CI, 70.4-80.0), respectively (Table 4).

KM curves for overall survival in the subgroups receiving an ERA at registration in the LT waitlist and LT data sets are shown in Figure 3C and D. One-year survival estimates were 90.4% (95% CI, 84.8-94.1) for the LT waitlist data set and 85.5% (95% CI, 77.3-90.9) for the LT data set. Five-year survival estimates were 74.3% (95% CI, 60.2-84.0) and 76.4% (95% CI, 64.7-84.6), respectively (Table 4).

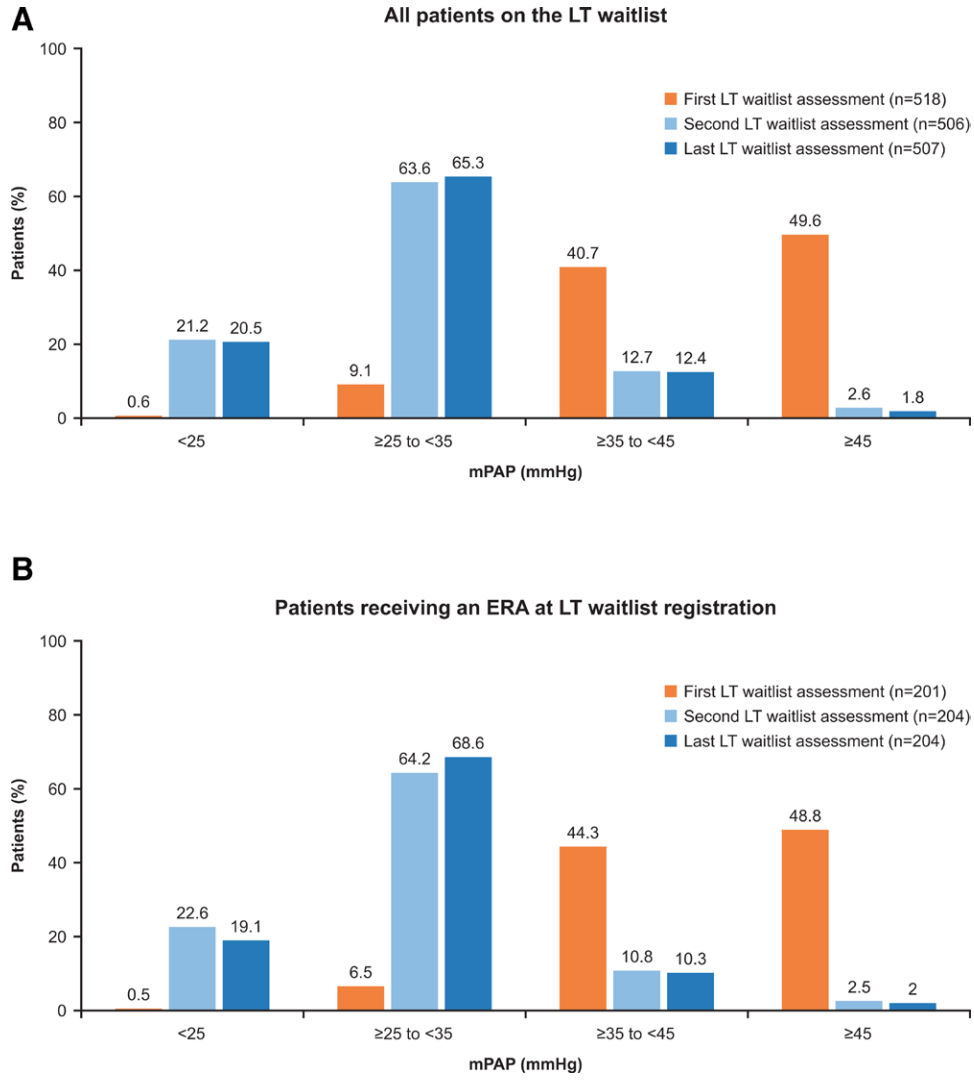


**FIGURE 2.** Distribution of mPAP at the first, second, and last assessments after joining the LT waitlist. A, All patients on the LT waitlist (percentages of patients with mPAP assessment recorded). B, Patients who were receiving an ERA at LT waitlist entry (percentages of patients with mPAP assessment recorded). Based on patients with nonmissing data. ERA, endothelin receptor antagonist; LT, liver transplant; mPAP, mean pulmonary arterial pressure; N, total number of patients with assessment recorded.

## DISCUSSION

We analyzed a large cohort of patients with PoPH registered on the LT waitlist of the US-based UNOS-OPTN Registry, of whom >90% had a MELD exception granted before joining the LT waitlist. Patient characteristics and liver disease severity were similar in both the overall LT waitlist data set and the subgroup who underwent LT (LT data set). Targeted therapy for PoPH was common but not universal, with approximately one-third of patients receiving oral monotherapy. In most patients with PoPH, hemodynamic parameters (mPAP and PVR) stabilized/improved on subsequent RHC assessments, notably remaining stable for a prolonged period (>12 mo).

Survival was similar in the LT waitlist and LT data sets of those receiving PAH treatment (versus those who were not) at LT waitlist registration. In these overall data sets, including their ERA-treated subgroups, 1-y survival estimates were higher in the LT waitlist data set (90.6% versus 86.4% in the LT data set), potentially reflecting early perioperative mortality associated with LT. A recent observational study demonstrated that 18 of 103 patients with PoPH undergoing LT died posttransplant, with most (14 patients) dying within 1 y of transplant.[21,22] In our analysis, 5-y survival estimates were higher in the LT data set versus the LT waitlist data set (75.6% versus 67.4%), suggesting a long-term survival benefit of LT in patients with PoPH. Five-year survival was favorable in those receiving an ERA at LT waitlist registration, supporting the value of managing hemodynamic parameters with medical treatment for patients with PoPH. These survival rates compare favorably against the 5-y rates of 50% and 40% observed in patients with PoPH in the REVEAL database[23,24] and 35% in a UK registry.[25] It was surprising that some patients with PoPH were on the LT waitlist for 5 y. The reasons for this are unclear. In the authors' clinical experience, for a patient with a PoPH MELD exception to remain on the LT waitlist, their MELD score would typically escalate every few months (based on the requirement for serial RHC assessments and the mortality equivalent increase in points awarded to patients with escalating waitlist durations) and should be sufficiently high to warrant LT within 2 y. The longer time on the LT waitlist in our analysis could be an anomaly because variability in

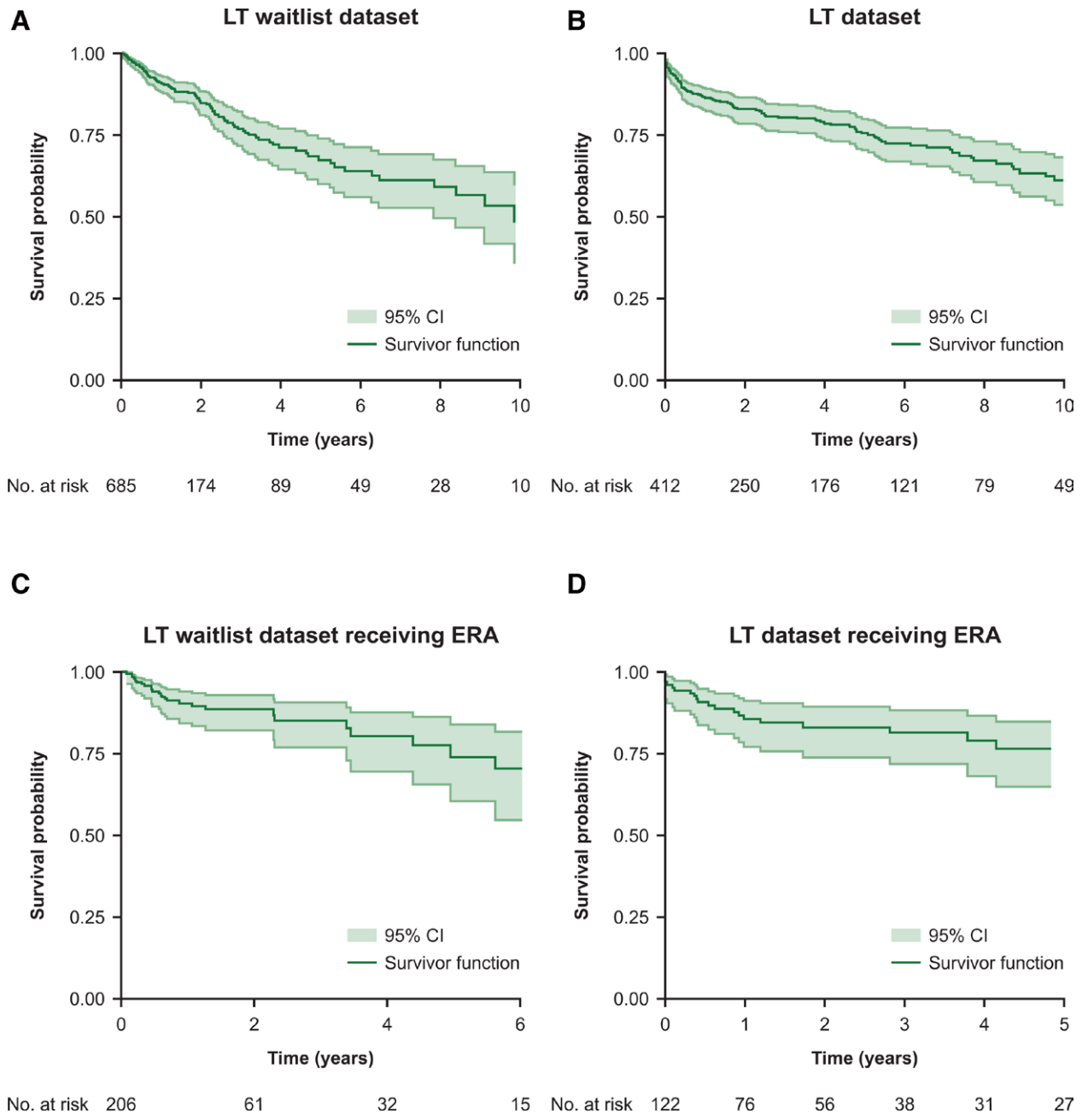


**FIGURE 3.** Kaplan-Meier survival curves for (A) time from LT waitlist registration to death in the LT waitlist data set; (B) time from LT to death in the LT data set; (C) time from LT waitlist registration to death in the subgroup of patients receiving an ERA at waiting list registration (LT waitlist data set); and (D) time from LT to death in the subgroup of patients receiving an ERA at waiting list registration (LT data set). Differences in time frames reflect the (low) number of patients at risk. ERA, endothelin receptor antagonist; LT, liver transplant.

applying MELD exceptions before 2010, or it could represent patients with stable hemodynamics and compensated cirrhosis who were not considered immediate candidates for LT but who remained on the LT waitlist. Further research into patient and disease characteristics that predict favorable post-LT outcomes, and the impact of the modality and intensity of PAH-targeted therapy on post-LT outcomes in PoPH, is needed to help make equitable and efficient use of this scarce resource.

Around three-quarters of LT waitlist data set patients received PAH treatment at enrollment, with approximately one-third receiving monotherapy. European Society of Cardiology/European Respiratory Society Guidelines strongly recommend that the standard PAH treatment algorithm be applied in patients with PoPH (assessing the severity of underlying liver disease, indication for LT, and potential effects of PAH medication on gas exchange) and that patients responding well to PAH treatment be eligible for LT consideration.[14] In our study, one-third of patients were not receiving PAH treatment upon entry to the LT waitlist, and usage of dual and triple therapy was relatively low (33% and 6% of patients, respectively [LT waitlist data set]) in this high-risk PoPH population. Our study analyzed data from a long time period (patient enrollment spanned 1996–2019), and some patients entered the LT waitlist before the introduction of current PAH treatments and

**TABLE 4.**

**KM survival estimates (95% CI) for time from LT waitlist registration to death in patients with PoPH in the LT waitlist and LT data sets**

| | 1-y survival | | 2-y survival | | 3-y survival | | 5-y survival | |
|---|---|---|---|---|---|---|---|---|
| | PAR | 1-y KM% (95% CI) | PAR | 2-y KM% (95% CI) | PAR | 3-y KM% (95% CI) | PAR | 5-y KM% (95% CI) |
| Overall data sets | | | | | | | | |
| LT waitlist data set[a] | 327 | 90.6 (87.6-92.9) | 175 | 84.8 (80.6-88.2) | 118 | 76.9 (71.2-81.7) | 65 | 67.4 (60.0-73.8) |
| LT data set[b] | 297 | 86.4 (82.6-89.5) | 251 | 83.0 (78.7-86.4) | 207 | 80.5 (76.0-84.3) | 153 | 75.6 (70.4-80.0) |
| Subgroup with ERA treatment | | | | | | | | |
| LT waitlist data set[a] | 108 | 90.4 (84.8-94.1) | 62 | 88.5 (82.1-92.7) | 40 | 85.2 (77.0-90.7) | 22 | 74.3 (60.2-84.0) |
| LT data set[b] | 78 | 85.5 (77.3-90.9) | 58 | 82.9 (74.1-89.0) | 39 | 81.2 (71.8-87.8) | 28 | 76.4 (64.7-84.6) |

[a]KM survival estimates are displayed as % (95% CI), from LT waitlist registration up to last information or LT date for patients who underwent LT.
[b]KM survival estimates are displayed as % (95% CI), from LT up to last information.
CI, confidence interval; ERA, endothelin receptor antagonist; LT, liver transplant; KM, Kaplan-Meier; PAR, number of patients at risk; PoPH, portopulmonary hypertension.

algorithms. Despite more limited treatment options in earlier periods, the low frequency of aggressive (double or triple) therapy indicates an opportunity for practice improvement and standardization. The use of PAH medication, with the goal of improving hemodynamics and RV function to facilitate a safe LT, has been a requirement for a MELD exception for patients with PoPH since 2006.[2,17] A recent analysis of waitlist mortality in LT candidates with PoPH showed that the severity of both hepatic and cardiovascular diseases, indicated by initial MELD score and PVR, respectively, predict waitlist mortality.[21] In patients with PoPH undergoing LT, optimized hemodynamics (mPAP and PVR) predict improved post-LT survival and graft failure.[12] Surveys of PoPH practice patterns support the widespread use of phosphodiesterase type 5 inhibitors (PDEi), ERAs, and parenteral prostacyclin therapy in these patients.[12,18] A longitudinal analysis of data from patients with PoPH and MELD exceptions from OPTN-UNOS showed a decline in the use of parenteral therapy and increased use of oral agents, ERA and PDE5i, between 3 time periods (2006–2010, 2011–2015, and 2016–2019).[26] Posttreatment, hemodynamic parameters improved over time and survival estimates (waitlist and post-LT) were similar across the 3 time periods.[26]

The known beneficial effect of hemodynamic optimization and our data on PAH-targeted therapy use in PoPH highlights a discrepancy between existing guidelines and real-world management strategies in PoPH. Undertreatment of patients with PoPH awaiting LT may contribute to adverse post-LT outcomes. Further efforts to clarify the relationship between treatment strategy, pre-LT hemodynamics, and post-LT outcomes in PoPH are warranted. Recently updated pulmonary hypertension guidance further clarifies the role of PAH-targeted therapy in eligible patients with PoPH,[14] although more data are needed to strengthen the evidence base for treatment recommendations.

Our analysis demonstrated that hemodynamic parameters (mPAP and PVR) improved or stabilized in most patients between the first and second RHC assessments following LT waitlist registration in UNOS-OPTN (median 9 mo between assessments) and were maintained over an extended period (median 14 mo between the first and last assessments). Patients on an ERA-containing or another regimen showed comparable hemodynamic improvement and stability; this is reassuring because ERA medications are the only PoPH-targeted therapy supported by a randomized controlled trial.[15] Our data showed sustained stability or improvement of hemodynamic parameters in patients with stable or improved mPAP/PVR at the first assessment on the LT waitlist. There may be an opportunity to reduce the frequency and burden of invasive RHC procedures for these very sick patients with liver disease who respond appropriately to PAH-targeted therapy. Further prospective evaluation of the RHC interval in patients with PoPH on the LT waitlist, and consideration for adjusting the frequency of hemodynamic assessments in patients with PoPH granted MELD exception points for achieving a low-risk hemodynamic state, may be warranted.

This study has limitations. Although it includes the largest cohort of patients with PoPH eligible for LT studied to date, the sample size of 685 is still relatively small. The selection criteria for identifying patients with PoPH from UNOS-OPTN, missing data (especially for hemodynamic parameters), and the retrospective analysis may have introduced bias. Another limitation is that only patients showing hemodynamic improvement after PAH therapy were eligible for a MELD exception, allowing LT waitlist entry. Our results may not be generalizable to all patients with PoPH, particularly those not responding adequately to PAH therapy or not registered on LT waitlists. During the long period of data capture, PAH treatment practices and MELD exception criteria were formally defined and updated. Consequently, selection bias and shifts in management strategies may have confounded the results, and the population studied may not truly represent the current clinical management and outcomes for patients with PoPH eligible for LT. We analyzed survival outcomes in the subset of patients receiving ERA treatment. Although it would have been interesting to look at outcomes with other therapeutic classes, we focused on ERAs because they are the only PAH treatment currently supported by data from a randomized controlled trial [15] and are unable to report on the possible relationship between other PAH treatments (ie, PDE-5i or prostanoids) and outcomes in this patient population. The small sample size precluded comparing outcomes across multiple treatment approaches. PAH treatment response was based on a longitudinal assessment of hemodynamic parameters, and interpretation may be limited by information lacking on other important metrics (functional class, structure and RV function on echocardiography, or 6-min walk distance).

In summary, our analysis represents the largest, most comprehensive national study of LT waitlist candidates with PoPH to date and provides new insights into their clinical characteristics, PAH treatment, and long-term outcomes.

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