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Transplantation for pulmonary arterial hypertension with congenital heart disease: Impact on outcomes of the current therapeutic approach including a high-priority allocation program

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Patients with end-stage pulmonary arterial hypertension due to congenital heart disease have limited access to heart-lung transplantation or double-lung transplantation. We aimed to assess the effects of a high-priority allocation program established in France in 2007. We conducted a retrospective study to compare waitlist and posttransplantation outcomes before versus after implementation of the high-priority allocation program. We included 67 consecutive patients (mean age at listing, 33.2 ± 10.5 years) with pulmonary arterial hypertension due to congenital heart disease listed for heart-lung transplantation or double-lung transplantation from 1997 to 2016. At one month, the incidences of transplantation and death before transplantation were 3.5% and 24.6% in 1997–2006, 4.8% and 4.9% for patients on the regular list in 2007–2016, and 41.2% and 7.4% for patients listed under the high-priority allocation program ($p < .001$ and $p = .0001$, respectively). Overall survival was higher in patients listed in 2007–2016 (84.2% and 61.2% at 1 and 10 years vs. 36.8% and

Abbreviations: ALAT, alanine-amino-transferase; ASAT, aspartate-amino-transferase; ASD, atrial septal defect; BMI, body mass index; CHD, congenital heart disease; CI, confidence interval; DLTx, double-lung transplantation; DSA, donor specific antibodies; ECLS, extra-corporeal life support; ES, Eisenmenger syndrome; FC, functional class; HPAP, high-priority allocation program; HLTx, heart-lung transplantation; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LAP, left atrial pressure; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PaO_2/FiO_2, ratio of partial pressure of oxygen in arterial blood over fraction of inspired oxygen; PVR, pulmonary vascular resistance; sdHR, subdistribution hazard-ratio; RAP, right atrial pressure; SaO_2, oxygen saturation of arterial blood; SDT, specific drug therapies; sPAP, systolic pulmonary artery pressure; WHO, World Health Organization; WU, Wood unit; 6'WT, 6-min walking test.

22.1%, p = .0001). Increased incidence of transplantation, decreased waiting list mortality, and improved early and long-term outcomes were observed in patients with pulmonary arterial hypertension due to congenital heart disease listed for transplantation in the recent era, characterized by implementation of a high-priority allocation program.

KEYWORDS
clinical research/practice, health services and outcomes research, heart disease: congenital, heart transplantation/cardiology, lung transplantation/pulmonology, organ allocation, organ procurement and allocation

1 | INTRODUCTION

Adults with pulmonary arterial hypertension (PAH) and unrepaired congenital heart disease (CHD), most notably Eisenmenger syndrome (ES), have better outcomes compared to patients with idiopathic PAH.[1] However, about 50% of patients with PAH-CHD die before the age of 35.[2-5] Changes in therapeutic strategies and specialized follow-up have nevertheless increased the life expectancy of these patients.[6] PAH-specific drug therapies (PAH-SDT) improve functional status and are associated with later listing for transplantation and reduced 10-year mortality.[2,3,5,7,8,9,10] However, the effects of PAH-SDT are limited and decrease over time in patients with PAH-CHD.[5] Heart-lung transplantation (HLTx) or double-lung transplantation (DLTx) with shunt closure is the only curative approach.[11] The appropriate timing of transplantation in patients with PAH-CHD remains a matter of debate.[11-13] High early posttransplantation mortality has been reported in patients with PAH-CHD. Thus, 5-year survival after HLTx was about 30%–40% and was comparable to 5-year survival in patients with ES.[2,11,14,15,16] Importantly, predicting the onset of heart failure in these patients is challenging. Heart failure is associated with a rapid deterioration in clinical status. Few options are available to support the heart. In particular, extra-corporeal life support (ECLS) is usually not recommended, since it increases the risk of perioperative bleeding.[12] Furthermore, the organ pool is particularly limited due to morphological and immunological factors, reducing access to transplantation for patients with PAH-CHD.[17] A national high-priority allocation program (HPAP) for heart and lung transplantation was implemented in France in 2007 to ensure that available organs go to those most at risk. A retrospective before-after study indicates that the HPAP has substantially improved survival of patients with PAH.[18] In the present study, we assessed potential associations of the HPAP with survival of patients with PAH-CHD listed for transplantation.

2 | MATERIALS AND METHODS

2.1 | Design

We conducted a retrospective before-after study to assess potential associations between implementation of the HPAP and outcomes while on the waiting list and after transplantation in patients with PAH-CHD. We included consecutive patients with PAH-CHD listed for HLTx or DLTx at a single tertiary center between 1997 and 2016, that is, 10 years before and 10 years after implementation of the HPAP. The study center was the Marie Lannelongue Hospital, which is a referral center for the surgical treatment of PAH and for the management of complex CHD (M3C network). All transplantations were performed at the Marie Lannelongue Hospital.

All patient data were collected prospectively by the transplantation team and entered into a database, which was reported to the French Data Protection Authority (CNIL #1154338, April 27, 2006). Data derived from our local database were linked to the CRISTAL database. CRISTAL is a national database initiated in 1996 and administered by the *Agence de la Biomédecine*. It prospectively collects data on all organ-transplant recipients in France, together with their outcomes and donor characteristics. Recipient and donor data are entered into the registry by transplant and procurement centers, respectively. Data collection is mandatory.

The study was conducted in compliance with the Declaration of Helsinki and was approved by our institutional review board (#CCML 2016–012), which waived the need for informed consent in compliance with French legislation on retrospective studies.

2.2 | Patients

From 1997 to December 2016, 67 patients with end-stage PAH and CHD were listed for HLTx or DLTx. The diagnosis of CHD was based on echocardiography and/or cardiac catheterization data in all patients. PAH was confirmed in each patient by standardized cardiac catheterization,[5] which was not routinely repeated at the time of listing. PAH was defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest combined with a pulmonary vascular resistance above 3 Wood units (WUs).[19] Selection for listing was based on an assessment of each individual patient during a multidisciplinary discussion that focused on functional class and other heart failure parameters.[20] In the preHPAP period, the organ allocation system in France was almost exclusively based on geography with successively local, regional, and national organ sharing, taking only donor and recipient ABO blood types into account. This system was associated with regional disparities in waitlist times and to differences in candidate profile across centers.[21] The

HPAP was implemented in 2004 for HTx, in September 2006 for HLTx, and in July 2007 for DLTx. Eligibility of PAH patients for HPAP listing is determined by the French national transplantation agency. Eligible patients are those who are on the waitlist for a cardiopulmonary transplant and whose clinical condition has become life-threatening, who are in an intensive care unit and in the immediate vicinity of a transplant center, in whom pulmonary vasodilator therapy is no longer effective, whose clinical condition remains compatible with a cardiopulmonary transplant, and who have none of the contraindications to transplantation given in international recommendations.[22] All requests for HPAP status are reviewed and approved by two independent experts mandated by the French national transplantation agency. In adults, HPAP listing is approved for a period of 8 days, renewable once. In children, HPAP status is conferred for an unlimited period.[18,21,22,23]

The patients were classified according to the Nice classification.[19,24] We included patients with ES, a prevalent systemic-to-pulmonary shunt, PAH and a history of surgery to correct or palliate a congenital heart defect, or segmental PH (e.g., pulmonary atresia with ventricular septal defect). The CHDs were classified as simple (e.g., single pretricuspid or posttricuspid shunt) or complex.[17] Heart failure was defined according to international guidelines based on the physical examination, transthoracic echocardiography findings, and biomarkers.[25]

Follow-up information was entered into the study database during outpatient clinic visits and readmissions. For the outcome analysis, follow-up of surviving patients was censored on December 31, 2019.

2.3 | Statistical analysis

The data are described as means ± SD for normally distributed variables, median (range) [interquartile range] for skewed continuous variables, and number (%) for categorical variables. To assess the effect of the HPAP, we compared the outcomes of patients listed before versus after 2007, when the HPAP was introduced. The patients were divided into three groups: patients listed between 1997 and 2006 (pre-HPAP group), patients listed between 2007 and 2016 on the HPAP (HPAP+ group), and patients listed between 2007 and 2016 on the regular list (HPAP− group). Outcomes in each of the two latter groups were compared to those in the pre-HPAP group. For bivariate analyses, and except for time-to-event outcomes, categorical variables were compared with Pearson's χ^2 test or Fisher's exact test. Comparisons of continuous variables relied on Student's *t* test for independent samples if its normality assumptions were satisfied (Shapiro-Wilk test) and on the Welch *t* test (if variances were heterogeneous) or the Mann-Whitney *U* test otherwise.

First, baseline data were described in the overall population and in each of the three groups. Baseline data and donor data were described for the patients who underwent transplantation during the study period. Baseline variables associated with the incidence of transplantation were analyzed using the Fine and Gray regression model, with death without transplantation and being delisted as competing risks.[26]

Associations between baseline variables and death on the waiting list were assessed using a Cox proportional hazards model with right censoring at the time of transplantation, delisting, or study completion. Only univariate analyses were done given a low event rate and a small sample size.

Kaplan-Meier survival curves with time since listing were plotted using months as the time scale. In transplanted patients, Kaplan-Meier survival curves with time since transplantation were plotted using years as the time scale. Differences in survival according to period of listing were assessed using the Log-rank test.

All reported *P* values are two-sided. Values of $p < .05$ were considered statistically significant. Risk estimations are reported with their 95% confidence intervals (95% CIs). Statistical analyses were performed using Stata® 11.2 software (StataCorp, College Station, TX) and R software v3.6.1.

3 | RESULTS

3.1 | Patient demographics

From 1997 to 2016, 67 patients with PAH-CHD were registered on the lung transplantation waiting list. Follow-up was 262.6 patient-years. There were 29 (43.3%) patients in the pre-HPAP group, 17 (25.4%) in the HPAP+ group, and 21 (31.3%) in the HPAP− group. Fifty-two (77.6%) patients had ES, 15 (22.4%) had no intracardiac shunt (either surgically closed or absent), and 25 (37.3%) had complex CHD.

Table 1 reports the main patient features at listing. Eight (11.9%) patients were listed before the age of 18. The primary reasons for listing were disease worsening despite medical therapy (*n* = 33, 49.3%), heart failure (*n* = 31, 46.3%), severe hemoptysis (*n* = 1, 1.5%), chronic respiratory failure (*n* = 1, 1.5%), and acute pulmonary artery dissection (*n* = 1, 1.5%). Other adverse events occurred in 24 (35.8%) patients (supra-ventricular rhythm disturbance, *n* = 9; syncope, *n* = 6; mild-moderate hemoptysis, *n* = 6; angina, *n* = 2; pulmonary in situ thrombosis, *n* = 2; aortic regurgitation, *n* = 1; and bronchial compression, *n* = 1). HPAP+ status was conferred on the day of listing for 7/17 (41.1%) patients and within 2 weeks after listing for 10/17 (58.9%) patients. Median time from listing to obtaining HPAP+ status was 11 days [0–105]. The reasons for conferring HPAP+ status were heart failure requiring inotropic support (*n* = 7, 41.2%), heart failure requiring ECLS support (*n* = 3, 17.6%), life-threatening uncontrolled hemoptysis (*n* = 3, 17.6%), acute pulmonary artery dissection (*n* = 1, 5.9%), clinical worsening despite maximal drug therapy (*n* = 1, 5.9%), heart failure and syncope (*n* = 1, 5.9%), and severe respiratory insufficiency (*n* = 1, 5.9).

3.2 | Waitlist outcomes

Figure 1 shows the patient outcomes. Transplantations were performed in 38 patients (56.7%) after a median waitlist time of 9.3 months (1.0–21.0) (0.0–49.3). HLTx (*n* = 28/38, 73.7%) was

TABLE 1 Characteristics of patients at transplant listing before and after implementation of the high-priority allocation program

	Pre-HPAP	HPAP implementation				
Variable	**Listing in 1997–2006 (*n* = 29)**	**Listing in 2007–2016 HPAP period (*n* = 38)**	***p* value pre-HPAP versus HPAP**	**Regular allocation: HPAP– group (*n* = 21)**	**HPAP allocation: HPAP+ group (*n* = 17)**	***p* value HPAP– versus HPAP+**
Age at listing (years), median [IQR]	34.1 [26.1–42.1]	34.7 [23.6–42.4]	.909	36.4 ± 9.0	29.4 ± 12.6	.041
Time on waiting list (months), median [IQR]	3.1 [0.8–12.5]	11.3 [0.9–24.9]	.271	14.3 [2.6–22.7]	2.9 [0.4–25.6]	.073
Death on list, *n* (%)	19 (65.5%)	4 (10.5%)	.0001	3 (14.3%)	1 (5.9%)	.613
Transplantation, *n* (%)	9 (31.0%)	29 (76.3%)	.0001	13 (61.9%)	16 (94.1%)	.026
History of heart surgery, *n* (%)	12 (41.4%)	16 (42.1%)	1.000	8 (38.1%)	8 (47.1%)	.821
Type of CHD, *n* (%)						
Simple	16 (55.2%)	26 (68.4%)	.267	13 (61.9%)	12 (70.6%)	.737
Complex	13 (44.8%)	12 (31.6%)		8 (38.1%)	5 (29.4%)	
Shunt position, *n* (%)						
Pretriscupid	6 (20.7%)	14 (36.8%)	.195	7 (33.3%)	7 (41.2%)	.129
Posttriscupid	9 (31.0%)	15 (39.5%)		11 (52.4%)	4 (23.5%)	
Combined pretricuspid and posttricuspid	5 (17.3%)	3 (7.9%)		2 (9.5%)	1 (5.9%)	
No shunt or closed shunt	9 (31.0%)	6 (15.8%)		1 (4.8%)	5 (29.4%)	
Female, *n* (%)	19 (65.5%)	27 (71.1%)	.827	16 (76.2%)	11 (64.7%)	.491
Weight (kg), mean ± SD	51.3 ± 7.9	51.6 ± 9.9	.905	52.4 ± 7.3	50.5 ± 12.6	.586
WHO-FC, *n* (%)						
III	12 (41.4%)	15 (39.5%)	1.000	13 (61.9%)	2 (11.8%)	.002
IV	17 (58.6%)	23 (60.5%)		8 (38.1%)	15 (88.2%)	
6'WT (m), median [IQR]	333 [194–376]	358 [318–420]	.119	351 [331–413]	367 [290–419]	.942
Heart failure, *n* (%)	27 (93.1%)	31 (81.6%)	.287	18 (85.7%)	13 (76.5%)	.678
Hemodynamics at listing						
sPAP (mm Hg), mean ± SD	108 ± 31	103 ± 27	.459	102 ± 21	102 ± 33	.977
mPAP (mm Hg), mean ± SD	71 ± 22	68 ± 20	.560	68 ± 17	68 ± 24	.966
RAP (mm Hg), median [IQR]	8 [6–10]	7 [3–11]	.235	6 [4–11]	8 [3–12]	.729
LAP (mm Hg), median [IQR]	8 [4–9]	8 [6–12]	.269	9 [5–11]	8 [7–12]	.961
Systemic cardiac output (L min^{-1} m^{-2}), mean ± SD	2.5 ± 0.8	2.9 ± 1.2	.147	2.8 ± 1.3	3.1 ± 1.0	.585
PVR (WU), median [IQR]	23.2 [18.8–33.2]	17.0 [11.3–25.7]	.081	16.3 [13.7–20.9]	18.8 [11.1–27.3]	.646

(Continues)

TABLE 1 (Continued)

Variable	Pre-HPAP	HPAP implementation				
	Listing in 1997–2006 (*n* = 29)	Listing in 2007–2016 HPAP period (*n* = 38)	*p* value pre-HPAP versus HPAP	Regular allocation: HPAP− group (*n* = 21)	HPAP allocation: HPAP+ group (*n* = 17)	*p* value HPAP− versus HPAP+
Aortic SaO_2 (%), median [IQR]	86 [75–90]	89 [76–91]	.396	85 [75–90]	90 [85–92]	.137
Blood tests at listing						
Hematocrit (%), mean ± SD	51.8 ± 8.0	46.2 ± 9.6	.018	50.5 ± 8.3	40.7 ± 8.5	.001
Creatinine clearance (mL min^{-1}), median [IQR]	63 [57–80]	76 [60–103]	.130	69 [55–103]	76 [66–103]	.419
Total bilirubin (μmol L^{-1}), median [IQR]	28 [18–39]	14 [9–22]	.002	13 [9–28]	15 [12–20]	.566
Ascites, *n* (%)	5 (17.2%)	5 (13.2%)	.735	3 (14.3%)	2 (11.8%)	1.000
Drug therapy at listing						
Number of PAH-SDT, *n* (%)						
0	17 (58.6%)	7 (18.4%)	.0001	6 (28.6%)	1 (5.9%)	.437
1	5 (17.2%)	2 (5.3%)		1 (4.8%)	1 (5.9%)	
2	6 (20.7%)	14 (36.8%)		7 (33.3%)	7 (41.2%)	
3	1 (3.5%)	15 (39.5%)		7 (33.3%)	8 (47.1%)	
IV prostacyclin, *n* (%)	13 (44.8%)	20 (52.6%)	.699	10 (47.6%)	10 (58.8%)	.718
Inotropic support, *n* (%)	11 (37.9%)	12 (31.6%)	.777	1 (4.8%)	11 (64.7%)	.0001
ECLS at listing, *n* (%)	0 (0.0%)	3 (7.9%)	.257	0 (0.0%)	3 (17.7%)	.079
Oro-tracheal intubation at listing, *n* (%)	2 (6.9%)	2 (5.3%)	1.000	0 (0.0%)	2 (11.8%)	.196

Abbreviations: 6'WT, 6-min walking test; CHD, congenital heart disease; ECLS, extracorporeal life support; HPAP, high-priority allocation program; IQR, interquartile range; IV, intravenous; LAP, left atrial pressure; mPAP, mean pulmonary artery pressure; PAH-SDT, pulmonary arterial hypertension specific drug therapy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, oxygen saturation of arterial blood; SD, standard deviation; sPAP, systolic pulmonary artery pressure; WHO-FC, World Health Organization Functional Class; WU, Wood unit.

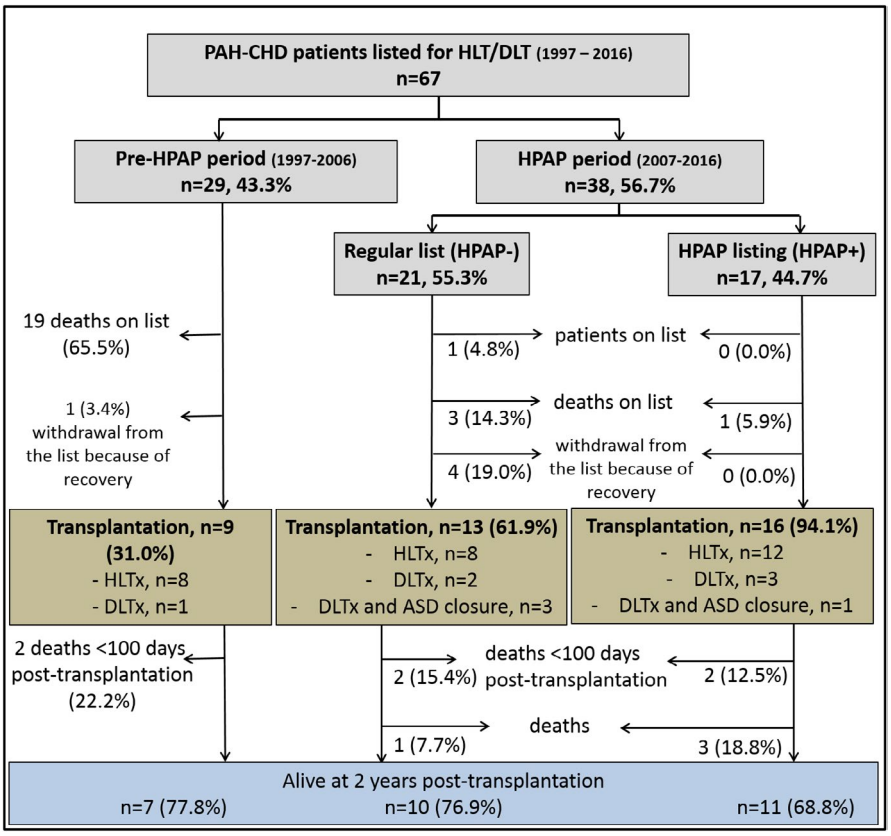

FIGURE 1 Flow-chart of the study population and outcomes while on the waiting list. ASD, atrial septal defect; DLTx, double-lung transplantation; HLTx, heart-lung transplantation; HPAP, high-priority allocation program; HPAP− group, patients listed during the HPAP period but according to the usual modalities; HPAP+ group, patients listed with HPAP status; PAH-CHD, pulmonary arterial hypertension-congenital heart disease; preHPAP, patients listed before the HPAP period [Color figure can be viewed at wileyonlinelibrary.com]

performed far more often than DLTx (n = 10/38, 26.3%). Median waitlist time was 9.9 months before DLTx and 9.1 months before HLTx (p = .8). Five (13.2%) patients were transplanted before the age of 18. Transplantations were performed in 10/17 (58.8%) patients who had HPAP status (HPAP+ group). One patient did not receive a transplant during the first 2 weeks after obtaining HPAP status and died 18 days after listing after losing HPAP+ status. Transplantations were performed via a median sternotomy (n = 20, 52.6%), clamshell incision (n = 13, 34.2%), or double anterolateral thoracotomy (n = 5, 13.2%). DLTx with percutaneous shunt closure was performed in 4 (10.5%) patients, with a median time between the two procedures of 5.2 months.

Table 2 reports the perioperative data. All patients included in the study received a transplant that had a negative cytotoxic donor lymphocyte crossmatch. Postoperative ECLS support was required in 12 (31.6%) patients for a median of 5 days in survivors (range 2–11 days). Postoperative ECLS support was more often required after DLTx versus HLTx (8; 80.0% vs. 4; 14.3%; p < .0001). Median postoperative inotropic support was 4 days in survivors (range 1–23 days). Median postoperative intubation duration in survivors was 7 days (range 1–82 days). Median ICU stay was 16 days (range 3–88 days) and median postoperative hospital stay was 39 days (range 14–132 days) in survivors.

3.3 | Incidence of transplantation

During the HPAP period, HPAP listing was associated with a trend toward a shorter time to transplantation (Table 2). Of the 17 HPAP+ patients, 7 (41.2%) were transplanted within 21 days after listing. HPAP listing was associated with a significantly higher incidence of transplantation, with a subdistribution hazard-ratio (sdHR) of 4.1 (2.2–7.5) (p < .001) compared to regular listing during both periods. The difference was most marked between the HPAP+ group and the pre-HPAP group (sdHR, 6.5 [2.9–14.6]; p < .001). The HPAP− group had a higher incidence of transplantation compared to the pre-HPAP group (sdHR, 2.6 [1.1–6.1]; p = .027). Finally, the HPAP+ group had a significantly higher incidence of transplantation compared to the HPAP− group (sdHR, 2.5 [1.2–5.0]; p = .011). At 1 month, the cumulative incidence of transplantation was 3.5% [0.0–10.2] in the pre HPAP group, 4.8% [0.0–14.1] in the HPAP− group, and 41.2% [16.8–65.6] in the HPAP+ group. The corresponding figures at 1 year were 13.8% [0.8–26.8], 33.3% [12.5–54.2], and 58.8% [34.1–83.5], respectively (Gray test, p < .001) (Figure 2). No other baseline variables were significantly associated with the incidence of transplantation.

3.4 | Waitlist mortality

Mortality while on the waitlist was 14.4%, 21.9%, and 34.2% at 1, 3, and 12 months, respectively. The incidence of death on waitlist was lower in patients listed during the HPAP period (at 1 and 12 months, 7.4% and 7.4% in the HPAP+ group, 4.9% and 10.6% in the HPAP− group, and 24.6% and 60.1% in the pre HPAP group, respectively; Log-rank test p = .0001, Figure 3A). Mortality was not significantly different between the HPAP+ and HPAP− groups (Log-rank test p = .9). Median survival on the waitlist in patients listed before versus after HPAP implementation was 0.3 and 6.2 years, respectively. WHO functional class IV, position of the shunt, plasma total bilirubin, PAH-SDT,

TABLE 2 Comparison of patients transplanted before versus after implementation of the high-priority allocation program (HPAP)

Variable	Pre-HPAP	HPAP implementation				
	Listing in 1997–2006 (n = 9)	Listing in 2007–2016 (n = 29) HPAP period	p value pre-HPAP versus HPAP period	Regular allocation: HPAP– group (n = 13)	HP allocation: HPAP+ group (n = 16)	p value HPAP– versus HPAP+
Time to transplantation (months), median [IQR]	12.5 [1.3–21.0]	7.9 [0.9–19.0]	.525	11.8 [2.6–17.7]	3.3 [0.3–26.2]	.329
Death <100 days after transplantation, n (%)	2 (22.2%)	4 (13.8%)	.613	2 (15.4%)	2 (12.5%)	1.000
Donor age (years), median [IQR]	41 [22–45]	38 [25–48]	.643	35 [26–48]	40 [25–50]	.614
Weight mismatch, n (%)	4 (44.4%)	5 (21.7%)	.226	1 (10.0%)	4 (30.8%)	.339
Gender mismatch, n (%)	1 (11.1%)	13 (44.8%)	.115	5 (38.5%)	8 (50.0%)	.711
Donor PaO_2/FiO_2 (mm Hg), median [IQR]	423 [400–461]	417 [384–487]	.631	421 [405–487]	409 [379–489]	.629
HLTx/DLTx, n (%)						
DLTx	1 (11.1%)	9 (31.0%)	.396	5 (38.5%)	4 (25.0%)	.688
HLTx	8 (88.9%)	20 (69.0%)		8 (61.5%)	12 (75.0%)	
Ischemic time HLTx, (min), median [IQR]	233 [190–261]	235 [208–251]	1.000	218 [206–265]	238 [217–247]	.847
Ischemic time DLTx right lung, (min), median [IQR]	180 (n = 1)	244 [225–310]		225 [198–244]	282 [242–320]	.221
Ischemic time DLTx left lung, (min), median [IQR]	300 (n = 1)	370 [322–435]		322 [297–345]	405 [373–440]	.142
ECLS posttransplantation, n (%)	1 (11.1%)	11 (37.9%)	.223	5 (38.5%)	6 (37.5%)	1.000
Reintervention for bleeding, n (%)	4 (44.4%)	8 (27.6%)	.423	3 (23.1%)	5 (31.3%)	.697
Tracheotomy, n (%)	1 (11.1%)	9 (31.0%)	.396	4 (30.8%)	5 (31.3%)	1.000
Post-op dialysis, n (%)	1 (11.1%)	9 (31.0%)	.396	3 (27.3%)	6 (46.2%)	.423
Mechanical ventilation duration in survivors (days), median [IQR]	5 [1–15]	8 [4–19]	.385	10 [3–16]	7 [4–30]	.701
Time to ICU discharge in survivors (days), median [IQR]	13 [7–39]	17 [7–33]	1.000	17 [9–23]	16 [6–39]	.584
Time to hospital discharge in survivors (days), median [IQR]	39 [26–67]	38 [30–58]	1.000	32 [28–50]	45 [31–61]	.338
Pretransplant immunosuppression, n (%)	0 (0.0%)	2 (6.9%)	1.000	0 (0.0%)	2 (12.5%)	.488
DSA the day of transplant, n (%); missing data: 12 (31.6%)	0/1	1/25	1.000	0/11	1/14	1.000
Minimal or mild acute cellular reject <1st year posttransplant, n (%)	5 (55.6%)	21 (72.4%)	.423	10 (76.9%)	11 (68.8%)	.697
Antibody mediated rejection <1st year posttransplant, n (%)	0 (0.0%)	10 (34.5%)	.079	3 (23.1%)	7 (43.8%)	.433

Abbreviations: DLTx, double-lung transplantation; DSA, donor specific-antibodies; ECLS, extracorporeal life support; HLTx, heart–lung transplantation; HPAP, high-priority allocation program; ICU, intensive care unit; IQR, interquartile range; PaO_2/FiO_2, ratio of partial pressure of oxygen in arterial blood over fraction of inspired oxygen; post-op, post-operative .

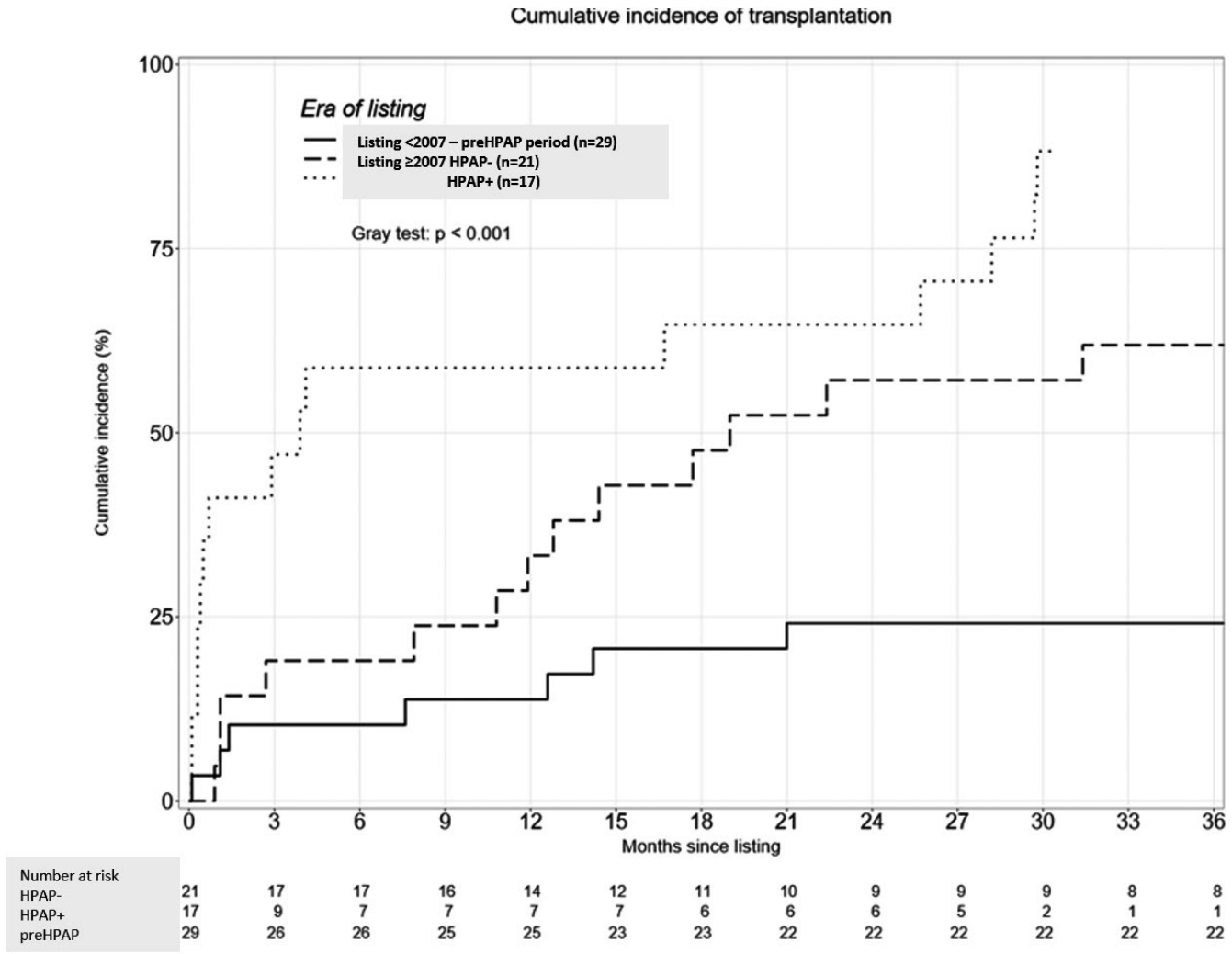

FIGURE 2 Cumulative incidence of transplantation according to a Fine and Gray regression model, with death before transplantation and being delisted as competing risks. HPAP, high-priority allocation program; HPAP− group, patients listed during the HPAP period but according to usual modalities; HPAP+ group, patients listed with HPAP status; preHPAP, patients listed before the HPAP period

inotropic support at listing and period of listing were significantly associated with the risk of death before transplantation (Table 3).

3.5 | Early mortality posttransplantation

In-hospital posttransplantation mortality occurred in 6 patients (15.8%), all within 100 days posttransplantation, with no significant difference before versus after HPAP implementation (22.2% and 13.8%, respectively; p = .6) and with no significant difference between HLTx versus DLTx recipients (5; 17.9% vs. 1; 10.0%, p = 1.0). HPAP allocation was not associated with a higher risk of early posttransplantation mortality (12.5% vs. 15.4%, p = .6).

3.6 | Long-term posttransplantation outcomes

Following transplantation, survival was 79.0%, 67.4%, and 67.4% at 1, 5, and 10 years, respectively, with a median survival of 11.2 years. Survival was not significantly different across the HPAP+, HPAP−, and preHPAP groups (Log-rank test p = .7, Figure 3B).

In the 32 patients alive 100 days posttransplantation, survival was 93.8%, 80.1%, and 80.1% at 1, 5, and 10 years, respectively, with a median conditional survival of 14.2 years. Survival conditional on survival 100 days posttransplantation was not significantly different across the HPAP+, HPAP−, and preHPAP groups (Log-rank test p = .5, Figure 3C).

Overall survival was higher in patients listed during the HPAP period when calculated from the day of listing (84.2%, 65.9%, and 61.2% at 1, 5, and 10 years vs. 36.8%, 22.1%, and 22.1% during the pre-HPAP period, Log-rank test p = .0001, Figure 3D). Overall survival calculated from the day of listing was not significantly different between the HPAP+ and HPAP− group (Logrank test, p = .6).

4 | DISCUSSION

In this retrospective study including 67 patients with PAH-CHD listed for HLTx or DLTx over a 20-year period in a single tertiary

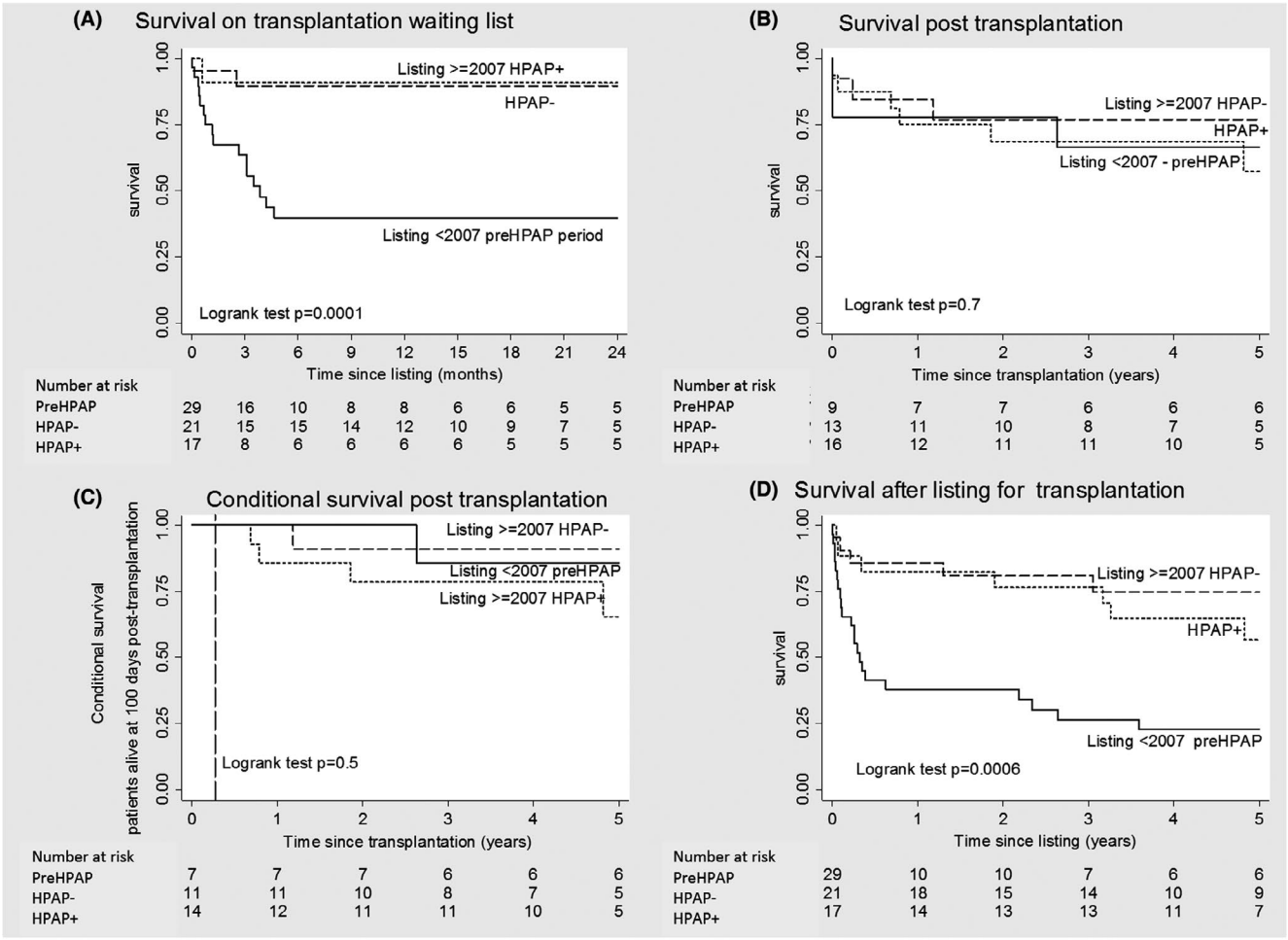

FIGURE 3 (A) Kaplan-Meier survival curve of patients on the waiting list (n = 67), with time since listing (months) as the time scale. Right censoring was set at the time of transplantation (n = 38), delisting (n = 5), or study completion (n = 1). (B) Kaplan-Meier survival curve after transplantation (n = 38), with time since transplantation (years) as the time scale. (C) Kaplan-Meier survival curve of transplanted patients, conditional on being alive 100 days posttransplantation (n = 32), with time since transplantation (years) as the time scale. (D) Kaplan-Meier survival curve of patients on the waiting list (n = 67), with time since listing (years) as the time scale. Right censoring was set at the time of delisting (n = 5) or study completion (n = 1). Deaths before and after transplantation were counted (intention-to-treat approach). HPAP, high-priority allocation program; HPAP− group, patients listed during the HPAP period but according to usual modalities; HPAP+ group, patients listed with HPAP status; preHPAP, patients listed before the HPAP period

specialized center, implementation of a national HPAP greatly improved both the incidence of transplantation and survival.

The number of transplantations in patients with ES has declined over the years across the world.[17,27,28] In a large multicenter international cohort study including 1098 patients with ES, 278 (25.3%) patients died, while only 6 (0.5%) underwent HLTx or DLTx over a median follow-up of 3.1 years. In our study of patients with PAH-CHD, before implementation of the HPAP, the incidence of transplantation was low and waitlist mortality was high. After HPAP implementation, the incidence of transplantation increased substantially. Thus, the HPAP was effective in improving access to transplantation.

Waitlist mortality was significantly lower after HPAP implementation and was also lower than previously reported.[29,30] Other factors that may have contributed to decrease mortality are improved timing of patient listing and better selection of eligible patients, as well as the shorter time to transplantation and absence of increased peri-operative mortality in the HPAP+ group. The strategy for deciding when to list has evolved in recent years. Listing is indicated before the onset of kidney and/or liver failure. In our cohort, plasma total bilirubin and hematocrit were higher at listing in the preHPAP period, suggesting that patients were more severely ill at baseline during this period. In addition, new supportive treatments are available for use before transplantation. During the HPAP period, 3 (7.9%) of our patients with severe decompensated heart failure were stabilized by ECLS support prior to transplantation (n = 2) or targeted medical therapy (n = 1).[31] PAH-SDTs were prescribed in our cohort starting in 1999 but became increasingly widely used, with 41.4% of patients receiving these drugs before HPAP implementation versus 81.6% afterward. As observed in many large cohort studies, PAH-SDTs may have contributed to increase waitlist survival in our patients.[2,3,8] PAH-SDTs may delay the need for

TABLE 3 Relationships between baseline variables and outcome by univariate Cox regression analysis with time since listing as the time scale and left censoring at transplantation or delisting

Variable	Available data	Reference	Modality	Univariate Cox analysis	
				Hazard ratio [95% CI]	Cox *p* value
Age at listing (years)	100%	Continuous variable		0.99 [0.95–1.04]	.825
History of cardiac surgery	100%	No	Yes	1.49 [0.64–3.46]	.355
Type of CHD	100%	Simple	Complex	1.92 [0.83–4.44]	.129
Position of the shunt	100%	Posttriscupid shunt	Combined pre and post	5.67 [1.46–22.05]	.012
			Pre-triscupid shunt	2.76 [0.76–9.99]	.123
			No shunt	4.08 [1.19–13.98]	.025
Sex	100%	Female	Male	2.25 [0.95–5.36]	.066
BMI (kg m^{-2})	100%	Continuous variable		0.88 [0.74–1.05]	.149
WHO-FC	100%	III	IV	3.97 [1.46–10.77]	.007
Ascites	100%	No	Yes	2.27 [0.73–7.02]	.154
sPAP (mm Hg)	98.5%	Continuous variable		0.99 [0.97–1.00]	.078
mPAP (mm Hg)	97.0%	Continuous variable		0.98 [0.96–1.00]	.076
RAP (mm Hg)	74.6%	Continuous variable		1.07 [0.99–1.16]	.070
LAP (mm Hg)	67.2%	Continuous variable		1.01 [0.92–1.11]	.820
Systemic output (L min^{-1} m^{-2})	71.6%	Continuous variable		0.58 [0.31–1.08]	.083
PVR (WU)	70.1%	Continuous variable		1.02 [0.99–1.06]	.119
Aortic SaO_2 (%)	100%	Continuous variable		0.99 [0.95–1.03]	.619
PA SaO_2 (%)	71.6%	Continuous variable		1.00 [0.95–1.05]	.950
Hematocrit (%)	94.0%	Continuous variable		1.02 [0.97–1.08]	.488
Creatinine clearance ≤60 mL min^{-1}	100%	No	Yes	1.71 [0.73–4.03]	.220
ALAT (IU L^{-1})	95.5%	Continuous variable		1.03 [0.98–1.07]	.216
ASAT (IU L^{-1})	82.1%	Continuous variable		1.01 [0.99–1.03]	.323
Total bilirubin (μmol L^{-1})	95.5%	Continuous variable		1.03 [1.01–1.05]	.016
PAH-SDT	100%	No	Single therapy	1.17 [0.42–3.26]	.768
			Double therapy	0.04 [0.00–0.32]	.003
			Triple therapy	0.11 [0.02–0.64]	.013
Inotropic support at listing	100%	No	Yes	2.67 [1.15–6.19]	.022
Oro-tracheal intubation at listing	100%	No	Yes	2.99 [0.68–13.20]	.149
Listed before 2007	100%	No	Yes	9.27 [2.73–31.40]	.001
High-priority graft allocation program	100%	No	Yes	0.18 [0.02–1.33]	.092
Period of Listing	100%	<2007	≥2007 HPAP−	0.11 [0.03–0.48]	.003
			≥2007 HPAP+	0.10 [0.01–0.76]	.026

Abbreviations: ALAT, alanine-amino-transferase; ASAT, aspartate-amino-transferase; BMI, body mass index; CI, confidence interval; mPAP, mean pulmonary artery pressure; PAH-SDT, pulmonary artery hypertension specific drug therapy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; WHO-FC, World Health Organization Functional Class; WU, Wood unit.

transplantation in patients with unstable ES[10] or improve organ failures, thereby eliminating contraindications to listing. However, only WHO status and era of listing with HPAP status were independently associated with waitlist mortality in a multivariable Cox regression analysis.

The time to transplantation was shorter in the HPAP+ group than in the HPAP− and preHPAP groups. In addition to the HPAP, the greater use of DLTx may have contributed to shorten the time to transplantation, since double-lung transplants are far more available than heart-lung transplants. However, median waitlist durations before DLTx and HLTx were similar in our cohort. The shift towards DLTx is in line with suggestions that PAH-CHD may be treatable by DLTx and cardiac repair provided the cardiac abnormalities are relatively simple and the function of both ventricles is

preserved.[15,20,32,33,34,35] In our cohort, DLTx accounted for 11.1% of transplantations before HPAP implementation compared to 31.0% afterward. The indications of DLTx were extended to patients with an absent or closed shunt and to those with atrial septal defects eligible for percutaneous closure. The morphological parameters must be suitable for DLTx, with limited heart dilation. In a period of organ scarcity, DLTx combined with percutaneous shunt repair may be an excellent alternative to HLTx in selected cases. In addition, transplantation of a single organ provides better early and long-term outcomes compared to multi-organ transplantation.[20,27,28,36,37]

Peri-operative mortality decreased to 13.8% after HPAP implementation versus 22.2% in the earlier period. This decrease is ascribable to multiple factors including improvements in peri-transplantation management, which requires the complementary skills of surgeons, anesthesiologists, pulmonologists, and intensivists. Hemostasis control during transplantation is challenging, especially with HLTx, during which access to the posterior mediastinum can be very difficult.[14] Reintervention for bleeding control was required in one of three patients. Postoperative supportive therapies have evolved markedly over the last two decades. Postoperative ECLS is more often used to facilitate heart function recovery, in particular after DLTx. Importantly, transplantation in patients in the HPAP+ group was not associated with higher peri-operative mortality.

Improved management of immunosuppression may have also contributed to the better outcomes reported in our cohort after HPAP implementation. During that period, the detection of donor-specific-antibodies improved, their prognostic value was demonstrated, and immunosuppressive strategies were enhanced accordingly.[38]

Long-term survival of HLTx recipients has improved throughout the world. The median survival for HLTx has increased to 6.5 years in the most recent era; much of this mortality occurs early after transplantation, with median survival conditional on survival to 1 year after transplantation being 12.8 years in the international registry.[27] Survival rates in our transplant recipients were 79.0%, 67.4%, and 67.4% at 1, 5, and 10 years, respectively, with a median survival of 11.2 years. A 2019 study from the United States found a 64.3% 5-year survival rate after HLTx in adults with PAH-CHD.[36] A 2020 study of patients with ES managed in specialized centers in Scandinavia showed 1-, 5-, and 10-year survival rates of 84.1%, 69.7%, and 55.8%, respectively.[17] Importantly, in our cohort, long-term survival conditional on survival 100 days posttransplantation was not different between patients listed before and during HPAP implementation. Survival in our cohort was higher than reported in adults who underwent primary DLTx in the more recent era (2010–2017; n = 29,872; median survival, 6.7 years).[27] Patients with PAH-CHD are generally young, as illustrated in our cohort by the mean age of 33.2 years at listing. Mean age at listing was not significantly different before and during HPAP implementation. In registry studies, mean age at DLTx and HLTx was 56 and 54 years, respectively, with comorbidities in up to 45% of patients.[16,39] The lower comorbidity burden among younger patients contributes to the better long-term outcomes. Their better long-term outcomes compared to patients without CHD encourage the prioritization of graft allocation to patients with PAH-CHD. HPAP implementation followed similar rules for patients with PAH but no CHD and resulted in similar outcome benefits. In 2016, the pediatric transplant allocation policy in the US was changed to prioritize CHD patients maintained on intravenous inotropes while downgrading patients with dilated cardiomyopathy in similar condition.[40] Contrary to our study, there was no difference in waitlist mortality or posttransplant survival despite this policy change. In France, HPAP+ status is conferred for an unlimited duration to children awaiting a heart and/or lung transplant. In France, the cumulative pediatric heart transplant incidence at 6 months increased between 1995–1998 and 2015–2017 from 48% to 65%, while the probability of death or being delisted because of aggravation decreased from 30% to 19%.[41] HPAP implementation resulted in similar outcome improvements after lung transplantation in non-CHD patients.[18]

Our study has several limitations. First, the decrease in mortality may be ascribable not only to the HPAP but also to other changes in the management of patients with PAH-CHD. The approach to these patients has become more active in recent years. Furthermore, the accumulation of experience over time contributes to improve outcomes. We kept the study period relatively short to limit bias due to improvements in overall management. The statistical analyses suggest a major improvement in outcomes after 2007 that is unlikely to be solely ascribable to improvements in management. However, given a low event rate and a small sample size, it cannot be definitively determined statistically if HPAP was responsible for the observed improvement in waitlist outcomes. Second, we did not analyze the outcomes of patients with PAH-CHD who were referred for listing but had absolute contraindications to transplantation. An analysis of the listing process and of the indications and contraindications of transplantation would have been useful. A previous report suggested that at least a quarter of patients with PAH-CHD were considered unsuitable for listing, and the outcomes of these patients are unclear.[32] Recognized contraindications to transplantation include previous multiple lateral thoracotomies, impaired renal and hepatic function, and multiple systemic-to-pulmonary collateral vessels.[12] The optimal time for transplantation listing remains difficult to determine, particularly given the considerable heterogeneity of patients with PAH-CHD in terms of clinical phenotype, anatomy, and course.[5,8,12,42] The assessment of indications for HLTx or DLTx, transplantation feasibility, and optimal timing should be performed early, by a specialized team, before the onset of multi-organ failure.[12] Scores such as the ERS-ESC and REVEAL2.0 that are designed to predict 1-year mortality in patients with PAH may be useful to determine the optimal time for listing.[43,44] However, a risk stratification score specific of patients with PAH-CHD remains to be developed.

5 | CONCLUSION

Implementation of an HPAP for patients with end-stage PAH-CHD was associated with a dramatic increase in the incidence of transplantation, decreased waiting list mortality, and improved early and long-term outcomes.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be made available on reasonable request.

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