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Severe primary graft failure: Are there lasting impacts? Analysis from the PHTS Database

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BACKGROUND: Primary graft failure (PGF) is a leading cause of early morbidity and mortality after heart transplantation (HTx). PGF is secondary to graft ischemia and ischemia-reperfusion injuries to the cardiomyocytes and vasculature of the donor heart after transplantation. Longer-term outcomes after PGF are not well studied.

METHODS: Patients with an HTx (January 1, 2010 to June 30, 2022) were identified using the Pediatric Heart Transplant Society registry. PGF was defined as death, retransplantation, or need for mechanical circulatory support within 72 hours of HTx. Kaplan-Meier analysis and Cox proportional hazard modeling were utilized.

RESULTS: Of the 4,982 patients with a primary HTx, 5.4% (n = 269) met criteria for PGF. Patients with PGF were younger, with higher proportion of congenital heart disease, longer cardiopulmonary bypass and ischemic times (IT), and more likely to be on extracorporeal membrane oxygenation or ventilator at HTx (all $p < 0.0001$, IT $p = 0.0006$). PGF resulted in lower overall survival (1 year: 54% vs 94%, $p < 0.001$). This remained true when conditional survival was examined at 30 and 90 days but not at 1 year ($p = 0.1143$). Freedom from rejection did not differ between the groups at overall or conditional on 30 days but was slightly higher for those with PGF at 90 and 365 days. There was no difference in freedom from coronary allograft vasculopathy (CAV). PGF was an independent predictor of overall graft loss (hazard ratios [HR] 4.7, $p < 0.0001$) and conditional survival to 30 days (HR 2.47, $p < 0.0001$) and 90 days (HR 1.6, $p = 0.012$) but not beyond 1 year.

CONCLUSIONS: Severe PGF is an independent predictor of early mortality post-HTx but subsequently does not further impact long-term survival, overall risk of rejection, or CAV. Understanding the impact of milder forms of PGF on survival and long-term outcomes is still needed. Methods to decrease the

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risk of PGF, such as alternative preservation and storage techniques, may impact early mortality post-HTx.

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Background

Heart transplantation (HTx) is a well-recognized therapy for end-stage heart failure in children and while the outcomes have improved over the last 20 years, there remains ongoing morbidity and mortality that limit the life span of both the graft and the recipient.[1] Primary graft failure (PGF) is one of the leading causes of early morbidity and mortality after HTx. It manifests as allograft dysfunction in the absence of other causes.

Previous reports in children have suggested the incidence of severe PGF, specifically in children requiring extracorporeal membrane oxygenation (ECMO), is approximately 5%.[1,2] Risk factors for the development of PGF have been identified as younger age, diagnosis of congenital heart disease (CHD), need for ECMO pretransplant, higher bilirubin, and graft ischemic time ≥4 hours. Similar findings have also been reported in a group of children < 1 year of age.[1,2] Regardless of recipient age, severe PGF is associated with high early mortality with 1-year survival approaching 50%.[1,2]

While the impact of PGF on early mortality in pediatrics has been described, these studies are almost a decade old, only focus on patients supported with post-transplant ECMO, and do not clarify if there are longer-term impacts on survival and post-HTx morbidities. This analysis is focused on a contemporary cohort of children from a multicenter, prospective longitudinal cohort, with a broader definition of severe PGF and includes outcomes that extend beyond early survival.

Materials and methods

The Pediatric Heart Transplant Society (PHTS) houses a prospective, multicenter, international, event-driven database, spanning 59 centers in 4 countries and including patients transplanted starting on January 1, 1993. Institutional review board approval was obtained at each institute and patient consent to participate was left to the discretion of each institution as the registry serves as a quality improvement resource for centers.

Patients transplanted between January 1, 2010 and June 30, 2022 were included. Patients with a retransplant or multiorgan transplant were excluded. Data are collected on all patients from the time of listing and HTx until their most recent follow-up, with data entry end-points occurring at death or transfer to a nonpediatric or non-PHTS transplant center. Pertinent recipient–related demographic and clinical variables are collected including but not limited to, age (at listing and HTx), sex, diagnosis, priority status at listing and at HTx, measures of hepatic and renal function, body mass index (BMI), need for mechanical circulatory support, ventilatory support, or inotropic requirements, use of induction therapy, and the occurrence of rejection and coronary allograft vasculopathy [CAV]. Donor characteristics were also collected including age, sex, race, cause of death, downtime (duration of cardiac arrest), and ischemic time.

Definitions

The PHTS defines acute rejection as a clinical event, diagnosed based on clinical findings, endomyocardial biopsy, or echocardiography, resulting in augmentation of immunosuppression therapy relative to baseline strategies for the patient. CAV was defined as the presence of an abnormal coronary evaluation by angiography.

As PGF is not an outcome in the PHTS database, for the purpose of this study, PGF was defined as the need for mechanical circulatory support (ECMO/ventricular assist device [VAD]), death, or retransplantation within 72 hours of HTx. This represents severe PGF as milder forms are not captured in the database.

Statistical analysis

Analysis was performed at the PHTS data coordinating center (Kirklin Solutions, Hoover, AL). Demographic and clinical characteristics are presented and compared between the patients of PGF or not. Continuous data are presented as median (quartile 1-quartile 3) and categorical data as frequency (percent). Comparisons were evaluated using Wilcoxon Rank Sum for continuous variables and chi-square tests for categorical variables.

Outcome analyses were conducted utilizing the Kaplan-Meier method and log-rank tests examining time to first event (survival, rejection, allograft vasculopathy), censoring on graft loss (death or retransplantation) or lost to follow-up. Multivariable Cox proportional hazard models were used to estimate hazards of PGF or not for post-HTx graft survival. Hazard ratios (HR) are presented with 95% confidence intervals (95% CI). Conditional survival to 30-, 90-, and 365-day post-HTx were also examined. For the multivariable models, categorical missing values were set to mode, and for continuous variables, the average value was used. If more than 20% of the data was missing, we excluded the variable from potential covariates. All analyses

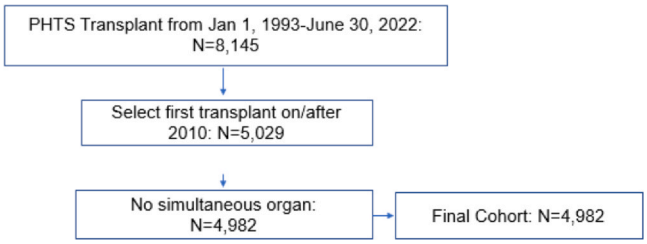

Figure 1 Flow diagram outlining the selection criteria for the study cohort. Final cohort consisted of 4,982 patients who underwent heart transplant only after 2010. PHTS, Pediatric Heart Transplant Society.

were performed with SAS 9.4 software (SAS Institute, Cary, NC).

A series of multivariable Cox proportional hazard models, using step-wise selection, with a p-value of 0.05 for selection into the model, was performed for the outcome of graft loss, conditional on survival to 30, 90, and 365 days were performed. Factors included in the model are outlined in Appendix 1. Variables that were significant in univariate analysis at $p < 0.1$ were included in the multivariable models.

All analyses were performed with SAS 9 software (SAS Institute, Cary, NC).

Results

Demographics and clinical characteristics

There were 4,982 patients eligible for this study (Figure 1). Tables 1 and 2 outline the cohort characteristics at listing and HTx. The median age at HTx was 5.2 (0.8-13.2) years with 44.8% (n = 2230) being female. Approximately one-third (28.8%) of those transplanted were < 1 year of age with an almost equal distribution of children with a diagnosis of CHD (n = 2,423, 48.6%) and cardiomyopathy (n = 2,416, 48.5%) (Table 1). At the time of HTx, 3.7% of patients were supported on ECMO and 29.1% on VAD. The median creatinine was 0.4 (0.3-0.6) and bilirubin was 0.6 (0.4-1.1) at HTx. The median cardiopulmonary bypass time (CPB) was 2.8 (2.1-3.6) hours and ischemic time was 3.6 (3.0-4.2) hours. Ischemic times between 4 and 6 hours occurred in 32.3% with 2.9% of patients having an ischemic time > 6 hours.

In this cohort, 5.4% (n = 269) meet the criteria for PGF with 238 patients on ECMO, 20 on VAD, and 11 who died within 72 hours of HTx. There were no patients that underwent retransplant in that time frame. This did not vary between those that were transplanted in the more recent era (2016-2022), where 5.6% of patients experienced PGF. Those with PGF were more likely to have CHD (65.1% vs 47.7%, $p < 0.0001$). At the time of HTx (Table 2), those with PGF were younger (2.9 (0.6 -9.7) vs 5.3 (0.8-13.3) years, $p < 0.0001$) with no difference in end-organ function, specifically creatine (p = 0.143) and bilirubin compared to those without PGF (p = 0.105). In addition, children with PGF were more likely to be on a ventilator (30.4% vs 15.3%, $p < 0.0001$) and ECMO (29.6% vs 2.2, $p < 0.0001$) but there was no difference in VAD use (p = 0.96). Lastly, those patients who experienced PGF were more likely to have an ABO-incompatible HTx (17.2% vs 9.3%, $p < 0.0001$), a longer bypass time [3.8 (2.9-5.1) vs 2.7 (2.1-3.5) hours, $p < 0.0001$], and longer ischemic time [3.8 (3.2-4.5) vs 3.6 (3.0-4.2) hours, p = 0.0006] (Table 2). There was a greater proportion of patients having an ischemic time between 4 and 6 hours (36.8% vs 32.1%) and > 6 hours (5.3% vs 2.8%) (p = 0.012). There was no difference in the proportion of donors with downtime, but the downtime was longer in donors with PGF (26.7 ± 29.4 vs 20.8 ± 22.4 minutes, p = 0.002) and the distribution of donor causes of death differed (p = 0.0290) (Table 3). Supplementary Table 1 highlights the non–risk-adjusted recipient and donor characteristics associated with PGF from univariate analysis.

Graft survival

Graft loss occurred in almost half of the group with PGF (47.2%) at a median time of 0.7 (0.1-4.5) years (Table 4). Graft loss was significantly lower in those without PGF (13.4%, $p < 0.0001$) and occurred on average later post-HTx, 3.7 (1.5-6.5) years ($p < 0.0001$). Death occurred early in the PGF group with almost a quarter (24.9%) of deaths occurring by 30 days post-HTx. There was ongoing attrition after this point with 1-year survival being 54% in those with PGF compared to 94.5% ($p < 0.0001$) in those without. Conditional survival to 30 and 90 days was significantly worse for those with PGF vs those without (1-year 72.6% vs 95.6%, $p < 0.0001$% and 84.0% vs 96.5%, p = 0.007, respectively). This did not hold true when conditional survival to 365 days was examined (1-year survival 97.6% vs 97.2%, p = 0.114) (Figure 2A-D).

Tables 5-8 list the multivariate results outlining the factors associated with overall survival and conditional survival. As highlighted in the tables, PGF is an independent predictor of overall survival (HR 4.72, 95% CI 3.87-5.74, $p < 0.0001$). It is also an independent predictor conditional on survival to 30 days (HR 2.47, 95% CI 1.87-3.26, $p < 0.0001$) and 90 days (HR 1.60, 95% CI 1.11-2.31, p = 0.012) but not 365 days. Other important independent predictors of mortality that also impacted overall and conditional survival to 60 and 90 days included race, a diagnosis of CHD, and CPB time. Tables 5-8 also highlight additional covariates at each time period with only race impacting all 4 conditions.

Post-transplant complications

Rejection

By 1-year post-transplant, 17.5% of the group with PGF experienced rejection compared to 21.9% in the non-PGF group (p = 0.041). When the time to first rejection was examined and dichotomized by the presence or absence of

Table 1 Patient Characteristics at Listing

Patient characteristics at listing	Overall (n =4982) N (%) or median (q1-q3)	PGF (n = 269) N (%) or median (q1-q3)	No PGF (n = 4713) N (%) or median (q1-q3)	*p*-value
Age (years) at listing	4.4 (0.5-12.9)	2.5 (0.3-9.3)	4.6 (0.5-13.0)	< 0.0001
Height (cm) at listing	107.0 ± 45.2 (*n* = 4,889)	93.6 ± 38.9 (*n* = 260)	107.7 ± 45.4 (*n* = 4,629)	< 0.0001
Weight (kg) at listing	26.2 ± 24.9 (*n* = 4,973)	18.7 ± 18.5 (*n* = 268)	26.7 ± 25.2 (*n* = 4,705)	< .0001
Sex at listing				0.67
F	2,230 (44.8)	117 (43.5)	2,113 (44.8)	
M	2,752 (55.2)	152 (56.5)	2,600 (55.2)	
Recipient race				0.57
1. White	3,180 (63.9)	178 (66.2)	3,002 (63.8)	
2. Black	880 (17.7)	48 (17.8)	832 (17.7)	
3. Other	915 (18.4)	43 (16.0)	872 (18.5)	
Missing	7		7	
Status at listing: combined countries				0.076
Priority	4,073 (81.8)	209 (77.7)	3,864 (82.0)	
Routine	909 (18.2)	60 (22.3)	849 (18.0)	
Primary etiology				< 0.0001
Cardiac tumor	13 (0.3)	1 (0.4)	12 (0.3)	
Cardiomyopathy	2,416 (48.5)	83 (30.9)	2,333 (49.5)	
Congenital HD	2,423 (48.6)	175 (65.1)	2,248 (47.7)	
Myocarditis	97 (1.9)	6 (2.2)	91 (1.9)	
Other, specify	33 (0.7)	4 (1.5)	29 (0.6)	
Serum albumin g/dl	3.6 (3.1-4.1) (*n* = 4,624)	3.4 (2.9-4.0) (n = 250)	3.6 (3.1-4.1) (*n* = 4,374)	0.004
Creatinine (mg/dl) at listing	0.4 (0.3-0.6) (*n* = 4,845)	0.4 (0.3-0.6) (*n* = 258)	0.4 (0.3-0.6) (*n* =4,587)	0.066
Bilirubin (mg/dl) at listing	0.7 (0.4-1.2) (*n* = 4,542)	0.7 (0.4-1.3) (*n* = 244)	0.7 (0.4-1.2) (*n* = 4,298)	0.547
AST (U/liter) at listing	36.0 (27.0-53.0) (*n* = 4,412)	36.0 (28.0-55.0) (*n* = 223)	36.0 (27.0-53.0) (*n* = 4,189)	0.281
ALT (U/liter) at listing	28.0 (18.0-43.0) (*n* = 4,662)	29.0 (19.0-42.0) (*n* = 248)	28.0 (18.0-43.0) (*n* = 4,414)	0.679
BNP (pg/ml) at listing	920.0 (262.4-2,386.0) (*n* = 2,550)	823.0 (158.0-1,459.0) (*n* = 127)	930.0 (264.0-2,409.0) (*n* = 2,423)	0.034
eGFR (ml/min/1.73 m^2) at listing	95.0 (73.0-121.2) (*n* = 4,779)	89.6 (63.8-112.9) (*n* = 253)	95.1 (73.4-121.4) (*n* = 4,526)	0.013
Patient in hospital at listing	3,826 (76.8)	212 (78.8)	3,614 (76.7)	0.42
Patient in ICU at listing	2,672 (61.5)	157 (64.6)	2,515 (61.3)	0.30
Ventilator at listing	1,047 (21.1)	76 (28.7)	971 (20.7)	0.002
VAD at listing	609 (12.3)	27 (10.0)	582 (12.4)	0.25
ECMO at listing	212 (4.3)	17 (6.3)	195 (4.2)	0.09
Inotropes at listing	3,048 (61.5)	159 (60.0)	2,889 (61.5)	0.62
Max PRA at listing (%)	0.0 (0.0-11.0) (*n* = 4,644)	0.0 (0.0-18.0) (*n* = 243)	0.0 (0.0-11.0) (*n* = 4,401)	0.442

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide, ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; F, female; HD, heart disease; ICU, intensive care unit; M, male; PGF, primary graft failure; PRA, panel reactive antibody; VAD, ventricular assist device.

PGF, there was no difference in freedom from rejection between the 2 cohorts (at 1-year 76.1% vs 76.9%) (Figure 3A). This was true when results were examined based on conditional survival at 30-day post-HTx (Figure 3B). However, in those patients that survived beyond 90- and 365-day post-HTx freedom from rejection was higher for those with PGF (Figure 3C and D).

Allograft vasculopathy

There was no difference in the freedom from allograft vasculopathy in those with and without PGF (10 years: 89.3% vs 81.5%, $p = 0.54$). This was true at baseline and when conditional on survival to 30, 90, and 365 days were examined (Figure 4A-D).

Table 2 Patient Characteristics at Transplant

Recipient patient characteristics	Overall (*n* = 4,982) N (%) or median (q1-q3)	PGF (*n* = 269) N (%) or median (q1-q3)	No PGF (*n* = 4,713) N (%) or median (q1-q3)	*p*-value
Age (years) at transplant	5.2 (0.8-13.2) (*n* = 4,982)	2.9 (0.6-9.7) (*n* = 269)	5.3 (0.8-13.3) (*n* = 4,713)	< 0.0001
Recipient height (cm) at transplant	109.4 ± 42.4 (*n* = 4,909)	96.4 ± 37.9 (*n* = 266)	110.2 ± 42.5 (*n* = 4,643)	< 0.0001
Recipient weight (kg) at transplant	27.4 ± 24.6 (*n* = 4,973)	19.8 ± 18.6 (*n* = 269)	27.9 ± 24.9 (*n* = 4,704)	< 0.0001
BSA (kg/m^2) at transplant	0.7 (0.4-1.4) (*n* = 4,909)	0.6 (0.3-1.0) (*n* = 266)	0.7 (0.4-1.4) (*n* = 4,643)	< 0.0001
BMI at transplant	16.9 (15.1-19.7) (*n* = 4,909)	16.4 (14.8-18.9) (*n* = 266)	7.0 (15.1-19.8) (*n* = 4,643)	0.006
Recipient blood type at transplant				0.33
A	1,795 (36.0)	103 (38.3)	1,692 (35.9)	
AB	208 (4.2)	13 (4.8)	195 (4.1)	
B	690 (13.8)	26 (9.7)	664 (14.1)	
O	2,285 (45.9)	127 (47.2)	2,158 (45.8)	
Unknown	4 (0.1)		4 (0.1)	
Status at transplant				0.007
Priority	4,601 (92.4)	237 (88.1)	4,364 (92.6)	
Routine	381 (7.6)	32 (11.9)	349 (7.4)	
Time on waitlist (months)	2.2 (0.8-4.9) (*n* = 4,982)	2.3 (1.0-5.1) (*n* = 269)	2.2 (0.8-4.9) (*n* = 4,713)	0.554
Creatinine (mg/dl)	0.4 (0.3-0.6) (*n* = 4,952)	0.4 (0.3-0.6) (*n* = 263)	0.4 (0.3-0.6) (*n* = 4,689)	0.143
Bilirubin (mg/dl)	0.6 (0.4-1.1) (*n* = 4,536)	0.7 (0.4-1.2) (*n* = 246)	0.6 (0.4-1.1) (*n* = 4,290)	0.105
eGFR (ml/min/1.73 m^2)	99.8 (77.8-128.1) (*n* = 4,887)	95.8 (70.4-120.5) (*n* = 261)	100.1 (78.1-128.4) (*n* = 4,626)	0.009
Transplant PRA: max	0.0 (0.0-11.0) (*n* = 4,577)	0.0 (0.0-24.0) (*n* = 238)	0.0 (0.0-11.0) (*n* = 4,339)	0.358
VAD at transplant	1,425 (29.1)	78 (29.2)	1,347 (29.1)	0.96
ECMO at transplant	180 (3.7)	79 (29.6)	101 (2.2)	< 0.0001
Ventilator at transplant	793 (16.1)	80 (30.4)	713 (15.3)	< 0.0001
Patient in hospital at transplant	4,103 (82.4)	233 (86.6)	3,870 (82.1)	0.06
Patient in ICU at transplant	2,399 (48.7)	146 (54.9)	2,253 (48.4)	0.011
Inotropes at transplant	2,913 (58.7)	146 (55.3)	2,767 (58.9)	0.245
Induction therapy at transplant	4,332 (87.3)	235 (87.7)	4,097 (87.3)	0.85
ABO-incompatible at transplant	482 (9.7)	46 (17.2)	436 (9.3)	< 0.0001
Cardio bypass time (hours)	2.8 (2.1-3.6) (*n* = 4,805)	3.8 (2.9-5.1) (*n* = 260)	2.7 (2.1-3.5) (*n* = 4,545)	< 0.0001
Donor ischemic time (hours)	3.6 (3.0-4.2) (*n* = 4,924)	3.8 (3.2-4.5) (*n* = 266)	3.6 (3.0-4.2) (*n* = 4,658)	0.0006
Donor ischemic time group (hours)				0.012
0- < 3	1,101 (22.4)	45 (16.9)	1,056 (22.7)	
3- < 4	2,088 (42.4)	109 (41.0)	1,979 (42.5)	
4- < 6	1,591 (32.3)	98 (36.8)	1,493 (32.1)	
≥6	144 (2.9)	14 (5.3)	130 (2.8)	
Missing	58	3	55	
Transplant time period				0.3061
Transplant 2010-2013	1,392 (27.9)	68 (25.3)	1,324 (28.1)	
Transplant 2014-2017	1,713 (34.4)	88 (32.7)	1,625 (34.5)	
Transplant 2018-June 30, 2022	1,877 (37.7)	113 (42.0)	1,764 (37.4)	

Abbreviations: BMI, body mass index; BSA, body surface area, ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; PGF, primary graft failure; PRA, panel reactive antibody; VAD, ventricular assist device.

Table 3 Donor Characteristics

Donor characteristics	Overall (n = 4,982) N (%) or median (q1-q3)	PGF (n = 269) N (%) or median (q1-q3)	No PGF (n = 4,713) N (%) or median (q1-q3)	p-value
Donor age (years)	6.0 (1.3-16.0) (n = 4,963)	4.0 (1.1-13.0) (n = 269)	6.0 (1.3-16.0) (n = 4,694)	0.034
Donor sex				0.99
F	2,032 (41.4)	110 (41.4)	1,922 (41.4)	
M	2,879 (58.6)	156 (58.6)	2,723 (58.6)	
Missing	71	3	68	
Donor blood type				0.30
A	1,567 (31.5)	96 (35.7)	1,471 (31.3)	
AB	109 (2.2)	7 (2.6)	102 (2.2)	
B	519 (10.4)	31 (11.5)	488 (10.4)	
O	2,773 (55.8)	135 (50.2)	2,638 (56.1)	
Missing	14		14	
Donor race				0.245
1. White	2,982 (61.1)	159 (60.0)	2,823 (61.2)	
2. Black	1,072 (22.0)	52 (19.6)	1,020 (22.1)	
3. Other	823 (16.9)	54 (20.4)	769 (16.7)	
Missing	105	4	101	
Donor BMI	18.6 (16.1-22.3) (n = 4,945)	17.6 (15.8-20.7) (n = 268)	18.7 (16.1-22.4) (n = 4,677)	< 0.001
Donor BSA (m^2)	0.9 (0.5-1.6) (n = 4,945)	0.7 (0.5-1.4) (n = 268)	0.9 (0.5-1.6) (n = 4,677)	0.0028
Donor weight (kg)	35.4 ± 28.3 (n = 4,961)	29.1 ± 23.5 (n = 268)	35.7 ± 28.6 (n = 4,693)	0.0025
Donor height (cm)	120.7 ± 43.8 (n = 4,945)	113.9 ± 41.5 (n = 268)	121.1 ± 43.9 (n = 4,677)	0.009
Donor cause of death				0.029
Anoxia	2,099 (42.3)	124 (46.1)	1,975 (42.1)	
CNS tumor	36 (0.7)	4 (1.5)	32 (0.7)	
Cerebrovascular	348 (7.0)	27 (10.0)	321 (6.8)	
Head trauma	2,250 (45.3)	101 (37.5)	2,149 (45.8)	
Other	229 (4.6)	13 (4.8)	216 (4.6)	
Missing	20		20	
Donor downtime yes	2,870 (69.9)	158 (70.9)	2,712 (69.8)	0.74
Donor duration of downtime (minutes)	15.0 (0.0-34.0) (n = 2,665)	20.0 (0.0-45.0) (n = 146)	15.0 (0.0-33.0) (n = 2,519)	0.077
Donor chest compression	2,688 (55.9)	157 (60.6)	2,531 (55.6)	0.11
Donor chest compression time (minutes)	22.0 (10.0-40.0) (n = 2,374)	30.0 (15.0-45.0) (n = 136)	22.0 (10.0-40.0) (n = 2,238)	0.010
Donor echocardiogram result				0.45
Abnormal	101 (2.1)	8 (3.1)	93 (2.0)	
Normal	4,621 (94.4)	243 (93.8)	4,378 (94.4)	
Unknown	175 (3.6)	8 (3.1)	167 (3.6)	
Missing	85	10	75	
Donor estimated LV eject fraction	65.0 (60.0-69.4) (n = 4,336)	63.0 (59.0-69.0) (n = 221)	65.0 (60.0-69.8) (n = 4,115)	0.200
Donor-specific antibodies	618 (13.0)	35 (14.3)	583 (12.9)	0.53
Donor history: cancer at procurement	17 (0.4)	2 (0.8)	15 (0.3)	0.25
Donor dobutamine	171 (3.6)	7 (2.7)	164 (3.7)	0.43
Donor dopamine	585 (12.4)	46 (17.9)	539 (12.1)	0.006
Donor epinephrine	605 (12.8)	37 (14.5)	568 (12.7)	0.40
Donor levophed	796 (16.8)	43 (16.8)	753 (16.8)	0.99
Donor milrinone	61 (1.3)	7 (2.8)	54 (1.2)	0.034
Donor neosynephrine	397 (8.4)	18 (7.0)	379 (8.5)	0.41
Donor T3	184 (3.9)	18 (7.1)	166 (3.7)	0.007
Donor T4	2,096 (44.0)	109 (42.6)	1,987 (44.1)	0.63
Donor vasopressin	2,396 (50.2)	139 (53.7)	2,257 (50.0)	0.25

Abbreviations: BMI, body mass index; BSA, body surface area; CNS, central nervous system; F, female; LV, left ventricular; M, male; PGF, primary graft failure.

Table 4 Outcomes Post-Transplant Dichotomized by the Presence or Absence of Primary Graft Failure

Characteristics	Overall (n = 4,982) N (%) or median (q1-q3)	PGF (n = 269) N (%) or median (q1-q3)	No PGF (n = 4,713) N (%) or median (q1-q3)	p-value
Graft loss	757 (15.2)	127 (47.2)	630 (13.4)	< 0.0001
Graft loss interval (years)	3.7 (1.4-6.5) (n = 4,982)	0.7 (0.1-4.5) (n = 269)	3.7 (1.5-6.5) (n = 4,713)	< 0.0001
Rejection time period (days)				0.041
0-30	536 (10.8)	27 (10.0)	509 (10.8)	
> 30-90	258 (5.2)	15 (5.6)	243 (5.2)	
> 90-365	285 (5.7)	5 (1.9)	280 (5.9)	
No rejection within 365 days	3,903 (78.3)	222 (82.5)	3,681 (78.1)	

Abbreviation: PGF, primary graft failure.

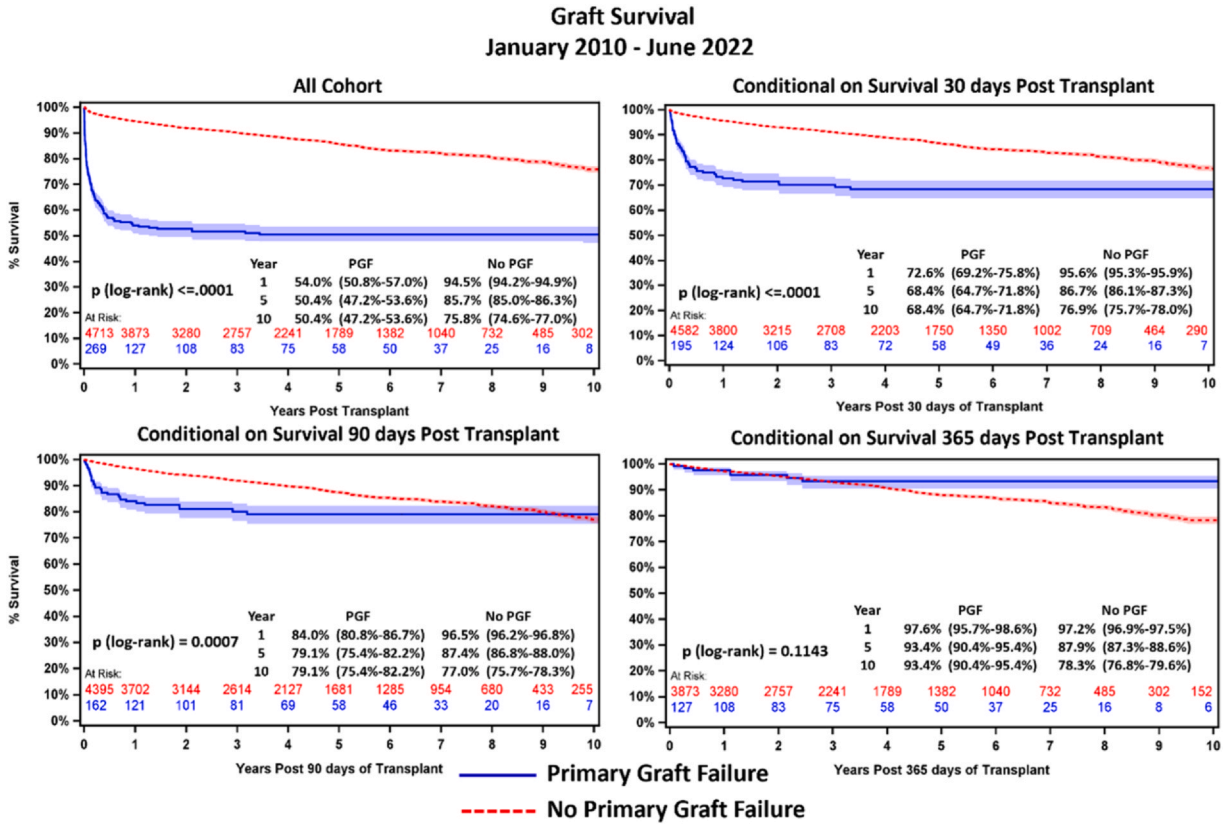

Figure 2 Kaplan-Meier survival analysis comparing outcomes between those with PGF (blue) and those without (red) for overall survival (A) and conditional on survival at 30 days (B), 90 days (C), and 365 days (D). Groups were compared using log-rank. Survival at 1, 5, and 10 years is reported for each condition. PGF, primary graft failure.

Discussion

This analysis of a contemporary cohort of children who underwent primary HTx revealed that approximately 5% of children will experience severe PGF. In addition, we identified that the impact of PGF is isolated within the first year post-HTx and that PGF is an independent risk factor for mortality. Lastly, we showed that the presence of severe PGF did not impact the development of CAV or early rejection. We also identified that those with PGF tended to be younger, require ECMO or a ventilator, differences in the distribution of donor causes of death, and have both longer CPB and ischemic times. While we did not perform a predictive model for the development of PGF, many of these characteristics align with what has been reported in other studies.[1,2]

Severe PGF in this multicenter, international study was associated with almost 50% graft loss. This is similar to previous reports from the United States that were conducted over a longer duration including a much older era (e.g., 1996-2015).[1] While this study centered on a more contemporary cohort, the impact of PGF on survival remains the same despite advances in care. The analysis also showed that PGF was an independent contributor to graft

Table 5 Final Multivariable Cox Proportional Hazard Model for Survival Post-Transplant (n = 4,982)

Covariates	Reference	HR (95% CI)	p-value
Recipient race—Black	White	1.42 (1.19-1.70)	0.0001
Recipient race—other	White	1.27 (1.05-1.54)	0.0161
Primary etiology—congenital HD	Cardiomyopathy	1.8 (1.53-2.11)	< 0.0001
Primary etiology—other	Cardiomyopathy	2.38 (1.63-3.47)	< 0.0001
Initial immunosuppression: induction therapy	No	0.77 (0.63-0.94)	0.0093
Primary graft failure	No	4.72 (3.87-5.74)	< 0.0001
Donor death cause—cerebrovascular	No	1.38 (1.07-1.77)	0.0122
EGFR at transplant 0-60	EGFR at transplant > 60	1.39 (1.14-1.70)	0.0010
Transplant 2010-2013	Transplant 2018-June 30, 2022	1.25 (1.03-1.53)	0.0273
Transplant 2014-2017	Transplant 2018-June 30, 2022	1.04 (0.85-1.26)	0.7287
Cardiopulmonary bypass time (hours)		1.12 (1.08-1.17)	< .0001

Abbreviations: CI, confidence interval; HD, heart disease; HR, hazard ratio.

Table 6 Final Multivariable Cox Proportional Hazard Model for Survival Post-Transplant, Conditional on Survival to 30 Days (n = 4,777)

Covariates	Reference	HR (95% CI)	p-value
Had HC rejection within 30 days post-transplant	No	1.81 (1.31-2.50)	0.0003
Recipient race—Black	White	1.53 (1.26-1.85)	< 0.0001
Recipient race—other	White	1.29 (1.04-1.59)	0.0204
Primary etiology—congenital HD	Cardiomyopathy	1.61 (1.36-1.92)	< 0.0001
Primary etiology—other	Cardiomyopathy	1.78 (1.13-2.81)	0.0134
Continuous invasive mechanical ventilation at transplant	No	1.27 (1.04-1.54)	0.0192
Primary graft failure	No	2.47 (1.87-3.26)	< 0.0001
Donor death cause—cerebrovascular	No	1.43 (1.08-1.88)	0.0111
Cardiopulmonary bypass time (hours)		1.1 (1.04-1.15)	0.0003

Abbreviations: CI, confidence interval; HC, hemodynamic compromise; HD, heart disease; HR, hazard ratio.

Table 7 Final Multivariable Cox Proportional Hazard Model for Survival Post-Transplant, Conditional on Survival to 90 Days (n = 4,557)

Covariates	Reference	HR (95% CI)	p-value
Had HC rejection within 90 days post-transplant	No	1.72 (1.26-2.35)	0.0007
Gender—male	Female	0.83 (0.70-0.99)	0.0346
Recipient race—Black	White	1.61 (1.31-1.98)	< 0.0001
Recipient race—other	White	1.29 (1.02-1.62)	0.0330
Primary etiology—congenital HD	Cardiomyopathy	1.6 (1.33-1.93)	< 0.0001
Primary etiology—other	Cardiomyopathy	1.45 (0.86-2.46)	0.1619
Primary graft failure	No	1.6 (1.11-2.31)	0.0121
Donor death cause—cerebrovascular	No	1.47 (1.10-1.97)	0.0100
Transplant 2010-2013	Transplant 2018-June 30, 2022	1.27 (0.98-1.64)	0.0716
Transplant 2014-2017	Transplant 2018-June 30, 2022	1.01 (0.78-1.30)	0.9660
Cardiopulmonary bypass time (hours)		1.09 (1.03-1.15)	0.0025

Abbreviations: CI, confidence interval; HC, hemodynamic compromise; HD, heart disease; HR, hazard ratio.

Table 8 Final Multivariable Cox Proportional Hazard Model for Survival Post-Transplant, Conditional on Survival to 365 Days (n = 4,000)

Covariates	Reference	HR (95% CI)	p-value
Had rejection within 365 days post-transplant	No	1.45 (1.13-1.86)	0.004
Had HC rejection within 365 days post-transplant	No	1.89 (1.34-2.66)	0.0003
Gender—male	Female	0.79 (0.65-0.97)	0.023
Recipient race—Black	White	1.81 (1.44-2.28)	< 0.0001
Recipient race—other	White	1.05 (0.78-1.40)	0.76

Abbreviations: CI, confidence interval; HC, hemodynamic compromise; HR, hazard ratio.

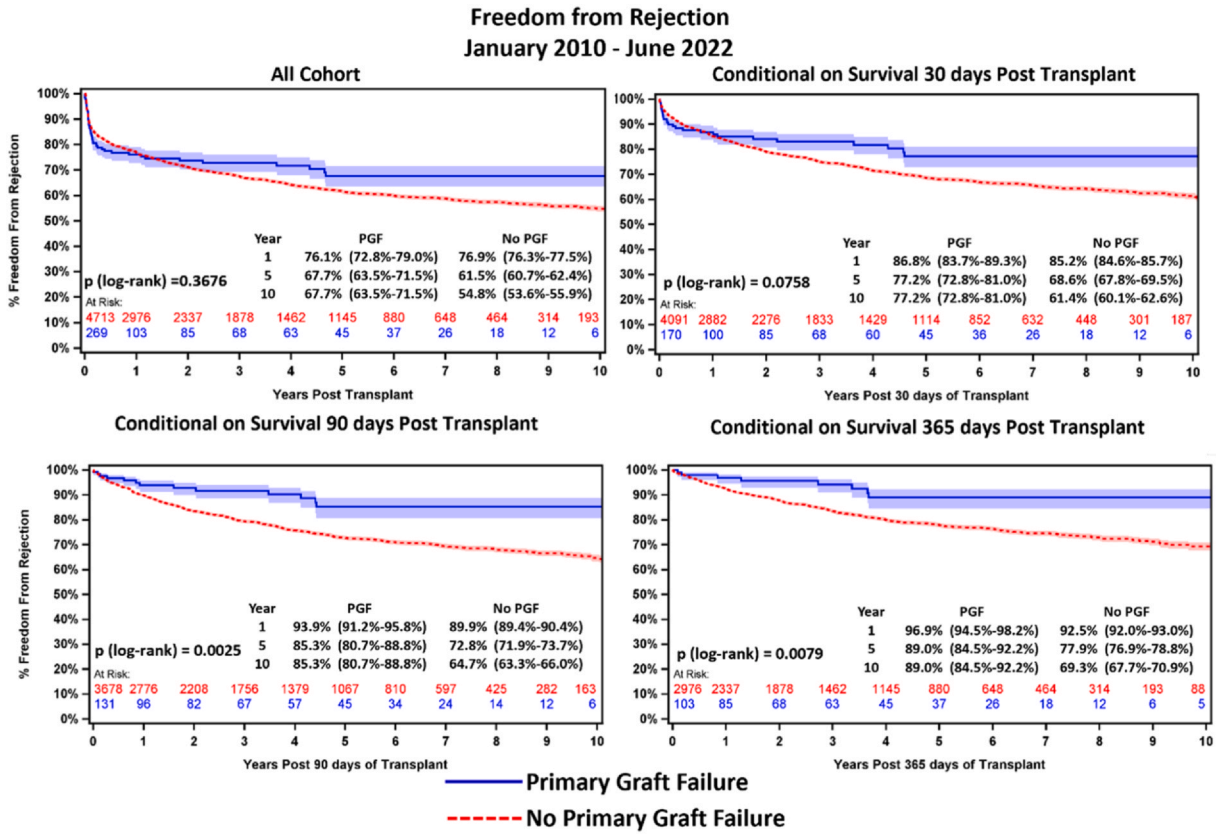

Figure 3 Time to first rejection dichotomized by the presence of PGF (blue) or absence of PGF (red) overall (A) and conditional on survival at 30 days (B), 90 days (C), and 365 days (D). Groups were compared using log rank. Freedom from rejection at 1, 5, and 10 years is reported. PGF, primary graft failure.

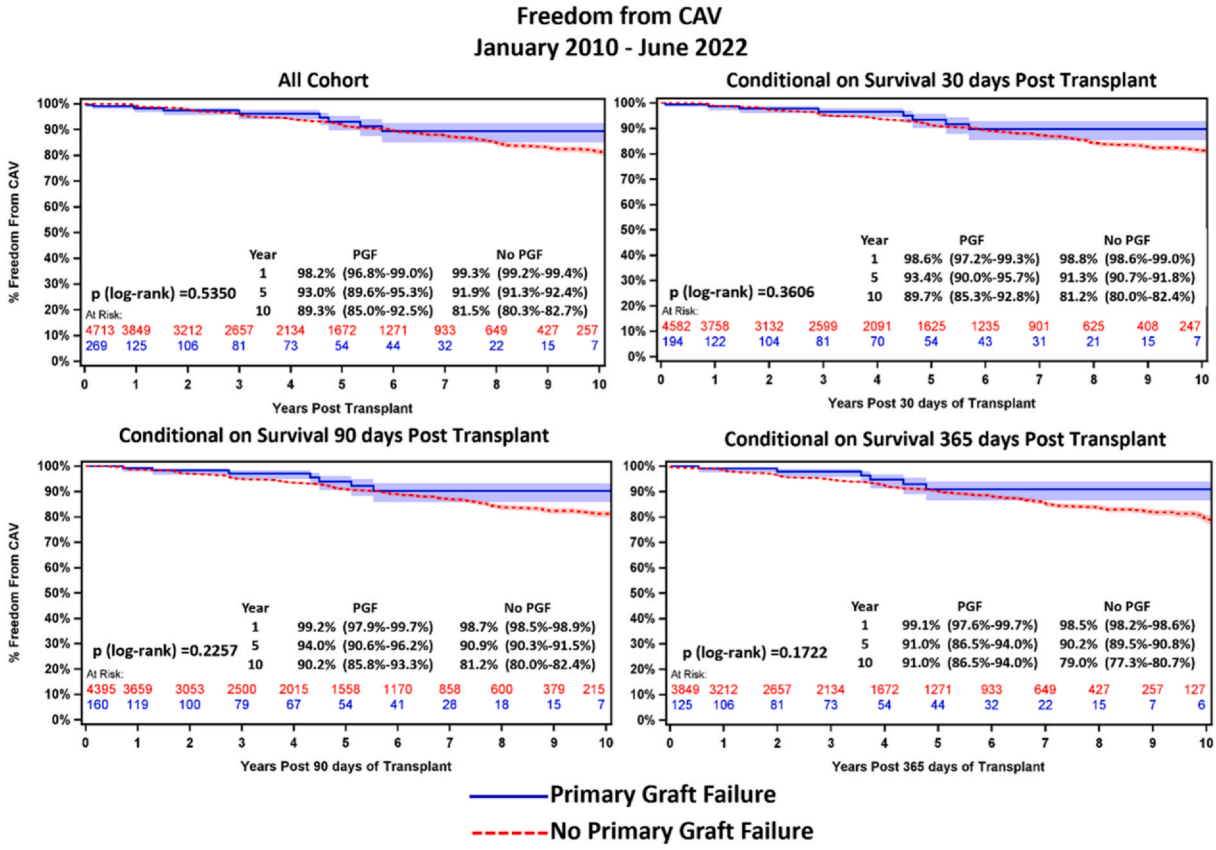

Figure 4 Time to first CAV dichotomized by the presence of PGF (blue) or absence of PGF (red) overall (A) and conditional on survival at 30 days (B), 90 days, (C) and 365 days (D). Groups were compared using log rank. Freedom from CAV at 1, 5, and 10 years is reported. CAV, coronary allograft vasculopathy; PGF, primary graft failure.

loss at 30-, 60-, and 90-day post-HTx but not at 365 days. As the impact of PGF is really in the first year post-HTx, strategies to reduce the incidence of PGF will have an important impact on early mortality. Other independent contributors to mortality included factors that have been reported in previous studies, including race, sex, presence of CHD, longer bypass times, ischemic times, and presence of rejection with hemodynamic compromise.[3-5]

The impact of PGF on other post-HTx morbidities is unknown. However, vascular and endothelial cell injury sustained to the graft during this process is thought to place the patient at risk of long-term comorbidities.[6] This analysis showed that, at least in the case of severe PGF, this does not seem to be the case. While this is encouraging, these results need to be interpreted with caution given the significant early mortality and the small number of patients surviving beyond the first year.

To date, the prevention of PGF has largely focused on recipient and donor selection. However, given the advances in perfusion technology, the impact of ischemic-reperfusion and poor donor preservation may be minimized.[7-9] This proposed benefit has been seen in multiple trials in adults examining the outcomes of both normothermic perfusion and controlled hypothermic preservation where the incidence of primary graft dysfunction has been reduced.[10-14] In pediatrics, due to size limitations of the current technologies, the outcomes of various device technologies are unknown. However, single-center reports have suggested that utilization of ex-situ perfusion allows for transplants in more complex patients, with less ischemic time and similar outcomes to lower-risk transplants.[7] Expanding these technologies to all pediatric-sized donors may reduce the incidence of PGF and have a significant impact on early survival post-HTx.

Limitations

As in all registry analyses, this study is limited by its retrospective nature. In addition, although we included deaths and use of VAD in our definition of PGF, which is an expansion from previous analysis, the focus remains on severe cases. More granular data are required to understand the impact of less severe forms of PGF, and currently, work is being done within the PHTS to expand data collection to allow for this analysis in the future. In addition, while the early need for MCS or death was classified as PGF, it is possible a misclassification error may have occurred and patients with right heart failure only due to pulmonary hypertension could be included in this cohort. Lastly, it is unclear why patients with PGF would have a lower freedom from rejection conditional on survival to 90 and 365 days. This may be reflective of an immortality bias as patients who died with PGF were not at risk of rejection or due to the smaller number of patients in the PGF group at these time points.

Conclusion

PGF is an independent predictor of early mortality post-HTx but does not impact long-term survival or the risk of rejection or CAV. Methods to decrease the risk of PGF, such as alternative preservation and storage techniques, may decrease the risk of PGF and in turn have a significant impact on early mortality post-HTx. Evaluation of milder forms of PGF is needed to understand the impact on long-term morbidities due to the early graft loss seen in this current cohort.

Author contributions

Conception and design: Jennifer Conway, Darren H. Freed, and Tara Pidborochynski. Analysis and interpretation of data: Jennifer Conway, Darren H. Freed, Tara Pidborochynski, James K. Kirklin, Ryan Cantor, and Hong Zhao. Manuscript Preparation: Jennifer Conway and Tara Pidborochynski. Manuscript revisions and final approval: Jennifer Conway, Darren H. Freed, Tara Pidborochynski, James K. Kirklin, Ryan Cantor, Hong Zhao, Aryaz Sheybani, Jacqueline Lamour, Lakshmi Gokanapudy Hahn, Leslie Collins, and Jessica Laks.

Disclosure statement

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Appendix 1. Covariates in the multivariable Cox proportional hazard model

Primary graft failure
Age at transplant
BMI at transplant
Cardiopulmonary bypass time (hours)
Donor ischemic time group
eGFR (ml/min/1.73 m^2) at transplant category
Initial immunosuppression: induction therapy

Max PRA at transplant > 10% or not	
Primary etiology	
Recipient blood type (AB, A, B, O)	
Recipient race (White, Black, other)	
Recipient sex	
Status at transplant	
ABO incompatible at transplant	
Transplant total bilirubin (mg/dl)	
Transplant creatinine (mg/dl)	
ECMO at transplant	
Transplant in hospital	
VAD at transplant	
Continuous invasive mechanical ventilation at transplant	
Rejection within 30 days post-transplant	Only included in 30 days post-transplant model
Rejection within 90 days post-transplant	Only included in 90 days post-transplant model
Rejection within 365 days post-transplant	Only included in 365 days post-transplant model
HC rejection within 30 days post-transplant	Only included in 30 days post-transplant model
HC rejection within 90 days post-transplant	Only included in 90 days post-transplant model
HC rejection within 365 days post-transplant	Only included in 365 days post-transplant model
Donor death cause—cerebrovascular	
Transplant era	

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HC, hemodynamic compromise; PRA, panel reactive antibody; VAD, ventricular assist device.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100184.

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