ORIGINAL RESEARCH

Risk Factors for Severe Primary Graft Dysfunction in Infants Following Heart Transplant

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BACKGROUND: Previous studies suggest that infant heart transplant (HT) recipients are at higher risk of developing severe primary graft dysfunction (PGD) than older children. We sought to identify risk factors for developing severe PGD in infant HT recipients.

METHODS AND RESULTS: We identified all HT recipients aged <1 year in the United States during 1996 to 2015 using the Organ Procurement and Transplant Network database. We linked their data to ELSO (Extracorporeal Life Support Organization) registry data to identify those with severe PGD, defined by initiation of extracorporeal membrane oxygenation support for PGD within 2 days following HT. We used multivariable logistic regression to assess risk factors for developing severe PGD. Of 1718 infants analyzed, 600 (35%) were <90 days old and 1079 (63%) had congenital heart disease. Overall, 134 (7.8%) developed severe PGD; 95 (71%) were initiated on extracorporeal membrane oxygenation support on the day of HT, 34 (25%) the next day, and 5 (4%) the following day. In adjusted analysis, recipient congenital heart disease, extracorporeal membrane oxygenation, or biventricular assist device support at transplant, recipient blood type AB, donor-recipient weight ratio <0.9, and graft ischemic time ≥4 hours were independently associated with developing severe PGD whereas left ventricular assist device support at HT was not. One-year graft survival was 48% in infants with severe PGD versus 87% without severe PGD.

CONCLUSIONS: Infant HT recipients with severe PGD have poor graft survival. Although some recipient-level risk factors are nonmodifiable, avoiding modifiable risk factors may mitigate further risk in infants at high risk of developing severe PGD.

Key Words: children ■ heart transplant ■ outcomes ■ pediatric ■ primary graft dysfunction ■ primary graft failure ■ survival

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Primary Graft Dysfunction

**CLINICAL PERSPECTIVE**

**What Is New?**
- Severe primary graft dysfunction (PGD) was identified in 7.8% of infant heart transplant recipients in the United States during 1996 to 2015 with no significant change in incidence over time.
- The risk of developing severe PGD varies 10-fold between the lowest and the highest risk infants; risk factors include recipient congenital heart disease, extracorporeal membrane oxygenation or biventricular mechanical support, undersized donor, and donor ischemic time >4 hours.
- Posttransplant survival following severe PGD was poor with continued risk of death and graft loss beyond the first few weeks; half of them died or lost their graft within a year of transplant.

**What Are the Clinical Implications?**
- Infant heart transplant recipients are known to have worse 1-year posttransplant survival compared with older children; because severe PGD is more frequent in infants, preventing severe PGD is important to narrow this survival gap.
- Early team discussion for best mechanical support strategy in each listed infant may decrease the need for emergent extracorporeal membrane oxygenation and lower the risk of severe PGD and posttransplant mortality.
- Hearts from donors with donor: recipient weight ratio <0.9 and with expected ischemic time >4 hours should be avoided in candidates with high-risk recipient profile.

**METHODS**

**Study Population**

The current study is a subgroup analysis limited to infants aged <1 year among children identified to have severe PGD by linkage of OPTN and ELSO registry data, previously described by us. In brief, we identified all infants aged <1 year who underwent HT in the United States between January 1, 1996 and December 31, 2015 using the OPTN database. The OPTN data include demographic and clinical variables at the time of HT and follow-up data in all HT recipients in the United States submitted by transplant centers, supplemented with death data from the social security master death file. These data are provided by the United Network for Organ Sharing to investigators for a nominal fee. We excluded children with multi-organ transplantation. Follow-up data were available until March 31, 2016.

Using the subject-level variables of HT center, date of birth, and date of HT in the OPTN data and the date of initiating ECMO in the ELSO registry, we identified infants initiated on ECMO for cardiac support within 2 calendar days following HT. ELSO registry is an international registry, with all current US pediatric HT centers as its members, that collects clinical data in all patients supported with ECMO at participating centers. Exclusion criteria included infants at risk of secondary graft dysfunction, ie, those with a positive cross-match attributable to the potential risk of acute antibody-mediated rejection and those with pulmonary vascular resistance >6 wood units attributable to a risk of posttransplant acute right heart failure.

**Study Design and Variables**

This was a retrospective cohort study with design similar to our previous study. The primary end point was development of severe PGD. The study protocol was approved by the Committee for Clinical Investigation at Boston Children’s Hospital and the Health Research Services Administration of the US Department of Health and Human Services with a waiver of consent. This report follows the supported by ECMO at the participating centers, allowed us to identify and analyze the vast majority of US pediatric HT recipients with severe PGD over a 20-year duration. One of the key observations of our analysis was that younger children, in particular infants aged <1 year at HT, were at higher risk of developing severe PGD compared with older children adjusted for other risk factors that we identified. Other studies have also suggested infant HT recipients to be at higher risk of developing severe PGD. Because of the potential that a subgroup analysis of our linked data with a focus on infant HT recipients may provide unique insights that could inform clinical care of infants waiting for HT, our aim for the current study was to describe risk factors for developing severe PGD in US infants aged <1 year at HT during 1996 to 2015.

**Nonstandard Abbreviations and Acronyms**

| Abbreviation | Description |
|--------------|-------------|
| BIVAD        | biventricular assist device |
| ELSO         | Extracorporeal Life Support Organization |
| HT           | heart transplant |
| OPTN         | Organ Procurement and Transplant Network |
| PGD          | primary graft dysfunction |
Severe PGD was defined as initiation of ECMO for cardiac support within 2 calendar days of HT surgery. This modification of the International Society for Heart and Lung Transplantation definition was considered since patients starting on ECMO on the second day would likely have the onset of PGD within 24 hours of HT. Baseline variables were defined at the time of HT. Recipient race/ethnicity was recorded as estimated glomerular filtration rate (in mL/min per 1.73 m²) using serum creatinine and the modified Schwartz equation for infants. There were no missing data for the variables of recipient age, sex, race/ethnicity, cardiac diagnosis, blood type, hemodynamic support (ie, inotrope support, ventilator, type of mechanical support), health insurance (ie, Medicaid), dialysis support at HT and the dates of transplant, death or retransplant. For children with missing serum creatinine (3.6%) or bilirubin (11.3%), multiple imputation using variables at transplant was used to impute glomerular filtration rate and serum bilirubin, respectively; 10 imputations were used for each missing value. Missing donor ischemic time (3.6%) was analyzed as an indicator variable.

### Statistical Analysis

Summary data are presented as median (interquartile range) and number (percentage). Baseline variables were compared between groups using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. We developed a multivariable logistic regression model using variables at transplant and forward selection to assess predictors of severe PGD retaining variables significant at the 0.10 level based on a likelihood ratio test. Interactions among variables at HT were analyzed to evaluate for effect modification. Kaplan Meier curves with a log rank test were used to compare survival between children who developed severe PGD and who did not. Cox regression was used to assess if infants who developed severe PGD were at higher risk of death or graft loss adjusted for baseline variables at transplant.

Data were analyzed using statistical software SAS version 9.4 (SAS Institute Inc, Cary, NC) and STATA version 15.0 (StataCorp LP, College Station, TX). All statistical tests were 2-sided and \( P<0.05 \) defined statistical significance. Dr Gauvreau had full access to the study data and takes responsibility for its integrity and the accuracy of data analysis. All authors have read and agree to the manuscript as written.

### RESULTS

#### Study Population

During the study duration, 1823 infants <1 year of age underwent HT in the United States. Of these, 1 with multi-organ transplantation and 104 from centers before they joined ELSO registry were excluded. The remaining 1718 infants formed the study cohort. Of these, 600 (35%) were <90 days old, 774 (45%) were female, and 1079 (63%) had congenital heart disease (CHD). We identified 143 infants supported by ECMO within 2 days of HT by linking the OPTN data with ELSO registry (Figure 1). Of these, 3 were supported by ECMO for respiratory failure and 6 were at high risk of graft dysfunction secondary to acute rejection or pulmonary hypertension early posttransplant. The remaining 134 infants required veno-arterial ECMO for cardiac support and thus met the criteria for severe PGD. Of these, 95 (71%) were initiated on ECMO support on the day of HT, 34 (25%) the following day, and 5 (4%) on the second posttransplant day. Their median age was 120 days, 52 (39%) were <90 days old, 42 (31%) were 91 to 180 days old and 40 (30%) were >180 days old. Cardiac diagnosis was CHD in 81% (46% with prior surgery, 35% unrepaird) and cardiomyopathy in 19%. A majority of patients with PGD (77%) were supported using a single ECMO run whereas 18% were supported using 2 ECMO runs. Median duration of ECMO support was 105 hours (interquartile range, 65–173 hours).

#### Incidence of Severe PGD

The overall incidence of severe PGD was 7.8% (95% CI, 6.6%–9.2%). The incidence during the 4 consecutive 5-year periods was 8.1% (95% CI, 5.4%–11.6%), 7.2% (95% CI, 4.7%–10.5%), 9.0% (95% CI, 6.6%–11.9%), and 7.0% (95% CI, 5.0%–9.4%), respectively (\( P=0.62 \)).

The incidence of severe PGD stratified by patient characteristics at HT is shown in Table 1. The incidence was 4% in infants with dilated cardiomyopathy, 10% in infants with CHD, 15% in those supported on ECMO or biventricular assist device (BIVAD) at HT, 2% in those supported on a left ventricular assist device (LVAD) and 21% in those supported on dialysis. A higher incidence of severe PGD was also noted in association with donor ischemic time ≥4 hours and with donor:recipient weight ratio <0.9 or >2.3 but not with donor left ventricular ejection fraction <0.45 or donor support using multiple inotropes.
Independent Risk Factors for Severe PGD

In a multivariable model, recipient risk factors associated with severe PGD (Table 2) were a cardiac diagnosis of CHD (with prior surgery or unrepaired), ECMO, or BIVAD support at transplant and blood type AB. Donor ischemic time ≥4 hours and HT using undersized donors with donor: recipient weight ratio <0.9 were also significantly associated with developing severe PGD. No interactions among risk factors were found to be statistically significant.

Figure 2A illustrates the observed incidence of severe PGD with different combinations of recipient-level risk factors if they received an HT using low-risk donor criteria as defined by the multivariable model (donor: recipient weight ratio 0.9–2.3 and donor ischemic time <4 hours). The effect of a higher risk donor (either donor: recipient weight ratio <0.9 or ischemic time ≥4 hours) to corresponding recipient risk profiles is illustrated in Figure 2B, showing a disparate effect of higher risk donor on recipients with different risk profiles. The incidence of severe PGD among infants with CHD supported on LVAD using such a donor was 2.7%, whereas it was 22% among infants supported on ECMO or BIVAD support using such a donor.

Posttransplant Survival

Death (or graft loss) before hospital discharge occurred in 42.5% of infants with PGD (55 deaths, 2 retransplants) and 8.8% of infants without severe PGD (P<0.001). Posttransplant graft survival at 1-year, 5-year, and 10-year posttransplant was 48%, 39%, and 33%, respectively, in infants with severe PGD and 87%, 75%, and 66%, respectively, in infants without severe PGD (P<0.001, log-rank test). Figure 3 illustrates Kaplan-Meier survival curves of infants with and without severe PGD during the first 3-months posttransplant (Figure 3A) and conditional upon surviving the first 3 months (Figure 3B), suggesting ongoing attrition in the PGD group well beyond the initial ECMO support period. In an analysis adjusted for baseline risk factors (cardiac diagnosis, mechanical support, renal dysfunction, hepatic dysfunction, and year of transplant), infants who developed severe PGD were at a significantly higher risk of death or graft loss compared with those who

Figure 1. Organ Procurement and Transplant Network data were used to extract the list of all US infants aged <1 year who received heart transplant during 1996 to 2015, who were then linked to the ELSO (Extracorporeal Life Support Organization) registry to identify those supported on ECMO posttransplant within 2 calendar days.

ECMO indicates extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; HT, heart transplant; and PGD, primary graft dysfunction.
Table 1. Incidence of Severe PGD by Baseline Characteristics

| Variable                          | PGD (n=134) | No PGD (n=1575) | P Value |
|-----------------------------------|-------------|-----------------|---------|
| Age at transplant, d              |             |                 | 0.521   |
| 0–90                              | 52 (9%)     | 548 (91%)       |         |
| 91–180                            | 42 (8%)     | 486 (92%)       |         |
| ≥181                              | 40 (7%)     | 541 (93%)       |         |
| Sex                               |             |                 | 0.787   |
| Male                              | 75 (8%)     | 860 (92%)       |         |
| Female                            | 59 (8%)     | 715 (92%)       |         |
| Diagnosis*                        |             |                 | <0.001  |
| Dilated cardiomyopathy            | 21 (4%)     | 550 (96%)       |         |
| Nondilated cardiomyopathy         | 5 (7%)      | 62 (93%)        |         |
| CHD, prior surgery                | 61 (10%)    | 569 (90%)       |         |
| CHD un repaired                   | 47 (10%)    | 441 (90%)       |         |
| Race/Ethnicity                    |             |                 | 0.521   |
| White                             | 91 (9%)     | 974 (91%)       |         |
| Black                             | 15 (6%)     | 241 (94%)       |         |
| Hispanic                          | 21 (7%)     | 277 (93%)       |         |
| Other†                            | 7 (8%)      | 83 (92%)        |         |
| Blood type                        |             |                 | 0.085   |
| O                                 | 65 (9%)     | 698 (91%)       |         |
| A                                 | 44 (7%)     | 601 (93%)       |         |
| B                                 | 13 (6%)     | 203 (94%)       |         |
| AB                                | 12 (14%)    | 73 (86%)        |         |
| Inotropes                         |             |                 | 0.928   |
| Yes                               | 74 (8%)     | 881 (92%)       |         |
| No                                | 60 (8%)     | 694 (92%)       |         |
| Ventilator                        |             |                 | 0.089   |
| Yes                               | 56 (9%)     | 538 (91%)       |         |
| No                                | 78 (7%)     | 1037 (93%)      |         |
| Mechanical support                |             |                 | <0.001  |
| ECMO                              | 25 (15%)    | 138 (85%)       |         |
| BIVAD                             | 4 (3%)      | 23 (85%)        |         |
| LVAD                              | 2 (2%)      | 84 (98%)        |         |
| None of the above                 | 103 (7%)    | 1330 (93%)      |         |
| Estimated GFR (mL/min per 1.73 m²)|             |                 | 0.016   |
| <40                               | 32 (9%)     | 344 (91%)       |         |
| ≥40                               | 94 (7%)     | 1201 (93%)      |         |
| Dialysis                          | 3 (21%)     | 31 (79%)        |         |
| Serum bilirubin (mg/dL)           |             |                 | 0.043   |
| <1.0                              | 69 (7%)     | 957 (93%)       |         |
| ≥1.0                              | 65 (10%)    | 618 (90%)       |         |
| Donor age (y) (n=134, 1574)       |             |                 | 1.000   |
| <1                                | 93 (8%)     | 1095 (92%)      |         |
| ≥1                                | 41 (8%)     | 479 (92%)       |         |
| Donor LV ejection fraction (n=100, 1214) |         |                 | 0.338   |
| <45%                              | 7 (11%)     | 59 (89%)        |         |
| ≥45%                              | 93 (7%)     | 1155 (93%)      |         |
| Donor number of inotropes (n=126, 1481) |         |                 | 0.700   |
| <3                                | 124 (8%)    | 1460 (92%)      |         |
| ≥3                                | 2 (9%)      | 21 (91%)        |         |

(Continued)
did not (hazard ratio, 5.08; 95% CI, 3.68–7.00). The higher risk of death or graft loss persisted in 3-month survivors of severe PGD (hazard ratio, 1.96; 95% CI, 1.32–2.91) in adjusted analysis.

**DISCUSSION**

In this study, we identified severe PGD in 7.8% of infant HT recipients in the United States during 1996 to 2015 with no significant change in incidence over time when assessed in consecutive 5-year periods. The risk of developing severe PGD was heterogeneous and varied 10-fold between the lowest and the highest risk recipients. The risk was lowest in infants with dilated cardiomyopathy and in those with CHD supported on an LVAD at the time of HT, and highest in infants with CHD supported on ECMO or BIVAD at transplant. Additional risk of developing severe PGD accrued in infants who received a donor heart from an undersized donor (donor:recipient weight ratio <0.9) or with donor ischemic time ≥4 hours. Posttransplant survival of infants with severe PGD was poor with continued patient and graft loss beyond the first few days and weeks posttransplant; half of them died or lost their graft within a year of HT. The finding that 3-month survivors of severe PGD remained at increased risk of death or graft loss was surprising and not previously noted in the larger pediatric cohort. Infants are known to have worse first-year survival after HT than older children but have the best conditional survival of all age-groups if they survive the first posttransplant year.\(^8\)\(^9\) Our findings underscore the importance of preventing severe PGD in infants in narrowing this first-year survival gap versus older children. Although some of the risk factors we identified are nonmodifiable, others point to potential approaches for lowering the risk of severe PGD in infant HT recipients.

Previous analyses of infant HT recipients have identified primary graft failure as the most common cause of early posttransplant mortality.\(^10\)\(^11\) Previous studies of severe PGD in pediatric HT recipients have also suggested a higher incidence in infants than in older children.\(^2\)\(^3\)\(^12\)\(^13\) For example, Tissot et al reported ECMO support within 48 hours of HT in 28 of 310 pediatric recipients; 24 of 28 were infants.\(^13\) In another study of HT recipients from 3 centers, Kaushal et al reported that 16 (17%) of 92 infants aged <1 year needed ECMO for primary graft failure.\(^3\) More recently, Godown et al linked OPTN data with US hospital billing data and found infants aged <1 year to be at higher risk for ECMO support within 24 hours posttransplant compared with older children.\(^12\) Our objective for the current study was to understand the heterogeneity of risk for developing severe PGD among infant HT recipients and to identify patterns, risk factors, and interactions that may have been overlooked in the larger, pediatric cohort. While some risk factors such as recipient diagnosis of CHD and ECMO or BIVAD support at HT are similar to those in our larger analysis of the pediatric cohort, the analysis found <3% of infants with CHD transplanted from LVAD support to have developed severe PGD irrespective of additional donor-related
The low incidence of severe PGD in infants with CHD supported by LVAD (Figure 2) suggests the presence of a protective signal associated with LVAD. The numbers are small however, and the 95% CI in the adjusted model includes 1. The potential protection is biologically plausible because infants surviving HT on LVAD support have had time for rehabilitation and end-organ recovery and usually present a healthier milieu for the donor heart. Because LVAD support is being increasingly used to support infants awaiting HT, whether it is truly associated with lower incidence of severe PGD will be of high interest in future analyses of more recent recipients. The association of recipient blood type AB with severe PGD is surprising and difficult to explain. An analysis of infant recipients in 1990s found that HT with a non-identical blood type donor was associated with worse short-term survival but this finding has not been replicated in subsequent analyses.\(^9\) It is certainly not factored in clinical decision-making when evaluating donor offers. On the contrary, the excellent outcomes of ABO-incompatible HT in infants argue against HT with a non-identical blood type as the likely explanation for this finding. It is possible that AB recipients may be at higher risk of receiving marginal donor hearts but if true, these donor characteristics are not well captured as currently analyzed.

This study has important implications. The results indicate that severe PGD remains an important post-transplant morbidity in infant HT recipients with no discernible change in incidence over 20 years but a targeted clinical approach to lower the risk may be feasible. First, while the cardiac diagnosis in HT candidates is not modifiable, how advanced support strategies are chosen when the infant gets sicker may have important implications for their posttransplant outcomes including the risk of severe PGD. Because the clinical decision around the timing and type of mechanical support is informed by a myriad of factors such as patient size, anatomic complexity, team expertise, and experience with specific support and local wait-list time, it is important to initiate these discussions during HT evaluation rather than when faced with a clinical emergency. Infants already supported on ECMO at the time of HT evaluation should be evaluated for feasibility of transitioning to a durable LVAD for improving their wait-list and posttransplant outcomes.\(^6\) Newer approaches to anticoagulation management in pediatric HT candidates supported on para-corporeal assist device support are associated with a significant decline in incidence of neurological sequelae and may play a role in these discussions.\(^7\) Second, the evaluation of donor offers for infant candidates should be

### Table 2. Multivariable Model for Severe PGD

| Variable                        | Odds Ratio | (95% CI)       | P Value |
|---------------------------------|------------|----------------|---------|
| Diagnosis (vs dilated cardiomyopathy) | 1.00       | 0.217 (0.66-5.36) | <0.001  |
| CHD, prior surgery              | 2.70       | <0.001 (1.59-4.58) |         |
| CHD unrepaired                  | 2.56       | <0.001 (1.47-4.43) |         |
| Mechanical support              |            |                | 0.001   |
| None                            | 1.00       | ...            |         |
| LVAD                            | 0.54       | 0.400 (0.13-2.29) |         |
| ECMO                            | 2.48       | <0.001 (1.51-4.01) |         |
| BIVAD                           | 3.56       | 0.020 (1.14-11.1) |         |
| Blood Type AB                   | 2.22       | 0.018 (1.15-4.29) | 0.018   |
| Donor: recipient weight ratio   |            |                | 0.071   |
| <0.9                            | 1.72       | 0.043 (0.22-2.91) |         |
| ≥2.3                            | 1.52       | 0.125 (0.89-2.61) |         |
| Ischemic time, h                |            |                | 0.008   |
| <4                             | 1.00       | ...            |         |
| ≥4.0                            | 1.79       | 0.002 (1.23-2.60) |         |
| Missing                         | 1.50       | 0.414 (0.57-3.99) |         |

\(^a\) P value for each variable was determined using the likelihood ratio test whereas those for individual categories for each variable (compared with the reference group) were determined using the Wald test. **BIVAD** indicates biventricular assist device; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; PGD, primary graft dysfunction.
considered in light of known recipient-level risk factors. Our results suggest that hearts from undersized donors (with donor:recipient weight ratio <0.9) and with expected ischemic time that exceeds 4 hours should be avoided in candidates with high-risk recipient profile. Longer-term, advances in infant ventricular assist devices and heart transplantation techniques may improve outcomes in this challenging patient population.
Figure 3. Graft survival in US infant heart transplant recipients with and without severe PGD during the first 3 months posttransplant (A) \((P<0.001, \text{ log rank test})\) and conditional upon surviving the first 3 months (B) \((P<0.001, \text{ log rank test})\).

PGD indicates primary graft dysfunction.
device technology and donor preservation may further reduce the risk of severe PGD in infant HT recipients.

Limitations

This study has several limitations. It linked 2 large clinical registries with inherent limitations of registry data. Only recipients reported to and registered in the ELSO registry for ECMO initiation after HT were identified. It is possible that some infants received a few hours of extracorporeal support immediately after HT followed by a rapid improvement in graft function and did not get reported to the ELSO registry. Infants who died because of severe PGD before ECMO initiation would also not be included in our analysis of severe PGD. The lack of granular detail about the type of specific CHD and CHD surgery is a limitation of both registries and we were unable to determine if infants with specific CHD diagnoses were at higher risk.

CONCLUSIONS

Severe PGD was identified in 7.8% of infant HT recipients in the United States during 1996 to 2015. The risk of developing severe PGD was heterogeneous, however, with independent recipient- and donor-level risk factors identified in this study. Identifying and avoiding modifiable risk factors may mitigate further risk in infants at high risk of developing severe PGD.

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Disclosures

None.

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