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Graft survival is better without prior surgery in cardiac transplantation for functionally univentricular hearts

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BACKGROUND: The effect of surgical history on graft outcomes in patients with functionally univentricular hearts (UH) is not well understood. We compared graft outcomes after heart transplantation in children with a UH between patients who received allografts without prior cardiac surgery (Group A) and patients who underwent transplantation after prior cardiac surgery (Group B).

METHODS: We reviewed all patients who received allografts for UH at our institution from 1990 to 2009. Differences in the probability of acute rejection (AR), incidence of graft vasculopathy (GV), and incidence of death or retransplantation were compared between Group A and Group B. Student's *t*-test, Mann-Whitney *U*-test, the log-rank test, logistic regression, and Cox proportional hazards modeling were used as appropriate.

RESULTS: During the study period, 180 patients with a UH received allografts: 105 in Group A and 75 in Group B at a median (interquartile range) age of 84 (47–120) days vs 584 (168–2,956) days, respectively ($p < 0.001$). The odds of AR were higher in Group B (odds ratio, 2.7, 95% confidence interval, 1.3–5.4). Group A had lower univariable risks of GV ($p = 0.034$) and graft loss ($p = 0.003$). Median graft survival was 18 years in Group A vs 8 years in Group B. The risk of graft loss after 5 years post-transplant was higher in Group B patients who were aged ≥ 1 year at time of transplant ($p < 0.001$).

CONCLUSIONS: Heart transplantation without prior cardiac surgery in patients with a UH was associated with better graft survival and lower probability of AR. The effect of age is complex and time-dependent, with age affecting outcomes after 5 years.

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Cardiac transplantation in infancy is used as primary treatment for hypoplastic left heart syndrome (HLHS) and other forms of functionally univentricular hearts (UH). Long-term survival is excellent, with median survival of > 18 years.[1–4] As the results of staged surgical palliation improved and donor availability remained a challenge, most infants with UH were treated with surgical palliation rather than transplantation.[5,6] However, a significant number of UH surgical palliations fail, requiring cardiac transplantation to be performed in children with a history of cardiac surgeries.[7–11]

Single and multicenter evaluations of children undergoing cardiac transplantation with and without prior surgery have shown mixed outcomes.[12,13] However, few studies have evaluated the effect of prior cardiac surgery on outcomes after transplantation specifically in patients with UH.[14] Investigation of this sub-group is relevant because surgical palliation outcomes are not remarkably better than those for primary transplantation.[15–17] To determine if cardiac surgery before transplantation in patients with UH is a

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risk factor for graft loss, we evaluated its effect on graft outcomes in our large, single-center population of patients with UH.

Methods

Study design

This was a retrospective record review of patients with UH who underwent cardiac transplant between 1990 and 2009 at our institution. Patients were enrolled in consecutive fashion. Era 1 was defined as 1990 to 1999 and Era 2 as 2000 to 2009. Those patients without cardiac surgery before transplantation were defined as Group A, and those who received allografts after prior cardiac surgery were defined as Group B.

Clinical data included demographics, donor and recipient weight, diagnosis, age at transplantation, ventricular morphology, the presence of a restrictive atrial communication, need for mechanical circulatory support (MCS) and/or mechanical ventilation before transplantation, date of transplantation, and date of graft loss or last known follow-up. Race was defined as Black, Caucasian, Hispanic, or other (Asian, Arab, mixed ethnicity, and unspecified).

Laboratory data at the time of transplantation included creatinine, human leukocyte antigen (HLA) panel reactive antibody (PRA), and retrospective recipient-donor crossmatch results. Glomerular filtration rate (GFR) was estimated using the Schwartz equation.[18] PRA testing was performed by testing recipient serum for complement-mediated lytic activity in the presence of anti-human immunoglobulin and dithiothreitol, by enzyme-linked immunosorbent assay, or by the Luminex test, depending on the era of transplantation. A PRA of $\geq 10\%$ was considered positive. Retrospective crossmatching was performed by mixing recipient serum with donor lymphoid tissue, excluding the presence of autoantibodies by autologous serum crossmatch with recipient B and T cells, and the donor-recipient crossmatch by immunoglobulin (Ig) G was considered positive if there was evidence of B- or T-cell cytotoxicity in the presence of dithiothreitol. Pre-transplant cytomegalovirus (CMV) serology was not included in the analysis due to the large number of infants with maternal anti-CMV IgG.

Graft outcomes included the number of acute rejection (AR) episodes, the diagnosis of graft vasculopathy (GV), the need for repeat transplantation, or death. AR was defined as any event that led to an augmentation of immunosuppression, usually with steroids or anti-lymphocyte therapy, as defined by the Pediatric Heart Transplant Study group (PHTS).[19] GV was defined by a maximal intimal thickness by intravascular ultrasound of > 0.3 mm or when angiography showed evidence of stenosis or distal pruning. Graft loss was defined as death or repeat transplantation. Immunosuppression and rejection surveillance protocols have been previously reported by our center and were largely unchanged throughout the study period, except that anti-lymphocyte globulin was used for induction until anti-thymocyte globulin was approved by the U.S. Food and Drug Administration in 1991.[20]

Statistical analysis

We hypothesized that the risk of graft loss would be higher in Group B. The primary outcome for this study was graft loss, as defined. Student's *t*-test, chi-square test, Mann-Whitney *U*-test, and logistic regression were used as appropriate. Kaplan-Meier survival curves and the log-rank test were performed to determine the incidence of GV and graft loss. Univariable Cox proportional hazards modeling was performed to identify potential pre-transplant risk factors for graft loss, including age $>$ 1 year, sex, race, transplantation era, donor-to-recipient weight ratio, number of pre-transplant cardiac operations, PRA $> 10\%$, graft ischemic time, United Network of Organ Sharing (UNOS) waiting list time, GFR, pre-transplant need for mechanical ventilation, and pre-transplant inotropic support. UNOS listing status was not included in the analysis because of the different age-based criteria for determining listing status. Patients with listing status of 1A and 1B were considered status 1 for the purpose of descriptive statistics. Univariable analysis of incidence of GV was compared between patients with by prior surgery, age $>$ 1 year, male sex, era of surgery 2000 to 2009, non-white race, and PRA $> 10\%$.

We also examined the effect of prior surgery and age by reclassifying the patients, both over the entire follow-up period and during the intervals of 0 to 5 years after transplant and $>$ 5 years after transplant, using Kaplan-Meier plots, log-rank tests, and Cox proportional hazards models to estimate hazard ratios (HRs). Patients were classified according to age $<$ 1 year at transplant in Group A, age $<$ 1 year at transplant in Group B, and age $\geq$ 1 year at transplant in Group B. Values of $p < 0.05$ were considered statistically significant.

Results

Study population

Between 1990 and 2009, 180 patients with UH underwent a first heart transplantation, with 105 patients in Group A and 75 in Group B. Of those in Group B, 36% had 1 surgery, 32% had 2 surgeries, 24% had 3 surgeries, and 8% had ≥ 4 surgeries. Operations included 24 pulmonary artery bandings, 37 systemic-pulmonary artery shunts, 9 stage I palliations (modified Norwood procedure or Damus-Kay-Stansel), 26 stage II palliations, 21 stage III (Fontan), 3 Fontan revisions, and 1 Blalock-Hanlon septectomy. Of the 9 patients in our study who had undergone stage I palliation, 6 went on to stage II and 2 went on to Fontan palliation before transplantation. Coarctation repair in borderline left ventricles was performed in 9 patients, 6 of whom had coinciding PA band placement.

The median (interquartile range [IQR]) time from transplant to last follow-up or graft loss was 6.6 (2.0–11.5) years overall and was 7.8 (2.6–11.7) years in Group A and 5.0 (1.6–10.6) years in Group B ($p = 0.13$). Group B patients underwent a median (IQR) of 2 (1–3) pre-transplant operations. The median (IQR) number of surgeries for Group B in Era 1 was 2 (1–3) compared with 3 (1–3) in Era 2 ($p = 0.004$). Racial distribution was black (3%), Caucasian (68%), Hispanic (17%), unknown (6 %), and other (5%).

Patients' characteristics are summarized in Table 1. Median (IQR) age at transplant was 84 (47–120) days in Group A vs 584 (168–2,956) days in Group B ($p < 0.001$).

Table 1 Patient characteristics

Characteristics[a]	Total ($N = 180$)	Group A ($n = 105$)	Group B (n = 75)
Age, days	120 (65–383)	84 (47–120)[b]	584 (168–2,956)[b]
Age			
< 1 year	135	103[c]	32[c]
> 1 year	45	2	43
Sex			
Male	114	71	43
Female	66	34	32
Single ventricle			
Right	138	99[c]	39[c]
Left[d]	41	6	35
UNOS status			
1	142	98[c]	44[c]
2	27	0	27
Era			
1990–1999	93	53	40
2000–2009	87	52	35
Ischemic time, min	257 ± 71	257 ± 72	256 ± 79
Waiting list time, days	74 (33–115)	72 (35–110)	79 (33–125)
GFR, ml/min/m^2	67.5	56.7 (39.3–74.1)[b]	94.3 (62.7–125.9)[b]

GFR, glomerular filtration group; Group A, no prior cardiac surgery; Group B, had prior cardiac surgery; UNOS, United Network of Organ Sharing.

[a]Continuous data are presented as the median (interquartile range) and mean ± standard deviation, and categoric data as number.

[b]$p < 0.001$ by Mann-Whitney *U*-test for difference between Group A and Group B. The *p* values for other continuous variables were not significant.

[c]$p < 0.001$ for difference in proportions between Group A and Group B by the chi-square test. The *p* values for other categoric variables were not significant.

[d]Ventricular morphology was indeterminate in 1 patient.

Significantly more patients were aged < 1 year at the time of transplant in Group A (98% vs 43%, $p < 0.001$). Only 2 patients in Group A were aged ≥ 1 year.

Group A had a significantly higher proportion of patients with a single right ventricle, and Group B had a significantly higher proportion of patients with a single left ventricle (Table 1). There was no difference in the median number of surgeries in Group B based on ventricular morphology ($p = 0.24$). Overall, patients with a single right ventricle were significantly younger than patients with a single left ventricle, being a median (IQR) age at transplant of 0.26 (0.16–0.48) years vs 3.8 (0.39–10.8) years, respectively ($p < 0.001$). When analyzed within Group B only, patients in Group B with a single right ventricle also were significantly younger than patients with a single left ventricle, being a median (IQR) age at transplant of 1.1 (0.47–3.8) years vs 4.4 (0.45–13.5) years, respectively ($p = 0.046$).

A PRA > 10% was present in 6 patients in Group A and in 6 patients in Group B, with 4 of the patients in Group B having undergone ≥ 3 prior surgeries. There was only one positive retrospective crossmatch out of 148 patients with available crossmatch data. Only 3 patients had a PRA > 50%. No patients with a PRA > 10% had a positive retrospective crossmatch. There was no difference in the proportion of patients in the 2 groups with a PRA > 10% based on ventricular morphology ($p = 0.15$). Previous surgeries in patients with a PRA > 10% included 1 stage I palliation, 3 aortopulmonary shunts, 2 stage II palliations, and 4 Fontan operations.

Acute graft rejection

AR data were available for 174 patients. There was at least 1 AR episode in 60% of Group A and in 80% of Group B (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.3–5.4). The odds of AR in the first year after transplant were higher in Group B (OR, 2.4; 95% CI, 1.3–4.4) and in patients aged > 1 year at the time of transplant (OR, 2.7; 95% CI, 1.3–5.4) in univariable analysis.

Graft loss

Graft loss occurred in 76 patients (42%). Overall graft survival was 86% at 1 year, 72% at 5 years, 59% at 10 years, and 44% at 15 years. Causes of graft loss are reported in Table 2. The incidence of GV was lower in Group A than Group B at 10 years (40% vs 46%, respectively; $p = 0.03$). Graft survival was similar at 1 year (86% vs. 87%) but was higher in Group A than in Group B at 5 years (76% vs 66%) and 10 years (68% vs 46%; $p = 0.002$; Figure 1). Median graft survival was 18 years in Group A and 8 years in Group B. Repeat transplantation was required in 7 in Group A and 8 in Group B ($p = 0.35$). Univariable hazards for graft loss are reported in Table 3. MCS and a positive retrospective

Table 2 Causes of Graft Loss in 76 patients

Cause of graft loss	Total No. (%)	Group A No. (%)	Group B No. (%)
Graft vasculopathy	10 (5.6)	5 (14.3)	5 (12.2)
Acute rejection	26 (14.4)	13 (37.1)	13 (31.7)
Graft failure			
Chronic	7 (3.9)	1 (2.9)	6 (14.6)
Primary	7 (3.9)	5 (14.3)	2 (4.9)
Infection	4 (2.2)	2 (5.7)	2 (4.9)
Hemorrhage	3 (1.7)	1 (2.9)	2 (4.9)
Other[a]	12 (6.7)	5 (14.3)	7 (17.1)
Unknown	7 (3.9)	3 (8.6)	4 (9.8)
Total	76 (42.2)	35 (19.4)	41 (22.8)

Group A, no prior cardiac surgery; Group B, had prior cardiac surgery.

[a]Includes multiorgan system failure, cerebrovascular accident, and post-transplant lymphoproliferative disorder.

donor-specific crossmatch were not included in the analysis because only 2 patients in the entire cohort required MCS at the time of transplant, and of the 148 with available crossmatch data, only 1 patient had a positive retrospective crossmatch.

Univariable risk of graft loss was significantly higher in Group B. Using Group A as a reference, patients with 1 or 2 prior surgeries (HR, 1.82; 95% CI, 1.10–3.02) and patients with $>$ 3 prior surgeries (HR, 2.43; 95% CI, 1.27–2.64) had increasingly higher risks of graft loss. There was no significant univariable association between graft loss and age $>$ 1 year, sex, era of transplantation, ventricular morphology, GFR, the presence of a restrictive atrial septal communication, race, pre-transplant inotropic support, donor-to-recipient weight ratio, PRA $>$ 10%, mechanical ventilation before transplantation, ischemic time, or waiting list time (Table 3). When repeat transplantation was removed as an end point, the overall incidence of death was higher in Group B ($p = 0.016$).

When data were classified according to age and prior cardiac surgery, patients aged $<$ 1 year in Group A had the best graft survival ($p = 0.017$; Figure 2A). Graft loss was more than twice as likely to occur in those aged $\geq$ 1 year in Group B (HR, 2.06; $p = 0.009$). There was a higher risk of graft loss in those aged $<$ 1 year Group B (HR, 1.75; $p = 0.054$; Table 4) compared with those aged $<$ 1 year in Group A. The odds of AR were also significantly higher in those aged $\geq$ 1 year in Group B compared with those aged $<$ 1 year of age in Group A (OR, 3.87; 95% CI, 1.49–10.06; $p = 0.005$) but not in those aged $<$ 1 year in Group B.

An analysis of the data in separate post-transplant intervals revealed no significant difference in graft survival between groups in the first 5 years after transplant ($p = 0.36$; Figure 2B). However, among those who survived to 5 years after transplant, patients aged $\geq$ 1 year at the time of transplant in Group B had a 6-fold higher incidence of graft loss than those aged $<$ 1 year in Group A (HR, 6.48; 95% CI, 2.63–15.92; $p < 0.001$; Figure 2C, Table 4).

Effect of era on graft outcomes

Table 1 reports the proportion of patients in Groups A and B who received allografts in Eras 1 and 2. In Group B, 22

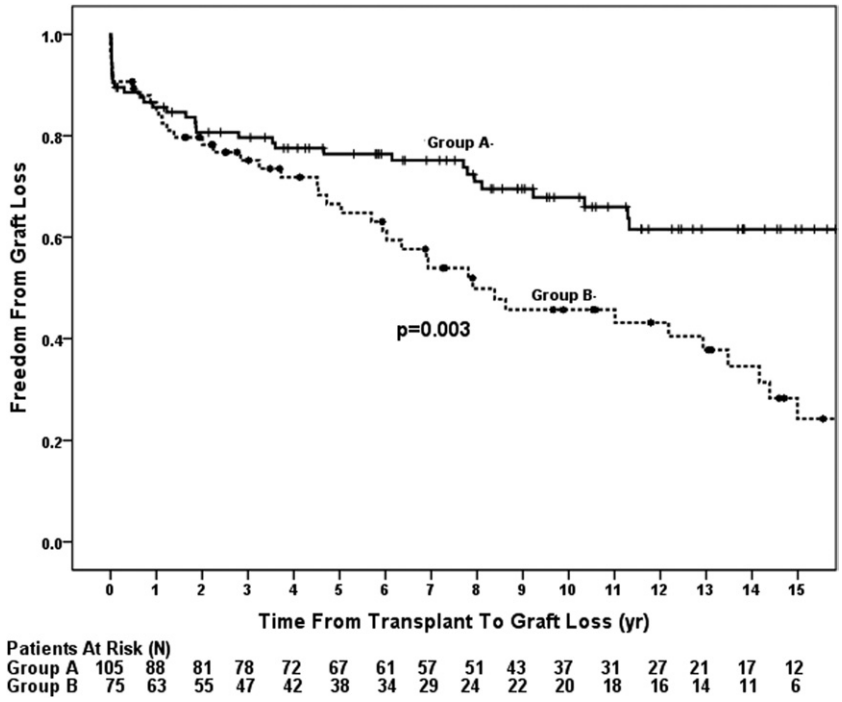

Figure 1 Post-transplant primary graft survival (freedom from death or repeat transplantation) comparing patients with (Group B) and without (Group A) surgery before transplantation. Patients with prior cardiac surgery had a higher incidence of graft loss compared with those without prior surgery.

Table 3 Univariable Cox Proportional Hazard Modeling of Risk Factors for Graft Loss

Pre-Tx characteristics	No. (%)	Model (*N*)	Events (*N*)	HR (95% CI)	*p*-value
Any surgery	75 (41.7)	180	76	1.98 (1.25–3.13)	0.004
Surgeries, No.		180	76	1.26 (1.06–1.50)	0.009
Age > 1 year	45 (25)	180	76	1.59 (0.97–2.61)	0.07
Male sex	114 (63)	180	76	0.64 (0.40–1.02)	0.06
Era 2000–2009[a]	87 (48.3)	180	76	0.98 (0.59–1.61)	0.94
Left ventricular morphology[b]		179	75	1.22 (0.73–2.06)	0.45
GFR (Schwartz)		170	69	1 (0.998–1.004)	0.56
Restrictive atrial septum	44 (24)	165	68	0.99 (0.57–1.72)	0.98
Non-white race	46 (26)	170	69	1.23 (0.72–2.11)	0.46
Inotropic support	22 (12)	170	69	1.52 (0.75–3.08)	0.25
Donor-to-recipient weight		168	67	0.97 (0.66–1.42)	0.86
PRA > 10%	12 (6.7)	156	60	1.45 (0.52–4.06)	0.48
Mechanical ventilation	10 (5.6)	169	69	1.51 (0.55–4.2)	0.43
Ischemic time		171	71	1.00 (0.997–1.003)	0.9
Waiting list time		180	75	1.00 (0.999–1.003)	0.46

CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NS, not significant; PRA, panel reactive antibody; Tx, transplant.
[a]Reference is Era 1990–1999.
[b]Reference is right ventricular morphology.

infants received allografts in Era 1 and 10 infants in Era 2. All patients who had undergone stage 1 palliation before transplantation received an allograft in Era 2. There was no difference in the proportion of patients with a PRA > 10%, 0.9 between eras, and there was no significant difference between eras in the odds of AR (OR, 0.56; 95% CI, 0.29–1.07). There were no univariable differences between eras for the risk of GV (HR, 1.29; 95% CI, 0.69–2.42) or graft loss (HR, 0.98; 95% CI, 0.59–1.61; Table 3).

Discussion

In this single-center retrospective analysis comparing outcomes of patients with UH undergoing cardiac transplantation, we found that surgery before transplantation was a significant risk factor for graft loss after transplantation. The most striking difference was found late, with 10- and 15-year graft survival of 68% and 57%, respectively, in Group A, and 46 % and 24%, respectively, in Group B (Figure 1). Half of patients in Group A were still alive 18 years after transplant whereas half of the patients in Group B had suffered graft loss by 8 years after transplant.

The interaction between a history of prior surgery and age at transplantation is complex. Although surgery before transplantation seems to be the most important risk factor (Figure 1 and Table 3), transplantation outside of infancy is also likely affecting outcomes, as demonstrated by our analysis in separate post-transplant intervals (Figure 2). There was no significant difference in early graft survival between infants and non-infants in Group B through 5 years; however, late graft loss accelerates for non-infants in Group B, so that by 10 years, there is a significant difference in graft survival between infants and non-infants in Group B (Figure 2A and C, Table 3).

We also found that the overall improved graft survival in Group A compared to infants in Group B was of borderline statistical significance (HR, 1.75; 95% CI, 0.99–3.10; $p = 0.053$; Table 4). Because there were only 32 infants in Group B, we were likely underpowered to determine a difference in graft survival between Group A and infants in Group B. We speculate that with more infant patients in Group B, we would have found a statistically significant difference between the 2 groups.

The overall graft survival of 86% at 1 year and 72% at 5 years is comparable to other series of patients receiving allografts primarily for single-ventricle physiology.[17,21] However, in contrast to prior reports, survival for Group A and Group B was nearly identical throughout the first year after transplant, signifying that peri-operative deaths did not play a role in outcome differences.[11,12,14] A report published by the PHTS showed that infants who received an allograft without prior surgery for HLHS had better early survival than infants with HLHS and prior surgery.[14] Comparison of late outcomes between the 2 studies are limited by the shorter duration of follow-up in the PHTS study, and differences in outcomes occurring > 9 years after transplant could not be evaluated.[14] The reasons for less early mortality in our center's population (87% 1-year graft survival in Group B vs 70% 1-year overall survival in the PHTS study) may be related to differences in ventricular morphology and/or clinical condition at the time of transplantation between the groups with prior surgery in the 2 studies.

A single-center study by Dionigi et al[13] compared 154 patients with primary transplantation for HLHS and 160 recipients after failed surgical palliation for complex congenital heart disease, 58 of whom had palliated UH and found no difference in long-term survival between the 2 groups. Graft outcomes in Group A were comparable to the Dionigi cardiomyopathy group but better than the non–operated-on infant HLHS group at 1 year, whereas graft

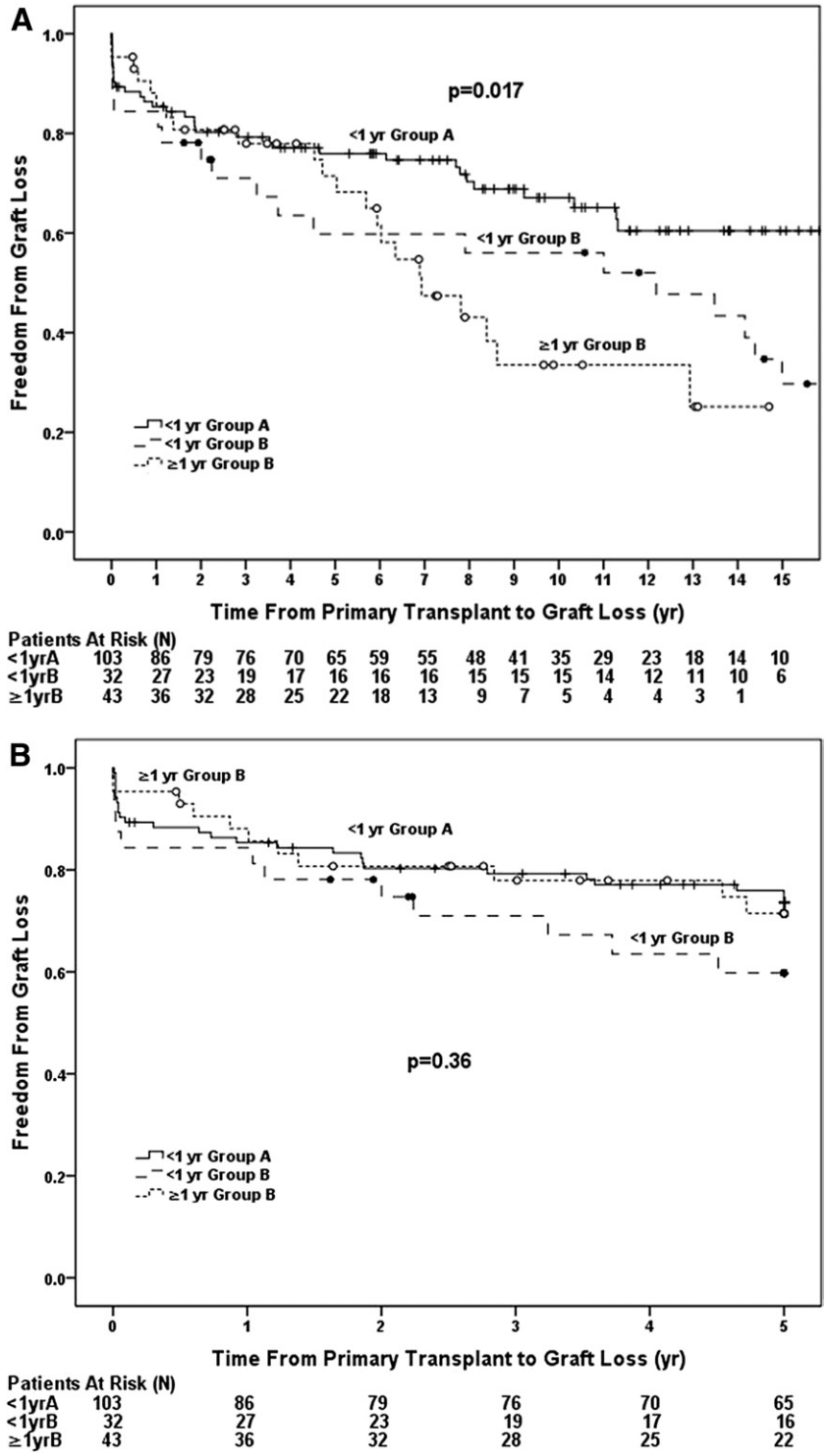

Figure 2 Groups were analyzed based on age and the presence of prior surgery and included patients aged < 1 year in Group A, aged < 1 year in Group B, and aged ≥ 1 year in Group B. (A) Overall incidence of graft loss was higher in patients with prior cardiac surgery and was highest in those with prior surgery who received an allograft outside of infancy. (B) Incidence of graft loss in the first 5 years after transplant. There was no difference in graft loss among the 3 groups through 5 years. (C) Incidence of graft loss in patients who survived 5 years after transplant. Patients in Group B the highest incidence of graft loss compared with those in Group A.

outcomes in Group B were slightly worse than those of the Dionigi group with complex congenital heart disease, which included a large proportion of patients with biventricular physiology.

A smaller study by Jacobs et al[9] comparing outcomes of primary heart transplantation in infants with HLHS vs rescue transplantation for failed surgical palliation in HLHS found that graft outcomes at 5 years were worse in the palliated group, with borderline significance; however, this study included only 8 patients who received an allograft after surgical palliation, which limits the potential for valid comparisons. The 10-year survival of 46% in Group B was

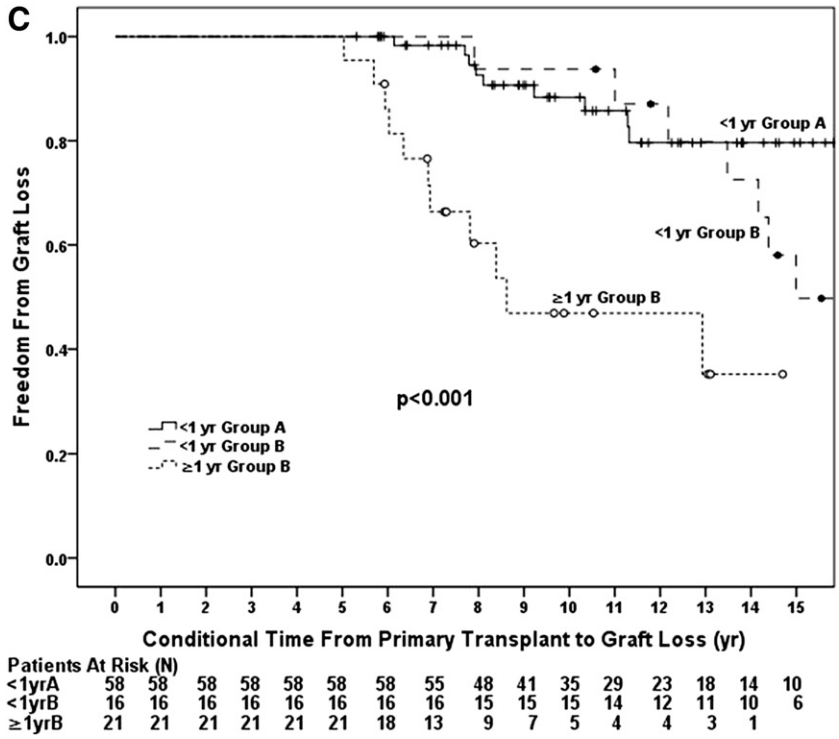

Figure 2 *(Continued)*

similar to that of patients reported by Chen et al[8] with complex congenital heart disease requiring pulmonary artery reconstruction at the time of transplant, which is not surprising because nearly all of our Group B patients required some form of pulmonary artery reconstruction. AR was less likely in Group A, which is consistent with prior studies and likely played a significant role in Group A's better long-term outcomes.[22] Whether Group A was less likely to have AR due to a more plastic immune system as a result of their young age, a lack of a previous sensitizing surgery, or a combination thereof, remains unclear.

Ventricular morphology was not associated with graft loss in univariate analysis. This finding could have been influenced by the larger proportion of patients with right ventricular morphology in Group A (72%) and the relatively few patients ($n = 9$) who had undergone a Norwood procedure, which is supported by a study from the PHTS database that found a previous Norwood procedure was highly associated with the presence and degree of HLA sensitization and that those with a PRA $> 50\%$ were at highest risk of poor outcomes.[23] The small number of patients that underwent Norwood palliation and the large proportion of infant transplants in our cohort likely explains why the PRA was elevated in only 7% of our population. Only 1 of the 9 patients who underwent Norwood palliation developed an elevated PRA, which may have been influenced by 3 Norwood patients who were aged < 1 year at the time of transplant. We found no difference in HLA sensitization based on ventricular morphology, which we speculate is due to the younger age of patients in our cohort with a single right ventricle.

Regardless of the reason for better outcomes in Group A, transplantation after palliative surgery is associated with worse long-term graft survival. The identification of prior cardiac surgery as a predictor of graft loss after transplant has implications for the management of children with UH.

Table 4 Cox Proportional Hazard Modeling of Risk Factors for Graft Loss

Variable	No. (events)	HR (95% CI)	*p*-value
Overall graft survival	178 (75)		
Age <1 year Group A	103		
Age <1 year Group B	32	1.75 (0.99–3.10)	0.053
Age ≥1 year Group B	43	2.06 (1.20–3.56)	0.009
5-year contingent graft survival	103 (28)		
Age <1 year Group A	65		
Age <1 year Group B	16	1.90 (0.70–5.15)	0.21
Age ≥1 year Group B	22	6.48 (2.63–15.92)	<0.001

CI, confidence interval; Group A, no prior cardiac surgery; Group B, had prior cardiac surgery; HR, hazard ratio.

Group A median graft survival was 18 years vs 8 years in Group B. Therefore, most infants who received an allograft without prior cardiac surgery for UH will experience graft loss at a much older age than most previously palliated transplant recipients. Limited donor supply makes it unrealistic to transplant all infants with single-ventricle physiology, which is reflected by the American Heart Association guideline recommendations that heart transplantation is not a feasible standard for any specific congenital heart lesion.[24]

Because some patients with staged palliation of UH live well into their adult years, better predictors of early surgical palliation failure, early ventricular failure, and interstage mortality are needed at the time of diagnosis in neonates with UH.[10,25] No one strategy for treatment of UH is ideal for all patients. Although some may point to waiting list mortality as the driving force in the decision to perform surgical palliation, outcomes from the time of stage I palliation must be taken into account as well. Risk factors that were predictive of adverse outcomes after stage I palliation in intermediate-term follow-up of the Single Ventricle Reconstruction Trial included obstructed pulmonary venous return, a lower right ventricular fractional area of change, a genetic syndrome, lower socioeconomic status, non-HLHS diagnosis, lower gestational age, and pre-Norwood surgery.[26] Consideration should be given to these data when determining a treatment strategy for an individual patient. Long-term follow-up and secondary analyses are still needed to determine risk factors for death or transplantation before stage I palliation to determine which children with UH will have acceptable long-term survival. Genetic data collected at the time of enrollment may also be of benefit in this endeavor.[27]

Among this study's limitations were that it was a retrospective study. Our single-center outcomes may not reflect the outcomes of the pediatric transplant population as a whole. We were also limited by the nature of the patient population. The inability to perform multivariable Cox proportional hazards modeling was due to a selection bias in the cohort because only 2 patients aged $>$ 1 year did not have surgery before transplantation. This selection bias is unavoidable in the analysis of these 2 populations because patients listed for primary transplantation without surgical palliation were likely receive a transplant or die on the waiting list before age 1 year.[16,21] We could not, therefore, fully determine whether age at the time of transplantation or prior cardiac surgery were independently responsible for the differences in long-term outcomes because very few patients are able to live $>$ 1 year without palliation or transplantation.

Another important note is that this study analyzed patients with UH from the time of transplantation and did not study outcomes from the time of listing or outcomes of surgical palliation from the time of the first surgery. Therefore, one cannot conclude from this study whether an initial strategy of palliation or transplantation achieves better overall outcomes.

In conclusion, patients with UH who have had surgery before undergoing transplantation have a higher risk of graft loss than those without prior surgery, with the largest effect on graft loss seen late in those with a history of prior surgery. The interaction between surgical history and age at transplantation is complex and time-dependent, with age affecting outcomes after 5 years.

Disclosure statement

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