Impact of antibodies against human leukocyte antigens on long-term outcome in pediatric heart transplant patients: An analysis of the United Network for Organ Sharing database

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Objectives: Controversy exists regarding the importance of circulating antibodies as determined by panel-reactive antibody screening as a risk factor for graft failure in pediatric patients undergoing heart transplantation. This study sought to determine the association of elevated anti-human leukocyte antibodies with long-term survival in pediatric heart transplant patients.

Methods: The United Network for Organ Sharing registry was queried for pediatric patients (aged < 18 years at listing) with panel-reactive antibody levels obtained before heart transplantation from 1987 through 2004. Survival analysis methods were used to assess the association of elevated panel-reactive antibodies with long-term graft and patient survival.

Results: Panel-reactive antibodies were obtained before transplantation from 3534 patients, median age 4 years (interquartile range 0–12 years). Most, 2711 (77%), had no detectible panel-reactive antibodies, 436 (12%) had panel-reactive antibodies of 1% to 10%, and 387 (11%) had panel-reactive antibodies greater than 10%. Patients with panel-reactive antibodies greater than 10% were more likely to be older ($P = .04$), have congenital heart disease ($P < .001$), and have a longer wait list time ($P = .006$). Patients with panel-reactive antibodies greater than 10% had significantly worse graft survival and patient survival than did patients with undetectable panel-reactive antibodies and panel-reactive antibodies of 1% to 10% ($P < .05$ for all). Controlling for confounding variables, elevated panel-reactive antibodies as a continuous variable and panel-reactive antibodies greater than 10% as a categorical variable were independently associated with decreased graft survival ($P = .04$ and $P = .02$, respectively).

Conclusions: Elevated panel-reactive antibodies are independently associated with worse long-term graft survival in pediatric patients undergoing heart transplantation. Further study is needed to determine the optimal management of this high-risk population. (J Thorac Cardiovasc Surg 2010;140:694-9)

Supplemental material is available online.

Heart transplantation in children is routinely performed in many institutions with excellent short- and medium-term survival.^{1,2} Long-term survival is still somewhat limited, with the median survival after transplantation being 11 to 16 years, depending on the age at transplant.³ Many pretransplant factors have limited posttransplant survival,

including the presence of congenital heart disease, renal insufficiency, and the use of extracorporeal life support.³ Additionally, the presence of antibodies directed against human leukocyte antigens (HLA) has been found to be associated with decreased survival in adults.⁴⁻⁷

However, there are very limited data on the effect of anti-HLA antibodies on survival after pediatric heart transplantation, and the available reports yield conflicting results. Several studies have demonstrated an increased risk of acute rejection among patients with elevated pretransplant anti-HLA antibodies,^{8,9} but others have not.¹⁰ Additionally, there has been some suggestion of decreased survival in this cohort of patients^{11,12}; however, this finding has not been consistent.^{10,13} The lack of consistent findings from these studies may be, in part, due to each study being a single center study of relatively small size.

Anti-HLA antibodies are typically measured in pretransplant patients with panel of reactive antibody (PRA) testing. PRA testing involves testing the potential recipient's serum against a panel of HLA antigens, either from lymphocytes or from purified HLA antigens.¹⁴ The results of PRA testing

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Abbreviations and Acronyms

ECMO	= extracorporeal membrane oxygenation
HLA	= human leukocyte antigen
PRA	= panel-reactive antibody
UNOS	= United Network for Organ Sharing
STAR	= Standard Transplant Analysis and Research
IQR	= interquartile range

are expressed as a percentage of reactivity. Conventionally, a PRA value of more than 10% is thought to be sensitive for identifying patients at increased risk for adverse outcomes.^{7,15}

The United Network for Organ Sharing (UNOS) maintains a database of all solid organ transplants in the United States. Data on pretransplant factors, including PRA levels, are recorded as are outcome data including graft and patient survival. Using the UNOS database, this study aimed to test the hypothesis that elevated pretransplant PRAs would be a risk factor for long-term graft and patient survival in pediatric patients undergoing heart transplantation.

METHODS

A retrospective analysis was performed on data obtained from the UNOS Standard Transplant Analysis and Research (STAR) files, with additional data provided by UNOS on crossmatch results. Data on heart transplants in the United States from October 1, 1987, with follow-up through May 15, 2008, were included for analysis. PRA data, expressed as a percentage, were available for transplants through June 1, 2004. Data were not available during that time period on the specific percentages of PRAs for HLA class I or class II antigens. The database was queried for pediatric patients (<18 years old at time of listing for heart transplantation) who underwent heart transplantation from October 1, 1987, through June 1, 2004, with PRA data before transplantation.

The most recent PRAs before transplantation were used for analysis. Patients were placed into 3 groups, 0%, 1% to 10%, or more than 10% PRAs. Additional data evaluated included demographic information, indication for transplantation, patient condition at transplantation including the use of inotropic medications or extracorporeal membrane oxygenation (ECMO), donor information, patient survival, and graft survival. The primary end point was graft survival and the secondary end point was patient survival.

Statistical Analysis

Data from the UNOS STAR files were imported into SPSS, version 16.0 (SPSS Inc, Chicago, Ill), for analysis. Baseline data are reported as means with standard deviations or as percentages, as appropriate. Baseline characteristics were compared among the 3 groups using an analysis of variance with the Bonferroni adjustment for multiple comparisons for continuous variables and a contingency table analysis for categorical variables. Kaplan–Meier survival curves were constructed and log–rank statistics were used to compare overall graft and patient survival among the different PRA groups. Cox proportional hazards models were used to assess the hazard ratios of graft and patient death in patients with elevated PRAs, while controlling for age, gender, diagnosis, year of transplant, inotropic medication at transplant, ECMO at transplant, mechanical ventilation at

transplant, donor age, donor weight, donor weight/recipient weight ratio, ischemic time, donor/recipient cytomegalovirus status, and crossmatch status. For the multivariable analysis, values of missing variables were replaced by the most common variable for categorical variables and the median value for continuous variables, as has been done previously.¹⁶

RESULTS

A total of 4176 pediatric patients underwent heart transplantation during the study period (1987–2004) with PRA data available for 3534 (85%). Patients with PRA data were older, weighed more, and waited longer for transplantation than patients without PRA data (Table E1). Most, 2711 (77%), had no detectable PRAs, 436 (12%) had PRAs of 1% to 10%, and 387 (11%) had PRAs greater than 10%. Patients with PRAs greater than 10% were more likely to be older, heavier, have congenital heart disease, be on inotropic support at transplant, wait longer for transplant, and have heavier donors ($P < .05$ for all) (Table 1). Evaluation of PRA level by age group demonstrated PRAs greater than 10% in 10% of patients aged 0 to 5 years, 12.4% of patients aged 6 to 13 years, and 11.8% of patients 13 years of age or older (Figure E1). Patients with PRAs greater than 10% were also more likely to have a positive crossmatch ($P < .001$) (Table 2).

Long-term graft survival was significantly less in patients with PRAs greater than 10%, median survival 7.1 years (interquartile range [IQR] 5.6–8.5 years), than in patients with PRAs of 1% to 10%, median survival 9.6 years (IQR 7.8–11.4 years) ($P = .003$), and patients with undetectable PRAs, median survival 9.8 years (IQR 9.1–10.4 years) ($P = .001$). Graft survival was not different between patients with undetectable PRAs and those with PRAs of 1% to 10% ($P = .75$). Patient survival was also significantly less in patients with PRAs greater than 10%, median survival 10.3 years (IQR 7.5–13.2 years), than in patients with PRAs of 1% to 10%, median survival 13.9 (IQR 11.0–16.8 years) ($P = .04$), and patients with undetectable PRAs, median survival 12.9 years (IQR 11.6–14.3 years) ($P = .014$). Patient survival was also not significantly different between patients with PRAs of 1% to 10% and those with undetectable PRAs ($P = .94$) (Figure 1). Among patients with elevated PRAs greater than 10%, survival was similar to that of patients with PRAs of 11% to 25%, 26% to 50%, and more than 50% (Figure E2).

A positive crossmatch was found in 320 (9%) patients. Patients with PRAs greater than 10% and a positive crossmatch had the worst overall graft and patient survival, which was significantly worse than that of patients with PRAs of 10% or less and a negative crossmatch ($P < .05$ for both) (Figure 2). Patients with PRAs greater than 10% with a negative crossmatch had worse graft and patient survival than did patients with PRAs of 10% or less; however, statistical significance was only reached for graft survival in patients with PRAs of 10% or less and a negative crossmatch.

TABLE 1. Patient characteristics

Characteristic	Undetectable PRA (n = 2711)	PRA 1%–10% (n = 436)	PRA > 10% (n = 387)	P value
Age, y	6.2 ± 6.3†	6.6 ± 6.2	7.1 ± 6.2†	.043
Weight, kg	24.4 ± 23.9†	25.4 ± 24.0	27.2 ± 23.9†	.043
Female	1174 (43)	178 (41)	165 (43)	.620
Year of transplant				<.001
1987–1992	634 (79)	110 (14)	58 (7)	
1992–1998	1115 (77)	196 (14)	136 (9)	
1999–2004	962 (75)	130 (10)	193 (15)	
Diagnosis				<.001
Congenital heart disease	1262 (47)	190 (44)	200 (52)	
Cardiomyopathy	1243 (46)	199 (46)	115 (30)	
Other	206 (8)	47 (12)	72 (19)	
Inotropic support*	875 (32)	133 (31)	157 (41)	.003
ECMO*	131 (5)	14 (3)	15 (4)	.258
Mechanical ventilation*	524 (19)	82 (19)	75 (19)	.966
Wait list time, mo	2.3 ± 4.6†	2.5 ± 5.7	3.5 ± 5.8†	.006

Data are shown as mean ± SD or n (%). ECMO, Extracorporeal membrane oxygenation. *Support at time of transplantation. †Difference between groups $P < .05$.

On multivariable analysis, PRAs greater than 10% were independently associated with decreased graft survival ($P = .02$) (Table 3). When we evaluated PRAs as a continuous variable, elevated PRAs were independently associated with decreased graft survival ($P = .04$). PRAs were not independently associated with patient survival.

DISCUSSION

This is the first study to demonstrate the incidence and outcome of a large cohort of pediatric patients with elevated pre-transplant anti-HLA antibodies. More than 75% of patients had no detectable PRAs whereas 11% had PRAs elevated more than 10%. Prior studies from adult patients have determined that risk factors for the development of anti-HLA antibodies include pregnancy, prior exposure to blood products or allograft material, prior transplant, and being on mechanical circulatory support.¹⁷ Similarly, our findings suggest that pediatric patients with elevated PRAs were more likely to be older and have congenital heart disease, many of whom would have undergone prior cardiac surgery with a risk of exposure to blood products and allograft material.

Additionally, patients undergoing transplantation in the most recent era (1999–2004) had more than twice the incidence of elevated PRAs as patients in the earliest era (1987–1992). This is likely related, in part, to techniques

used for PRA measurement, which have changed over time. Complement-dependent cytotoxicity assay was likely used virtually exclusively in the early era and has been replaced in most centers by more sensitive techniques such as flow cytometry.¹⁷ In addition, the complexity of patients at high risk for PRA development, such as patients undergoing transplantation after failed Fontan palliation and patients undergoing retransplantation, has also increased over time.^{3,18} Importantly, year of transplant was controlled for in the multivariable analysis and elevated PRA remained independently associated with worse graft survival.

We did not find an increased risk of elevated PRAs among patients supported with ECMO. Yang and associates¹⁹ reported previously that 3 (31%) of 13 pediatric transplant patients supported by ECMO had elevated PRAs, but elevated PRAs did not develop in any additional patients receiving ECMO support. Whether the shorter duration of support for pediatric patients on extracorporeal life support as a bridge to transplantation as opposed to adults on left ventricular assist devices accounts for these differences or whether other factors may contribute to this finding merits future inquiry.

Importantly, patients with elevated antibodies as determined by greater than 10% PRAs had significantly worse overall patient and graft survival. Those with undetectable

TABLE 2. Donor and transplant characteristics

Characteristic	Undetectable PRA (n = 2711)	PRA 1%–10% (n = 436)	PRA > 10% (n = 387)	P value
Donor age, y	9.0 ± 10.9	9.4 ± 10.9	10.2 ± 11.0	.110
Donor weight, kg	29.4 ± 24.3*	31.5 ± 25.7	33.0 ± 25.3*	.016
Donor/recipient weight ratio	1.5 ± 1.1	1.5 ± 0.9	1.4 ± 0.7	.225
Ischemic time, h	3.6 ± 1.3	3.5 ± 1.4	3.5 ± 1.4	.387
Crossmatch positive	155 (6)†	34 (8)‡	131 (34)† ‡	<.001
Donor CMV positive	471 (17)	72 (17)	67 (17)	.967
Donor CMV positive/recipient CMV negative	98 (4)	10 (2)	8 (2)	.130

Data are shown as mean ± SD or n (%). CMV, Cytomegalovirus. *Difference between groups $P < .05$. † and ‡ indicate difference between groups $P < .001$.

FIGURE 1. Kaplan-Meier survival curve with log-rank statistics for graft and patient survival. PRA, Panel-reactive antibody.

PRAs had a median graft survival over 2.5 years longer than those with PRAs greater than 10%. Additionally, those with PRAs greater than 10% were significantly more likely to have a positive crossmatch. Although the presence of a positive crossmatch shortened graft and patient survival, patients with elevated PRAs and a negative crossmatch still had worse graft survival than patients without elevated PRAs and a negative crossmatch. It is important to note that the survival in patients with a positive crossmatch and low PRAs was similar to that of patients with a negative crossmatch and high PRAs. These findings are consistent with the concept that patients with elevated PRAs may have shortened graft survival even in the setting of a negative crossmatch.

The association of PRA elevation greater than 10% and worse graft survival were independent of pretransplant status, year of transplantation, donor factors, crossmatch status, and rejection episodes in the first year after transplant. It is also important to note that the survival of patients with PRAs of 0% to 10% was virtually identical to that of patients with undetectable PRAs.

Prior pediatric studies have been limited by the small number of patients with elevated PRA levels,⁸⁻¹³ thus limiting the power of these studies to detect important differences in long-term survival. Feingold and colleagues¹³ described 36 patients with PRAs greater than 10% and found that patients with elevated PRAs had a decreased freedom from coronary allograft vasculopathy, but no statistically significant difference in survival. Holt and coworkers⁹ described the outcomes of 17 patients who underwent transplantation with PRAs greater than 10%. This cohort had a high incidence of rejection (92%), a 1-year survival of 85%, and a 3-year survival of 73%. There was no control group of patients with lower PRAs for this study, but the rates of rejection are higher and survival lower than recent cohorts from the International Society for Heart and Lung Transplantation.³ The current study is benefited by including more than 3500 pediatric patients with a long duration of follow-up, which allowed for clinically important differences to be detected. Furthermore, this study strengthens the notion that pediatric patients sensitized

FIGURE 2. Kaplan-Meier survival curve with log-rank statistics for graft and patient survival by crossmatch status. PRA, Panel-reactive antibody.

TABLE 3. Cox proportional hazard models of graft and patient survival

	Hazard ratio (95% CI)	P value
Graft survival		
PRAs > 10%	1.196 (1.025–1.396)	.02
PRAs, continuous variable	1.003 (1.000–1.006)	.04
Patient survival		
PRAs > 10%	1.128 (0.95–1.339)	.17
PRAs, continuous variable	1.002 (0.999–1.005)	.27

CI, Confidence interval.

with anti-HLA antibodies are a high-risk population at increased risk for earlier graft failure. The precise mechanism by which increased PRAs lead to earlier graft failure are likely multifaceted, including an increased likelihood of a positive crossmatch,²⁰ early graft dysfunction,²¹ acute rejection,^{15,21–24} and the earlier development of coronary allograft vasculopathy.^{13,15}

Limitations

This study has several limitations. Data on different techniques for measuring PRAs were not assessed, and thus whether different threshold percentages for PRAs should be used with different techniques cannot be determined. Likewise, the more sensitive tests such as flow cytometry or Luminex,²⁴ may detect some antibodies that, while present, are not clinically important.²⁵ Finally, data were not available on different patient management strategies such as the use of a prospective crossmatch, the use of a virtual crossmatch, or antibody reduction strategies.²⁶ Data were also not available on patients who did not survive to transplantation. Although the study is benefited by the large number of patients included and long duration of follow-up data, patient management likely varied considerably among different centers and over time. This variation could affect outcome, and given the limitations of the database, could not be completely controlled for in the multivariable models used.

CONCLUSIONS

The majority of pediatric heart transplant patients do not have elevated PRAs before transplantation. PRAs greater than 10% are more common in patients who are older, have congenital heart disease, and are receiving inotropic support at transplant. Elevations in PRAs greater than 10% are independently associated with worse long-term graft survival in pediatric heart transplant patients. Further study is needed to determine the optimal management of this high-risk population.

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and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

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FIGURE E1. Panel-reactive antibody level by age group. *PRA*, Panel-reactive antibody.

FIGURE E2. Kaplan–Meier survival curve with log–rank statistics for graft and patient survival with panel-reactive antibody levels greater than 10%. *PRA*, Panel reactive antibody.

TABLE E1. Characteristics of patients with and without PRA data

Characteristic	No PRA data (n = 642)	PRA data (n = 3534)	P value
Age, y	5.6 ± 6.2	6.6 ± 6.2	.04
Weight, kg	22.0 ± 22.6	25.2 ± 23.7	.004
Female	285 (44)	1517 (43)	.49
Year of transplant			<.001
1987–1992	196 (20)	802 (80)	
1993–1998	183 (11)	1447 (88)	
1999–2004	263 (17)	1285 (83)	
Diagnosis			.048
Congenital heart disease	324 (50)	1652 (47)	
Cardiomyopathy	276 (43)	1557 (44)	
Other	42 (7)	325 (9)	
ECMO*	31 (5)	160 (5)	.74
Mechanical ventilation*	141 (22)	681 (19)	.11
Wait list time, mo	2.1 ± 5.2	2.6 ± 5.0	.02

Data are shown as mean ± SD or n (%). PRA, Panel-reactive antibody; ECMO, extracorporeal membrane oxygenation. *Support at time of transplantation.