Predicting Graft Loss by 1 Year in Pediatric Heart Transplantation Candidates

An Analysis of the Pediatric Heart Transplant Study Database

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Background—Pediatric data on the impact of pre–heart transplantation (HTx) risk factors on early post-HTx outcomes remain inconclusive. Thus, among patients with previous congenital heart disease or cardiomyopathy, disease-specific risk models for graft loss were developed with the use pre-HTx recipient and donor characteristics.

Methods and Results—Patients enrolled in the Pediatric Heart Transplant Study (PHTS) from 1996 to 2006 were stratified by pre-HTx diagnosis into cardiomyopathy and congenital heart disease cohorts. Logistic regression identified independent, pre-HTx risk factors. Risk models were constructed for 1-year post-HTx graft loss. Donor factors were added for model refinement. The models were validated with the use of patients transplanted from 2007 to 2009. Risk factors for graft loss were identified in patients with cardiomyopathy (n=896) and congenital heart disease (n=965). For cardiomyopathy, independent risk factors were earlier year of transplantation, nonwhite race, female sex, diagnosis other than dilated cardiomyopathy, higher blood urea nitrogen, and panel reactive antibody >10%. The recipient characteristic risk model had good accuracy in the validation cohort, with predicted versus actual survival of 97.5% versus 95.3% (C statistic, 0.73). For patients with congenital heart disease, independent risk factors were nonwhite race, history of Fontan, ventilator dependence, higher blood urea nitrogen, panel reactive antibody >10%, and lower body surface area. The risk model was less accurate, with 86.6% predicted versus 92.4% actual survival, in the validation cohort (C statistic, 0.63). Donor characteristics did not enhance model precision.

Conclusions—Risk factors for 1-year post-HTx graft loss differ on the basis of pre-HTx cardiac diagnosis. Modeling effectively stratifies the risk of graft loss in patients with cardiomyopathy and may be an adjunctive tool in allocation policies and center performance metrics. (***Circulation*. 2015;131:890-898. DOI: 10.1161/CIRCULATIONAHA.114.009120.)**

Key Words: heart transplantation ■ pediatrics ■ risk assessment ■ risk factors

Survival rates for pediatric heart transplant (HTx) recipients have continued to increase over the last 15 years.[1] However, the decision to list patients with known risk factors for mortality, particularly in the context of limited donor availability,[2] remains one of the most significant challenges facing clinicians. Several retrospective studies have identified risk factors for post-HTx mortality and primary graft failure,[2–7] but variable reports of significant risk factors have complicated clinicians' ability to adequately assess postoperative risk. Although helpful in clinical decision making, the presence of a dichotomous risk factor does not allow the accurate prediction of an individual patient's overall HTx risk. Clinicians must account for the relative contributions of multiple, coexisting clinical variables to gauge the probability of survival. Until recently, clinically useful multivariable models predicting graft loss after pediatric HTx were lacking. Newly published models using the Organ Procurement and Transplantation Network (OPTN) data set have demonstrated good predictive ability,[7,8] but the spectrum and granularity of information available in the OPTN database have limitations for pediatric patients. Further complicating matters are the differing pediatric pre-HTx cardiac diagnoses;

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patients with congenital heart disease (CHD) and patients with cardiomyopathy are distinctly different populations, and they may possess dissimilar risk factors for graft loss after HTx. Risk factor analysis and modeling in each individual disease cohort would better illustrate disease-specific risk factors and allow better clinical evaluation of an HTx candidate's mortality risk.

The Pediatric Heart Transplant Study (PHTS) has been recording comprehensive preoperative and postoperative data on pediatric HTx patients since 1993 for research purposes. Although the PHTS has previously published analyses of risk factors among patient subgroups,[5,6,9–18] it has never examined risk factors in detail among the entire population of pediatric transplant recipients. Given this background, using the available data from the PHTS group, we aimed to identify independent risk factors for 1-year graft loss in pre-HTx children after stratifying by disease pathogenesis (CHD and cardiomyopathy) and to assess our ability to accurately predict graft loss using available risk factor data.

Methods

Patient Population and Data Collection

Data were collected on patients listed for HTx between January 1, 1996, and December 31, 2009, at 35 institutions participating in the PHTS. Demographic, clinical, and event data were collected on all HTx recipients at the participating centers. The data were collected through the use of coded event forms and sent to the data analysis center at the University of Alabama at Birmingham, where the information was entered into the database, verified, and corrected as needed, as described previously.[19] Institutional review boards from the participating centers approved all studies. The study excluded those subjects who received multi–solid-organ transplants. Follow-up on all patients was complete through December 31, 2009. All factors that were recorded for >75% of enrolled patients were included in analysis; New York Heart Association class and hemodynamic characteristics at pre-HTx cardiac catheterization were excluded because <75% patients reported them. Missing values were addressed by imputing the means of the existing data.

CHD was defined as any disease resulting from structural heart abnormalities developing before birth. Cardiomyopathy was defined as any nonstructural myopathic disease.

Glomerular filtration rate was the only variable that required additional transformation and was calculated with the modified Schwarz equation.[20,21]

Outcome Measure

The a priori primary outcome measure was graft loss within 1 year from the date of HTx.

Statistical Analysis

We examined data using standard descriptive statistics, including mean and standard deviation.

Pediatric patients undergoing HTx between 1996 and 2006 were stratified into disease-specific cohorts for cardiomyopathy and CHD. Univariable analyses were then performed to identify risk factors for graft loss with the use of parametric or nonparametric tests as appropriate for each variable. Continuous variables were assessed in their original scale, along with several key transformations (square, log linear, and inverse) to determine optimal fit in the model. Significant risk factors ($P<0.10$) were included in logistic regression analysis with forward stepwise selection for graft loss using only recipient factors. Multivariable odds ratios with 95% confidence intervals for graft loss were calculated for each factor. The final model covariates included only those that were significant in the multivariable analysis ($P<0.05$). In addition, on the basis of previous experience with the database and a known, era-dependent improvement in transplantation survival, a term was included in the model a priori to adjust outcomes from previous years for era to avoid era-dependent bias in evaluating other risk factors. The actual term was (2009−year of transplantation); it is abbreviated as year of transplantation in the model for simplicity. The variable was designed to drop out of the model after 2009 (ie, no improved or worsened risk based on year of transplantation after 2009). After the identification of independent risk factors and model completion, the analysis was repeated including recipient, donor, and recipient-donor mismatch factors. Each model was validated against a diagnosis-matched PHTS cohort transplanted from 2007 to 2009. The discriminatory ability of the resulting models in the validation cohort was assessed with receiver-operating characteristic curves. χ^2 Analysis assessed predicted versus observed risk by risk decile. Hosmer-Lemeshow statistics assessed the goodness of fit for each model. Additionally, Kaplan-Meier survival analysis was performed to evaluate prescribed patient subsets. The log-rank test was used to determine significant differences in survival between strata.

Results

Patient Characteristics

During the study period, 2714 patients underwent HTx. Specific demographic, clinical, and event indexes are shown in Table 1. During the modeling period from 1996 to 2006, 896 patients with cardiomyopathy were transplanted with 215 lost grafts (24%) by 1 year after HTx. In the CHD cohort, 965 patients were transplanted with 340 (35%) 1-year graft losses. In the validation period from 2007 to 2009, 483 additional patients with cardiomyopathy were transplanted (44 lost grafts at 1 year after HTx) and 370 patients with CHD were transplanted (52 lost grafts). Relevant patient characteristics and differences between the stratified modeling and validation cohorts are summarized in Table 2.

Cardiomyopathy Risk Factor Analysis and Modeling

For patients with cardiomyopathy in the modeling cohort, univariable analysis revealed several recipient and donor factors that were significantly associated with graft loss at 1 year after HTx (Table 3).

Multivariable logistic regression identified the following variables as independent predictors for graft loss: year of transplantation, nonwhite race, female sex, diagnosis other than dilated cardiomyopathy, higher blood urea nitrogen (BUN), and higher panel reactive antibody (PRA; Table 3).

Results of the univariable analyses including recipient and donor factors are also shown in Table 3. Ischemic time, older donor age, younger recipient age, year of transplantation, race, sex, diagnosis other than dilated cardiomyopathy, higher BUN, and higher PRA were found to be independent risk predictors by multivariable logistic regression (Table 3).

The cardiomyopathy risk models are included in Table 3. Internally, model performance was very good, with equivalent predicted versus actual graft loss of 9% for both the recipient-only and recipient+donor models (C statistic, 0.71 and 0.72, respectively). To validate the recipient factor model, it was applied to patients with cardiomyopathy who were transplanted from 2007 to 2009. Model accuracy was very good, with 2.7% predicted graft loss at 1 year and 4.7% actual graft

Table 1. Recipient and Donor Characteristics Included in the Analysis

Recipient	Donor
Demographics	Demographics
Sex	Sex
Race	Race
Age	Age
Blood type	BSA
Type of heart disease	Use of vasoactive support
BSA	Ischemic time
Body mass index	Clinical condition at death
Status at transplantation	Donor blood group
UNOS Status	Hypertension
Ventilator, VAD, ECMO	Diabetes mellitus
Inotropes, high or low	Cancer
Serum creatinine	Abnormal echocardiogram
Serum BUN	Cerebrovascular injury
Previous surgery	Recipient-donor mismatches
PRA	Sex
Clinical condition at listing	Race
Recipient blood group	Age
Failure to thrive	Blood type
Renal Insufficiency	BSA (ratio)
Arrhythmia	
Asthma/Pulmonary	
CVA	
Diabetes mellitus	
Serum creatinine	
Serum BUN	
GFR	
Date of transplantation	

BSA indicates body surface area; BUN, blood urea nitrogen; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; PRA, panel reactive antibody; UNOS, United Network for Organ Sharing; and VAD, ventricular assist device.

loss; the model demonstrated good discriminatory ability, with a C statistic of 0.73 (Figure I in the online-only Data Supplement); and the Hosmer-Lemeshow goodness-of-fit statistic demonstrated good calibration (P=0.40). The overall predicted graft loss versus observed graft loss by risk decile were not significantly different (Table I in the online-only Data Supplement). The addition of donor characteristics did not change the predictive accuracy or discriminatory ability of the model.

Practical Application of the Cardiomyopathy Model

Table 4 demonstrates how the cardiomyopathy risk models could be used to obtain an estimate of risk. We emphasize that these are estimates derived from a population-based study; they are not comprehensive measures of individual risk. Each patient and his or her individual clinical status need to be further considered, and the results of these models should serve only as a starting point for risk stratification. Table 4 demonstrates 2 hypothetical recipients with and without hypothetical donors. With the use of the independent risk factors identified and the logistic model, each patient's risk of graft loss as predicted by the model is shown. The first 2 columns detail a relatively low-risk patient: a teenaged white male patient with dilated cardiomyopathy, normal renal function, and 0% PRA. From his characteristics, the model predicts only a 4.7% chance of graft loss at 1 year after HTx. His predicted high chance of survival does not change with an optimal donor organ; however, if the donor organ has a prolonged ischemic time and the donor is older, the predicted chance of graft death increases to 13.5%. The third and fourth columns detail a higher-risk patient: a 5-year-old black female patient with myocarditis, impaired renal function, and a 20% PRA. Her baseline risk of graft loss is predicted to be 23.1%. Her baseline risk is both positively and negatively modifiable on the basis of characteristics of her donor graft; an optimal organ improves her risk of graft loss from 23.1% to 18.3%, whereas a suboptimal graft increases her risk of graft loss to 28.9%.

CHD Risk Factor Analysis and Modeling

The results of the bivariate analyses in the CHD modeling cohort revealed several recipient factors significantly associated with graft loss at 1 year after HTx (Table 5). After multivariable logistic regression, the following recipient variables were found to be independent significant predictors of 1-year graft loss: nonwhite race, history of Fontan palliation, ventilator dependence at transplantation, higher BUN, higher PRA, and lower body surface area (Table 5).

Results of the bivariate analyses that included recipient and donor factors are also shown in Table 5. Multivariable logistic regression found the following recipient and donor factors to be independent predictors of 1-year post-HTx graft loss: higher donor vasoactive support, older donor age, nonwhite race, history of Fontan palliation, ventilator dependence, higher BUN, higher PRA, and lower body surface area.

The resulting CHD risk models are included in Table 5. Internally, both the recipient and recipient+donor models performed fairly (C statistic, 0.64 and 0.66, respectively). When applied to the validation cohort, the model demonstrated only fair discriminatory ability, with a C statistic of 0.63 (Figure II in the online-only Data Supplement); model calibration was good (Hosmer-Lemeshow P=0.64). Predicted versus actual survival by risk decile is shown in Table II in the online-only Data Supplement. Similarly, it performed with only fair accuracy and with higher predicted (13.4%) than actual (7.6%) 1-year graft loss. The addition of donor characteristics to the model did not change predictive accuracy or discrimination, and the model continued to predict graft loss frequencies in the validation cohort that were higher than actually occurred. To investigate the cause of the overprediction of graft loss by the CHD model, survival analysis was performed on both the modeling and validation cohorts. Notably, the validation cohort of recent patients with CHD has a higher 1-year waitlist survival (78% versus 69%; P=0.004) and post-HTx survival rate than did the derivation cohort (Figure).

Table 2. Patient Information and Comparison Between Modeling and Validation Cohorts

	CMP			CHD		
	1996–2006 (n=896)	2007–2009 (n=483)	*P* Value	1996–2006 (n=965)	2007–2009 (n=370)	*P* Value
Recipient						
Demographics						
Male, n (%)	441 (49)	246 (51)	0.5439	601 (62)	203 (55)	0.0132
White, n (%)	595 (67)	306 (63)	0.2419	765 (79)	280 (76)	0.1575
Age, y	7.8 (1.4–14.0)	6.7 (1.2–13.3)	0.0761	41.3 (0.21–8.9)	1.3 (0.35–8.0)	0.6558
BSA, m^2	0.83 (0.44–1.42)	0.87 (0.47–1.44)	0.3260	0.43 (0.27–0.91)	0.46 (0.29–0.85)	0.8989
Status at HTx						
UNOS status 1, n (%)	728 (82)	438 (94)	<0.0001	756 (79)	325 (90)	<0.0001
Ventilator, n (%)	166 (19)	101 (20)	0.2851	199 (21)	97 (26)	0.0276
VAD, n (%)	109 (12)	134 (28)	<0.0001	20 (2)	21 (6)	0.0006
ECMO, n (%)	64 (7)	23 (5)	0.0828	68 (7)	23 (6)	0.5900
BUN, mg/dL	16.0 (11.0–21.0)	14.0 (9.0–20.0)	0.0002	14.0 (10.0–21.0)	15.0 (10.0–22.0)	0.2456
GFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	77.0 (59.9–97.6)	81.70 (62.4–101.8)	0.0132	65.9 (46.4–88.7)	73.5 (56.2–96.2)	0.0003
Maximum PRA, %	0 (0–0) (maximum 100)	0 (0–0) (maximum 100)	0.6225	0 (0–2) (maximum 100)	0 (0–4) (maximum 100)	0.5971
Heart disease pathogenesis, n (%)						
Dilated CMP	706 (79)	355 (74)	0.0259	…	…	…
Restrictive CMP	106 (12)	56 (12)	0.8966	…	…	…
Myocarditis	61 (7)	35 (7)	0.7603	…	…	…
Fontan	…	…	…	135 (14)	75 (20)	0.0048
Donor						
Male, n (%)	511 (58)	287 (61)	0.3066	519 (65)	201 (55)	0.9
White, n (%)	673 (79)	299 (68)	<0.0001	678 (76)	208 (61)	<0.0001
Age, y	8.4 (2.4–17.0)	8.7 (1.7–17.2)	0.6899	2.0 (0.36–8.0)	1.9 (0.50–9.4)	0.9423
BSA, m^2	1.0 (0.60–1.7)	1.1 (0.54–1.7)	0.8711	0.57 (0.37–1.04)	0.56 (0.37–1.09)	0.3207
Ischemic time, min	201.0 (161.0–240.0)	199.0 (167.0–240.0)	0.4823	238.0 (195.0–289.0)	236.0 (189.0–285.0)	0.5720
Vasoactive support, n (%)	646 (72)	314 (65)	0.0063	644 (67)	249 (67)	0.8641

BSA indicates body surface area; BUN, blood urea nitrogen; CHD, congestive heart disease; CMP, cardiomyopathy; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; HTx, heart transplantation; PRA, panel reactive antibody; UNOS, United Network for Organ Sharing; and VAD, ventricular assist device.

Discussion

This analysis is the first to stratify a large data set of pediatric HTx patients by pretransplantation cardiac diagnosis in an effort to better discern risk factors unique to different heart disease populations and then use those group-specific risk factors to model disease-specific risks of graft loss. We demonstrated that nonidentical factors contribute to the risk of early graft loss in both the CHD and cardiomyopathy subgroups. Several similarities and differences between the 2 disease cohorts warrant further discussion.

Risk Factors

Elevated BUN, indicative of renal dysfunction, is a risk factor for graft loss for both patients with cardiomyopathy and patients with CHD. This finding corroborates that of multiple previous studies of the influence of renal dysfunction on outcome in HTx candidates,[3,7,18] but this finding confirms that renal dysfunction is a risk factor for poor outcome regardless of pre-HTx heart disease pathogenesis. Similarly, a recipient PRA >10% is a risk factor for poor outcome and is consistent with the findings of a recent report from the PHTS on PRA,[22] but it now confirms that PRA is an independent risk factor across disease pathogeneses.

A few striking differences in risk factors are present between the cardiomyopathy and CHD cohorts. Ventilator dependence, frequently cited in previous reports as a risk factor for poor outcome, is an independent risk factor only for patients with CHD, not for those with cardiomyopathy. The cause of this discrepant result is unclear. Respiratory failure in patients with cardiomyopathy may typically occur primarily because of cardiac insufficiency and resolve completely after HTx with normal cardiac function. In contrast, although many children with CHD also have cardiac insufficiency, specific abnormalities of pulmonary blood flow may lead to pulmonary vascular and parenchymal changes, previous surgical palliation may have resulted in direct lung parenchymal or diaphragm damage, and airway abnormalities are more likely to be present.[23] All of these possible reasons for respiratory failure in patients with CHD would not be expected to improve immediately after HTx. Alternatively, ventilator dependence in CHD may be the best indicator of failed palliative surgery and increased overall morbidity at the time of HTx. The true nature of the

Table 3. Cardiomyopathy Modeling Cohort Risk Factors and Odds Ratios

	Univariable		Recipient-Only Multivariable		Recipient+Donor Multivariable	
Risk Factor	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Nonwhite race	1.55 (0.96–2.51)	0.0710	1.83 (1.10–3.05)	0.0210	1.76 (1.05–2.96)	0.0334
Female sex	1.50 (0.93–2.43)	0.0954	1.67 (1.00–2.77)	0.0489	NS	0.1042
Nondilated cardiomyopathy	1.73 (1.03–2.91)	0.0364	2.03 (1.07–3.84)	0.0302	2.71 (1.53–4.79)	0.0006
BUN (higher)	1.30 (1.16–1.44)	<0.0001	1.31 (1.16–1.47)	<0.0001	1.34 (1.20–1.51)	<0.0001
PRA (higher)	1.18 (1.03–1.35)	0.0151	1.21 (1.05–1.39)	0.0082	1.22 (1.06–1.41)	0.0068
Later year of transplantation*	0.996 (0.992–1.001)	0.1100	0.995 (0.990–0.999)	0.0226	0.995 (0.990–1.000)	0.0312
Recipient age (years, younger, log scale)	0.93 (0.79–1.09)	0.3523	NS	0.3537	0.79 0.65–0.96)	0.0200
Ischemic time (longer)	5.98 (2.07–17.27)	0.0010	N/A		4.38 (1.47–13.07)	0.0081
Donor age squared (per 10 y older)†	1.086 (1.027–1.15)	0.0084	N/A		1.086 (1.030–1.15)	0.0028

BUN indicates blood urea nitrogen; CI, confidence interval; and PRA, panel reactive antibody.

The following cardiomyopathy model equations result from the above analysis:

Recipient factors only:

$\ln(\text{odds of graft loss}) = -3.43 + 0.60_{\text{Nonwhite}} + 0.51_{\text{Female}} + 0.71_{\text{Nondilated cardiomyopathy}} + 0.27 \times (\text{BUN}) + 0.19 * (\text{PRA}) - 0.01 \times (\text{transplantation year})$.

Recipient and donor factors:

$\ln(\text{odds of graft loss}) = -3.94 + 0.57_{\text{Nonwhite}} + 1.00_{\text{Nondilated cardiomyopathy}} - 0.23 \times \ln(\text{age in years at transplantation}) + 0.29 \times (\text{BUN}) + 0.20 \times (\text{PRA}) - 0.01 \times (\text{transplantation year}) + 1.48 \times (\text{ischemic time in minutes}) + 0.0008 \times (\text{donor age in years})^2$.

*Indicates the decreased risk associated with a transplantation in 2006 compared with 1996.

†Increased risk associated with an increase in donor age from 1 to 10 years.

risk conferred by ventilator dependence remains unclear and warrants further study.

Additionally, for indeterminate reasons, female sex is a risk factor in patients with cardiomyopathy but not among those with CHD. Likewise, low recipient body surface area is a risk factor in patients with CHD but not in those with cardiomyopathy. That is, for patients with CHD, recipient age does not appear to be a significant risk factor for graft loss, suggesting that although young patients may also be small, the risk of poor outcome at HTx is conferred by small body size, not young age. In patients with cardiomyopathy, body surface area is not a risk factor for poor outcome, and when donor factors are included in the model, younger recipient age actually decreases risk. This suggests that although patient size and age vary together in pediatric HTx patients, their influence on post-HTx risk may be in opposition to each other, and the more influential of the 2 factors depends on the type of heart disease present.

Cardiomyopathy Model Performance and Implications

The cardiomyopathy predictive model performs well in risk stratification and provides a multifaceted tool for clinicians. On an individual-patient level, this tool would aid clinicians in baseline estimation of risk. As previously discussed, this population-derived tool should not be taken as an absolute and exact measure of individual risk but should instead be used as an estimate from which to further examine each individual's risk given the patient's clinical situation. Patients and families could be more accurately counseled on their own risk factors in undergoing HTx on the basis of known population-based risks. Other transplantation disciplines have

Table 4. Cardiomyopathy Model Demonstration With Predicted Risk of 1-Year Graft Loss Based on Patient Characteristics

Recipient				
Year of transplantation	2009	2009	2009	2009
Age, y	15	15	5	5
Race	White	White	Black	Black
Sex	Male	Male	Female	Female
Diagnosis	DCM	DCM	Myocarditis	Myocarditis
BUN, mg/dL	15	15	40	40
PRA (maximum), %	0	0	20	20
Donor				
Ischemic time, min	180	300	180	300
Age, y	10	30	4	12
Probability of graft loss at 1 y				
Recipient factors, %	4.7	4.7	23.1	23.1
Recipient+donor factors, %	4.7	13.5	18.3	28.9

BUN indicates blood urea nitrogen; DCM, dilated cardiomyopathy; and PRA, panel reactive antibody.

Table 5. CHD Modeling Cohort Risk Factors and Odds Ratios

	Univariable		Recipient-Only Multivariable		Recipient+Donor Multivariable	
Risk Factor	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Nonwhite race	1.50 (1.02–2.19)	0.0369	1.50 (1.01–2.22)	0.0427	1.53 (1.03–2.27)	0.0337
Fontan	1.35 (0.87–2.10)	0.1841	1.82 (1.09–3.03)	0.0211	1.87 (1.12–3.13)	0.0169
BUN (higher)	1.21 (1.08–1.35)	0.0010	1.16 (1.03–1.31)	0.0134	1.15 (1.02–1.30)	0.0186
PRA (higher)	1.10 (1.03–1.17)	0.0076	1.10 (1.02–1.18)	0.0100	1.09 (1.01–1.17)	0.0208
Ventilator at transplantation	1.99 (1.37–2.87)	0.0002	1.66 (1.12–2.46)	0.0119	1.61 (1.08–2.40)	0.0199
BSA (higher)	0.62 (0.42–0.92)	0.0186	0.51 (0.32–0.81)	0.0042	0.32 (0.18–0.58)	0.0001
Donor pressors	1.30 (0.91–1.86)	0.1543	N/A		1.46 (1.00–2.12)	0.0488
Donor age squared (per 10 y, older)*	1.022 (0.995–1.050)	0.4239	N/A		1.095 (1.057–1.134)	0.0096

BSA indicates body surface area; BUN, blood urea nitrogen; CHD, congestive heart disease; CI, confidence interval; and PRA, panel reactive antibody.

The following CHD model equations result from the above analysis:

Recipient factors only:

$\ln(\text{odds of graft loss}) = -1.78 + 0.40_{\text{Nonwhite}} + 0.60_{\text{Fontan}} - 0.68^{*}(\text{BSA}) + 0.51_{\text{Ventilator}} + 0.15\times(\text{BUN}) + 0.09\times(\text{PRA})$.

Recipient+donor factors:

$\ln(\text{odds of graft loss}) = -1.84 + 0.43_{\text{Nonwhite}} + 0.63_{\text{Fontan}} - 1.14\times(\text{BSA}) + 0.47_{\text{Ventilator}} + 0.14\times(\text{BUN}) + 0.08\times(\text{PRA}) + 0.0009\times(\text{donor age in years})^{2} + 0.38_{\text{Donor pressors}}$.

*Increased risk associated with an increase in donor age from 1 to 10 years.

shown that uniformity in communication of health-risks is lacking, and patients often have imperfect information on specific risks before making decisions.[24] An accurate risk model would facilitate provider dissemination of the most accurate information on population-based risk factors to recipients and families. The model could also be useful in further refinement of the current allocation system. Previous reports have demonstrated an apparent disconnect between medical urgency and pediatric HTx listing status, likely as a result of the significant heterogeneity within the status 1A (highest priority) group.[25] The model allows further stratification of patients within the current allocation groups, which would be a potential asset to future modifications to the allocation system.

The cardiomyopathy risk predictor model derived in this study may also allow secondary agencies to more appropriately assess outcome metrics for individual HTx centers. Current metrics use 1-year survival as a benchmark, and their prediction models include variables that may not correlate with graft loss

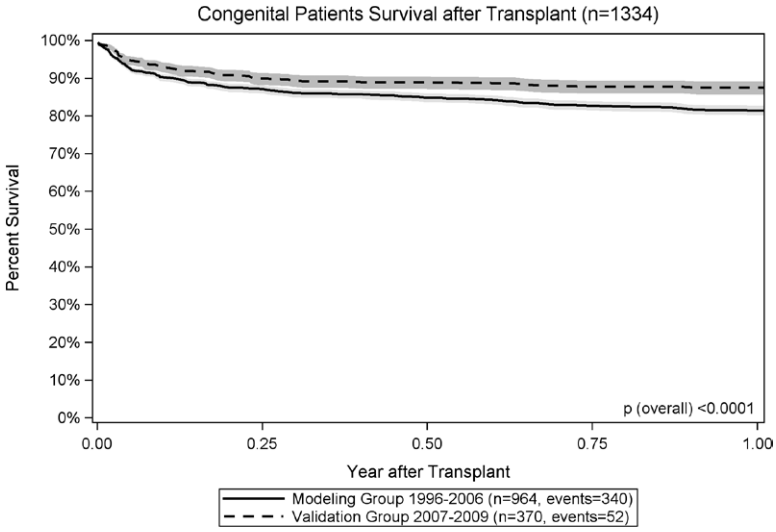

Figure. Freedom from posttransplantation graft loss in patients with congenital heart disease stratified by year of heart transplantation.

and exclude variables that do. At the time this manuscript was prepared, the US Scientific Registry of Transplant Recipients (SRTR) used the following factors for adjusting 1-year graft loss: recipient bilirubin, cardiac index, pulmonary artery pressure, previous solid-organ transplant, race, sex, weight, extracorporeal membrane oxygenation (ECMO) at transplantation, and ventilator dependence.[26] Both the SRTR model and the PHTS cardiomyopathy recipient-only model include race and sex. However, some significant independent risk factors found in our analysis are not included in the SRTR model, including heart disease diagnosis, BUN (or other marker of renal function), and elevated PRA. Furthermore, weight, ECMO at HTx, and ventilator dependence were included in the SRTR model but were not found to be significant in this analysis. The differences between the SRTR model and the findings of this study are noteworthy, and the inclusion of independent risk factors found in this analysis could enhance performance metrics and overall evaluation of center performance in cardiomyopathy HTx patients. Unfortunately, some SRTR risk factors were not historically collected in the PHTS, which currently prohibits a direct comparison of PHTS and SRTR model performance. However, recent revisions to the PHTS data fields will allow future comparisons that will be of significant interest. Currently, the SRTR publically reports the outcomes of each transplantation center, both in absolute terms and in comparison with expected survival using statistically derived model predictions. Given that the SRTR model does not include all significant risk factors, some of which were identified in this analysis, the predicted percent survival of the SRTR is likely imprecise. The extent to which these potential errors may affect overall center data is unknown. Nonetheless, because these limitations are likely underappreciated by patients and families, public availability of such data could result in false impressions or unfounded assumptions about the performance (good or bad) of a program. Because providing more transparency in individual center performance is of growing interest to reduce information asymmetry so that patients can make better-informed decisions about the institutions from which they seek care, perhaps a reconsideration of the current method used to convey this sensitive performance data is warranted.

CHD Model Performance

Although the risk factors found in the CHD analysis are significant, the ability to accurately predict outcome in patients with CHD was limited. Although this may be multifactorial, the survival analysis of patients with CHD implies that recently improved CHD survival may contribute to the model consistently overpredicting graft loss. Furthermore, the improved survival in the CHD validation cohort, both on the wait list and after HTx, occurred despite having significantly more Fontan patients and nonwhite patients (both independent risk factors for graft loss) than in the CHD modeling cohort. Explanation of the survival improvement warrants future study. Are CHD outcomes actually better regardless of patient characteristics, or have recent listing patterns changed in ways not discernable in this analysis so that providers have become increasingly conservative and the highest-risk patients are no longer being listed and undergoing HTx? Future studies designed to examine changing patterns in the selection of patients for listing may answer this question and would help identify a cohort of patients with CHD for whom transplantation would be unsuccessful. As for CHD risk prediction, remodeling with current-era patients with CHD and prospective validation could improve the ability to predict graft loss in these patients.

Previous Models

Almond and colleagues[7] recently published a model for outcome after pediatric HTx that warrants specific comparison. The Almond et al model used the OPTN database and found 4 independent risk factors for in-hospital mortality after pediatric HTx: CHD as an underlying pathogenesis, level of hemodynamic support, renal dysfunction, and serum bilirubin. Although both seek to describe preoperative factors that increase risk after HTx, there are distinct and important differences between the 2 studies. Almond et al included all pediatric patients in 1 cohort in deriving risk factors and found that heart disease pathogenesis is itself a risk factor. That specific finding served as a primary assumption in formulating the question addressed in our analysis: Given that disease pathogenesis strongly affects survival, do other pathogenesis-specific risk factors differentially affect survival but become masked when pathogenesis is included as a risk factor in the analysis? Thus, the main difference between the 2 studies is the a priori stratification by pathogenesis. The models should therefore not be viewed as competitors but rather as complementary, with the present analysis refining and extending the findings of Almond et al. Importantly, the insight into disease-specific risk factors gained from this analysis highlights differing factors that warrant consideration when performing pre-HTx evaluations. In addition, the models differ with respect to outcome measured in that the Almond et al study assessed in-hospital mortality as opposed to 1-year graft loss in the present study. We specifically chose 1-year graft loss because this is the metric by which centers are evaluated in the United States. Furthermore, the source data for each study differ significantly. Some data fields that may be important, specifically serum bilirubin, are included in the OPTN database but have only recently been collected in the PHTS study and could not be included in the present analysis. However, the PHTS otherwise offers advantages over the OPTN database. The PHTS is a database designed specifically for research, which allows accuracy and granularity that are not available in the administrative OPTN database. Finally, the predictive performance of the Almond et al model exceeded ours, which is a likely result of reduced statistical power after stratification by disease. In addition, a reduction in power after stratification could lead to a lack of identification of some risk factors as a result of type II error. For instance, Almond et al found ECMO before HTx to be a predictor of in-hospital mortality, whereas the present study did not. In the present study, type II error may be present, and the risk factors found may not constitute a completely comprehensive list. This may be a consequence of analyzing a smaller pediatric transplantation cohort but still would be a justifiable cost to gain the disease-specific insights provided by our models. However, it may be that the sample size is adequate and that after stratification by disease, factors associated with ECMO such as mechanical ventilation in congenital patients are the main drivers of risk, and ECMO is only

an associated factor. In toto, then, the reader is again reminded not to consider these models as final risk estimators but rather as initial estimates, which, when added to other clinically relevant data, provide a more complete risk estimator for each individual transplant candidate.

Limitations

Several limitations require brief discussion. This is a registry-based study of a broad, diverse patient cohort. Despite attempts to examine relationships between specific risk factors, the nature of registry-based research at times may decrease our ability to discern specific relationships. Second, some specific variables of interest such as serum bilirubin were not collected throughout the PHTS study or, like pulmonary vascular resistance, were not reported consistently enough to be included. Furthermore, some variables such as PRA have historically used different measurement methodologies, and the differential impact of these methodologies could not be accurately studied. Third, some variables collected in the PHTS database such as BUN as a marker of renal function are nonspecific. To address this, we included more specific estimates such as glomerular filtration rate when possible, and in this case, BUN was the independent risk factor whereas glomerular filtration rate did not remain in the models. Fourth, this is a retrospective study with all the inherent limitations. Finally, despite the fact that we used the entire PHTS database, our patient numbers are still relatively limited because of the overall low incidence of pediatric heart disease requiring transplantation. This limitation in study power is further exacerbated by stratifying patients into disease-based cohorts and further reducing sample size. Type II error is possible, and risk factors that were not shown to be significant in this study should not necessarily be dismissed as unimportant.

Conclusions

This analysis identified independent risk factors for post-HTx graft loss among pediatric HTx recipients, and these risk factors differed between patients with cardiomyopathy and patients with CHD. With the use of these risk factors, a population-based risk stratification for early graft loss can be accurately modeled for patients with cardiomyopathy. For patients with cardiomyopathy, this model could be used to augment or replace the SRTR model currently used for benchmarking center performance in the United States. Accurate prediction of short-term risk could also help to maximize overall pediatric survival by optimizing future organ allocation rules. We hope to make this model available online for clinician use in the future.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This is the most detailed study of risk factors for graft loss in pediatric heart transplantation patients published; it uses data from the Pediatric Heart Transplant Study. Previous studies of risk factors in pediatric patients have consistently demonstrated that the cause of heart disease is a risk factor for poor outcome, but none have attempted to evaluate and compare risk factors for transplantation outcome within individual disease pathogeneses. Unlike all previous studies of pediatric risk factors, before analysis, the data were stratified into 2 cohorts: congenital heart disease and myopathies. By doing this, disease-specific risk factors were determined that were previously unappreciated. Furthermore, it was discovered that risk factors differ significantly between disease groups. These new risk factors allowed disease-specific multivariable models that will aid in pediatric pre–heart transplantation risk stratification and which could assist with improved assessment of center performance.

Predicting Graft Loss by 1 Year in Pediatric Heart Transplantation Candidates: An Analysis of the Pediatric Heart Transplant Study Database

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SUPPLEMENTAL MATERIAL

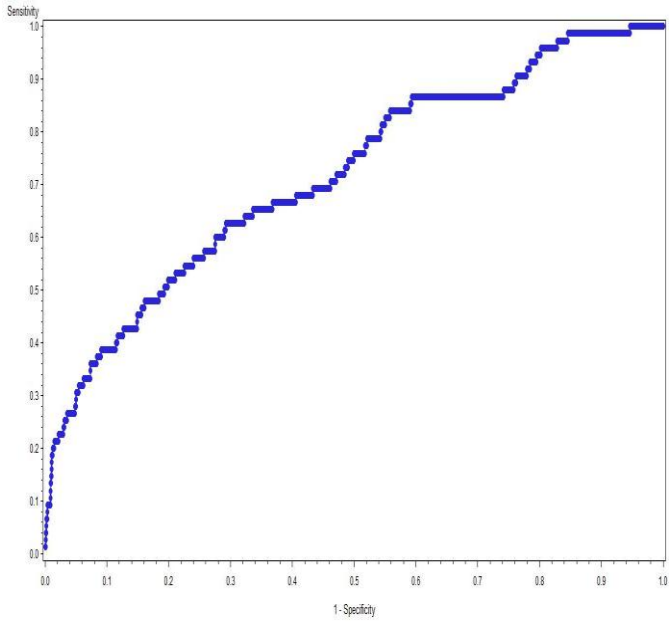
Supplement Table 1. Cardiomyopathy Model: Observed v. Predicted Mortality in modeling and validation cohorts by decile

	1996-2006 (n=896)		2007-2009 (n=483)	
Decile	Predicted 1 Year Mortality	Observed 1 Year Mortality	Predicted 1 Year Mortality	Observed 1 Year Mortality
0	1.9	1	0.5	1
1	2.7	4	0.7	0
2	3.4	5	0.9	3
3	3.9	2	1.1	1
4	4.7	9	1.3	2
5	5.6	4	1.5	3
6	6.7	7	1.8	2
7	8.5	7	2.4	7
8	12.0	9	3.3	3
9	25.5	27	6.9	7
Overall	75.0	75	20.3	29

Supplement Table 2. Congenital Model: Observed v. Predicted Mortality in modeling and validation cohorts by decile

	1996-2006 (n=1061)		2007-2009 (n=273)	
Decile	Predicted 1 Year Mortality	Observed 1 Year Mortality	Predicted 1 Year Mortality	Observed 1 Year Mortality
0	6.3	5	2.6	1
1	10.0	11	4.2	4
2	11.7	15	4.7	3
3	13.8	9	5.5	2
4	15.4	18	6.2	4
5	16.8	15	6.8	3
6	18.7	16	7.9	5
7	21.2	25	9.1	4
8	25.0	28	10.7	11
9	36.2	33	14.6	9
Overall	175.0	175	72.4	46

Supplement Figure 1. ROC curve for the CMP model's discrimination in the validation cohort.



Supplement Figure 2. ROC curve for the CHD model's discrimination in the validation cohort.