Cumulative Effect of Preoperative Risk Factors on Mortality After Pediatric Heart Transplantation

Matthew J. O'Connor, MD, Andrew C. Glatz, MD, MSCE, Joseph W. Rossano, MD, Robert E. Shaddy, MD, Rachel Ryan, RN, Chitra Ravishankar, MD, Stephanie Fuller, MD, Christopher E. Mascio, MD, J. William Gaynor, MD, and Kimberly Y. Lin, MD

Division of Cardiology and Division of Pediatric Cardiothoracic Surgery, University of Pennsylvania Perelman School of Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Background. **Risk assessment in heart transplantation is critical for candidate selection, but current models inadequately assess individual risk of postoperative mortality. We sought to identify risk factors and develop a scoring system to predict mortality after heart transplantation in children.**

Methods. **The records of patients undergoing heart transplantation at our institution from 2010 through 2016 were reviewed. Clinical characteristics were recorded and compared between survivors and nonsurvivors. We used Cox proportional hazard modeling of factors associated with postoperative mortality to develop a risk factor score.**

Results. **There were 74 patients who underwent heart transplantation at a mean age of 8.8 ± 6.6 years. Congenital heart disease was the most common indication, comprising 48.6% of the cohort. Overall mortality was 18.9%, with 10 of 14 dying within 30 days of the operation or during the initial postoperative admission (early mortality). Preoperative factors associated with overall mortality were single-ventricle congenital heart disease (hazard ratio [HR], 3.2; $p = 0.042$), biventricular assist device (HR, 4.8; $p = 0.043$), history of four or more sternotomies (HR, 3.9; $p = 0.023$), panel reactive antibody exceeding 10% (HR, 4.4; $p = 0.013$), any previous operation at another institution (HR, 3.2; $p = 0.038$), and pulmonary vein disease (HR, 4.7; $p = 0.045$). Each risk factor was assigned a point value, based on similar magnitude of the HRs. A score of 4 or higher predicted mortality with 57% sensitivity and 90% specificity.**

Conclusions. **In this single-center pediatric cohort, postheart transplantation mortality could be predicted using patient-specific risk factors. The cumulative effect of these risk factors predicted mortality with high specificity.**

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Heart transplantation (HT) remains the definitive therapy for end-stage heart failure in children. Outcomes after pediatric HT are favorable, with median survival exceeding 20 years for some age groups, and HT may offer superior survival and quality of life [1]. However, certain patients undergoing HT continue to experience disproportionately high mortality, including infants [2], infants with single-ventricle (SV) congenital heart disease (CHD) [3], highly sensitized patients [4], and patients with Fontan physiology [5–7]. Offering life-prolonging therapy with the potential for significant early mortality is a complex decision-making process involving the balancing of short-term and long-term risks, which may vary widely among individual patients. Furthermore, assessing and quantifying the contributions of relatively rare abnormalities to overall postoperative risk may be one of the most challenging aspects of candidate selection in pediatric HT.

We hypothesized that patients at higher risk of post-HT mortality could be identified, with high specificity, by using preoperative factors not currently accounted for in commonly used risk models. Furthermore, we hypothesized that the accumulation of perioperative risk factors is associated with increased mortality after HT and that these risk factors could be used to develop a risk scoring system for this population.

Patients and Methods

The records of all patients aged younger than 21 years undergoing HT at Children's Hospital of Philadelphia between January 1, 2010, and August 31, 2016, were reviewed as part of a quality-improvement initiative. Multiple organ transplants were excluded. Our local

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Address correspondence to Dr O'Connor, Division of Cardiology, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104; email: oconnorm@email.chop.edu.

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Abbreviations and Acronyms

biVAD = biventricular assist device
CHD = congenital heart disease
CI = confidence interval
CM = cardiomyopathy
ECMO = extracorporeal membrane oxygenation
HR = hazard ratio
HT = heart transplant
ISHLT = International Society for Heart and Lung Transplantation
MCS = mechanical circulatory support
OR = odds ratio
PLE = protein-losing enteropathy
PRA = panel reactive antibody
SV = single ventricle
UNOS = United Network for Organ Sharing
VAD = ventricular assist device

Institutional Review Board reviewed this initiative and deemed it to be exempt from review. Demographic data were collected, as were indications and anatomic diagnoses leading to HT and classification of physiology (for patients with CHD) at the time of HT. Other pre-HT clinical variables included inpatient status, mechanical circulatory support with extracorporeal membrane oxygenation or ventricular assist device (VAD), dialysis, renal dysfunction, hepatic dysfunction, mechanical ventilation, number of sternotomies before HT, and whether patients had undergone any prior cardiac operations at another institution.

Renal dysfunction was defined as an estimated glomerular filtration rate of less than 45 mL · min^{-1} · 1.73 m^{-2} using the modified Schwartz formula, based on the serum creatinine obtained closest to the time of HT. Hepatic dysfunction was defined as a total bilirubin, obtained closest to the time of HT, of 2 mg/dL or more.

Pulmonary vein abnormalities were defined as any form of anomalous pulmonary venous connection or the presence of pulmonary vein obstruction, or both. Anti-human leukocyte antigen antibody status at the time of HT was recorded, with positive status defined as a class I or class II panel reactive antibody (PRA) of more than 10%, using single-bead antigen methodology. The retrospective crossmatch status was recorded, with a positive crossmatch defined as a positive flow cytometric or cell-dependent cytotoxicity crossmatch assay, or both.

Postoperative clinical factors were also collected. Early (operative) mortality was defined as death within 30 days of HT or during the hospitalization for HT. Follow-up was ascertained through death or date of the most recent clinical encounter in which the patient was known to be alive.

Standard summary descriptive statistics were used and are reported as mean ± SD for normally distributed continuous variables, median (range) for skewed continuous variables, and count (percentage of total) for categoric variables. Associations between covariates and early mortality were assessed using logistic regression testing, with the strength of the association expressed as an odds ratio (OR) with 95% confidence intervals (CIs). Because all outcomes for early mortality occurred within a specified time frame after HT, a time-dependent analysis was not used for this outcome. Associations between covariates and overall mortality were assessed using Cox regression testing, with the strength of the association expressed as a hazard ratio (HR) with 95% CIs. An attempt to identify factors independently associated with the outcome of interest for both outcomes was made using multivariable regression modeling.

A score to predict the risk of overall mortality was generated by including nonoverlapping covariates significantly associated with overall mortality in univariable Cox regression testing. The value of the point score for each covariate was based on the relative magnitude of the HR. The ability of the resultant score to discriminate outcomes was summarized with sensitivity and specificity values.

The optimal discriminatory cutpoint was assessed using receiver operating characteristic curve analysis, with an emphasis on maximizing specificity to avoid false positives. Because of the exploratory nature of this study, the score and risk factors did not undergo internal or external validation. Finally, a visual representation of the differing survivor experiences based on the risk score was displayed using Kaplan-Meier curves, and the differences were tested by log-rank test. Statistical significance was established a priori at a two-tailed α of less than 0.05. Analyses were performed using STATA 10 software (StataCorp, College Station, TX).

Results

Between January 1, 2010, and August 31, 2016, 74 patients (28 females [37. 8%]), underwent HT. Mean age was 8.8 ± 6.6 years. Age grouping and diagnoses leading to HT are presented in Table 1. Adolescents (27 patients [36.5%]) were the most common age group, and 15 (20.3%) were neonates or infants. Patients with CHD represented 48.6% of the cohort, with 16 CHD patients having Fontan physiology at the time of HT (44.4% of patients with CHD). Of the Fontan patients, 4 had protein-losing enteropathy (PLE), 3 had plastic bronchitis, 7 had ventricular dysfunction, 1 had ventricular dysfunction and plastic bronchitis, and 1 had ventricular dysfunction and PLE.

Early mortality occurred in 10 patients (13.5%), with an additional 4 (5.4%) experiencing late mortality. The overall unadjusted mortality rate was 18.9%. Survival post-HT was 86% (95% CI, 76% to 92%) at 1 year and 78% (95% CI, 63% to 87%) at 5 years. For patients experiencing early mortality, death occurred at a median of 8 days (range, 1 to 360 days) after HT. Patients with late mortality died at a median of 3.2 years (range, 2.3 to 5.4 years) after HT. Median follow-up was 2.7 years (range, 2 days to 6.1 years). Causes of early mortality were multiorgan system dysfunction (3 patients), graft dysfunction (5 patients), hemorrhage (1 patient), and pulmonary hypertension