

CLINICAL RESEARCH

Validation of a Simple Score to Determine Risk of Early Rejection After Pediatric Heart Transplantation



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ABSTRACT

OBJECTIVES This study aimed to develop a reliable and feasible score to assess the risk of rejection in pediatric heart transplantation recipients during the first post-transplant year.

BACKGROUND The first post-transplant year is the most likely time for rejection to occur in pediatric heart transplantation. Rejection during this period is associated with worse outcomes.

METHODS The United Network for Organ Sharing database was queried for pediatric patients (age <18 years) who underwent isolated orthotopic heart transplantation from January 1, 2000 to December 31, 2012. Transplantations were divided into a derivation cohort (n = 2,686) and a validation (n = 509) cohort. The validation cohort was randomly selected from 20% of transplantations from 2005 to 2012. Covariates found to be associated with rejection ($p < 0.2$) were included in the initial multivariable logistic regression model. The final model was derived by including only variables independently associated with rejection. A risk score was then developed using relative magnitudes of the covariates' odds ratio. The score was then tested in the validation cohort.

RESULTS A 9-point risk score using 3 variables (age, cardiac diagnosis, and panel reactive antibody) was developed. Mean score in the derivation and validation cohorts were 4.5 ± 2.6 and 4.8 ± 2.7 , respectively. A higher score was associated with an increased rate of rejection (score = 0, 10.6% in the validation cohort vs. score = 9, 40%; $p < 0.01$). In weighted regression analysis, the model-predicted risk of rejection correlated closely with the actual rates of rejection in the validation cohort ($R^2 = 0.86$; $p < 0.01$).

CONCLUSIONS The rejection score is accurate in determining the risk of early rejection in pediatric heart transplantation recipients. The score has the potential to be used in clinical practice to aid in determining the immunosuppressant regimen and the frequency of rejection surveillance in the first post-transplant year. (J Am Coll Cardiol HF 2015;3:670-6)
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The first post-transplant year is the most likely time for rejection to occur in pediatric heart transplantation (1). Early rejection is a significant cause of morbidity and mortality in pediatric heart transplantation (1,2) as evidenced by its association with increased risk of late rejection, graft loss, and patient death (3-5). Despite a declining rate of early rejection due to the use of induction therapy, tacrolimus, and new immunosuppressive regimens, early rejection continues to occur in approximately 20% to 30% of transplantation recipients (1,6-8).

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Multiple risk factors have been identified as increasing the risk of early rejection (2). However, a simple method to risk stratify pediatric heart transplantation recipients has not been developed. The object of this study was to design and validate a clinically derived rejection score that could be used to assess risk of early rejection in pediatric heart transplantation recipients.

METHODS

A retrospective analysis was performed using data obtained from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research files. Heart transplantations performed in the United States from January 1, 2000, to December 31, 2012 were included for analysis. The study end date of December 31, 2012 was chosen to allow for 1 year of follow-up. The database was queried for pediatric heart transplantations in patients who were age 17 or younger. Transplantations were included if they had valid reporting of the presence of treated rejection within the first post-transplant year; biopsy confirmation of rejection was not required. Transplantations were excluded if they were performed in patients who were age 18 years or older, were not isolated heart transplantation, or had <1 year of follow-up reported. A validation group was randomly selected from 20% of the transplantations done between 2005 and 2012. The validation cohort was removed from the derivation cohort. The primary endpoint was early rejection, which was defined as rejection that required treatment in the first post-transplant year. The Medical University of South Carolina Institutional Review Board approved the study.

STATISTICAL ANALYSIS. All pre-transplantation variables present in the UNOS database were assessed for association with early rejection using univariate statistics (chi-square for categorical variables and Student *t* test for continuous variables).

Continuous variables were converted to categorical variables using previously published cutoffs for the purposes of the multivariable logistic model (1,9,10). For panel reactive antibodies (PRAs), the most recently reported PRA before transplantation was used. The variables associated with rejection in univariate analysis ($p < 0.2$) were entered into a multivariable logistic regression analysis. Variables with $\geq 20\%$ of missing data were excluded from the multivariable model.

Covariates were eliminated from the model if they were not independently associated with early rejection, which was defined as a p value of < 0.05 . The model's goodness of fit was tested with the Hosmer-Lemeshow test and the receiver-operating area under the curve (c-statistic).

Remaining covariates associated with rejection were assigned points based on the relative weight of their odds ratio in the final multivariable logistic regression model to derive a formula for the "rejection score." A score was then calculated for all transplantations in the derivation and validation groups. The association of the rejection score with early rejection was assessed using weighted regression analysis and logistic regression in both the derivation and validation cohorts. In weighted regression analysis, correlations between model-predicted rejection rates and actual rejection rates within each respective rejection score were assessed, and weights were given based on the number of patients in each respective rejection score. Rejection scores were subsequently classified as low, medium, and high, and the predicted and actual rates of rejection among these 3 groups were compared.

All statistics was performed using SPSS version 21 (IBM, Armonk, New York).

RESULTS

A total of 4,106 isolated heart transplantations were performed between 2000 and 2012 in pediatric patients. Of those, 3,195 (78%) had adequate reporting of early rejection, and therefore, were used for further analysis. Average recipient age was 6.9 ± 6.2 years. The average donor age was 9.5 ± 9.4 years. Recipient race was Caucasian in 1,822 (57%) transplantations, and donor race was Caucasian in 1,854 (58%) transplantations. An underlying cardiac diagnosis of cardiomyopathy was present in 1,652 (51%) transplantations, and congenital heart disease was present in 1,233 (39%) transplantations. Two hundred fourteen (7%) patients had re-transplantations, and 112 (3%) transplantation patients had other conditions.

ABBREVIATIONS AND ACRONYMS

ECMO = extra-corporeal membrane oxygenation

HLA = human leukocyte antigen

PRA = panel reactive antibody

UNOS = United Network for Organ Sharing

VAD = ventricular assist device

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