EDITORIAL COMMENT

Taking First Steps Toward Modeling Risk of Rejection in Children*

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Pediatric cardiologists envy our colleagues who treat adults with respect to their feasibility of performing clinical trials, gathering data that results in evidence-based clinical guidelines with class I recommendations, and generating validated risk prediction models, such as the Framingham Risk Score, the Seattle Heart Failure Model, and the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) risk score (1,2). Pediatric heart transplantation practitioners are used to relying on data generated from multicenter registries and databases, and on data from single-center studies to help guide management decisions. Our patients do not present in great enough numbers to allow us to easily conduct multicenter, randomized, blinded, placebo-controlled trials. Fortunately, the pioneers in our field had the foresight to create registries and databases, such as the Pediatric Cardiomyopathy Registry and the Pediatric Heart Transplant Study (PHTS) database (3,4). These registries, in addition to the Organ Procurement and Transplantation Network (OPTN) database and the International Society for Heart and Lung Transplantation (ISHLT) registry, have been essential in developing an understanding of the risk and outcomes in pediatric heart failure and transplantation. Although data generated from these registries have helped us to better understand risk factors for adverse outcomes, very few analyses have provided us with a risk score. Until now, pediatric heart transplantation risk prediction models have been limited to a risk prediction model for 30-day and 1-year post-transplant mortality, and a risk prediction model for in-hospital mortality following heart transplantation (5,6).

In this issue of JACC: Heart Failure, Butts et al. (7) add a risk prediction score for early rejection (defined as a treated rejection in the first post-transplant year) to the pediatric literature using the OPTN database. Their objective was to develop and validate an easy to calculate risk score that was able to assign a predicted rate of early rejection. This approach was shown to be feasible in an adult transplant population (8). Logistic regression was used to find univariate risk factors for treated rejection in the first year post-transplant in patients younger than 18 years of age. Variables found to be significant in the univariate analysis were entered into a multivariable model, and the significant odds ratios from the multivariable model were used to calculate the risk score. Regression analysis was then used to associate the predicted rejection score with the observed rejection rates. This was performed using 2 cohorts within the OPTN dataset: a derivation cohort and a validation cohort. The derivation and the validation cohorts were similar, except for a lower incidence of rejection (37.5% in the derivation cohort and 23.4% in the validation cohort), fewer patients on inotropes, and fewer male patients in the validation cohort than the derivation cohort. Another difference was that the validation cohort only included patients from 2005 to 2012, whereas the derivation cohort included patients from 2000 to 2012. This is important because the rejection rate dropped from >50% in 2000 to >20% in 2012 (Figure 2 of Butts et al. [7]).

The final multivariable model found that year of transplantation, age at transplantation, diagnosis of congenital heart disease, and the panel reactive antibody were all significant risk factors; rejection risk
scores were calculated based on the odds ratio from these variables. Year of transplantation was left out of the score for practical reasons. The risk of rejection ranged from 10.6% for a score of 0% to 40%, for a score of 9. Calibration and discrimination of the model were adequate based on the Hosmer-Lemeshow statistic and the c-index, respectively. The R² values for the predicted and observed rejection rates in both the derivation and validation cohorts were very good despite the previously mentioned differences between the 2 groups. The investigators were successful in creating and validating the first tool to combine multiple known risk factors for rejection into a score that could predict a child’s chance of rejection within a year following transplantation.

Although this pediatric rejection risk score is similar to the adult score created by Kilic et al. (8) in 2012, the variables included in the rejection score in children differ from the variables in the adult rejection score. Risk factors that were included in the adult rejection score, but were not predictors of early rejection in children, included race, sex, and human leukocyte antigen mismatch. Conversely, a diagnosis of congenital heart disease was included in the risk score in children but did not reach significance to be included in the score for adults (diagnosis failed to improve the explanatory power of the model in the adults study) (8). The fact that there are different risk factors for early rejection between adults and children should not surprise anyone, because of the differences in indications for transplantation, age, immunological maturity and memory, sensitizing events, and the social environment.

The similarities between the adult and pediatric risk scores were the methods used to derive the score, and, more importantly, the variables and outcomes not incorporated into the model and score. Mehra (9) wrote an editorial about the adult risk score in 2012, and his comments about unincorporated variables and problems with the model endpoint in the adult rejection score are relevant to the pediatric risk score. These unincorporated variables include the different eras during the study period, induction therapy, and maintenance immunosuppression. Problems with the risk model endpoint include potential variability in the diagnosis of rejection, the type of rejection (acute cellular rejection [ACR] vs. antibody mediated rejection [AMR]), and the severity of rejection.

**DIFFERENT ERAS**

The incidence of early rejection decreased steadily over the study period, which is consistent with data from the ISHLT registry and the PHTS database (10,11). This lower risk of rejection seems to be coincidental with the increasing use of induction therapy and the use of newer forms of maintenance immunsuppression (10,11). The model did not incorporate induction therapy or maintenance immunsuppression as variables, which are important considerations, because induction therapy, tacrolimus, and the initial use of mycophenolate have been shown to be protective against early rejection (11).

**DIAGNOSIS OF REJECTION**

There is variation between pediatric heart transplantations centers with respect to rejection surveillance protocols. Some centers biopsy every 1 to 2 weeks early after transplantation, while other centers may not perform a first biopsy until 6 weeks post-transplantation (12,13). It is also unknown how a diagnosis of rejection was made in any individual patient. Differences between thresholds for diagnosing a “treated rejection” could influence the accuracy of the model. Patients could have been diagnosed with rejection on a clinical basis without obtaining a biopsy, or rejection may have been diagnosed in an asymptomatic patient with normal hemodynamics, but who had a positive biopsy. In addition, some centers might adjust maintenance steroid doses in response to low histological grades of rejection (<2R), whereas a similar biopsy may not result in a change in immunsuppression at a different center.

**SEVERITY AND TYPE OF EARLY REJECTION**

Early rejection could have been mild and treated with a change in maintenance immunsuppression or oral steroids. Early rejection could also have been moderate or severe and treated with high-dose steroids, antithymocyte globulin, plasmapheresis, or intravenous immunoglobulin. Regardless of the type of treatment or severity rejection, all early rejection episodes are the same in the eyes of the risk score. The severity of rejection has significance because mortality 2 years after an episode of rejection with severe hemodynamic compromise was 38%, as reported by Pahl et al. (14) in 2001, and the incidences of rejection with severe hemodynamic compromise and death from rejection have not declined like less severe forms of rejection (10,14,15). In addition, it is important to remember that this model is specific to early rejection. The score does not predict who is at risk for recurrent rejection or late rejection, both of which have been shown to be risk factors for mortality (16,17). The investigators correctly state in the limitations that they could not determine if a patient had ACR or AMR. This limitation is important to
mention because biopsies showing severe AMR (ISHLT grade pAMR) have been associated with increased cardiovascular mortality and a higher risk of developing cardiac allograft vasculopathy (18).

OTHER UNINCORPORATED VARIABLES

Although the R² values for predicted versus expected rejection rates showed a close correlation, there were variables that were not incorporated into the model that could have an impact on an individual’s risk of rejection. One example is a patient’s social environment, which plays a critical role in graft outcomes. It is extremely challenging to accurately incorporate an individual patient’s social environment into a model generated from the OPTN database. An individual patient’s social environment must be taken into account separately from this risk score when generating an overall rejection risk assessment.

NEED FOR VALIDATION IN EXTERNAL COHORTS

We know from the adult experience with risk scores that the predicted risk can be inaccurate in certain subpopulations. One example is the American College of Cardiology/American Heart Association risk model, which has overestimated coronary artery disease risk in multiple cohorts (19). Therefore, to better understand whether the risk prediction tool created by Butts et al. (7) will overestimate or underestimate risk of rejection, this model must be validated in other cohorts. Validation in additional cohorts has the potential for refinement of the risk score by incorporation of variables not included in the risk score, such as the type of induction therapy, the type of maintenance immunosuppression, and the presence of a positive donor-specific cross match. Depending on the validation cohort, it may be possible for risk scores to be simultaneously developed for additional outcomes, such as rejection with severe hemodynamic compromise, recurrent rejection, and/or late rejection, which are endpoints associated with mortality (14,16,17). It may also be possible to develop risk models specifically for ACR, AMR, and mixed rejection, although this requires detailed collection of rejection data and will become more difficult if the rejection rate continues to decline. The PHTS database would be a practical choice for an additional validation cohort, because it would allow for incorporation of additional variables and model different types and severity of rejection. A recent report from the PHTS states that “risk factors analyses and impact on decision-making regarding candidacy for transplantation and post-transplantation outcomes” will be one of its key issues (20). Although a multicenter, prospective study designed specifically to develop a risk score would be the ideal way to prospectively validate the risk model, such a study is unlikely to happen. Although a multicenter clinical trial bears many challenges in the pediatric population, a clinical drug trial in the next 5 to 10 years is possible and would be an excellent opportunity for further evaluation of this model if such a trial becomes a reality.

Pediatric heart transplantation practitioners have learned through experience and registry studies how to incorporate different risk factors to develop a general sense of a patient’s risk of rejection. However, this risk score is the first tool developed to quantify that risk in an individual child. Although the impact of this score on clinical decision-making will likely be small in its current form, we should view it with skeptical optimism. Despite its limitations, this is an excellent first step in the development of a risk score for rejection in a pediatric heart transplantation population. The investigators now face the challenge of making progress on further validation and refinement of the score by incorporating additional variables and modeling the rejection endpoints that are most highly associated with adverse outcomes. Such refinement and validation of the score would provide more confidence in its ability to help tailor rejection surveillance frequency and immunosuppression regimens.

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REFERENCES


