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Have risk factors for mortality after heart transplantation changed over time? Insights from 19 years of Cardiac Transplant Research Database study

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Racial disparities

BACKGROUND: The Cardiac Transplant Research Database (CTRD) collected data from 26 U.S. institutions from January 1, 1990 to December 31, 2008 providing the opportunity for construction of a comprehensive multivariable model of risk for death after transplantation. We analyzed risk factors for death over 19 years of experience to determine how risk profiles have changed over time and how they interact with age.

METHODS: A multivariable parametric hazard model for death was created for 7,015 patients entered into the CTRD. Variables collected over 19 years of experience were examined as potential risk factors and tested for interaction with date of transplantation to determine if their relative risk (RR) changed over time.

RESULTS: The hazard for death post-transplant occurred in 2 phases: an early phase of acute risk lasting <1 year, and a late phase of relatively low, gradually increasing risk (<0.1 event/year). In the early phase, predictive models showed that ventricular assist device (VAD) at the time of transplant did not increase the RR of death for recipient transplant at 30 years of age, but the RR of death was increased by 60% ($p = 0.04$) at 60 years of age. Of the late-phase variables found to be risk factors, the RR of age, date of transplant and pulmonary vascular resistance changed with respect to transplant year. The overall risk of death dropped importantly over the study period, but the RR of all other variables remained unchanged. RR was 2.6 ($p < 0.0001$) for 25-year-old African-American (AA) versus non-AA recipients and 1.6 for 60-year-old AA recipients ($p = 0.02$).

CONCLUSION: Over 19 years, the baseline risk of death has decreased, but the specific risk factors and the magnitudes of their RR have remained unchanged. Therefore, despite advances in clinical management and improvement in overall survival, the risk profile for death after cardiac transplantation is similar to that in 1990.

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Cardiac transplantation is the "gold standard" in the treatment of end-stage heart disease. Improvements in donor management, heart preservation, understanding donor–recipient immunologic mismatches as well as new and evolving immunosuppressive strategies have not only decreased the chances of rejection and allograft loss, but

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they have also minimized long-term morbidity quality of life and long-term survival.[1] The Cardiac Transplant Research Database (CTRD) has been the first, most comprehensive database for heart transplant recipients since its creation in 1990.[2–7] Most of the well-known pre- and post-transplant risk factors associated with poor outcome after heart transplantation in adults have been characterized by CTRD studies, including pre-transplant pulmonary hypertension, renal insufficiency,[2,8] rejection associated with gender mismatch,[3] HLA mismatch[4] and cytomegalovirus (CMV) infection.[5] The CTRD enrolled patients from 26 institutions between January 1, 1990 and December 31, 2008, encompassing 2 decades of data. The purpose of this current study was to determine time-related risk factors for death as a function of transplant year, age and time post-transplantation, in order to answer the question of how risk factors for mortality have changed over 19 years of experience and how specific risk factors for death interact. To accomplish this objective, we constructed parametric multivariable models in the hazard domain to estimate the risk for a given event at any point in time as a function of transplant year and age at time of transplant, while correcting for an array of covariables. The creation of parametric risk models also allows the determination of risk factors for as many as 3 concomitant phases across time.[9] This methodology was used to determine changes in the contribution of specific risk factors across time without assuming a constant risk ratio within a given time interval.

Methods

Patient population

A retrospective analysis was conducted using the CTRD, an event-driven database incorporating follow-up data from 26 institutions. Data collection included, but was not limited to, pre-transplant donor and recipient factors, peri-operative factors and post-transplant characteristics. The demographic variables collected on all patients included age, race, gender, height, weight, body mass index (BMI), pre-transplant heart disease and transplant date. Clinical variables collected included, but were not limited to, detailed history of immunosuppressants and non-immunosuppressant medications, rejection history, including number and severity of treated rejections, lipid levels, presence of diabetes mellitus, hypertension, history of tobacco use, CMV serology and infections. Data were collected on detailed forms at the time of transplantation and at the time of specific clinical events, including diagnosis of infection, rejection, malignancy or death. The forms were then forwarded to the data coordinating and analysis center at the University of Alabama at Birmingham, where the data were entered, corrected and verified as needed. Participating institutions obtained approval from their local institutional review boards for submission of the patient data used in these studies. Data from 7,013 primary orthotopic heart transplants over the age of 18 were collected between January 1990 and December 2008.

Statistical analysis

Descriptive statistics were computed for each variable. Baseline proportions were calculated for discrete variables, and mean ± standard deviation were calculated for continuous variables. Groups were compared using chi-square and *t*-tests, respectively. Outcomes were assessed within groups with paired *t*-testing. $p < 0.05$ was considered significant. Actuarial freedom from events was assessed non-parametrically using the Kaplan–Meier method. To determine time-related risk factors we employed a fully parametric multiphase hazard model.[9] This method was chosen because it allows estimation of the instantaneous risk for a given event at a specific point in time, which has greater utility in the context of this study because it is not limited by assumption of a constant hazard ratio across a time interval, which is a limitation of the semi-parametric Cox regression method. Instead, as we have implemented the approach, a parametric multivariable model can be constructed that allows identification of up to 3 concomitant, but overlapping phases of hazard over time, each encompassing a unique set of risk factors with a continuous distribution (shaping function) of risk. This information can be used to generate nomograms of the estimated risk as a function of time under a given set of initial conditions. For additional details, see http://my.clevelandclinic.org/professionals/software/hazard/default.aspx.

Results

Overall survival and risk factors for death

From 1990 to 2008, follow-up data from a total of 7,013 primary heart transplants at 26 institutions were entered into the CTRD, ultimately encompassing 41,217 patient-years of heart transplant experience. To determine risk factors for death as a function of time, the instantaneous probability of death at a given time (*t*) was calculated as part of a multivariable parametric hazard model incorporating 2 phases (Figure 1). The early-phase hazard for death was predominant from Time 0 (the date of transplant) to 1-year post-transplantation. It was characterized by a period of maximal risk for death occurring nearly immediately

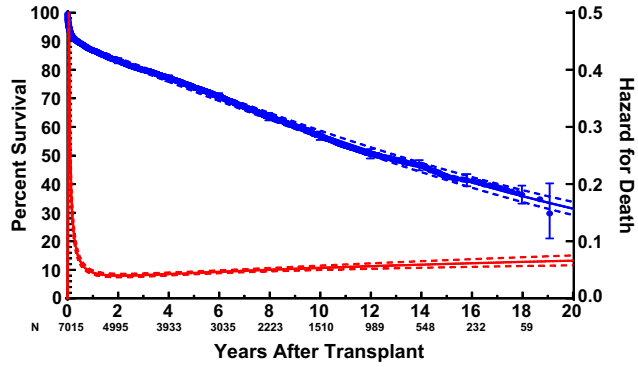

Figure 1 Actuarial survival, predicted survival from the multivariable model, and the hazard for death for all patients included in the study. The closed circles depict actuarial survival by the Kaplan–Meier (product limit) method, with error bars representing standard error of the mean. The solid line superimposed onto the Kaplan–Meier plot shows the predicted survival as determined by the multivariable model, with the dotted line representing the 70% confidence limits of the model. Note that the 2 plots are essentially indistinguishable, indicating that the calculated survival is not significantly different from actuarial survival. The bottom plot shows the hazard for death (right axis) as a function of time.