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Race and ethnic differences in the epidemiology and risk factors for graft failure after heart transplantation

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BACKGROUND: Contemporary epidemiology of chronic graft failure (GF) after heart transplantation (HT) is not well described. Moreover, differences in the epidemiology of GF based on race/ethnicity remain poorly understood, despite clear evidence of inferior survival of ethnic minorities after HT.

METHODS: The incidence of GF and the population-attributable risk (PAR) of independent risk factors for GF were assessed in 15,255 patients (76% men; mean age 52 ± 12 years) who underwent primary HT from 2004 to 2012.

RESULTS: During a median follow-up of 4.7 years (interquartile range, 2.3–7.1 years), GF developed in 2,926 patients (19.2%), corresponding to an incidence rate of 39.8/1,000 person-years (95% confidence interval, 38.4–41.3). Blacks were more likely to develop GF than Hispanics or whites, with incidence rates of 55.1, 42.2, and 36.5/1,000 person-years, respectively. After multivariable adjustment, black race was associated with a higher risk of GF (hazard ratio, 1.4; 95% confidence interval, 1.2–1.6; $p < 0.001$). Blacks and Hispanics were more likely to have risk factors for GF, including low education, public insurance, allosensitization, higher human leukocyte antigen mismatch, non-adherence, and history of rejection requiring hospitalization (all $p < 0.001$). Rejection requiring hospitalization carried the highest population-attributable risk in all groups, with the highest fraction in blacks (25.8%) compared with whites (18.6%) and Hispanics (15.6%). Socioeconomic and donor risk factors conferred relatively less risk of GF.

CONCLUSIONS: Black HT recipients have the highest risk of GF, with immunologic factors conferring the greatest proportion of that risk. Racial differences in risk factors for GF after HT require further study.

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Heart transplantation (HT) remains the therapy of choice for select patients with end-stage heart failure. Median conditional survival now exceeds 10 years for recipients who survive the first year after HT.[1] However, approximately 20% of deaths after the first year are due to graft failure (GF), which often results from processes that include cellular or antibody-mediated rejection and cardiac allograft vasculopathy (CAV).

Despite this overall trend toward improved outcomes after HT, disparities in survival based on race/ethnicity are

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well recognized. Several studies have demonstrated shorter graft and patient survival in HT recipients who are of racial/ethnic minority background.[2–4] The exact mechanisms for these disparities remain unclear; however, suggested explanations include socioeconomic, biological, and immunologic factors.[5,6] Understanding the epidemiology of GF, including the influence of risk factors associated with GF, are imperative to further improve outcomes and bridge disparities after HT. The population-attributable risk (PAR) is often used to describe the proportion of disease risk in a population that can be attributed to the causal effects of a risk factor or set of factors.[7] Thus, our objective for this study was to assess the epidemiology of incident GF by examining the race-related risk factor profile and PAR for GF in a contemporary cohort of HT recipients.

Methods

Study population

All individuals aged $\geq$18 years who were listed for their first HT were identified in the Organ Procurement and Transplantation Network (OPTN) database, which includes deidentified data on all patients listed for a HT in the United States. Analysis was limited to patients listed between June 30, 2004 (when follow-up information on graft status was first reported to the OPTN) and September 2012. The Health Resources and Services Administration and the United States Department of Health and Human Services provide oversight to the activities of the OPTN contractor, the United Network of Organ Sharing.

We compared baseline characteristics of patients listed for primary HT during the study period, excluding patients listed for a repeat HT or for multiorgan transplantation. Race was reported by the transplantation centers as white, black, Hispanic/Latino, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, multiracial, or other. Ethnicity was reported as Hispanic or non-Hispanic. For all Hispanic patients in the study, race and ethnicity variables were identical; therefore, all white patients in this analysis were non-Hispanic white, and all black patients were non-Hispanic black. Because of the small sample size of minority patients with race/ethnicity other than black or Hispanic ($<$4.5% of the sample), these patients were excluded.

Study definitions

Incident graft failure

Follow-up data on HT recipients is provided to the OPTN 6 months after transplant and then annually thereafter. On the follow-up form that is reported annually to the OPTN, transplant centers are asked to document allograft status as "functioning" or "failed." GF is defined as having occurred when "an organ is removed, a recipient dies, or a recipient is placed on a chronic allograft support system."[8] We identified patients with GF that occurred at least 180 days after transplant to attempt to exclude patients with primary allograft dysfunction. Thus, GF includes patients living with allograft dysfunction, patients listed for repeat transplantation, and patients who died or did not have further information regarding their outcome of GF. Patients were monitored from the date of transplant until death, retransplantation, or date of last known follow-up provided by United Network of Organ Sharing, with follow-up through September 2012.

Risk factors for incident graft failure

Clinical, socioeconomic, and immunologic variables were defined at the time of listing for waiting list factors, whereas donor-related variables were defined at the time of transplant, and post-transplantation outcomes were defined at the time of follow-up. Variables compared between race/ethnic groups included clinical (recipient age, gender, creatinine), socioeconomic factors (education, primary insurance payer), immunologic (allosensitization, human leukocyte antigen [HLA] mismatch, non-adherence to medications, any episodes of rejection requiring hospitalization, CAV), and donor (donor age, ischemic time) factors. Transplant centers are asked to document "Was there evidence of non-compliance with immunosuppression medication during this follow-up period that compromised the patient's recovery?" on the annual follow-up form. For the purposes of our analysis, any report of "yes" to this question during the total follow-up period for any patient was considered "non-adherence."

Risk factor definitions for calculation of PAR

For the PAR calculation, continuous predictors that were univariate predictors of GF were dichotomized using clinically relevant cutoff points. Age was dichotomized at the median age of the cohort, education at high school level or less, insurance as public (Medicare, Medicaid, Veterans Affairs) vs private, allosensitization as panel reactive antibody (PRA) level $\geq$10%, HLA mismatch at $\geq$ 5 loci based on the cohort median, ischemic time as $\geq$4 hours,[9] and donor age as $\geq$30 years.[10] Medication non-adherence, history of rejection requiring hospitalization, and presence of CAV were collapsed into binary predictors (yes or no).

Statistical analysis

Continuous variables were compared using the Mann-Whitney rank sum test, and categorical variables were compared using the chi-square test. Cumulative event rates were obtained using the Kaplan-Meier method and were compared using the log-rank statistic. Univariate and adjusted hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were obtained using Cox proportional hazards regression models to identify significant predictors of GF. The proportional hazards assumption was tested and verified for all risk factors using Schoenfeld residual correlation analysis. Subsequently, race/ethnicity-stratified analysis was performed to obtain rate ratio (RR) estimates for the significant risk factors.

We also calculated adjusted (multivariable) PARs using a Poisson regression model with incident GF as the outcome and the factors already described as predictors.[11,12] Briefly, the predicted number of cases is calculated for the full model (N_{full}), which equals the actual number of cases. Next, the effect of the risk factor of interest is "removed" by setting the value of the covariable to 0, and the predicted number of events is calculated ($N_{removed}$). The adjusted PAR for the risk factor then becomes $PAR_{adjusted} = 1 - (N_{removed}/N_{full})$. PARs are not presented if the adjusted RR and corresponding 95% CI for the risk factor failed to reach a p-value of 0.2. Age and gender were included in regression models for multivariable PAR calculation, but the PARs of these variables were omitted from the tables because they cannot be