Impact of Diabetes Mellitus on the Association of Vascular Disease Before Transplantation With Long-term Transplant and Patient Outcomes After Kidney Transplantation: A Population Cohort Study

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Background: Advances in kidney transplantation have led to considerable improvements in short-term transplant and patient outcomes, but there are few data regarding long-term transplant outcomes in patients with vascular comorbid conditions. This study examined the association of vascular disease before transplantation with transplant and patient survival after transplantation and evaluated whether this association was modified by diabetes.

Study Design: All deceased donor kidney transplant recipients recorded in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) for 1990 to 2012.

Predictor: Vascular disease burden.

Outcomes: All-cause mortality and overall transplant loss. Potential interactions between diabetes and vascular disease for mortality and transplant loss were assessed using 2-way interaction terms.

Results: Of 7,128 recipients with 58,120 patient-years of follow-up, 854 (12.0%) and 263 (3.7%) had vascular diseases at 1 and 2 or more sites, respectively. Overall survival for recipients without vascular disease 15 years after transplantation was 65% compared with 35% and 22% among recipients with vascular disease at 1 and 2 or more sites, respectively ($P < 0.001$). Compared with recipients without vascular disease, adjusted HRs for mortality and transplant loss were 1.75 (95% CI, 1.39-2.20; $P < 0.001$) and 1.61 (95% CI, 1.30-1.99; $P < 0.001$), respectively, for recipients with 2 or more vascular diseases. Among recipients without diabetes but with 2 or more vascular diseases, adjusted HRs for mortality and transplant loss were 2.10 (95% CI, 1.56-2.82; $P < 0.001$) and 1.84 (95% CI, 1.39-2.42; $P < 0.001$), respectively, compared with those without vascular disease. Similar associations were not observed for recipients with diabetes mellitus (P for interaction < 0.001).

Limitations: Selection bias and unmeasured residual confounders, such as the severity/extent of comorbid conditions likely to be present.

Conclusions: The impact of vascular disease on long-term outcomes was modified by the presence of diabetes, whereby excess risks for death and transplant loss are more apparent in recipients without diabetes.

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Dialysis patients on the transplant waiting list are at heightened risk for death attributed mainly to vascular disease. The annual vascular-related mortality rate of transplantation candidates on the deceased donor waiting list is >8% and increases with cumulative time on dialysis therapy.[1,2] Although there may be a modest survival advantage with transplantation for those with vascular disease, death from vascular causes remains a significant impediment to improving long-term outcomes after transplantation.[1,3,4] In Australia and New Zealand, cardiovascular disease (CVD) and other vascular diseases contribute to >30% of deaths with a functioning transplant, with similar mortality patterns being observed worldwide.[3,5,6]

Given the higher risk for posttransplantation mortality among transplantation candidates with comorbid conditions, selection criteria are imposed on patients with end-stage kidney disease to be placed on the transplant waiting list. These criteria are to ensure that patients are deemed medically and surgically suitable to undergo and benefit from kidney transplantation. However, guidelines for kidney transplantation suitability vary considerably between countries and jurisdictions, and the level of evidence is currently insufficient to support these recommendations. In Australia, eligibility for deceased donor transplant waitlisting requires an expected survival of at least 80% at 5 years, whereas in other countries, including the United States, Canada, and the United Kingdom, patients with expected survival of 5 years or more or who have a reasonable probability of surviving past the current waiting time for transplantation are eligible for waitlisting.[7,8] These proposals were made without evidence for the long-term expected survival for recipients with coexisting comorbid conditions.

Accurate contemporary data are therefore required to generate quality evidence of the expected short- and long-term survival among kidney transplant recipients with vascular comorbid conditions. The aim of this study was to determine the impact of vascular disease burden on longer-term transplant and patient survival after kidney transplantation and determine whether this association was modified by diabetes.

Methods

Study Population

Primary adult deceased donor kidney transplant recipients 18 years or older in Australia and New Zealand for 1990 to 2012 were included using data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Recipients of multiple organ transplants and those who have received prior transplants were excluded. Approval of the study by the research ethics committee and informed consent were not required because only deidentified information was used for analysis.

Exposure Factor

ANZDATA collects information about the clinical presence, suspicion, or absence of vascular diseases, as per local nephrologist diagnosis, at 3 sites: CVD, peripheral vascular disease (PVD), and cerebrovascular disease. Those who were recorded as having "suspected" disease were recorded as having the disease for the main analyses. Sensitivity analyses excluding recipients with suspected disease were also undertaken. Recipients were categorized according to the number of affected vascular disease sites (ie, the presence of 0, 1, or ≥2 vascular disease sites of CVD and/or PVD and/or cerebrovascular disease). There were no missing data for prevalent vascular disease. ANZDATA does not verify the presence or details of vascular disease reported by each center.

Data Collection

Baseline characteristics recorded by ANZDATA included the following: recipient age, sex, race, body mass index, waiting time pretransplantation, diabetes status, smoking history, and cause of end-stage kidney disease; donor age and type; and immunologic characteristics such as peak percentage panel-reactive antibody and number of HLA antigen mismatches and transplant-related factors, such as total ischemic time, use of induction therapy, transplantation era, and types of initial immunosuppressive agents.

Clinical Outcomes

The primary clinical outcome was all-cause mortality. Secondary outcomes included overall transplant loss, death-censored transplant loss, death with a functioning transplant, and cause-specific mortality (including CVD, infection mortality, cancer, and other vascular disease–related mortality). Other vascular disease mortality included death from cerebrovascular accident, withdrawals resulting from cerebrovascular or PVD-related comorbid conditions, pulmonary embolus, bowel infarction, and ruptured aortic aneurysm.

Statistical Analyses

Baseline characteristics were expressed as number and proportion, mean ± standard deviation, and median with interquartile range, when appropriate. Comparisons of baseline characteristics and clinical outcomes between vascular diseases were made by χ^2 test and analysis of variance for categorical and continuous variables, respectively. Mortality rates with 95% confidence intervals (CIs) between 0 and 1, more than 1 and 5, and more than 5 and 10 years according to vascular disease were calculated and expressed per 100 recipients. Patient and transplant survival at 5, 10, 15, and 20 years according to vascular disease status were calculated using Kaplan-Meier methods. Associations between vascular disease and outcomes were examined using multivariable Cox proportional hazards regression analyses. The proportional hazards assumptions of all Cox regression models were checked graphically by plotting Schoenfeld residuals, with no evidence of departures from proportional hazards. Covariates associated with each clinical outcome with $P < 0.10$ in unadjusted analyses were included in multivariable-adjusted analyses, although donor age, recipient age, race, and transplantation era were included in all models because of their established relationship with these outcomes. Results were expressed as hazard ratio (HR) with 95% CI. Potential effect modifications between vascular disease and diabetes or transplantation era were examined for each clinical outcome using 2-way interaction terms in multivariable-adjusted models.

Competing-Risk Analyses

Competing-risk regression analyses were also undertaken for death-censored transplant loss, death with a functioning transplant, and cause-specific mortality by taking into account the informative nature of censoring due to competing risk. Associations between vascular disease and these outcomes were examined using multivariable subdistribution hazards models.[9] Developments of the clinical outcomes over time, cumulative incidence functions, were investigated using the method of Fine and Gray.[10] Results were expressed as subdistribution HR with 95% CI. The Fine and Gray models were checked graphically by plotting Schoenfeld residuals, without evidence of departures from proportionality. Covariates included in the competing-risk models were identical to those adjusted for in the Cox regression models.

Sensitivity Analyses

Sensitivity analyses were conducted to examine associations between vascular disease and outcomes following exclusion of recipients with suspected (ie, unconfirmed) vascular disease and following separation of specific sites of vascular disease. All analyses were undertaken using SPSS, version 10, statistical software program (SPSS Inc) and Stata (version 11; StataCorp LP).

Results

Study Population

Of 7,128 recipients included, 6,011 (84.3%) had no recorded vascular disease at the time of transplantation,