Delayed Graft Function and the Risk of Death With Graft Function in Living Donor Kidney Transplant Recipients

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Background: The link between delayed graft function (DGF) and death with graft function (DWGF) in living donor kidney transplant recipients presently is unknown.

Study Design: Retrospective cohort study.

Setting & Participants: 44,630 adult living donor kidney recipients (first transplants only) in the US Renal Data System from January 1, 1994, to December 31, 2004.

Predictor: DGF, defined as the need for dialysis therapy in the first week after transplant.

Outcome: Time to DWGF.

Measurements: Kaplan-Meier curves were constructed to assess the impact of DGF on DWGF. Recipients with DGF were 1:1 propensity score matched to those without DGF, and time-dependent Cox proportional hazards models were used to examine factors associated with DWGF. Subgroup and sensitivity analyses also were conducted.

Results: DWGF occurred in 3,878 patients during 3.9 years' (median) follow-up. In patients with DGF, survival with graft function at 1, 3, 5, and 10 years was 91.9%, 86.8%, 81.6%, and 61.7%, respectively (in patients without DGF, these values were 98.0%, 95.2%, 91.6%, and 80.1%, respectively; $P < 0.001$ compared with the DGF group). In a fully adjusted time-dependent Cox model, HRs for DWGF in patients with DGF (vs without DGF) were 6.55 (95% CI, 4.78-8.97), 3.55 (95% CI, 2.46-5.11), 2.07 (95% CI, 1.53-2.81), and 1.48 (95% CI, 1.26-1.73) at 0-1, 1-3, 3-12, and longer than 12 months posttransplant, respectively. Propensity score analysis showed similar results. Inferences were unchanged after adjustment for kidney function and acute rejection at 6 months and 1 year posttransplant. Cardiovascular and infectious causes of DWGF were more prevalent in patients with DGF. The association was more marked in female recipients and robust to various sensitivity analyses.

Limitations: The impact of lesser decreases in early graft function could not be evaluated.

Conclusions: DGF is associated with an increased risk of DWGF in living donor kidney recipients. The mechanisms underlying this relation require further study.

Am J Kidney Dis 56:961-970.

INDEX WORDS: Delayed graft function; kidney transplant; living donor; survival.

It is widely accepted that kidney transplant offers greater longevity in patients with end-stage renal disease (ESRD) compared with dialysis therapy.[1] Moreover, living donor kidney transplants are associated with more favorable transplant and patient outcomes than deceased donor kidney transplants.[2,3] Despite the decrease in mortality in patients with ESRD after transplant, survival of kidney recipients remains inferior to that in the general population.[4] Since death with graft function (DWGF) accounts for up to 50% of all graft losses,[5-8] strategies that reduce the risk of DWGF likely will improve outcomes.

The negative influence of delayed graft function (DGF) on the survival of deceased donor kidney transplant recipients has been well established.[9] DGF in living donor kidney transplant recipients has received less attention. The incidence of DGF in these patients is approximately 4%-10% compared with 2%-50% for deceased donor kidney recipients.[10] DGF may increase the risk of acute rejection in living donor kidney recipients, but it appears to have only a modest impact on the risk of graft failure.[11,12] Unlike deceased donation, factors such as brain death,

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Received February 21, 2010. Accepted in revised form June 25, 2010. Originally published online as doi:10.1053/j.ajkd.2010.06.024 on September 27, 2010.

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0272-6386/10/5605-0020$36.00/0
doi:10.1053/j.ajkd.2010.06.024

cardiopulmonary arrest, inotropic/vasopressor support, and prolonged cold ischemia time are either irrelevant or have a minor role in determining early graft function in living donor donation.

In an analysis of national registry data from 1988-1997, Ojo et al[6] identified DGF as an independent risk factor for DWGF. We recently have confirmed and further explored this relation in a contemporary cohort of deceased donor kidney recipients.[13] The primary aim of the present study is to determine the association of DGF and DWGF in living donor kidney recipients. In light of the potential for confounding, both conventional and propensity score models were used to estimate the DGF-DWGF relation in this patient population. Secondary aims include examination of cause-specific DWGF and evaluation of prespecified subgroups.

METHODS

Setting and Participants

This is a retrospective cohort study using the US Renal Data System (USRDS). All adult patients with ESRD who received living donor kidney transplants in the United States from January 1, 1994, to December 31, 2004, (followed up until June 30, 2005) were eligible for study inclusion. Exclusion criteria included: (1) age younger than 18 years, (2) multiorgan transplant recipients (including kidney-pancreas), (3) retransplants, (4) deceased donor kidney recipients, and (5) kidney transplants that never functioned (ie, primary nonfunction). The Research Ethics Board at the Toronto General Hospital, University Health Network, approved the study.

Exposure and Outcome Measurements

The exposure of interest was the development of DGF posttransplant. DGF was defined in the USRDS as the need for at least 1 dialysis session within the first week after kidney transplant. The outcome of interest was DWGF, defined as graft failure due to patient death. This was ascertained in the USRDS by identifying individuals for whom dates of death and graft failure were identical. Graft failures not caused by patient death were censored.

Potential Confounders

The following potential confounders were examined in multivariable statistical models: (1) recipient factors (ie, age, sex, race, cause of ESRD, peak panel-reactive antibody level, body mass index [kg/m^2], and time on dialysis therapy before transplant); (2) donor factors (ie, age, sex, race, and preoperative serum creatinine level); and (3) transplant factors (ie, cold ischemia time, number of HLA antigen mismatches, type of induction therapy, and transplant year). Moreover, adjustments for estimated glomerular filtration rate (eGFR) based on the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation at 6 months and 1 year were made to account for the influence of achieved kidney function on the association of DGF and DWGF. Patients with missing data for recipient/donor sex, recipient race, time on dialysis therapy, or DGF status were excluded (158 individuals [0.35% of the initial cohort]).

Additional Analyses

The relation between DGF and DWGF was examined in prespecified patient subgroups. In addition, the following sensitivity analyses were performed: (1) adjustment for baseline comorbid conditions at dialysis therapy initiation (from the Centers for Medicare & Medicaid Services [CMS] 2728 form), (2) adjustment for type of immunotherapy at the time of hospital discharge, (3) adjustment for clustering by transplant center, (4) exclusion of pre-emptive kidney transplants, (5) cohort restriction to "low-risk" transplant candidates (ie, age $<$50 years, cause of ESRD other than diabetes or hypertension, and waiting time $\leq$2 years), and (6) alternate definitions of DWGF that include deaths occurring within 1, 2, 7, or 30 days after transplant loss.

Statistical Analysis

Frequencies within categories of each study variable and their distributions were compared across DGF groups. Time to DWGF, stratified by DGF status, was assessed using the Kaplan-Meier method, and differences across survival curves were evaluated using the log-rank test.[14] Risk of DWGF in patients with versus without DGF was modeled in a Cox proportional hazards regression analysis, adjusting for potential confounders.[15] Because a violation of the proportional hazards assumption was noted in the first year posttransplant, a time-dependent Cox model was fitted by partitioned follow-up time into periods when the assumption was not violated (ie, 0-1, 1-3, 3-12, and $>$12 months).

To improve comparability between DGF groups, a multivariable logistic regression model was used to generate a propensity score for each individual in the data set.[16] All covariates listed in Table 1 were included in the model. Propensity scores subsequently were used to optimally match a patient with and a patient without DGF with similar probabilities of developing DGF.[17] A caliper width of 0.015 was used (which represents the maximal allowable "distance" in propensity scores for each pair), and non-DGF kidney recipients were sampled without replacement. The effectiveness of bias reduction was assessed using the absolute standardized difference, expressed as a percentage of the pooled standard deviation.[18] A value closer to zero for a given baseline characteristic indicates greater balance in the distribution of that characteristic across the DGF and non-DGF groups.

Heterogeneity of the DGF-DWGF association across prespecified subgroups was examined using interaction terms in the Cox model conditional on 1-year transplant survival. A similar strategy was used to determine the impact of acute rejection by 6 months and 1 year posttransplant on the relation between DGF and DWGF in models conditional on 6-month and 1-year transplant survival, respectively. Adjustment for clustering by transplant center was achieved using the robust variance estimator of Lin and Wei.[19] All statistical