Mortality and Allograft Loss Trends Among US Pediatric Kidney Transplant Recipients With and Without Focal Segmental Glomerulosclerosis

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Background: Pediatric patients with focal segmental glomerulosclerosis (FSGS) have high rates of disease recurrence and allograft failure after kidney transplantation, but there are few data for long-term survival posttransplantation.

Study Design: Retrospective cohort study.

Setting & Participants: 12,303 pediatric patients (aged <18 years), including 1,408 (11%) patients with FSGS, who received a first kidney transplant in 1990 through 2009 and were followed up through June 2015 were identified from the US Renal Data System database.

Predictors: Primary cause of end-stage renal disease, FSGS or other.

Outcomes: All-cause patient mortality and allograft loss.

Results: All-cause mortality significantly improved for patients with FSGS who underwent transplantation in the 2000s versus the 1990s (6.72 vs 12.24 deaths/1,000 patient-years; HR, 0.55; 95% CI, 0.39-0.78; $P < 0.001$). Reductions in allograft loss were less dramatic (75.91 vs 89.05 events/1,000 patient-years; HR, 0.85; 95% CI, 0.74-0.98; $P = 0.02$). After adjusting for baseline characteristics at the time of transplantation, patients with FSGS had similar rates of death compared with patients without FSGS (HRs of 0.81 [$P = 0.6$] and 1.06 [$P = 0.2$] among those who underwent transplantation in the 2000s and 1990s, respectively) despite higher rates of allograft loss (HRs of 1.17 [$P = 0.03$] and 1.27 [$P < 0.001$], respectively). Among patients who underwent transplantation in the 2000s, further adjustment for allograft failure as a time-varying covariate demonstrated a lower rate of death among patients with FSGS compared with those without FSGS (HR, 0.70; $P = 0.02$).

Limitations: Lack of information about certain risk factors for mortality, including duration of chronic kidney disease; missing data; and potential primary disease misclassification.

Conclusions: Survival of pediatric kidney transplant recipients with FSGS improved between the 1990s and 2000s and was similar to that of recipients without FSGS. Interestingly, adjustment for allograft failure showed greater survival for pediatric patients with FSGS who underwent transplantation in the 2000s as compared with others, suggesting that effective interventions to decrease allograft loss due to disease recurrence may improve patient survival.

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Focal segmental glomerulosclerosis (FSGS) is one of the top causes of end-stage renal disease (ESRD) in children and the third most common diagnosis among US pediatric kidney transplant recipients.[1,2] Posttransplantation treatment of children with FSGS is complicated by primary disease recurrence in 15% to 64% of patients,[3-8] which has been linked to increased risk for allograft loss.[9-11] Allograft loss and return to dialysis therapy is one of the most important risk factors for mortality.[12,13]

Data for long-term survival of pediatric kidney transplant recipients with ESRD secondary to FSGS are limited. Despite the added complexity of this disease, a study using the North American Pediatric Renal Transplant Cooperative database found no difference in survival between pediatric kidney transplant recipients with and without FSGS at 5 years.[11] Similarly, an analysis of the US Renal Data System (USRDS) database of pediatric patients who underwent transplantation from 1983 through 2006 showed similar mortality rates between patients with FSGS and those with congenital anomalies of the kidney and urinary tract.[12] These results contrast with findings in adults: using the USRDS database, a study found that patients with FSGS have increased rates of death compared with patients with ESRD secondary to autosomal dominant polycystic kidney disease, a primary kidney disease that does not recur.[14] One explanation for the difference in results is that the USRDS study in adults included patients who underwent transplantation within a 16-year period (1996 through 2011), but the pediatric USRDS study used a 24-year period, which may have concealed changes in mortality risk over time, particularly because outcome reporting was less reliable in the 1980s in the USRDS database.[15]

In this study, we described time trends of all-cause mortality in pediatric kidney transplant recipients with ESRD secondary to FSGS (FSGS-caused ESRD) compared with those with other causes of ESRD (other-caused ESRD) over 2 decades: 1990 through 1999 and 2000 through 2009. We also examined time trends of allograft loss in patients with FSGS-caused ESRD and other-caused ESRD and the impact of allograft loss on patient survival. We hypothesized that rates of allograft loss and all-cause mortality for all patients improve during the 2 decades,

and that patients with FSGS-caused ESRD have higher rates of death in part due to higher rates of allograft loss. Our goal is to gain a more complete understanding of the long-term morbidity and mortality of childhood FSGS that results in ESRD and transplantation.

Methods

Data Sources and Study Population

We obtained data from the USRDS database for patients who received a first kidney transplant before the age of 18 years from 1990 through 2009 and were followed up through June 30, 2015, to ensure a minimum follow-up of 5 years. The earliest inclusion time point of 1990 was selected due to improvements in the completeness and validity of outcome reporting within the USRDS database after the 1980s.[15] The USRDS Standard Analytic Files (SAF).PATIENTS, SAF.MEDEVID, SAF.WAITLIST_KI, SAF.TX, and SAF.DEATH were used. Variables included in the USRDS files, as well as the data collection methods and validation, are listed on the USRDS website (www.usrds.org). Patients who did not have a listed cause of ESRD under the USRDS variable "PDIS" (primary disease causing ESRD) were excluded (n = 680). Additionally, those with a history of nonkidney organ transplantation or simultaneous dual-organ transplantation were also excluded (n = 313). The total number excluded was 993 patients of 13,296 (7.5%). Patients were followed up from the time of first kidney transplantation until death or June 30, 2015.

Outcomes and Variables

Our outcomes included: (1) patient death, from date of first kidney transplantation to death, censored by end of study follow-up on June 30, 2015; and (2) allograft failure censored by death or end of study follow-up, with the premise that death is a noninformative event for allograft failure. Outcomes were determined for patients who underwent transplantation during the 2 different times, 1990 through 1999 and 2000 through 2009.

Primary cause of ESRD, stratified into FSGS-caused ESRD and other-caused ESRD, was the main exposure. We defined the cohort with FSGS-caused ESRD using the codes 5811 and 5811Z (focal glomerulonephritis/focal glomerulosclerosis with nephrotic syndrome); 5818Z (focal glomerulosclerosis with nephrotic syndrome); 5819 and 5819Z (nephrotic syndrome/nephrosis); 5821 (focal glomerulonephritis, focal sclerosing glomerulonephritis); 5821A, 5821Y, and 5821Z (focal glomerulosclerosis, focal sclerosing glomerulonephritis); and from the variable "PDIS" in the USRDS core data set. A prior validation study determined that selection of a specific glomerular disease subtype had a high positive predictive value (>90%) but low sensitivity (≤30%).[16] Thus, codes representing the main clinical manifestations of FSGS, nephrotic syndrome/nephrosis (5819 and 5819Z), were included. All other patients were defined as having other-caused ESRD.

Covariates in our analyses included age at first kidney transplantation (0-5, 6-11, or 12-17 years), sex, race (white, black, other, or unknown), ethnicity (Hispanic, non-Hispanic, or unknown), and duration of dialysis therapy before transplantation (preemptive kidney transplantation, <6 months, 7-12 months, or >1 year).

Statistical Methods

Patient demographic and clinical characteristics at the time of kidney transplantation were described by frequencies and percentages for categorical variables. Chi-square tests were used to examine differences between baseline characteristics among patients with FSGS-caused and other-caused ESRD, stratified by decade of first kidney transplantation. We computed rates of all-cause mortality and allograft loss from the number of events and person-time observed. Kaplan-Meier plots were created to depict unadjusted estimates of patient and allograft survival, stratified by primary cause of ESRD and time period when kidney transplantation first took place. As sensitivity analysis, time periods were stratified into 5-year periods: 1990 through 1994, 1995 through 1999, 2000 through 2004, and 2005 through 2009. The unadjusted effect of the time period of first kidney transplantation (1990 through 1999 vs 2000 through 2009) on mortality and allograft survival was examined by Cox proportional hazards analyses, stratified by cause of ESRD.

Cox proportional hazards models were used to examine the relationship between primary cause of ESRD and (1) all-cause mortality and (2) allograft failure, stratified by time period of first kidney transplantation. For the outcome of all-cause mortality, time-to-event analysis started at the date of the first kidney transplantation until the date of death, censored for the end of the study period. Model 1 was the unadjusted model including primary cause of ESRD. Model 2 included additional baseline clinical and demographic characteristics at the time of first kidney transplantation: age at first kidney transplantation, sex, race, ethnicity, and duration of dialysis therapy before transplantation. In model 3, we added to model 2 allograft failure as a time-varying variable to examine whether associations between primary cause of ESRD and patient mortality were potentially mediated by allograft failure. Dialysis modality (hemodialysis vs peritoneal dialysis) and the interaction term age at first kidney transplantation × duration of dialysis therapy before transplantation were not included in the models because they did not significantly change model estimates of the primary predicator (primary cause of ESRD) and did not have $P < 0.05$. For allograft failure, time-to-event analysis started at the date of the first kidney transplantation until allograft failure, censored for death or end of the study period. Models 1 and 2 were performed as described for unadjusted and adjusted hazard ratios (HRs).

Missing data were found for the covariates race (n = 426 [3%]) and ethnicity (n = 2,547 [21%]), shown in Table 1,