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

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Abstract

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 on long-term survival post-transplantation.

Study Design—Retrospective cohort study.

Setting & Participants—12,303 pediatric patients (age <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 (ESRD), FSGS or other.

Outcomes—All-cause patient mortality and allograft loss.

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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 per 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 per 1,000 patient-years; HR, 0.85; 95% CI, 0.74–0.98; $p = 0.02$). After adjusting for baseline characteristics at time of transplantation, patients with FSGS had similar rates of death compared to 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 to those without FSGS (HR, 0.70; $p = 0.02$).

Limitations—Lack of information on 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 the 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 to others, suggesting that effective interventions to decrease allograft loss due to disease recurrence may improve patient survival.

Index Words

focal segmental glomerulosclerosis (FSGS); segmental glomerulosclerosis; pediatrics; child; infant; adolescent; mortality; graft survival; kidney transplantation; transplant outcomes; end-stage renal disease (ESRD); USRDS; renal transplant recipient

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} Post-transplantation treatment of children with FSGS is complicated by primary disease recurrence in 15%–64% of patients^{3–8}, which has been linked to increased risk for allograft loss^{9–11}. Allograft loss and return to dialysis is one of the most important risk factors for mortality^{12,13}.

Data on long-term survival of pediatric kidney transplant recipients with ESRD secondary to FSGS is 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 years¹¹. 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 tract¹². These results contrast with findings in adults: using the USRDS database, a study found that patients with FSGS have increased rates of death compared to patients with ESRD secondary to autosomal dominant polycystic kidney disease, a primary kidney disease that does not recur¹⁴. 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 as outcome reporting was less reliable in the 1980s in the USRDS database¹⁵.

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 to those with other causes of ESRD (other-caused ESRD) over two decades: 1990–1999 and 2000–2009. We also examined the 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 over 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 on 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 duration 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 1980s¹⁵. 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 non-kidney organ transplantation or simultaneous dual organ transplantation were also excluded (n=313). Total number excluded was 993 patients of 13,296 (7.5%). Patients were followed up from 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 two different time periods, 1990–1999 and 2000–2009.

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 GN); 5821A, 5821Y, and 5821Z (focal glomerulosclerosis, focal sclerosing GN) and from the variable “PDIS” (primary disease causing ESRD) in the USRDS core dataset. 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 prior to transplantation (pre-emptive kidney transplantation, <6 months, 7–12 months, or 1 year).

Statistical Methods

Patient demographic and clinical characteristics at time of kidney transplantation were described by frequencies and percentages for categorical variables. Chi-square tests were used to examine the 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 a sensitivity analysis, time periods were stratified into 5-year periods: 1990–1994, 1995–1999, 2000–2004, and 2005–2009. The unadjusted effect of the time-period of first kidney transplantation (1990–1999 versus 2000–2009) 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 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 prior to 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 was potentially mediated by allograft failure. Dialysis modality (hemodialysis versus peritoneal dialysis) as well as the interaction term age at first kidney transplantation*duration of dialysis prior to transplantation were not included in the models as they did not significantly change the model estimates of the primary predictor (primary cause of ESRD), nor had a p of <0.05. For allograft failure, time-to-event analysis started at the date of first kidney transplantation until allograft failure, censored for death or the end of the study period. Models 1 and 2 were performed as described above for unadjusted and adjusted hazard ratios (HRs).

Missing data were found for the covariates race ($n=426$ [3%]) and ethnicity ($n=2547$ [21%]), shown in Table 1, which were grouped as “other” and “non-Hispanic” categories in the Cox regression models, respectively. Complete case analysis was performed. SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for all statistical analyses. This study was approved

by the Emory University Institutional Review Board with waiver of informed consent as the USRDS database contains only de-identified information.

Results

Patient Characteristics

The study cohort was assembled as summarized in Figure 1. A total of 12,303 pediatric patients underwent transplantation from 1990 through 2009, with 5527 patients in the decade 1990–1999 and 6776 patients in the decade 2000–2009. The number of patients with FSGS-caused ESRD included 558 (10%) in 1990–1999 and 850 (13%) in 2000–2009. Baseline demographic and clinical characteristics at time of transplantation are presented in Table 1. Patients with FSGS-caused ESRD compared to other-caused ESRD tended to be significantly older at time of transplantation ($p < 0.001$ for both patients who underwent transplantation in the 1990s and the 2000s) and more equal in male to female distribution ($p = 0.005$ and $p = 0.009$ among those having transplantation in the 1990s and 2000s, respectively). There was a significantly greater proportion of black patients in those with FSGS-caused ESRD (31.72% vs. 16.10% and 34.35% vs. 16.84% among those having transplantation in the 1990s and 2000s, respectively). In the 2 decades, patients with FSGS were also significantly less likely to have undergone preemptive transplantation (24.55% vs. 38.00% and 10.47% vs. 28.10%, respectively) and had longer dialysis duration prior to transplantation (32.80% vs. 29.10% and 48.18% vs. 42.12%, respectively, were dialyzed for 1 year). Comparisons of patients across the 2 decades showed greater proportions of patients with “unknown” race and ethnicity classification in the 1990s. The proportion of patients who underwent pre-emptive transplantation decreased in the later decade, and correspondingly, the duration of dialysis prior to transplantation increased.

Time Trends in All-Cause Mortality and Allograft Failure

Median follow-up was 19.04 (interquartile range [IQR], 16.52–21.96) years and 9.83 (IQR, 7.56–12.36) years for patients transplanted between 1990–1999 and 2000–2009, respectively. Death rate improved over the two decades for both patients with FSGS-caused ESRD and other-caused ESRD. In patients with FSGS-caused ESRD, death rate improved from 12.24 deaths per 1,000 patient-years among those who underwent transplantation in the 1990s to 6.72 deaths per 1,000 patient-years among those received a transplant in the 2000s (HR, 0.55; 95% confidence interval [CI], 0.39–0.78; $p < 0.001$). Similarly, in patients with other-caused ESRD, death rate improved from 9.61 to 5.94 deaths per 1,000 patient-years (HR, 0.62; 95% CI, 0.54–0.71; $p < 0.001$).

Allograft survival also improved over the two decades for both patients with FSGS-caused ESRD and other-caused ESRD, although the change was smaller in magnitude, particularly for patients with FSGS. Allograft failure rate for FSGS-caused ESRD was 89.05 versus 75.91 events per 1,000 patients-years among those who underwent transplantation in the 1990s and 2000s, respectively (HR, 0.85; 95% CI, 0.74–0.98; $p = 0.02$). In patients with other-caused ESRD, allograft failure rate improved from 62.29 to 48.03 events per 1,000 patient-years (HR, 0.77; 95% CI, 0.73–0.82; $p < 0.001$).

Crude patient and allograft survival for patients with FSGS-caused ESRD and other-caused ESRD are presented in Figures 2 and 3. Survival probabilities are shown in Table S1.

Association Between ESRD Cause and Mortality

Patients with FSGS-caused ESRD who underwent transplantation in the 1990s had a 29.7% increase in mortality compared to patients with other-caused ESRD who had transplantation in the same period (HR, 1.297; 95% CI, 1.072–1.554; $p=0.01$), shown in the unadjusted Model 1, Table 2. Among patients who underwent transplantation in the 2000s, this differential risk is no longer seen (HR, 1.133; 95% CI, 0.843–1.523; $p=0.4$). Adjustments for baseline characteristics at time of transplantation (age at first kidney transplantation, sex, race, ethnicity, and duration of dialysis prior to transplantation) eliminated the differential risk for death between patients with FSGS-caused ESRD and all others who underwent transplantation in either decade (Model 2, Table 2). When allograft failure was entered into the model as a time-varying covariate, the risk of mortality among patients with FSGS-caused ESRD compared to others further decreased. In this fully adjusted model, patients with FSGS-caused ESRD who underwent transplantation in the 2000s had a statistically significant 30% reduction in mortality compared to other patients who had transplantation in the same decade (Model 3, Table 2).

Association Between ESRD Cause and Allograft Failure

Allograft failure was significantly higher for patients with FSGS-caused ESRD compared to patients with other-caused ESRD, regardless of the time period of transplantation. Among those who underwent transplantation in the 1990s, patients with FSGS-caused ESRD had a 37% increase in allograft loss compared to other-caused ESRD (HR, 1.37; 95% CI, 1.24–1.52; $p<0.001$). Interestingly, the magnitude of difference is even greater among those who had transplantation in the 2000s, with an increased allograft loss of 64% as shown in Model 1, Table 2 (HR, 1.64; 95% CI, 1.48–1.81; $p<0.001$). The differential risk is found even after adjustments for baseline characteristics (Model 2, Table 2).

Sensitivity analysis of patient and allograft survival with the cohort stratified by 5-year time periods showed similar trends over time (Table S2 and Figures S1 and S2). Complete-case analysis excluding patients with missing race or ethnicity information ($n=2777$) showed similar associations and HR estimates for both mortality and allograft loss (Table S3).

Discussion

This study was a large retrospective analysis of 12,303 pediatric patients, including 1,408 with FSGS-caused ESRD, who received a first-time kidney transplant between 1990 and 2009 in the United States. We found that pediatric patients who underwent transplantation in the more recent decade had improved survival compared to those who had transplantation in the 1990s. Long-term mortality rates among those who had transplantation in the 2000s were similar between those with FSGS-caused ESRD and other-caused ESRD, despite consistently worse allograft survival among patients with FSGS. When adjusted for the presence of allograft loss, pediatric patients with FSGS who had transplantation in the 2000s had lower mortality risk compared to other patients who underwent transplantation during

the same period, suggesting that allograft loss played a significant role in the survival of patients with FSGS during this era.

Previous research has highlighted the increased morbidity of FSGS-caused ESRD. In both adults and children, FSGS is associated with increased rates of disease recurrence and allograft loss^{3-11,17,18}. In our study of patients younger than 18 years, we confirmed that FSGS was significantly associated with increased allograft failure rates, although we were unable to ascertain the cause of allograft failure and whether primary disease recurrence contributed to increased allograft failure rates due to limits of the USRDS database. Even though allograft survival improved in pediatric patients with FSGS who underwent transplantation in the 2000s compared to the 1990s, patients with FSGS continued to have significantly worse allograft survival relative to other pediatric patients who had kidney transplantation. In fact, the differential risk for allograft survival between patients with and without FSGS was even more prominent among those who underwent transplantation in the 2000s, with negative implications for patient well-being. This suggests that up to the 2000s there were not yet significant advances in the treatment of FSGS-specific risks for allograft failure, of which primary disease recurrence is likely a major cause. In fact, in an analysis examining risk factors for allograft loss comparing patients with versus without FSGS, recurrence of primary disease was the only cause of allograft failure that differed between the two groups¹¹.

Data on long-term survival of pediatric patients with FSGS post-transplantation is much more limited. A large scale study of pediatric kidney transplant recipients using the USRDS database found patients with FSGS to have similar mortality risk as patients with congenital anomalies of the urinary tract¹². In that study, the cohort included incident transplantation patients between 1983 to 2006, a large time-span during which data collection changed significantly within the USRDS¹⁵. We restricted our analysis to patients who underwent transplantation starting from 1990 through 2009 to reduce issues of data incompleteness, which was more common in the 1980s. We further stratified our analysis by decades in which the first kidney transplantation occurred, to ascertain time trends in mortality. We found that patients with FSGS had similar mortality risk compared to all others after adjustment for clinical and demographic characteristics. We had predicted patients with FSGS would have worse survival due to the high risk of disease recurrence. This unexpected finding is good prognostic information for young patients afflicted with this disease. In fact, when we further adjusted for allograft failure, we found that among patients who underwent transplantation in the 2000s, patients with FSGS had significantly lower rates of mortality compared to others. This suggested that allograft loss is a potential mediator of patient survival in FSGS, and that a focus on interventions to decrease allograft loss due to disease recurrence may improve patient survival.

Our study had important limitations. First, important risk factors for mortality such as duration of chronic kidney disease and treatments provided, comorbid conditions, body mass index, and income status could not be assessed due to the lack of these details from the early USRDS data. Because the most common causes of ESRD in children are congenital diseases, which have a slower progression to ESRD than FSGS², the duration of chronic kidney disease and its management prior to transplantation may be particularly important to

study for a more complete understanding of the factors important to mortality. Second, racial and ethnicity data were less complete for the patients who underwent transplantation in the 1990s. Our sensitivity analyses, which employed complete case analysis for the missing data, did not result in different findings. Finally, errors of coding in our main predictor variable, primary cause of ESRD, may affect the validity of our analyses. Layton *et al* reported high positive predictive value of >90% but low sensitivity of 30% of using the USRDS for the selection of a specific glomerular disease subtype¹⁶. We included two codes (5819 and 5819Z) that describe the principal manifestations of FSGS, nephrotic syndrome/nephrosis, to increase the sensitivity of identifying the FSGS cohort. These two codes identified 19 patients out of 1,408 (0.7%). Although FSGS is the primary histologic subtype in nephrotic syndrome to cause ESRD², there is a possibility that a portion of the 19 patients do not have histologic FSGS.

Notwithstanding the limitations of our study, the present analysis adds crucial information on long-term patient and allograft survival as well as changes over time using one of the largest cohort of pediatric patients with FSGS in the United States. Further delineating the underlying risk factors for mortality in patients with FSGS will require prospective studies with clearly defined disease cohorts, more complete descriptors of patient characteristics, and details of disease management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Derivation of cohort of pediatric patients <18 years of age from the USRDS database who received a first kidney transplant in 1990 through 2009. FSGS, focal segmental glomerulosclerosis.

Figure 2. Kaplan-Meier survival plots of allograft survival by primary cause of ESRD and time-period of first kidney transplantation among pediatric kidney transplant recipients. ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis

Figure 3. Kaplan-Meier survival plots of patient survival by primary cause of ESRD and time-period of first kidney transplantation among pediatric kidney transplant recipients. ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis

Table 1

Characteristics of pediatric incident kidney transplant recipients 1990 through 2009 by primary cause of ESRD

Characteristic	1990–1999 (n=5527)			2000–2009 (n=6776)		
	FSGS (n=558)	Other causes (n=4969)	P*	FSGS (n=850)	Other causes (n=5926)	P*
Age at Tx			<0.001			<0.001
0–5 year	10.29 (57)	20.90 (1030)		9.20 (78)	22.26 (1316)	
6–11 years	30.14 (167)	25.81 (1272)		24.65 (209)	23.08 (1364)	
12–17 years	59.57 (330)	53.29 (2626)		66.16 (561)	54.66 (3231)	
Sex			0.005			0.009
Male	53.76 (300)	59.91 (2977)		54.12 (460)	58.83 (3486)	
Female	46.24 (258)	40.09 (1992)		45.88 (390)	41.17 (2440)	
Race			<0.001			<0.001
White	57.71 (322)	69.49 (3453)		58.12 (494)	73.30 (4344)	
Black	31.72 (177)	16.10 (800)		34.35 (292)	16.84 (998)	
Other	3.94 (22)	6.58 (327)		7.18 (61)	9.11 (540)	
Missing	6.63 (37)	7.83 (389)		0.35 (3)	0.74 (44)	
Ethnicity			0.7			0.9
Non-Hispanic	49.10 (274)	44.44 (2208)		76.00 (646)	73.74 (4370)	
Hispanic	8.42 (47)	9.08 (451)		23.53 (200)	23.37 (1385)	
Missing	42.47 (237)	46.49 (2310)		0.47 (4)	2.89 (171)	
Dialysis duration before Tx			<0.001			<0.001
Pre-emptive Tx	24.55 (137)	38.00 (1888)		10.47 (89)	28.10 (1665)	
<6 months	20.25 (113)	17.47 (868)		19.41 (165)	14.98 (888)	
6–12 months	22.40 (125)	15.44 (767)		20.94 (178)	14.80 (877)	
1 years	32.80 (183)	29.10 (1446)		49.18 (418)	42.12 (2496)	

Note: Values are given as number (percentage)

* Univariate analyses were performed with Chi-square test for categorical variables.

ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; Tx, transplantation

Table 2

Hazard ratios for all-cause mortality and allograft loss in pediatric kidney transplant patients, comparing FSGS-caused ESRD versus other-caused ESRD, stratified by period of first kidney transplantation.

	All-cause Mortality		Allograft Loss	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Model 1				
1990–1999	1.29 (1.07–1.55)	0.01	1.37 (1.24–1.52)	<0.001
2000–2009	1.13 (0.84–1.52)	0.4	1.64 (1.48–1.81)	<0.001
Model 2				
1990–1999	1.06 (0.88–1.28)	0.6	1.17 (1.01–1.34)	0.03
2000–2009	0.81 (0.60–1.09)	0.2	1.27 (1.14–1.41)	<0.001
Model 3				
1990–1999	0.95 (0.79–1.15)	0.9		
2000–2009	0.70 (0.52–0.94)	0.02		

Note: The referent group for all models is ESRD secondary to other, non-FSGS causes. Model 1: unadjusted model. Model 2: plus clinical and demographic covariates at time of transplant: age at transplantation (0–5, 6–11, 12–17 years), sex, race (White, Black, other), ethnicity (non-Hispanic*, Hispanic), duration of dialysis prior to transplantation (pre-emptive transplantation or <6, 7–12, or ≥1 year). Model 3: plus allograft failure as time-varying variable

CI, confidence interval; FSGS, focal segmental glomerulosclerosis; HR, hazard ratio

* Non-Hispanic includes those with unknown ethnicity