Uncovering a Long-term Graft Survival Advantage Afforded by Infant Renal Transplants—An Organ Procurement and Transplantation Network Database Analysis

Daniel Tancredi, PhD[1] and Lavjay Butani, MD[1]

Background. Renal transplants (Tx) are performed infrequently in infants, due to concerns related to poor outcomes. The aim of our study was to compare graft failure rates in infant (<1 y) renal Tx recipients compared with older children. **Methods.** Retrospective cohort study of pediatric renal Tx recipients from 2000 to 2015, using the Organ Procurement and Transplant Network database. A log-linear event history regression model for time to graft failure, adjusting for age group and important confounders, was used to estimate post-Tx graft failure probabilities. **Results.** In 2696 Tx followed for a median of 6.1 y, 704 failures were observed. Significant predictors of graft failure were year of Tx (for each year after 2000, rates were 8.6% lower), Black race-ethnicity (63% higher compared with Whites), and number of HLA matches. For infants (n=27), estimated graft failure percentage (95% confidence interval) within the first 1-, 2-, and 5-y post-Tx were 10.4 (0.1–21.1), 11.9 (1.2–22.6), and 16.4 (4.9–27.9). For the 1- to 11-y-olds (n=1429), these were 3.8 (3.0–4.6), 6.3 (5.4–7.3), and 13.6 (12.2–15.0), respectively, and for the 12+ y olds (n=1240), they were 3.8 (3.1–4.5), 8.1 (7.2–9.0), and 19.9 (18.1–21.7), respectively (*P*<0.001 for 5-y graft failure rate across age groups). **Conclusions.** Infant renal Tx recipients experience a higher graft failure rate in the first year, compared with older cohorts, but over longer intervals, cumulative failure rates are comparable or even lower. To minimize early graft losses such Tx should be performed in experienced centers.

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INTRODUCTION

Renal transplants (Tx) are infrequently performed in very young children and account for a small minority of all pediatric Tx reported in large national registries.[1,2] This is even more pronounced in the infant (<1 y) recipient age group, which received approximately 1 percent of primary kidney single-organ transplants in the Organ Procurement and Transplantation Network (OPTN) database through December 31, 1999, and since then have received fewer than half of 1%. An overwhelming majority of such recipients were exposed to a period of pre-Tx dialysis.[1] Knowing the adverse effects of the uremic environment on neurodevelopmental outcomes and growth and the dramatically higher risk of all cause and cardiovascular morbidity and mortality during dialysis, all of which are accentuated in this youngest of all pediatric age groups,[2] makes it imperative to minimize exposure to dialysis in this vulnerable population, when possible. This is even more important considering the added benefit of preemptive Tx on long-term graft survival.[3]

One of the main reasons why infant Tx remain uncommon is because of technical challenges in performing surgery resulting from the small recipient and donor size, leading to a higher risk of graft thromboses[4,5] historically contributing to lower patient survival.[6] Over the decades, however, with increased experience and improved technical surgical expertise, such considerations may no longer hold true. Moreover, in the long-term, by, among other factors, more expeditiously correcting the uremic environment, infant Tx may afford a greater survival benefit to recipients, compared with Tx in older age groups, resulting in reduced age-related disparities in graft failure over longer horizons.

However, there are no data reporting absolute and relative outcomes in this youngest of all Tx recipient population. The

objective of our study was to compare graft failure in infant recipients of kidney Tx compared with older pediatric recipients at various time points after Tx. Our hypothesis was that infant recipients would have comparable graft survival both in the short and long term and may, in fact, fare better than Tx in older age groups, possibly due to greater family investment in the care of these children, leading to better adherence with the treatment regimen. If true, such Tx, especially preemptive, would be preferred to exposing children to pre-Tx dialysis while awaiting attainment of their growth to a bigger size to potentially mitigate historically observed higher surgical complication rates.

MATERIALS AND METHODS

We conducted a retrospective cohort analysis of the OPTN database, to identify children (age < 18 y at the time of Tx) who had received their first kidney-only Tx between January 1, 2000 and December 31, 2015. To be included in the study, we also required that the recipient have a graft that had not failed on the day of the surgical procedure, so as to be able to analyze our primary outcome measure (d to graft failure) using survival analyses. We modeled the probability of graft failure over various post-Tx time periods, among the different pediatric age-at-transplant categories. The secondary outcome measure was differences in causes of graft failure among the pediatric age categories. Children were categorized, based on their age at the time of Tx, as infants (age < 1 y), preteens (1–11 y), and teenagers (12–17 y).

Data pertaining to donor and recipient demographics, and peri-Tx characteristics were compared among age groupings using Pearson Chi-square or Fisher exact tests for categorical variables and the Kruskal-Wallis test for continuous variables.

Kaplan-Meier curves for the primary outcome, time to graft failure (graft loss or patient death), were estimated for each of the 3 age groups. A log-linear event history regression model for time to graft failure with time to graft failure with age-group specific piecewise constant baseline failure rates (for 1–7 d, 7–30 d, 30–183 d, and 183+ d intervals post-Tx) and statistically adjusting for important confounders, was applied to the selected cohort. Because of the small sample size in the infant group, to reduce imbalance and promote complete overlap across the 3 age groups of interest, we excluded records with key patient or disease characteristics infrequently seen in any one of the age groups, as is standard practice.[7] Predictive margins based on the event history regression analysis results were used to estimate age-group specific probabilities of failure over various follow-up intervals, to illustrate how postsurgery failure rates differ over time and between age groups, while statistically holding the distribution of covariates constant. Sensitivity analyses were conducted using alternative age groupings, including moving the relatively sizeable 1-y-old group from the middle group to the youngest group or subdividing the middle group by age into 2 groups.

For the primary outcome measure, the following recipient, donor, and Tx-related characteristics were accounted for in the multivariate models—recipient sex, self-reported race-ethnicity, cause of chronic kidney disease (CKD), donor age and cause of death, OPTN region where the Tx occurred, donor source (deceased or living), need for pre-Tx dialysis, number of HLA mismatches, year of Tx, pre-Tx hypoalbuminemia, and cold ischemia time.

Datasets were assembled using SAS (Cary, NC) and statistical analysis was conducted in Stata/SE (College Station, TX) statistical software. All available data were used, and the resulting precision of estimates is reflected by the width of the confidence interval (CI).

The study was granted an exempt status from the University of California Davis Institutional Review Board.

RESULTS

Descriptive Data

Using the OPTN database, 2696 pediatric renal Tx met the inclusion criteria, of whom 27 were in infant recipients. An additional 16 patients (7 preteens, 9 teens, and no infants) that would have otherwise been included were excluded because the graft did not survive to postoperative day 1, with no statistically significant association between the 3-level age-group variable and survival to postoperative day 1 (Fisher Exact $P = 0.54$).

Of the 11 OPTN geographic regions, infant Tx were performed in only 6 regions, with an overwhelming majority being done in regions 5 (n = 9) and 7 (n = 10). The number of infant Tx remained steady over the study period, ranging from 0 in many of the years to a peak of 5 in 2006. There was no trend in the number of infant Tx over time.

Table 1 depicts data comparing Tx in infant recipients with the 2 older cohorts. Infant recipients were more likely to be male, have structural causes of CKD and have hypoalbuminemia; they were also more likely to receive infant and living donor kidneys. The majority of infant (and all other pediatric) recipients had experienced a period of pre-Tx dialysis. At the time of Tx, infant recipients had a median (interquartile range) weight of 9.1 (8.2–11.0) kg. This corresponds to the 50th percentile weight for an 8.5-mo-old healthy male and a 10.5-mo-old healthy female infant. The median cold ischemia time was significantly longer in infant Tx recipients, especially when compared with the preteens.

Age-group specific unadjusted (Kaplan-Meier) estimates of graft-free failure over the first 60 mo of follow-up are shown in Figure 1. At 5 y, survival estimates (95% CI) are 88.9% (69.4–96), 90.3% (88.5–91.8), and 82.5% (80.0–84.6) for the infants, preteens, and teenagers, respectively, with infant losses occurring relatively early post-Tx compared with the other age groups. As shown in Table 1, the unadjusted graft failure rate, during the entirety of the follow-up period, was highest in the teenage cohort (30.6% over a mean follow-up period of 6.4 y). When accounting for the variable follow-up duration among the 3 cohorts, unadjusted graft failures/100 person years of follow-up (95% CI) remained the highest for the teenage group at 4.8 (4.3–5.2), compared with the 2 younger cohorts ($P < 0.001$).

Tables 2 and 3 show the data from the event history regression analyses pertaining to the primary outcome measure.

As shown in Table 2, statistically significant predictors of graft failure rates were year of Tx with a lower rate in the more contemporaneous period (for each y after 2000, graft failure rates were 8.6% lower), a 29% higher rate in recipients from region 10 (compared with region 5), a 63% higher rate in recipients of Black race-ethnicity (compared with Whites), and a much lower rate in children who received 0, 1, and 2

Demographic and peri-Tx-related data across age groups

	Recipient age at Tx			
	<1 y (n, 27)	1–11 y (n, 1429)	12–17 y (n, 1240)	*P*
Region no. (%)				0.01
1	2 (7)	108 (7.6)	92 (7.4)	
2	4 (15)	230 (16.1)	188 (15.2)	
5	9 (33)	312 (21.8)	319 (25.7)	
7	10 (37)	260 (18.2)	190 (15.3)	
10	1 (4)	269 (18.2)	250 (20.2)	
11	1 (4)	250 (17.5)	201 (16.2)	
Race/ethnicity no. (%)				0.24
White	16 (59)	937 (65.6)	761 (61.4)	
Black	5 (19)	193 (13.5)	168 (13.5)	
Hispanic	4 (15)	231 (16.2)	244 (19.7)	
Other	2 (7)	68 (4.8)	67 (5.4)	
Female no. (%)	5 (19)	503 (35.2)	536 (43.2)	<0.001
Serum albumin no. (%) (g/dL)				<0.001
<2.5	2 (7)	60 (4.2)	27 (2.2)	
2.5–3.4	8 (30)	347 (24.3)	253 (20.4)	
3.5+	17 (63)	1022 (71.5)	960 (77.4)	
Cause of CKD no. (%)				<0.001
Structural	20 (74)	956 (66.9)	626 (50.5)	
Glomerular	4 (14)	311 (21.8)	483 (39.0)	
Other	3 (11)	162 (11.3)	131 (10.6)	
Pre-Tx dialysis (%)	20 (74)	931 (65.2)	800 (64.5)	0.57
Receiving infant donor Tx	1	2	3	0.049
Age of adult donor[a]				
Median (Q1, Q3)	30 (25, 33)	31 (25, 37)	33 (23, 40)	0.004
Donor type no. (%)				<0.001
Living	21 (78)	1012 (70.8)	735 (59.3)	
Died from head trauma	5 (19)	357 (25.0)	426 (34.4)	
Died from cerebrovascular event	1 (4)	60 (4.2)	79 (6.4)	
HLA mismatch level no. (%)				<0.001
0	0 (0)	38 (2.7)	51 (4.1)	
1	4 (15)	88 (6.2)	61 (4.9)	
2	7 (26)	348 (24.4)	223 (18.0)	
3	11 (41)	441 (30.9)	348 (28.1)	
4	2 (7)	179 (12.5)	179 (14.4)	
5	2 (7)	210 (14.7)	244 (19.7)	
6	1 (4)	125 (8.7)	134 (10.8)	
Recipient weight (kg)				
Median (Q1, Q3)	9.1 (8.2, 11.0)	17.1 (12.0, 24.9)	52 (43.1, 63.3)	<0.001
Cold ischemia time not available no. (%)	10 (37)	330 (23.1)	239 (19.3)	0.008
Cold ischemia time (h)				
Median (Q1, Q3)	2.8 (0, 4.2)	1.3 (0.5, 6.3)	2.1 (0.6, 10.2)	<0.001
Follow-up duration (y)				<0.001
Mean ± SD	8.7±5.4	7.3±4.4	6.4±3.9	
Median (Q1, Q3)	9.7 (4.8, 12.0)	6.9 (3.9, 10.6)	5.8 (3.2, 8.9)	
Graft losses (failure or death) during follow-up no. (%)	8 (30)	317 (22.2)	379 (30.6)	<0.001
Unadjusted graft failures/100 person years of follow-up (no. 95% CI)	3.4 (1.0, 5.8)	3.0 (2.7, 3.4)	4.8 (4.3, 5.2)	<0.001
Leading causes of graft loss no. (%)				
• Chronic rejection	2 (28.5)	131 (51.8)	134 (41.2)	
• Acute rejection	0	36 (14)	77 (23.6)	
• Surgical/urologic complications	1 (14.3)	11 (4)	6 (2)	
• Thromboses	1 (14.3)	19 (7.5)	9 (2.8)	
• Infection	2 (28.5)	12 (4.7)	16 (4.9)	

[a]For adult donors, the age was restricted to include only adult donor Tx where the donor age was between 18 and 46 y (to promote comparability across the groups).
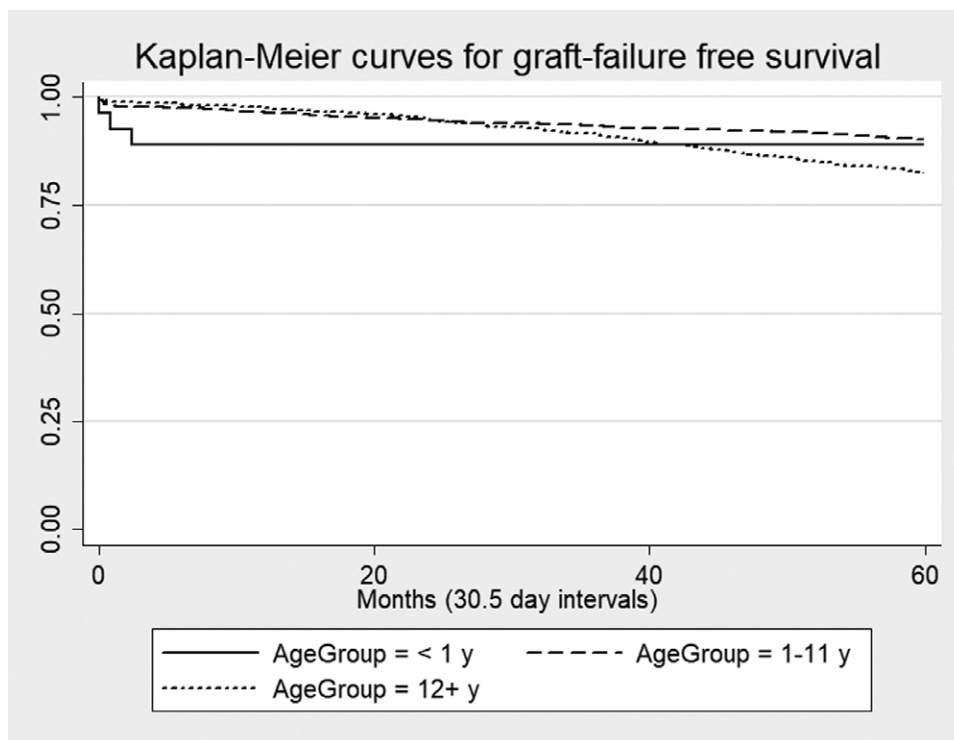CKD, chronic kidney disease; Tx, renal transplant.

FIGURE 1. Kaplan-Meier curves for graft-free survival in various age groupings.

HLA mismatched kidneys, compared with those who received 3 HLA antigen mismatched kidneys.

Table 3 illustrates the complex effect of age groups on graft failure, at various time points after Tx.

For infants, the graft failure percentage was highest in the first post-Tx year (10.4%; 95% CI, 0–21.1) and was substantially higher than the graft failure percentage in the older pediatric cohorts (3.8% for each of the 2 older cohorts), although this was not statistically different. Compared with the first post-Tx year, failure rates progressively declined over time in infant recipients such that the cumulative graft failure percentage in infants by 5 y was 16.4% (95% CI, 4.9–27.9). In stark contrast, graft failure percentages increased over time for the older pediatric cohorts. By 5-y post-Tx, statistically significant differences were noted in graft failure percentages among the age groups, with the teenagers having the higher cumulative graft failure rate (19.9, 95% CI, 18.1–21.7; $P < 0.0001$). In sensitivity analysis, moving the 1-y-olds to the youngest age group improved survival percentages by 2 to 4 percentage points, depending on the time-point, with the 5-y failure percentage for the 0- to 1-y-olds, decreasing to 13.9 (10.6–17.2).

Causes of Graft Loss

Statistical comparison data pertaining to differences in causes of graft loss are not provided since the very small number of graft losses in infants precludes meaningful interpretation of statistical data. Nevertheless, as shown in Table 1, there appear to be substantive differences in causes of graft loss among the 3 age groups, with chronic rejection being the leading cause in each group. Overrepresented in the infant age group were infections, surgical/urologic complications, and thromboses as causes of graft loss.

DISCUSSION

Infant Tx remain infrequent, even in the current era, as demonstrated by the very small numbers of such Tx registered in the OPTN database, a mandatory requirement for all Tx centers in the United States. Moreover, most infant Tx recipients are exposed to a period of pre-Tx dialysis. Although there are many potential reasons for this, such as the time required to optimize recipient nutritional status (as evidenced by the higher prevalence of hypoalbuminemia in infants in our study), find a suitable donor, and prepare the recipient for the Tx, especially addressing urologic considerations (since a very large percentage of infant recipients have structural anomalies with associated bladder dysfunction), a large consideration, historically, has been the technical challenge in performing surgery due to the small recipient size. This has led to a higher reported incidence of thrombosis, graft loss, and lower patient survival.[4,6]

Whether these considerations remain true in the current era, an era that has seen remarkable advancements in surgical techniques and a growing experience among pediatric Tx surgeons, remains unknown, and was a gap that we attempted to address with our study, using the comprehensive OPTN database. The most recent study exploring this issue was published in 2018, but was based on a single-center experience, and included transplants that were performed over a very long duration, starting from 1984.[8] Finally, the study included Tx recipients who were under 2 y of age and not just infants. As can be expected, based on the epidemiology of CKD in this age group, the majority of recipients were male, received living donor kidneys, and had structural renal conditions, similar to what we describe. Only a small minority (20%) of these recipients received preemptive Tx. Graft thromboses were seen in 3% of the recipients over the entire study period and

Adjusted incidence rate ratios for terms other than age group and follow-up time category from multiple log-linear model of graft failure loss[a]

	Adjusted incidence rate ratio (95% CI) %	P
Each y of Tx after 2000	0.92 (0.90–0.93)	<0.001
Region (compared with region 5)		
1	1.12 (0.80–1.56)	0.52
2	0.97 (0.76–1.25)	0.83
7	1.21 (0.94–1.55)	0.14
10	1.29 (1.01–1.64)	0.04
11	1.16 (0.90–1.48)	0.25
Race-ethnicity (compared with White)		
Black	1.63 (1.34–1.98)	<0.001
Hispanic	1.14 (0.91–1.42)	0.25
Other	1.30 (0.90–1.86)	0.16
Female sex (compared with male)	1.11 (0.96–1.29)	0.16
Serum albumin g/dL (compared with 3.5+)		
<2.5	1.16 (0.82–1.65)	0.40
2.5–3.4	0.90 (0.75–1.08)	0.27
Cause of CKD (compared with structural)		
Glomerular disease	0.85 (0.72–1.01)	0.07
Other	0.92 (0.72–1.17)	0.50
Receipt of pre-Tx dialysis	1.01 (0.87–1.18)	0.87
Receipt of infant donor Tx	2.52 (0.80–7.90)	0.11
Every h of CIT	1.00 (0.99–1.02)	0.88
CIT not available	0.93 (0.78–1.14)	0.54
Number of HLA mismatches (compared with 3)		
0	0.43 (0.24–0.77)	0.005
1	0.64 (0.45–0.91)	0.01
2	0.81 (0.67–0.99)	0.04
4	0.86 (0.65–1.14)	0.30
5	1.20 (0.92–1.56)	0.18
6	1.24 (0.84–1.51)	0.43
Donor cause of death (compared with living donor)		
Head trauma	1.21 (0.92–1.58)	0.17
Cerebrovascular accident/stroke	1.25 (0.87–1.82)	0.23

[a]The model used also included main effects and interactions for age group and for follow-up interval (0–7 d, 8–30 d, 30–183 d, 184+ d).
CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; Tx, renal transplant.

declined over time, as did graft failure from technical reasons. A prior study from the same group, highlighted the very high mortality in this age group in patients who started dialysis, such that only 53% of infant recipients who started dialysis survived to receive a Tx by 2 y.[9]

Our study clarifies outcomes in the contemporary era in infant recipients and reiterates the low-frequency of such procedures and the high incidence of dialysis exposure before

Tx, which based on prior studies can lead to suboptimal outcomes.[3] Such Tx are concentrated in a few geographic areas, likely reflecting the comfort level and expertise of Tx teams in a few centers, in performing these technically challenging procedures and caring for these children. This study adds to the literature, by demonstrating the comparable long-term graft survival in infants, compared with older children. Although we did note a higher risk of graft failure in the very early Tx period in infants compared with the older pediatric cohorts, beyond the first post-Tx year, differences in graft survival among the age groups declined such that over time, infant Tx fared as well, if not better, than the teenagers. This could very well be due to the well-documented higher nonadherence rates leading to poorer graft survival in the teenage population.[10] Analysis of the causes of graft loss confirm the disproportionate occurrence of graft thromboses and surgical/urologic complications as a cause of graft loss in infant Tx recipients, compared with older cohorts, attesting to the challenge in performing such complex surgical procedures in such small patients, and of meticulous attention to post-Tx management.

Limitations of our study include the small number of infant Tx during the study period (a result of how infrequently this procedure is performed even today), and the even smaller number of graft losses, precluding meaningful statistical comparisons. Finally, we are limited by the level of detail to the data available in the OPTN database and rely on the reporting center on the accuracy of the data reported, especially pertaining to the cause(s) of graft loss in the Tx recipients, which can sometimes be subjective and opinion based. Nevertheless, our study illustrates good outcomes in the long-term, in infants, compared with older children and serves as an optimistic reminder for Tx centers to not delay performing Tx solely based on recipient size. However, we would be remiss in not highlighting the technical challenges associated with Tx in recipients of such a small size, and caution centers from performing such procedures unless team members have the technical expertise and experience in caring for this high-risk population. The consequences of graft thrombosis and resulting graft loss can be devastating, especially in infants, potentially exposing them to a prolonged period of dialysis, sensitizing them to HLA antigens and creating technical problems with subsequent vascular anastomoses, making the possibility of future Tx difficult.

However, in the presence of surgical experience and expertise, avoiding dialysis at all costs in this population, can only be beneficial. Regional differences in graft failure rates could be hypothesized to be related to this issue since the highest graft loss was seen in the OPTN Region that performed the fewest infant Tx during the study period.

Effect of age on graft failure over time: marginal estimates following multiple log-linear regression model of graft failure

Time post-Tx	Graft failure % (95% CI) by age groupings			P
	Infants	Preteenagers	Teenagers	
1 d–1 y	10.4 (0–21.1)	3.8 (3.0–4.6)	3.8 (3.1–4.5)	0.49
1 d–2 y	11.9 (1.2–22.6)	6.3 (5.4–7.3)	8.1 (7.2–9.0)	0.02
1 d–5 y	16.4 (4.9–27.9)	13.6 (12.2–15.0)	19.9 (18.1–21.7)	<0.001

CI, confidence interval; Tx, renal transplant.

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REFERENCES

1. Chua A, Cramer C, Moudgil A, et al; NAPRTCS investigators. Kidney transplant practice patterns and outcome benchmarks over 30 years: the 2018 report of the NAPRTCS. *Pediatr Transplant.* 2019;23:e13597.

2. United States Renal Data System. 2018 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018. Available at https://adr.usrds.org/2020/end-stage-renal-disease/7-%20esrd-among-children-and-adolescents. Published 2020. Accessed January 10, 2021.

3. Butani L, Perez RV. Effect of pretransplant dialysis modality and duration on long-term outcomes of children receiving renal transplants. *Transplantation*. 2011;91:447–451.

4. Harmon WE, Stablein D, Alexander SR, et al. Graft thrombosis in pediatric renal transplant recipients. A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation*. 1991;51:406–412.

5. van Lieburg AF, de Jong MC, Hoitsma AJ, et al. Renal transplant thrombosis in children. *J Pediatr Surg*. 1995;30:615–619.

6. Sheldon CA, Churchill BM, McLorie GA, et al. Evaluation of factors contributing to mortality in pediatric renal transplant recipients. *J Pediatr Surg*. 1992;27:629–633.

7. Imbens GW, Rubin DB. *Assessing Overlap in Covariate Distributions. In Causal Inference for Statistics, Social, and Biomedical Sciences: An Introduction*. Cambridge University Press; 2015.

8. Chavers BM, Rheault MN, Matas AJ, et al. Improved outcomes of kidney transplantation in infants (age < 2 years): a single-center experience. *Transplantation*. 2018;102:284–290.

9. Rheault MN, Rajpal J, Chavers B, et al. Outcomes of infants <28 days old treated with peritoneal dialysis for end-stage renal disease. *Pediatr Nephrol*. 2009;24:2035–2039.

10. Hamilton AJ, Plumb LA, Casula A, et al. Associations with kidney transplant survival and eGFR decline in children and young adults in the United Kingdom: a retrospective cohort study. *BMC Nephrol*. 2020;21:492.