

National Trends Over 25 Years in Pediatric Kidney Transplant Outcomes



WHAT'S KNOWN ON THIS SUBJECT: Kidney transplantation is the optimal treatment of children with end-stage renal disease. The field of pediatric kidney transplantation has changed over time with regard to immunosuppression, surgical technique, organ allocation policy, and rates of living donor transplantation.



WHAT THIS STUDY ADDS: Outcomes after pediatric kidney transplantation in the United States have improved over time, independent of changes in recipient, donor, and transplant characteristics. These improvements were most dramatic within the first posttransplant year and among the most highly sensitized patients.

abstract

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OBJECTIVE: To investigate changes in pediatric kidney transplant outcomes over time and potential variations in these changes between the early and late posttransplant periods and across subgroups based on recipient, donor, and transplant characteristics.

METHODS: Using multiple logistic regression and multivariable Cox models, graft and patient outcomes were analyzed in 17 446 pediatric kidney-only transplants performed in the United States between 1987 and 2012.

RESULTS: Ten-year patient and graft survival rates were 90.5% and 60.2%, respectively, after transplantation in 2001, compared with 77.6% and 46.8% after transplantation in 1987. Primary nonfunction and delayed graft function occurred in 3.3% and 5.3%, respectively, of transplants performed in 2011, compared with 15.4% and 19.7% of those performed in 1987. Adjusted for recipient, donor, and transplant characteristics, these improvements corresponded to a 5% decreased hazard of graft loss, 5% decreased hazard of death, 10% decreased odds of primary nonfunction, and 5% decreased odds of delayed graft function with each more recent year of transplantation. Graft survival improvements were lower in adolescent and female recipients, those receiving pretransplant dialysis, and those with focal segmental glomerulosclerosis. Patient survival improvements were higher in those with elevated peak panel reactive antibody. Both patient and graft survival improvements were most pronounced in the first posttransplant year.

CONCLUSIONS: Outcomes after pediatric kidney transplantation have improved dramatically over time for all recipient subgroups, especially for highly sensitized recipients. Most improvement in graft and patient survival has come in the first year after transplantation, highlighting the need for continued progress in long-term outcomes. *Pediatrics* 2014;133:594–601

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KEY WORDS

renal transplantation, kidney disease, pediatric, temporal trends

ABBREVIATIONS

aHR—adjusted hazard ratio per year
CI—confidence interval
DCGS—death-censored graft survival
DGF—delayed graft function
ESRD—end-stage renal disease
FSGS—focal segmental glomerular sclerosis
KT—kidney transplantation
PNF—primary nonfunction
PRA—panel reactive antibody
SRTR—Scientific Registry of Transplant Recipients

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End-stage renal disease (ESRD) affects 5 to 10 children per million per year and increases mortality risk by 30-fold compared with the general pediatric population.¹ Kidney transplantation (KT) has emerged as the optimal treatment of pediatric patients with ESRD, providing a significant survival advantage over dialysis.^{1,2} Approximately 800 children in the United States undergo KT each year, representing about 5% of all kidney transplants performed nationally.³

The field of pediatric KT has evolved over the past 25 years, including changes in immunosuppression, surgical technique, organ allocation policy, and rates of living donor transplantation.⁴ However, the relationship between these changes and post-KT outcomes remains unclear, both in terms of which patient phenotypes have been affected and when any changes in outcomes have occurred (ie, early versus late post-KT).

The objective of this study was to examine changes in pediatric KT outcomes over the last 25 years. In particular, our work sought to assess trends in graft survival, rates of primary nonfunction (PNF) and delayed graft function (DGF), and patient survival independent of concurrent variations in recipient and donor characteristics, to compare the early and late posttransplant periods with regard to trends in graft and patient survival, and to evaluate whether any changes in graft and patient survival differ in particular recipient subgroups.

METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR), a national registry of all solid organ transplants. As previously described,⁵ the SRTR includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration

of the U.S. Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. The present work was approved as exempt by the Johns Hopkins Medicine Institutional Review Board.

Study Population

All pediatric (ie, recipient <18 years old) kidney-only transplants between 1987 and 2012 were identified in the SRTR. Etiology of renal disease was categorized as focal segmental glomerular sclerosis (FSGS), other glomerular diseases, congenital anomalies of the kidney and urinary tract, or other/missing diagnosis, based on clinical knowledge and precedent set by the SRTR program-specific regression models (available at www.srtr.org).

Transplants were categorized into 4 time periods (1987–1993, 1994–2001, 2002–2004, and 2005–2012) to reflect changes in immunosuppression practices over time (in general, increased use of tacrolimus and mycophenolate mofetil, decreased use of cyclosporine and azathioprine, and introduction of interleukin-2 receptor monoclonal antibodies)⁴ and implementation in 2005 of the Share-35 allocation policy, which includes preference to pediatric recipients in the allocation of organs from deceased donors under age 35.⁶

Outcome Ascertainment

Death-censored graft survival (DCGS) was defined as the time between date of KT and either date of graft failure (marked by retransplantation or return to dialysis) or last date of follow-up with a functioning graft, censoring for death and administrative end of study. PNF was defined as graft survival <90 days, and DGF was defined as the need for dialysis within the first week after KT. Patient survival was defined as the time from KT to death or last follow-up, censoring for administrative end of

study. Death and graft loss ascertainment were supplemented by linkage to data from the Centers for Medicare and Medicaid Services. Death ascertainment was also supplemented by linkage to the Social Security Death Master File.

Statistical Analysis

Rates of PNF and DGF were compared over time by using multiple logistic regression models. DCGS and patient survival were estimated and compared across year and transplantation period using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models. Multivariable Cox models were used to compare survival, which was censored at 5 years after KT to avoid artifactual comparison of late survival time in those with long follow-up to early survival time in those with only shorter follow-up. Results are presented as the change in expected outcomes with each more recent year of transplantation (ie, a comparison of transplants performed in a given year with those performed 1 year before). All multivariable models were adjusted for recipient (age, gender, race, peak panel reactive antibody [PRA], previous transplant history, preemptive status, and etiology of renal disease) and donor (age, living versus deceased) characteristics and HLA mismatch. Cold ischemia time was also included in deceased donor transplant Cox models. Missing data in the included covariates were handled using the missing indicator method, in which missing data are categorized as unknown, thereby allowing patients with missing data to still contribute all other data points to the models.

Based on visual inspection of the survival curves, the changes in survival over time appeared to be most pronounced in the first year after KT. This finding was quantified using a time-dependent Cox model in which the

year of transplantation coefficient was split into 2 time-varying coefficients, one representing the first year after KT and the second representing subsequent post-KT time. To determine whether changes in survival differed across recipient subgroups, interaction terms between the year of transplantation variable and the following characteristics were evaluated: recipient age, gender, race, peak PRA, previous transplant history, preemptive status, and etiology of renal disease, donor type, and HLA mismatch. All tests were 2-sided, with statistical significance set at $\alpha = 0.05$. Analyses were performed by using Stata 12.1/SE (Stata Corp, College Station, TX).

RESULTS

Study Population

Of 17 446 pediatric kidney transplants performed in the United States during the study period, 8501 (48.7%) were living donor transplants, and 8945 (51.3%) were deceased donor transplants. Living donor transplants were less common after 2005, as were zero-HLA mismatched transplants (Table 1). Although the percentage of transplants performed preemptively (before initiation of dialysis) increased over time, the length of pretransplant dialysis for those not undergoing preemptive transplantation remained steady. The percentage of transplants that were repeat transplants decreased over time, and for deceased donor transplants, the cold ischemia time also decreased over time.

Graft Survival Over Time

DCGS improved dramatically over time, with 1-year graft survival of 97.0% for transplants performed in 2010 compared with 80.9% in 1987, 5-year graft survival of 77.9% for transplants performed in 2006 compared with 59.0% in 1987, and 10-year graft survival of 60.2% for transplants performed in 2001

compared with 46.8% in 1987. The median graft survival improved from 7.2 years for transplants performed in 1987 to 12.3 years for transplants performed in 1998 (the most recent year for which a median survival is available).

The 1-, 5-, and 10-year graft survival also improved dramatically across transplantation periods (Table 2 and Fig 1A). The rate of improvement in unadjusted graft survival since 2005 (hazard ratio per year, 0.86; 95% confidence interval [CI], 0.82–0.90; $P < .001$) was also greater than the rate of improvement before 2005 (hazard ratio, 0.95; 95% CI, 0.94–0.96; $P < .001$) ($P < .001$). These improvements in DCGS remained after concurrent changes in recipient, donor, and transplant characteristics over time were adjusted for, with the risk of graft loss decreasing by 5% (adjusted hazard ratio per year [aHR], 0.95; 95% CI, 0.94–0.96; $P < .001$) with each more recent year of transplantation.

PNF and DGF Over Time

Rates of PNF and DGF declined over time and across transplantation periods (Table 2). The rate of PNF decreased from 15.4% in 1987 to 3.3% in 2011. The rate of DGF decreased from 19.7% in 1987 to 5.3% in 2011. After concurrent changes in recipient, donor, and transplant characteristics over time were adjusted for, the odds of PNF decreased by 10% (adjusted odds ratio per year, 0.90; 95% CI, 0.89–0.91; $P < .001$) and the odds of DGF decreased by 5% (adjusted odds ratio, 0.95; 95% CI, 0.94–0.96; $P < .001$) with each more recent year of transplantation.

Patient Survival Over Time

Patient survival after pediatric KT also improved significantly over time, with 1-year survival of 99.0% after transplants performed in 2010 compared with 95.1% in 1987, 5-year survival of 96.9% after transplants performed in 2006 compared with 90.2% in 1987, and 10-year survival of 90.5% after transplants

performed in 2001 compared with 77.6% in 1987. Similarly, the 1-, 5-, and 10-year patient survival also improved across transplantation periods (Table 2 and Fig 1B). These improvements in patient survival remained after concurrent changes in recipient, donor, and transplant characteristics over time were adjusted for, with the risk of death decreasing by 5% (aHR, 0.95; 95% CI, 0.94–0.97; $P < .001$) with each more recent year of transplantation.

Early Versus Late Posttransplant Improvement

Temporal improvements in DCGS were significantly more pronounced in the first year after KT compared with beyond 1 year ($P < .001$). The risk of graft loss in the first year after KT decreased by 9% (aHR, 0.91; 95% CI, 0.91–0.92; $P < .001$) with each more recent year of transplantation, whereas the risk of graft loss beyond the first year after KT decreased by 2% (aHR, 0.98; 95% CI, 0.97–0.98; $P < .001$) with each more recent year of transplantation.

Temporal improvements in patient survival were also significantly more pronounced in the first year after KT compared with beyond 1 year ($P = .002$). The risk of death in the first year after KT decreased by 6% (aHR, 0.94; 95% CI, 0.92–0.95; $P < .001$) with each more recent year of transplantation, whereas the risk of death beyond the first year after KT decreased by 3% (aHR, 0.97; 95% CI, 0.96–0.99; $P < .001$) with each more recent year of transplantation.

Differential Improvement Over Time Across Recipient Subgroups

The improvement in DCGS over time was similar between living donor and deceased donor transplants (both aHRs, 0.95; 95% CI, 0.94–0.96; $P < .001$). Likewise, no significant interaction was identified between year of transplantation and recipient race, peak PRA, previous transplant history, or HLA mismatch ($P > .05$).

TABLE 1 Recipient, Donor, and Transplant Characteristics for Pediatric (<18 years old) Kidney Transplants Performed Between 1987 and 2012 (*n* = 17 446), Stratified by Transplantation Period

	Transplantation Period			
	1987–1993 (<i>n</i> = 3942)	1994–2001 (<i>n</i> = 5460)	2002–2004 (<i>n</i> = 2310)	2005–2012 (<i>n</i> = 5734)
Mean recipient age (SD)	10.7 (5.1)	11.1 (5.0)	11.1 (5.1)	11.3 (5.2)
Recipient gender (% female)	40.6	40.8	40.3	41.2
Recipient race (%)				
Caucasian	65.4	60.2	54.5	51.2
African American	16.7	19.0	19.9	18.9
Hispanic	14.2	16.4	20.8	24.8
Other	3.7	4.3	4.7	5.1
Preemptive transplant (%)	12.7	25.6	25.9	27.5
Median years of dialysis ^a (IQR)	1.1 (0.5–2.4)	1.3 (0.6–2.4)	1.5 (0.7–2.6)	1.3 (0.7–2.5)
Etiology of renal disease				
FSGS	6.4	9.9	11.9	12.9
Other glomerular	21.9	14.5	12.2	9.7
CAKUT	28.7	34.5	38.4	38.4
Other/missing	42.9	41.2	37.5	38.9
Previous transplant (%)	16.0	11.7	10.0	8.8
Median peak PRA (%) (IQR)	3 (0–13)	0 (0–6)	0 (0–4)	0 (0–6)
Donor type (% living)	49.4	55.0	54.4	40.1
Mean donor age (SD)	28.8 (14.1)	32.2 (12.6)	31.5 (12.1)	27.6 (11.4)
Zero HLA mismatch (%)				
Living donor	7.0	5.1	3.9	3.5
Deceased donor	3.6	4.4	4.8	2.4
Median hours of cold ischemia time ^b (IQR)	22.0 (15.0–29.0)	18.0 (13.0–24.0)	14.6 (10.0–20.0)	12.4 (8.8–17.5)

CAKUT, congenital anomalies of the kidney and urinary tract; IQR, interquartile range.

^a Among those not undergoing preemptive transplantation.

^b Among deceased donor transplants.

for all interaction terms), suggesting that the rate of improvement in DCGS over time was similar across each of these recipient subgroups. The annual improvement in DCGS was slightly attenuated among recipients age 13 to 17 ($P = .05$), female recipients ($P < .001$), recipients who received pretransplant dialysis

($P = .01$), and recipients with FSGS ($P = .03$), although significant improvements in DCGS were still seen in each of these recipient subgroups (Table 3).

As with DCGS, a similar improvement in patient survival over time was seen after both living donor (aHR, 0.96; 95% CI, 0.94–0.98; $P < .001$) and deceased

donor (aHR, 0.96; 95% CI, 0.94–0.98; $P < .001$) transplantation. In addition, no significant interaction was identified between year of transplantation and recipient age, gender, race, etiology of renal disease, previous transplant history, pretransplant dialysis history, or HLA mismatch ($P > .05$ for all interaction terms), suggesting that the rate of improvement in patient survival over time was similar across each of these recipient subgroups. However, patients with the highest peak PRA (81% to 100%) experienced a significantly larger annual improvement in patient survival compared with patients with lower peak PRA ($P = .01$) (Table 3).

DISCUSSION

In this national study examining pediatric KT over a 25-year period, we found dramatic improvements over time in rates of PNF and DGF and in patient and graft survival, even when concurrent changes in recipient, donor, and transplant characteristics were adjusted for. In other words, the improvements over time are not merely due to changes in selection of recipients or donors or matching of the two. Although at first glance the improvements over time may appear to be quite modest, one must remember that the changes presented are per year (ie, the differential risk experienced by patients transplanted 1 year apart). Thus, for example, a 5% decrease in the risk of death and graft loss per year would translate into approximately a 40% difference in risk between patients transplanted 1 decade apart.

Most improvement in patient and graft survival came in the first year after transplantation, and improvement after 1 year was more modest. These improvements were seen across all subgroups examined, although highly sensitized recipients experienced a more pronounced improvement in patient survival, whereas several recipient subgroups, specifically adolescent and

TABLE 2 Outcomes Among Pediatric (<18 years old) Kidney Transplants Performed Between 1987 and 2012 (*n* = 17 446), Stratified by Transplantation Period

	Transplantation Period			
	1987–1993 (<i>n</i> = 3942)	1994–2001 (<i>n</i> = 5460)	2002–2004 (<i>n</i> = 2310)	2005–2012 (<i>n</i> = 5734)
DCGS (%)				
1-year	84.0	92.6	95.1	95.3
5-year	65.9	75.1	77.3	78.6
10-year	48.8	55.6	—	—
DGF (%)	14.5	10.0	7.3	7.5
PNF (%)	11.6	5.2	2.8	2.7
Patient survival (%)				
1-year	96.5	98.4	98.5	98.9
5-year	92.4	95.2	95.2	96.6
10-year	85.8	89.1	—	—

—, indicates data are not yet available.

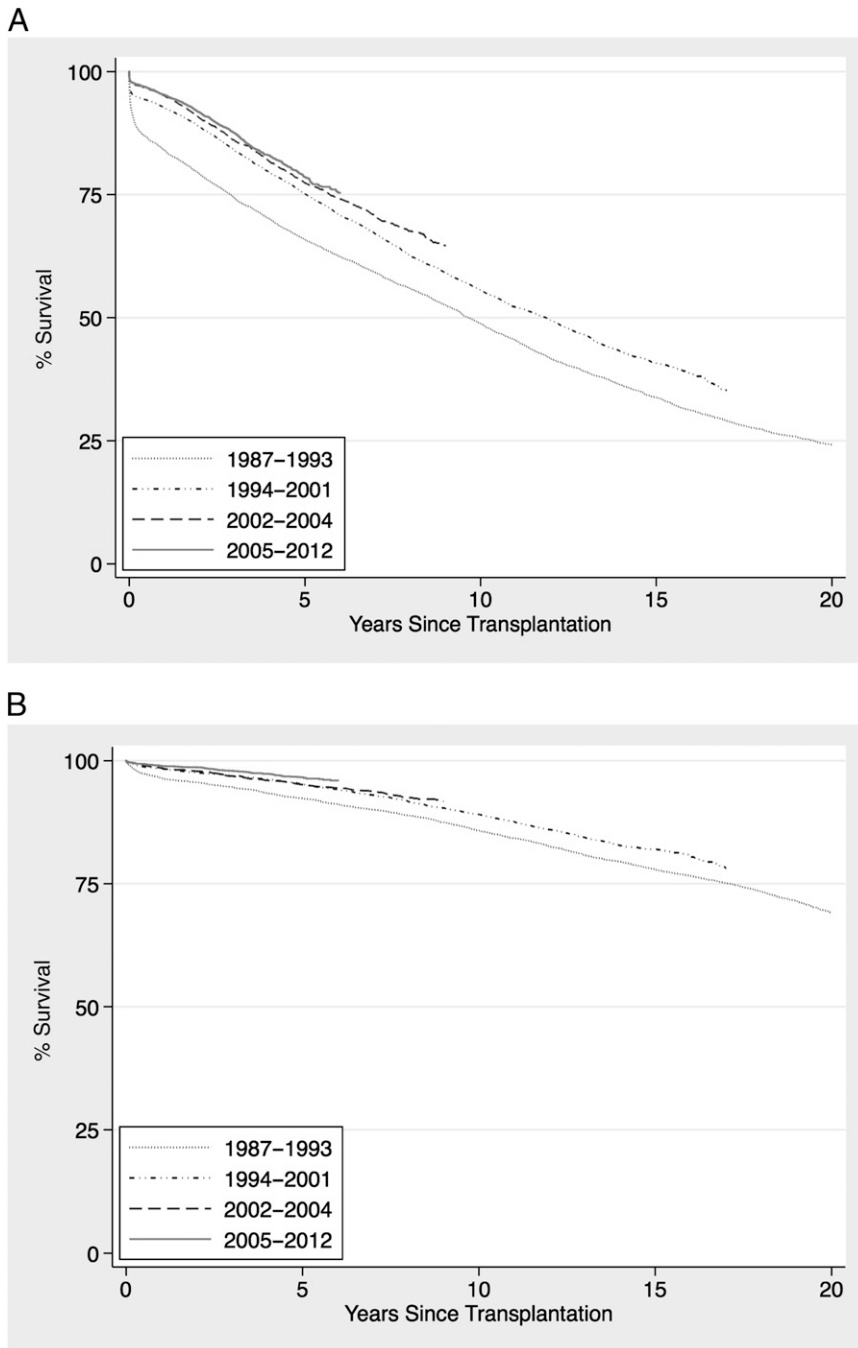


FIGURE 1 A, Death-censored graft survival, and B, Patient survival after pediatric kidney transplantation (1987–2012), stratified by transplantation period.

female recipients and those with pre-transplant dialysis and a diagnosis of FSGS, saw improvements in graft survival that were less dramatic than those seen in other recipient subgroups.

Our findings build on previous work reporting improvements (typically in

unadjusted analyses) in graft survival over time in pediatric KT.^{4,7–14} Significant changes in donor characteristics have been seen in the field of pediatric KT, most notably since 2005, when the Share-35 policy was implemented. While previous kidney allocation policies

also provided preference for children, the Share-35 policy established the preferential allocation of grafts from deceased donors under age 35 to pediatric candidates and eliminated the requirement for a minimum waiting period before benefiting from this preference. This policy change has seemingly led to a shift toward HLA-mismatched and deceased donor grafts for pediatric recipients,^{15–17} raising concerns about the potential effects of these changes on outcomes after pediatric KT. Interestingly, despite this shift, we found that unadjusted graft survival has continued to improve, and at an even greater rate, since 2005.

Although such changes in organ allocation policy, as well as changes in donor and recipient selection, probably contribute to changes in unadjusted patient and graft survival over time, these factors are reliably measured in the national SRTR registry and are accounted for in our adjusted analyses. What remains after this adjustment, other than a small amount of unmeasured confounding that is unlikely to cause significant bias, should reflect longitudinal improvements in transplant care that have occurred over time. These improvements are probably due to significant advances in immunosuppression,^{4,9,18–20} surgical technique,^{4,18,21} alloantibody detection and desensitization strategies,^{4,21} and infectious disease prevention and treatment.^{4,18} Finally, other latent factors that have improved over time, such as crossmatch technology and interdisciplinary collaboration in post-transplant care, may also contribute to the temporal improvements in outcomes.

Improvements in graft survival are vital given the substantial progress that has been achieved in the long-term survival of pediatric patients with ESRD.¹ Currently patient survival after pediatric

TABLE 3 Differential Improvements Over Time in Death-Censored Graft Survival and Patient Survival Across Various Subgroups of Pediatric (<18 years old) Kidney Transplant Recipients Between 1987 and 2012 (*n* = 17 446)

DCGS		
	aHR (95% CI)	<i>P</i>
All patients	0.95 (0.94–0.96)	<.001
Recipient age		
0–2 years	0.94 (0.92–0.96)	<.001
3–5 years	0.93 (0.91–0.95)	<.001
6–12 years	0.94 (0.93–0.95)	<.001
13–17 years	0.96 (0.95–0.96)	<.001
Recipient gender		
Female	0.96 (0.95–0.97)	<.001
Male	0.94 (0.93–0.95)	<.001
Dialysis history		
Preemptive	0.94 (0.92–0.95)	<.001
Pretransplant dialysis	0.95 (0.95–0.96)	<.001
Etiology of renal disease		
FSGS	0.97 (0.95–0.98)	<.001
Other glomerular	0.95 (0.94–0.96)	<.001
CAKUT	0.94 (0.93–0.95)	<.001
Other/missing	0.95 (0.94–0.96)	<.001
Patient Survival		
	aHR (95% CI)	<i>P</i>
All patients	0.95 (0.94–0.97)	<.001
Peak PRA		
0%–20%	0.96 (0.95–0.97)	<.001
21%–80%	0.96 (0.93–0.98)	.002
81%–100%	0.90 (0.86–0.94)	<.001

CAKUT, congenital anomalies of the kidney and urinary tract; IQR, interquartile range.

KT greatly outpaces graft survival. For example, whereas the 10-year patient survival after a transplant in 2001 was 90.5%, the 10-year graft survival from the same time point was just 60.2%. In this study, improvements in patient and graft survival were similar in magnitude, corresponding to an approximate 5% decrease in both the risk of death and graft loss with each more recent year of transplantation. Given the current discrepancy between patient survival and graft survival, an even greater rate of improvement in graft survival will be needed to better match patient survival and thereby minimize the need to return to dialysis or undergo retransplantation.²²

Our finding of a lower rate of improvement in graft survival among adolescent and female recipients and those with pretransplant dialysis and a diagnosis of FSGS is consistent with the lower graft survival

in general seen among adolescent recipients,^{7,9–12,23–27} female recipients,^{8,14} those receiving pretransplant dialysis,^{8,14,27,28} and those with FSGS.^{12,29} Unfortunately, these pediatric recipients who tend to have poorer graft survival also appear to be experiencing a slightly attenuated rate of improvement, although significant improvements did still remain across all subgroups. In addition, although African American race is associated with poorer graft survival,^{7–9,12,14,27,30} African American recipients notably experienced a rate of improvement in graft survival similar to that of other recipient groups. Similarly, higher-risk transplants based on peak PRA, previous transplant history, and HLA mismatch also saw a similar rate of improvement in graft survival compared with other lower-risk transplants. Highly sensitized patients experienced an even

more pronounced improvement in patient survival over time.

The limited improvement in long-term graft survival, compared with the improvement seen within the first year after transplantation, may be related to the exceptionally high risk of graft loss seen during late adolescence and early adulthood,^{31,32} although a similar disparity between short-term and long-term improvement has also been identified in adult recipients.^{33,34} This high-risk period, which is typically attributed to poor adherence to immunosuppression,^{35–42} alterations in health insurance coverage,^{43–45} or difficulties with transition between pediatric and adult post-transplant care,^{39,46–51} may explain the dampened improvements that were seen in long-term graft survival despite more impressive short-term improvements.

CONCLUSIONS

Over the past 25 years, pediatric KT outcomes have improved significantly for all the recipient subgroups examined in this study, reflecting dramatic longitudinal improvements in transplant care. However, adolescent and female recipients, those receiving pretransplant dialysis, and those with FSGS have had a less pronounced rate of improvement in graft survival. Progress in long-term patient and graft survival also appears to be modest compared with progress in short-term survival. In addition, patient survival still far exceeds graft survival, meaning most pediatric recipients will eventually face either retransplantation or a return to dialysis. Continued progress in outcomes after pediatric KT, much like the dramatic improvements seen over the past 25 years, is therefore needed to reach the goal in which a child with ESRD may receive a single kidney transplant that will last a lifetime.

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SNAKES ON THE BRAIN: *Like many people, I have a healthy fear of snakes. While hiking, particularly in the Southwest, I am always on the lookout for the stray rattlesnake. I am not afraid of spiders, the dark, or the basement at night, and no snake has ever harmed me or a member of my family, so I have never known why I am afraid of them. According to an article in The New York Times (Science: October 31, 2013), I can blame special neurons in the pulvinar. The pulvinar is a region in the thalamus that receives visual input. Evidently, primates have specialized cells in the pulvinar not found in other species that allow them to see and respond to snakes extremely quickly. In one experiment, trained macaque monkeys had electrodes implanted in the pulvinar and were then shown various images. When shown images of other monkeys, shapes, or faces, the neurons did not fire. However, when shown images of snakes, the neurons fired despite the fact that the monkeys had been raised in a primate facility and had never seen a snake. The work augments previous studies demonstrating that primates were exceptionally adept at identifying snakes. One hypothesis is that during primate evolutionary development, snakes were a dangerous enemy. Primates swinging through trees or resting in bushes would have a survival advantage if they could recognize and quickly startle to a dangerous foe. While I do not often rest in trees or worry much about being eaten by a snake, the neurons in my brain still recognize the shape of a snake and contribute to my fears. Of course, these fears can be overcome. One of my sons, who presumably has the same type of neurons as I do, loves snakes and has had a pet ball python for almost 15 years. Regardless, I am glad that I at least have some plausible biologic explanation for my seemingly irrational fear.*

Noted by WVR, MD