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Order of Donor Type in Pediatric Kidney Transplant Recipients Requiring Retransplantation

Kyle J. Van Arendonk, MD¹, Nathan T. James, ScM¹, Babak J. Orandi, MD, MSc¹, Jacqueline M. Garonzik-Wang, MD¹, Jodi M. Smith, MD, MPH², Paul M. Colombani, MD, MBA¹, and Dorry L. Segev, MD, PhD^{1,3}

¹Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

²Department of Pediatrics, University of Washington School of Medicine, Seattle, WA

³Department of Epidemiology, Johns Hopkins University School of Public Health, Baltimore, MD

Abstract

Background—Living donor kidney transplantation (KT) is encouraged for children with end-stage renal disease due to superior long-term graft survival compared with deceased donor KT. Despite this, there has been a steady decrease in the use of living donor KT for pediatric recipients. Due to their young age at transplant, most pediatric recipients eventually require retransplantation, and the optimal order of donor type is not clear.

Methods—Using the Scientific Registry of Transplant Recipients, we analyzed first and second graft survival among 14,799 pediatric (<18 years old) recipients undergoing KT between 1987–2010.

Results—Living donor grafts had longer survival compared to deceased donor grafts, similarly among both first (adjusted hazard ratio [aHR]=0.78, 95% CI: 0.73–0.84; p<0.001) and second (aHR=0.74, 95% CI: 0.64–0.84; p<0.001) transplants. Living donor second grafts had longer survival compared to deceased donor second grafts, similarly following living donor (aHR=0.68, 95% CI: 0.56–0.83; p<0.001) and deceased donor (aHR=0.77, 95% CI: 0.63–0.95; p=0.02) first transplants. Cumulative graft life of two transplants was similar regardless of the order of deceased donor and living donor transplantation.

Conclusions—Deceased donor KT in pediatric recipients followed by living donor retransplantation does not negatively impact the living donor graft survival advantage and provides similar cumulative graft life compared to living donor KT followed by deceased donor retransplantation. Clinical decision-making for pediatric patients with healthy, willing living donors should consider these findings in addition to the risk of sensitization, aging of the living donor, and deceased donor waiting times.

Keywords

pediatric kidney transplantation; donor selection; graft survival; donor type; retransplantation

Address for Correspondence: Dorry Segev, MD, PhD, Director of Clinical Research, Transplant Surgery, Johns Hopkins Medical Institutions, 720 Rutland Ave, Ross 771B, Baltimore, MD 21205, 410-502-6115 (tel) 410-614-2079 (fax), dorry@jhmi.edu.

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INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for pediatric patients with end-stage renal disease (ESRD) (1, 2), but because of their longevity these recipients almost inevitably outlive their grafts and require a second transplant. For example, among 11–17 year-old recipients, five-year patient survival is 95.9%, while five-year graft survival is 68.4% (3). Similarly, a survey of pediatric recipients who had survived into adulthood found that over half had undergone retransplantation within a mean follow-up of 13.2 years (4).

Since graft survival in pediatric KT recipients is better with living donor kidneys compared to deceased donor kidneys (5–7), conventional counseling has been to use the “best donor first”: if a living donor is available, a living donor transplant should be performed first in order to maximize the chance of success. If multiple living donors are available, the solution is self-evident, since subsequent transplants could also occur from living donors. However, if only one living donor is available, the most advantageous timing strategy for use of the living donor (as the first donor, or as the second donor should a first deceased donor transplant fail) remains unclear. Beyond arguments regarding risks to the living donor, deceased donor transplantation has become a quite viable option for pediatric candidates in the context of recent Share-35 prioritization, after which there has been a trend away from living donation among pediatric recipients (7–9). This age-based allocation priority often does not apply when these patients need a second transplant, as many are no longer pediatric patients at that time. Furthermore, given that retransplant patients are often sensitized (10, 11), choosing a living donor as the second donor makes possible the use of living donor desensitization regimens (12, 13).

To better understand the relationship between donor type order and pediatric KT outcomes, we used national registry data to (1) compare the likelihood of retransplantation following failure of a first transplant according to first transplant donor type, (2) compare graft survival according to transplant number and donor type, and (3) compare the expected cumulative graft life of two transplants according to order of donor type.

RESULTS

Retransplantation: By First Transplant Donor Type

Of patients receiving their first KT before age 18 ($n=14,799$), 7589 patients (51.3%) received a first living donor KT, and 7210 patients (48.7%) received a first deceased donor KT (Figure 1). Among patients with failure of a first living donor KT ($n=2713$), 59.2% underwent retransplantation and 10.6% died (before retransplantation) within five years after graft failure (Figure 2). Median time to retransplantation after first living donor graft failure was 1.3 years (interquartile range [IQR]: 0.3–2.9). Of the 1663 patients who underwent retransplantation after first living donor graft failure, 43.8% were retransplanted with another living donor graft, while 56.2% were retransplanted with a deceased donor graft (Figure 1).

Among patients with failure of a first deceased donor KT ($n=3059$), 42.5% underwent retransplantation and 13.3% died (before retransplantation) within five years after graft failure (Figure 2). Median time to retransplantation after first deceased donor graft failure was 2.0 years (IQR: 0.7–4.2). Of the 1418 patients who underwent retransplantation after first deceased donor graft failure, 74.3% were retransplanted with another deceased donor graft, and 25.7% were retransplanted with a living donor graft (Figure 1).

Graft Survival: By Donor Type and Transplant Number

Death-censored graft survival (DCGS) of living donor grafts was longer than deceased donor grafts among first transplants (adjusted hazard ratio [aHR] for graft loss=0.78, 95% CI: 0.73–0.84; $p<0.001$) as well as second transplants (aHR=0.74, 95% CI: 0.64–0.84; $p<0.001$) (Figure 3A). No statistically significant interaction was identified between donor type and transplant number ($p=0.4$), suggesting that the graft survival advantage associated with living donor grafts held similarly in first and second transplants.

Repeat Transplant Recipient Characteristics

Among patients who received two or more grafts, peak panel reactive antibody (PRA) was increased at second transplants compared to first transplants, and second transplants more frequently had zero human leukocyte antigen (HLA) mismatches (Table 1). Living donor transplants were more frequently performed preemptively, and the median time between first graft failure and receipt of second transplant was longer for those receiving a deceased donor second transplant compared to living donor second transplant.

Second Graft Survival: By Order of Donor Type

DCGS of living donor second grafts was similar following first deceased donor (DL group) compared to first living donor (LL group) transplantation (aHR=1.00, 95% CI: 0.78–1.28; $p=1.0$) (Table 2, Figure 3B). Likewise, DCGS of deceased donor second grafts was also similar following first deceased donor (DD group) compared to first living donor (LD group) transplantation (aHR=0.90, 95% CI: 0.78–1.03; $p=0.1$).

DCGS of living donor second grafts was longer than deceased donor second grafts following both first living donor (LL vs. LD) (aHR=0.68, 95% CI: 0.56–0.83; $p<0.001$) and first deceased donor (DL vs. DD) (aHR=0.77, 95% CI: 0.63–0.95; $p=0.02$) transplantation. This graft survival advantage of a living donor second graft compared to deceased donor second graft was similar regardless of first transplant donor type ($p=0.4$).

Cumulative Graft Life of Two Transplants

The cumulative graft lives, by percentiles, of D+L (first deceased donor and second living donor transplant, added by percentile to avoid biased selection of only those with failed first grafts) and L+D (first living donor and second deceased donor transplant, using similar methods) were generally similar (Figure 3C). Cumulative graft lives of 7.9, 20.1, and 34.5 years for the D+L group (25th, 50th, and 70th percentile, respectively) were comparable to 9.7, 21.0, and 33.5 years for the L+D group.

DISCUSSION

This national observational study examining the order of donor type in pediatric KT recipients revealed several important findings. First, the magnitude of improvement in graft survival among living donor grafts compared to deceased donor grafts was similar among first and second transplants, meaning the graft survival advantage of a living donor KT compared to deceased donor KT was not significantly attenuated among second transplants. Second, among pediatric KT recipients who underwent retransplantation, graft survival of a living donor second graft was similar regardless of the first transplant donor type, suggesting that on average receiving a first deceased donor KT does not negatively impact the graft survival of a living donor second graft (more so than receiving a first living donor KT). Finally, the cumulative graft life of two transplants, using percentiles for first and second graft survival among all pediatric KT recipients (including the first graft survival estimates, importantly, in those who have not yet required retransplantation), was similar regardless of the order of living donor and deceased donor transplantation.

Living donor grafts have been repeatedly shown to have improved graft survival over deceased donor grafts (5–7), including in the setting of retransplantation (14). Specifically in the pediatric population, kidneys from living donors under age 55 have been shown to provide superior graft survival compared to deceased donors kidneys (5). Our study confirmed that living donor grafts clearly provide superior graft survival compared to deceased donor grafts among both first and second transplants. Given the improved outcomes of living donor grafts, living donor KT is typically encouraged for primary pediatric KT when available, as well as for retransplants that may be required. The increased longevity of these grafts could, in the best-case scenario, allow some patients to avoid retransplantation altogether. Living kidney donation can also shorten or eliminate time on dialysis since transplantation can be scheduled in advance and does not require waiting for a high-quality deceased donor organ to become available.

Despite these benefits of living donor KT, most pediatric KT recipients eventually require retransplantation, and for this reason a difficult decision must be made, in particular among those with only one living donor available—should an available living donor graft be utilized for primary KT or alternatively “saved” for potential retransplantation? Implementation of the Share-35 allocation policy in 2005, in which grafts from deceased donors under age 35 are preferentially allocated to pediatric patients, has decreased pediatric waiting time for a deceased donor graft and increased the use of deceased donor KT in children (7–9). A concomitant decrease in the rate of pediatric living donor KT after Share-35 has suggested that some pediatric candidates may in fact be waiting for deceased donor grafts rather than utilizing available living donors (15).

The living donor-first approach is thought to avoid potential sensitization from a first deceased donor graft that could negatively impact survival of a subsequent living donor graft. In this study, both first deceased donor and living donor grafts did lead to increased sensitization. However, living donor second graft survival was similar following a first deceased donor or living donor graft and still exhibited a significant improvement compared to deceased donor second graft survival. Primary deceased donor KT could also lead to such high sensitization that retransplantation becomes exceedingly difficult. Indeed, those recipients with first deceased donor graft failure were less frequently retransplanted compared to those with first living donor graft failure. The extent to which this difference may be due to sensitization, however, is unclear. Receipt of a first living donor KT is likely a surrogate for availability of additional potential living donors as well as other factors associated with an increased likelihood of transplantation (16), independent of differences in sensitization. Finally, a recent study using OPTN data found no association between the degree of HLA mismatch of a first deceased donor graft and the development of sensitization with high PRA at listing for retransplantation (17), and the extent to which sensitization will even hinder retransplantation in the future is unclear given recent advances in desensitization protocols (13).

Given the risk of death and other adverse outcomes known to be associated with prolonged dialysis, this study evaluated only the outcome of graft survival from the individual patient perspective (i.e., the perspective of a child who could undergo either living donor or deceased donor KT). We recognize that other outcomes (growth, long-term cardiovascular morbidity, etc.) and other perspectives (societal, etc.), although not the focus of this study, may be equally valid choices. In addition, although specific age groups within the pediatric population may have different risks and needs with regard to KT, we chose to evaluate the question of donor type order from the simplified view of a homogeneous pediatric population, all of whom face the similar question of how to best utilize a living donor organ in the context of age-based priority for deceased donor organs. We acknowledge that decisions regarding donor type order may be significantly affected by the age of the

transplant candidate. Unfortunately, an in-depth analysis of precisely how this decision may vary across patient age was limited by inadequate sample sizes for the DL and LD subgroups across all age strata.

When examining donor type order from the chosen perspective, our findings suggest that the increasingly common decision to forego primary living donor KT if a deceased donor graft becomes available might be a reasonable one. The expected cumulative graft life in those receiving a living donor graft after a deceased donor graft was similar compared to those receiving the reverse donor type order. This finding may be due to the disproportionately high rate of graft failure seen among 17–24 year-olds (18, 19). Given this high-risk age period, it could theoretically be optimal to save one's "best" graft—the living donor graft—until after passage through late adolescence and early adulthood. However, the mean age at second transplantation in this study was still well within that age period shown to have the highest risk of graft loss.

An alternative explanation of our findings may be an exceptionally strong beneficial effect of undergoing pre-emptive retransplantation, enabled by the remaining availability of a living donor at that time. In addition, the benefit of a living donor graft may be diminished in the setting of recurrent disease such as focal segmental glomerular sclerosis (FSGS) (20). Given the frequency of such diagnoses prone to recur in the pediatric population, the superiority of living donor grafts may be somewhat attenuated in this population (although clearly still superior, as shown in this study), thus swaying the overall benefit towards receiving a high-quality deceased donor organ first, while still enjoying the advantage of Share-35 status. Finally, differential improvements in deceased donor and living donor graft survival over time (for example, if changes in immunosuppression have led to more dramatic improvements in deceased donor compared to living donor graft survival over time) could also have affected our findings, although likely minimized by the inclusion of transplant year in each of our multivariable models.

The results of this study must be interpreted carefully given the inherent limitations of applying observational data to clinical decision-making. First, a direct comparison of cumulative graft life in the DL and LD groups is a biased one due to the selection bias inherent in entering these cohorts and the exclusion from these groups of those patients with the longest first graft survival (who therefore have not yet required retransplantation). We avoided this bias through our comparison of the D+L and L+D groups, showing similar cumulative graft life between the two groups when examining all the available percentiles of graft survival times for first and second grafts.

Second, in addition to considering the expected cumulative graft life of two transplants, one must also consider the time that will be spent on dialysis after first graft failure and before retransplantation. The age-based allocation priority given by Share-35 often no longer applies at the time that retransplantation is required (as they may no longer be pediatric patients at that time), meaning that the waiting time for a deceased donor transplant will likely be significantly longer as an adult (after loss of a first living donor graft, for example) compared to as a pediatric patient (at the time of their first deceased donor transplant). Indeed, the patients in this study who received a second living donor KT did more frequently undergo pre-emptive retransplantation and generally spent less time back on dialysis after first graft loss. However, a close examination of waiting time between first and second KT is complex because some patients may wait for a deceased donor kidney for various periods of time before proceeding with living donor retransplantation while others may undergo immediate living donor retransplantation. In addition, organ allocation policies, including the precise delineation of how younger transplant candidates are provided

preference for deceased donor kidneys, have changed over time and may also continue to change in the future.

Finally, and perhaps most importantly, the direct application of these results to clinical decision-making requires an assumption that an available living donor's health status at the time of primary KT will not change prior to graft failure and the need for retransplantation. "Saving" one's available living donor for retransplantation induces an inherent risk that one's living donor, healthy and eligible for donation at the time of primary KT, may develop health conditions over time or even die prior to graft failure, precluding donation when retransplantation is needed. This inability to determine the future availability of living donors makes the decision to forego primary living donor KT a risky one. At the very least, the approach of living donor retransplantation (instead of primary KT) would mean that one's living donor will be older (perhaps 10–15 years or more) at the time of donation, which may negatively impact second transplant survival given the association between older living donor age and KT outcomes (21). Although our study provides important data to guide pediatric KT candidates and their families who face this choice between primary living donor KT or acceptance of an available deceased donor KT, these results must be interpreted in the context of these other variables not accounted for in an observational study.

In conclusion, deceased donor KT followed by living donor retransplantation does not negatively impact the benefit of a living donor graft used in the setting of retransplantation and appears to provide similar cumulative graft life compared to living donor KT followed by deceased donor retransplantation. These findings must be carefully interpreted within the confines of applying observational data to clinical decision-making but nonetheless suggest that the conventional living donor-first approach to pediatric kidney transplantation may not be the only acceptable timing strategy for utilization of a pediatric candidate's available living donor.

MATERIALS AND METHODS

Study Population

All kidney-only transplants completed between 1/1987 and 7/2010 in patients who received a KT prior to age 18 were identified in the Scientific Registry of Transplant Recipients (SRTR), which includes data on all donor, wait-listed candidates, and transplant recipients in the U.S. (22).

Outcome Ascertainment

DCGS was defined as the time between transplantation and either graft failure (marked by retransplantation or return to dialysis) or last follow-up with a functioning graft, censoring for death and administrative end of study. Death ascertainment was supplemented by linkage to the Social Security Death Master File; death and graft loss ascertainment were also supplemented by linkage to data from the Centers for Medicare and Medicaid Services. To assess whether differential patient survival after deceased donor and living donor KT could alter the results of the study, a sensitivity analysis examining all-cause graft loss (including death as a graft failure) rather than death-censored graft loss was performed, and inferences were unchanged.

Graft Survival: By Donor Type and Transplant Number

DCGS of all first and second grafts was compared, stratified by donor type. An interaction term between donor type and transplant number was used to test for modification of the living donor graft survival advantage by graft number.

Second Graft Survival: By Order of Donor Type

DCGS of second grafts was compared according to the order of donor type of the first two transplants among patients undergoing retransplantation: those who received two deceased donor transplants (DD group), those who received a deceased donor followed by living donor transplant (DL group), those who received living donor followed by deceased donor transplant (LD group), and those who received two living donor transplants (LL group). An interaction term was used to test for modification by first transplant donor type of the graft survival advantage of a living donor second transplant.

Cumulative Graft Life of Two Transplants

In examining graft survival among repeat transplant recipients, first grafts by definition have failed, making analysis of second grafts somewhat biased. In comparing donor type order, this bias is important because those in the LD group by definition have lost their living donor graft, which on average has a longer potential graft survival than a deceased donor graft, which those in the DL group have necessarily lost. Furthermore, those patients with the best primary living donor graft survival (who therefore have not yet required retransplantation) are by design excluded from a direct comparison of cumulative graft life in DL and LD recipients because this comparison requires the first graft to have already been lost.

To account for this bias, the n^{th} percentiles of graft survival times for *all* first living donor grafts (regardless of graft outcome – survival or failure) were added to the n^{th} percentiles of second deceased donor grafts (among those with a preceding living donor graft) (L+D group). Likewise, the n^{th} percentiles of graft survival times among *all* first deceased donor grafts (regardless of eventual graft outcome) were added to the n^{th} percentiles of second living donor grafts (among those with a preceding deceased donor graft) (D+L group). These cumulative graft lives for the L+D and D+L groups were plotted on the x-axis against each particular n^{th} percentile on the y-axis. For example, the x-axis value for the D+L group at the 40th percentile on the y-axis consisted of the 40th percentile of graft survival time for all first deceased donor grafts added to the 40th percentile of graft survival time for all second living donor grafts among those with a preceding deceased donor graft. As such, this analysis represents what would have been expected to be the ultimate combined survival of both grafts, using information not only from patients who lost their first graft but also from patients who still have a functioning first graft, thereby addressing the selection bias of a simpler direct comparison of DL and LD recipients.

Statistical Analysis

Death and retransplantation following first graft failure were explored as time-dependent competing events using cumulative incidence functions through the *stcompet* STATA module (23). DCGS was compared using Kaplan-Meier survival estimates and multivariable Cox proportional hazards models adjusting for recipient (age, sex, race, insurance, diagnosis, dialysis history, and peak PRA), donor (age and race), and transplant (HLA mismatch and year) factors. All tests were two-sided with statistical significance set at $\alpha = 0.05$. Analyses were performed using STATA 12.1/SE (College Station, Texas).

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ABBREVIATIONS

CAKUT	congenital anomalies of the kidney and urinary tract
DCGS	death-censored graft survival
DD	two deceased donor transplants
DL	deceased donor followed by living donor transplant
ESRD	end-stage renal disease
FSGS	focal segmental glomerular sclerosis
HLA	human leukocyte antigen
aHR	adjusted hazard ratio
IQR	interquartile range
KT	kidney transplantation
LD	living donor followed by deceased donor transplant
LL	two living donor transplants
OPTN	Organ Procurement and Transplantation Network
PRA	panel reactive antibody
SRTR	Scientific Registry of Transplant Recipients

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Figure 1.
Donor Type in First and Second Kidney Transplants among Primary Pediatric Kidney Transplant Recipients.

Figure 2. Patient Survival and Incidence of Retransplantation after First Graft Loss, Stratified by Donor Type of First Transplant, among Patients Receiving a Primary Pediatric Kidney Transplant.

Figure 3*.

A. Death-Censored Graft Survival, Stratified by Transplant Number and Donor Type, among Recipients of a Primary Pediatric Kidney Transplant, B. Death-Censored Graft Survival of Second Kidney Transplants, Stratified by Order of Donor Type, among Recipients of a Primary Pediatric Kidney Transplant who Underwent Retransplantation, and C. Cumulative Graft Life, by Percentiles, of the First Two Transplants in the D+L and L+D Groups.

* DD: two deceased donor grafts; LD: living donor graft followed by deceased donor graft; DL: deceased donor graft followed by living donor graft; LL: two living donor grafts; D+L: n^{th} percentile of graft survival times for all first deceased donor grafts added to n^{th} percentile for second living donor grafts among those with a preceding deceased donor graft; L+D: n^{th} percentile of graft survival times for all first living donor grafts added to n^{th} percentile for second deceased donor grafts among those with a preceding living donor graft

Table 1

Recipient, Donor, and Transplant Characteristics among Pediatric Kidney Transplant Recipients (1987–2010) who Underwent Retransplantation, Stratified by Order of Donor Type and Graft Number.

	DD n = 1044		DL n = 360		LD n = 922		LL n = 705	
	Graft	Number	Graft	Number	Graft	Number	Graft	Number
	1	2	1	2	1	2	1	2
Mean Recipient Age (SD)	11.2 (4.8)	18.4 (7.0)	11.0 (5.3)	19.1 (7.2)	10.9 (5.1)	18.6 (6.9)	10.9 (5.1)	20.1 (6.6)
Recipient Sex (% Female)	41		47		42		44	
Recipient Race (%)								
Caucasian	50		66		66		81	
African-American	29		16		17		6	
Hispanic	17		14		15		10	
Other	4		4		2		2	
Pre-emptive Status* (%)	8	8	10	18	18	8	22	25
Public Insurance† (%)	83	84	81	71	75	75	67	48
Etiology of Renal Disease								
FSGS	12		14		11		7	
Other Glomerular	14		16		16		17	
CAKUT	24		29		30		32	
Other/Missing	50		40		43		44	
Median Peak PRA* (%) (IQR)	3 (0–10)	64 (15–93)	3 (0–14)	33 (4–81)	0 (0–5)	53 (9–91)	0 (0–4)	15 (0–69)
Median Wait‡ (years)	2.3		1.2		2.0		0.6	
Mean Donor Age‡ (SD)	24.3 (15.9)	28.8 (15.1)	24.2 (16.2)	35.5 (11.0)	35.9 (8.6)	28.5 (14.4)	37.5 (8.5)	37.3 (11.6)
Donor Race (%)								
Caucasian	73	70	76	67	67	72	82	83
African-American	14	14	12	14	17	13	6	6
Hispanic	11	13	10	14	15	13	9	8
Other	2	3	2	4	1	2	2	3
Zero HLA Mismatch* (%)	4	16	7	13	4	18	5	11

	DD n = 1044		DL n = 360		LD n = 922		LL n = 705	
	Graft	Number	Graft	Number	Graft	Number	Graft	Number
	1	2	1	2	1	2	1	2
Median Transplant Year	1993	2002	1993	2003	1993	2003	1994	2004

DD: two deceased donor grafts; LD: living donor graft followed by deceased donor graft; DL: deceased donor graft followed by living donor graft; LL: two living donor grafts

PRA: panel reactive antibody

HLA: human leukocyte antigen

FSGS: focal segmental glomerulosclerosis

CAKUT: congenital anomalies of the kidney and urinary tract

^{*}Missing in 5% of records

[†]Missing in 1% of records

[‡]Time between first graft failure and receipt of second transplant

Graft Survival among Pediatric Kidney Transplant Recipients who Underwent Retransplantation, Stratified by Order of Donor Type and Graft Number.

Table 2

	DD n = 1044		DL n = 360		LD n = 922		LL n = 705	
	Graft Number		Graft Number		Graft Number		Graft Number	
	1	2	1	2	1	2	1	2
DCGS (%)								
One-Year	66.6	86.8	80.0	92.3	75.8	86.6	90.8	94.9
Five-Year	31.6	59.6	50.3	72.4	42.5	61.5	70.2	75.6
Ten-Year	10.4	38.4	22.8	50.4	15.5	38.4	35.7	57.5
Median DCGS (years)	2.7	7.2	5.0	10.8	4.1	7.5	7.9	10.8

DD: two deceased donor grafts; LD: living donor graft followed by deceased donor graft; DL: deceased donor graft followed by living donor graft; LL: two living donor grafts

DCGS: death-censored graft survival