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ORIGINAL ARTICLE

Association of age with risk of first and subsequent allograft failure and mortality among young kidney transplant recipients in the USA – a retrospective cohort study

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SUMMARY

Adolescent age may be a high-risk period for kidney allograft failure. However, the knowledge on this topic is limited mostly to the first transplant. Among 20 960 patients aged ≤21 years at the first kidney transplantation from the US Renal Data System, we evaluated the association of age at the first kidney transplant with risk for the first and subsequent graft failures (1st, 2nd, and 3rd) using the conditional risk set model for recurrent time-to-event data. The median age was 15 (interquartile range: 9–18) years, and 18% received transplants twice or more during a median follow-up of 9.7 years. The risk for graft failures was highest in 16 to <18 years old with an adjusted hazard ratio (aHR) of 1.93 (95% CI, 1.73–2.15; reference: <3 years). When separately analyzed, the highest risk was observed in 17, 19, and 21 years old for the first, second, and third transplant, respectively. Those 16 to <18 years were also strongly associated with the highest risk for death after returning to dialysis (aHR, 4.01; 95% CI, 2.82–5.71). Adolescent recipients remain at high risk for allograft failure for a long time, which may result in high mortality risk, even though they surpass this high-risk period soon after the first transplant.

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Key words
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Introduction

Kidney transplantation is the preferred renal replacement therapy in children and is beneficial for survival, growth, development, and quality of life [1,2]. Despite the improvement in surgical techniques and the progress in immunosuppressive therapies, long-term graft failure remains a major concern in kidney transplant among children and young adults [3,4]. Among several risk factors for graft failure, transplantation during adolescence has been associated with a high graft failure rate [4,5]. Nevertheless, adolescence is the most common age for transplantation in children and young adults [6]. Thus, a continuous effort to understand the impact of age at transplantation on graft failure is needed for the management of kidney transplant in this population.

A number of studies have investigated the association between age and graft failure risk [7–14]. Some studies showed a high risk for graft failure associated with adolescent age at kidney transplantation [7–10]. This association between age at transplant and graft failure is considered to be a long-term association because of the excellent short-term graft survival in pediatric transplant recipients [2]. Other studies instead examined the association between current age (irrespective of age of transplant) and graft failure as a short-term association, and also found a high risk for graft failure in adolescence [11–14]. Although these prior studies have consistently shown a high graft failure risk in adolescents, most results were obtained from only the first or second transplant, and no studies took into account repeated transplants and graft failures. Considering many children and young adults with end-stage renal disease (ESRD) require repeated kidney transplants in their lifetime [15], the risk for graft failure associated with adolescence needs to be assessed with consideration for repeated transplants and graft failures [16]. Moreover, there are scarce data on the association between age at transplantation and mortality.

We hypothesized that adolescent age at the first kidney transplant is a risk factor for first-time and subsequent graft failure. To examine this, we conducted a retrospective cohort study by means of the analytical model for recurrent time-to-event data, using a cohort which consists of young kidney transplant recipients from the United States Renal Data System (USRDS). We also examined the association between age at transplantation and mortality.

Materials and methods

This study was approved by the Institutional Review Board of University of California Irvine with waiver of informed consent because the USRDS contains only deidentified information.

Study population and data sources

A total of 21 075 patients who received a first kidney transplant at the age of 21 years old or younger (range 0–21 years) between January 1, 1995 and June 29, 2016 were identified from the USRDS database. Among them, 115 who received combined transplantation during the follow-up period were excluded. A total number of 20 960 patients were identified for the main analytical cohort. Patients were followed from the time of the first transplant until death, loss to follow-up, or the end of follow-up (June 30, 2016), whichever occurred first.

Information on death, transplant, recipient age, sex, race, ethnicity, Medicaid use, initial renal replacement modality, primary cause of ESRD, comorbidities, donor type, blood type of recipient and donor, donor age, human leukocyte antigen (HLA) type of recipient and donor, panel reactive antibodies (PRA), and cold ischemia time was obtained from the USRDS Patients file (PATIENTS), the Treatment History file (RXHIST), the Medical Evidence file (MEDEVID) which contains data from the Centers for Medicare and Medicaid Services Medical Evidence form (CMS 2728), the Transplant file (TX), and the TXUNOS files which contain detailed data on kidney transplant from the Organ Procurement and Transplant Network (OPTN)/the United Network for Organ Sharing (UNOS).

Statistical analysis

Characteristics at the time of the first and second transplant were summarized across age categories, and expressed as number (proportions), mean ± SD, or medians (interquartile range), as appropriate.

The primary outcome was graft failure, which included the first and subsequent graft failures during the follow-up period. We used the Prentice, Williams and Peterson (PWP) model for the analysis of recurrent events [17]. The PWP model is a time-to-event analysis, and analyses ordered multiple events by stratification based on the numbers of episodes [18,19]. In the present study, all patients were at risk for the first stratum, and only those who experienced graft failure and received subsequent

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transplant were at risk for successive stratum. We used the PWP model with gap time which estimates time to each graft failure event from the time of corresponding transplant, that is, from first transplant to first event, from second transplant to second event, from third transplant to third event, with an assumption of a renewal process [18]. We did not include the fourth and fifth transplant (a total of 31 transplants) for analyses because strata with too small number of events makes the PWP model unstable [18]. We accounted for within-person effect for graft failure due to multiple event data using robust standard errors [20]. The effects of age to multiple graft failure events were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We categorized age at the first transplant into eight groups, that is, <3, 3 to <6, 6 to <10, 10 to <13, 13 to <16, 16 to <18, 18 to <20, and ≥20 years. As a sensitivity analysis, age was modeled as a continuous variable, and its association with graft failure was estimated using a restricted cubic spline function with four knots placed at the 5th, 35th, 65th, and 95th percentile of age.

We also examined the association of age at transplant with graft failure for the first, second, and third transplant separately using Cox regression models. Both categorical and continuous variables for age at each transplant were used for the analyses. For the second transplant, we newly stratified age into eight groups, that is, <10, 10 to <13, 13 to <16, 16 to <18, 18 to <20, 20 to <22, 22 to <27, and ≥27 years. We did not assess categorical age at the third transplant because of a small number of patients ($N = 403$). We defined patients with prolonged time to second transplantation from the first graft failure as patients having a time to second transplantation greater than the median for our second transplant cohort (1.8 years). We then evaluated the association of age at the first transplant with prolonged time to the second transplant using logistic regression models among patients who underwent a second transplant.

As a secondary outcome, we examined the association between age at the first transplant and overall mortality using a Cox regression model. Given the survival benefit of transplantation, we considered two mortality periods: the risk of death with a functioning graft and the risk of death after returning to dialysis. Thus, we separated the outcome into death with functioning graft and death after returning to dialysis, and performed the same analyses. Patients were censored for death, loss to follow-up, or the end of follow-up in the graft failure analyses; for loss to follow-up or the end of follow-up in the mortality analyses. All analyses included unadjusted, case mix-adjusted, and fully adjusted models. The unadjusted model consisted of categorized age. The case mix-adjusted model included categorized age plus, sex, race (white, black, other races), ethnicity (Hispanic or non-Hispanic), Medicaid coverage as an indicator of lower income status, dialysis vintage (preemptive transplant, >0 to <12, 12 to <36, ≥36 months), primary cause of ESRD (congenital anomalies of the kidney and urinary tract, primary glomerulonephritis, focal segmental glomerulosclerosis, secondary glomerulonephritis, other causes), comorbidities (hypertension, heart disease, nonrenal anomaly), and transplant year (1995–1999, 2000–2004, 2005–2009, 2010–2016) as covariates. The fully adjusted model included recipient blood type (O, A, B, AB), donor age (<20, 20 to <30, 30 to <40, ≥40 years), HLA mismatch number (0, 1, 2, 3, 4, 5, 6), peak PRA (<5, 5 to <85, ≥85%), cold ischemia time (living donor transplant, >0 to <12, 12 to <18, 18 to <24, ≥24 h) in addition to all covariates in the case mix-adjusted model. The frequency of missing data was 4%, 4%, 5%, 16%, and 7% in recipient blood type, donor age, HLA mismatch number, peak PRA, and cold ischemia time, respectively. Missing categories were added to the categories above and were used for analyses. Analyses were performed using STATA MP, version 13.1 (Stata Corp, College Station, TX, USA).

Results

Patients characteristics and crude graft failure, mortality rate

A total of 20 960 patients were included for analyses. Median age at the first transplant was 15 (interquartile range: 9–18) years old. Among all patients, 59% were male, 28% received transplant as a first renal replacement modality, 54% received a first transplant after 2005, and 50% received a living donor transplant as a first transplant (Table 1). Median age at the second transplant was 23 (interquartile range: 17–27) years old, and median time from the first to the second transplant was 8.1 (interquartile range: 4.7–11.8) years with no trend across age strata, where median (interquartile rage) time was 8.5 (4.2–12.6), 7.9 (4.6–12.1), 7.9 (4.5–11.4), and 8.2 (5.1–11.6) years in <6, 6 to <13, 13 to <18, and ≥18 years old at the first transplant, respectively (P for trend = 0.87). Patients who received a second transplant had higher peak PRA and were less likely to receive living donor transplantation compared to those who received a first transplant (Table S1).

Among 20 960 patients, 3850 (18%) patients received kidney transplants twice or more and up to five times

Table 1. Characteristics at the first kidney transplant.

		Age (years)							
	All	<3	3 to <6	6 to <10	10 to <13	13 to <16	16 to <18	18 to <20	≥20
N (%)	20 960	1638 (8)	1670 (8)	2185 (10)	2321 (11)	3778 (18)	3522 (17)	2858 (14)	2988 (14)
Male (%)	12 263 (59)	1151 (70)	1068 (64)	1274 (58)	1267 (55)	2101 (56)	2032 (58)	1650 (58)	1720 (58)
Race (%)									
White	14 851 (71)	1281 (78)	1194 (71)	1572 (72)	1623 (70)	2647 (70)	2405 (68)	1961 (69)	2168 (73)
Black	3894 (19)	186 (11)	270 (16)	375 (17)	425 (18)	720 (19)	743 (21)	609 (21)	566 (19)
Other	2215 (11)	171 (10)	206 (12)	238 (11)	273 (12)	411 (11)	374 (11)	288 (10)	254 (9)
Hispanic (%)	4728 (23)	287 (18)	381 (23)	478 (22)	551 (24)	915 (24)	855 (24)	636 (22)	625 (21)
Medicaid (%)	7999 (38)	752 (46)	847 (51)	1039 (48)	973 (42)	1485 (39)	1280 (36)	869 (30)	754 (25)
Preemptive transplant (%)	5906 (28)	425 (26)	512 (31)	777 (36)	771 (33)	1115 (30)	911 (26)	761 (27)	634 (21)
Dialysis vintage (months)	14 (7–26)	15 (9–22)	20 (9–37)	14 (7–27)	13 (6–24)	13 (6–23)	14 (7–25)	14 (7–27)	16 (8–30)
Primary cause of ESRD (%)									
Primary GN	2670 (13)	28 (2)	51 (3)	140 (6)	212 (9)	445 (12)	523 (15)	543 (19)	728 (24)
FSGS	2523 (12)	25 (2)	129 (8)	274 (13)	267 (12)	479 (13)	495 (14)	447 (16)	407 (14)
CAKUT	5652 (27)	806 (49)	682 (41)	797 (36)	771 (33)	1005 (27)	746 (21)	484 (17)	361 (12)
Secondary GN	1238 (6)	3 (0)	13 (1)	46 (2)	128 (6)	221 (6)	281 (8)	224 (8)	322 (11)
Others	8877 (42)	776 (47)	795 (48)	928 (42)	943 (41)	1628 (43)	1477 (42)	1160 (41)	1170 (39)
Comorbidities (%)									
Hypertension	7496 (36)	291 (18)	373 (22)	613 (28)	692 (30)	1308 (35)	1423 (40)	1280 (45)	1516 (51)
Heart disease	583 (3)	42 (3)	47 (3)	51 (2)	54 (2)	113 (3)	85 (2)	88 (3)	103 (3)
Nonrenal anomaly	563 (3)	62 (4)	74 (4)	100 (5)	68 (3)	92 (2)	84 (2)	50 (2)	33 (1)
Transplant year									
1995–1999	4579 (22)	322 (20)	336 (20)	506 (23)	534 (23)	781 (21)	722 (20)	651 (23)	727 (24)
2000–2004	4995 (24)	372 (23)	349 (21)	511 (23)	580 (25)	917 (24)	754 (21)	711 (25)	801 (27)
2005–2009	5299 (25)	412 (25)	394 (24)	510 (23)	561 (24)	1042 (28)	1000 (28)	683 (24)	697 (23)
2010–2016	6087 (29)	532 (32)	591 (35)	658 (30)	646 (28)	1038 (27)	1046 (30)	813 (28)	763 (26)
Recipient blood type (%)									
O	9703 (46)	776 (47)	783 (47)	1047 (48)	1041 (45)	1790 (47)	1687 (48)	1279 (45)	1300 (44)
A	7100 (34)	538 (33)	548 (33)	679 (31)	796 (34)	1281 (34)	1140 (32)	998 (35)	1120 (37)
B	2543 (12)	177 (11)	223 (13)	272 (12)	283 (12)	422 (11)	435 (12)	371 (13)	360 (12)
AB	767 (4)	65 (4)	54 (3)	87 (4)	84 (4)	131 (3)	125 (4)	106 (4)	115 (4)

Table 1. Continued.

	All	Age (years)							
		<3	3 to <6	6 to <10	10 to <13	13 to <16	16 to <18	18 to <20	≥20
Missing	847 (4)	82 (5)	62 (4)	100 (5)	117 (5)	154 (4)	135 (4)	104 (4)	93 (3)
Donor age (years)	31 ± 13	28 ± 11	27 ± 11	28 ± 12	30 ± 12	30 ± 12	30 ± 13	33 ± 13	35 ± 14
HLA mismatch number (%)									
0	512 (2)	16 (1)	20 (1)	26 (1)	35 (2)	70 (2)	72 (2)	106 (4)	167 (6)
1	603 (3)	45 (3)	40 (2)	53 (2)	66 (3)	89 (2)	95 (3)	93 (3)	122 (4)
2	2236 (11)	244 (15)	159 (10)	231 (11)	242 (10)	348 (9)	303 (9)	331 (12)	378 (13)
3	6122 (29)	608 (37)	524 (31)	619 (28)	657 (28)	1031 (27)	838 (24)	853 (30)	992 (33)
4	3149 (15)	182 (11)	257 (15)	358 (16)	353 (15)	602 (16)	586 (17)	403 (14)	408 (14)
5	4410 (21)	269 (16)	370 (22)	456 (21)	512 (22)	880 (23)	865 (25)	575 (20)	483 (16)
6	2787 (13)	164 (10)	218 (13)	313 (14)	312 (13)	544 (14)	593 (17)	351 (12)	292 (10)
Missing	1141 (5)	110 (7)	82 (5)	129 (6)	144 (6)	214 (6)	170 (5)	146 (5)	146 (5)
Peak PRA (%)									
<5%	13 858 (66)	1035 (63)	1090 (65)	1446 (66)	1507 (65)	2559 (68)	2367 (67)	1888 (66)	1966 (66)
5 to <85%	3622 (17)	312 (19)	295 (18)	375 (17)	417 (18)	592 (16)	565 (16)	509 (18)	557 (19)
≥85%	201 (1)	16 (1)	10 (1)	19 (1)	15 (1)	32 (1)	27 (1)	36 (1)	46 (2)
Missing	3279 (16)	275 (17)	275 (16)	345 (16)	382 (16)	595 (16)	563 (16)	425 (15)	419 (14)
Living donor (%)	10 474 (50)	1037 (63)	806 (48)	1012 (46)	1074 (46)	1683 (45)	1363 (39)	1555 (54)	1944 (65)
Cold ischemia time (h)	14 (9–19)	13 (9–18)	13 (9–18)	13 (9–18)	13 (9–19)	14 (9–19)	13 (9–19)	14 (10–21)	17 (11–23)

Dialysis vintage is only for patients whose initial renal replacement modality was dialysis. Cold ischemia time is only for patients who received deceased donor transplant. Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median (interquartile range).

CAKUT, congenital anomaly of the kidney and urinary tract; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HLA, human leukocyte antigen; PRA, panel reactive antibodies.

during the median follow-up period of 9.7 (interquartile range: 4.9–14.6) years (Fig. S1). One-, five-, and ten-year graft survival rate was 94%, 77%, and 59% for the first transplant, respectively. The graft survival rate was slightly better in the first transplant than the second and the third transplant (Fig. 1). The median graft survival time was 13.0, 10.8, and 9.0 years in the first, second, and third transplant, respectively. The graft survival rate improved over time between 1995 and 2016 (Table 2). Similarly, crude graft failure and mortality rate showed decreasing secular trends (Fig. 2).

Risk for graft failure

Among the 20 960 patients, there were 25 213 transplants. In the recurrent event analysis, the risk for graft failure sharply increased after age 6 years with a peak at the age group of 16 and 17 years old, where the fully adjusted HR was 1.93 (95% CI, 1.73–2.15; reference: <3 years old) (Fig. 3). This association was robust in restricted cubic splines across all levels of adjustment (Fig. S2).

A total of 8035 (out of 20 960 transplants), 1240 (out of 3850 transplants), and 120 (out of 403 transplants) graft failures were observed in the first, second, and third transplant, respectively (Fig. S1). Crude graft failure rates were 5.3, 6.8, and 8.1 per 100 patient-years for the first, second, and third transplant, respectively. Age of 16 and 17 years was associated with the highest risk for graft failure in the first transplant; the fully adjusted HR was 1.99 (95% CI, 1.77–2.23; reference: <3 years old; Fig. S3a). In the second transplant, age of 18 and 19 years was associated with the highest risk for graft failure; the fully adjusted HR was 2.28 (95% CI, 1.71–3.03; reference: <10 years old; Fig. S3b). In the restricted cubic spline, the highest risk for graft failure was observed in 17, 19, and 21 years old for the first, second, and third transplant, respectively (Fig. 4). Deceased donor transplant had higher risk for graft failure in the first and second transplant compared to living donor transplant, where the fully adjusted HR was 1.20 (95% CI, 1.08–1.32) and 1.68 (95% CI, 1.34–2.11), respectively. The higher risk in deceased donor transplant among those who underwent the second transplant was consistent regardless of the donor type in the first transplant; that is, the fully adjusted HRs were 1.61 (95% CI, 1.13–2.31) and 1.70 (95% CI, 1.21–2.41) in living and deceased donor at the first transplant, respectively. The J- and U-shaped associations between age and the risk for graft failure in the first and second transplant were consistent in living and deceased donor transplant, though the risks in adolescents and young adults were noticeable in living donor transplant (Fig. S4).

Risk for a prolonged time to second transplantation from the first graft failure

Among 3850 patients who underwent second transplantation, median time to second transplantation from the first graft failure was 1.8 (interquartile range: 0.4–4.3)

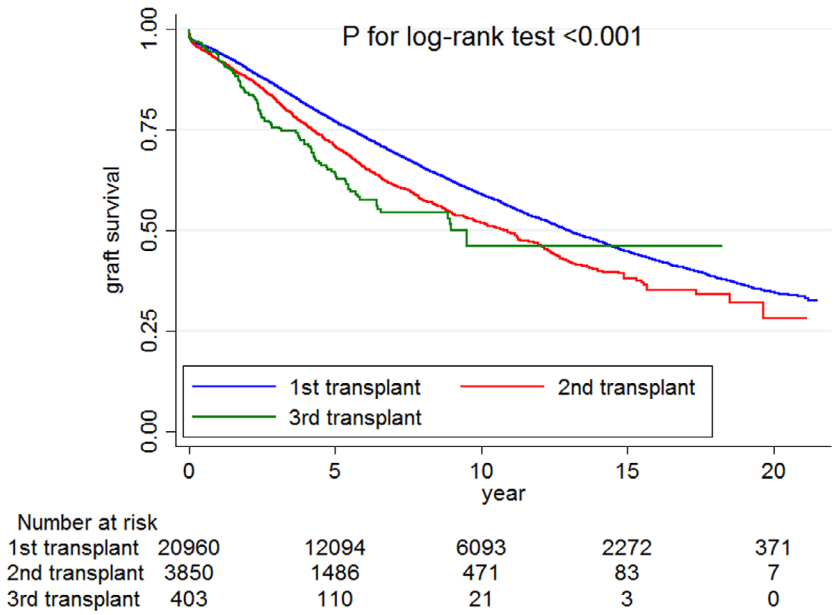

Figure 1 Kaplan–Meier survival curve for graft failure.

Table 2. One-, five- and ten-year graft survival rates.

	1st transplant			2nd transplant			3rd transplant		
	1 year	5 year	10 year	1 year	5 year	10 year	1 year	5 year	10 year
All	94 (94–95)	77 (76–78)	59 (58–60)	92 (91–93)	71 (69–73)	52 (50–54)	93 (90–95)	64 (58–70)	46 (37–55)
Transplant year									
1995–1999	91 (91–92)	73 (71–74)	54 (52–55)	83 (77–87)	59 (52–65)	39 (32–45)	NA	NA	NA
2000–2004	93 (93–94)	74 (73–75)	58 (56–59)	90 (87–92)	64 (60–68)	47 (43–51)	89 (72–96)	40 (24–56)	NA
2005–2009	95 (94–95)	78 (77–79)	61 (59–62)	91 (89–93)	69 (66–72)	52 (48–55)	92 (85–96)	70 (60–78)	57 (45–67)
2010–2016	97 (96–97)	84 (83–85)	NA	95 (94–96)	78 (75–81)	NA	94 (90–97)	66 (55–75)	NA

Values are given as percentage (95% confidence interval). Survival rates were not assessed because of small sample size ($N < 10$).
NA, not assessed.

years. Age of 16 and 17 years was associated with a prolonged time to second transplantation, where the fully adjusted odds ratio was 3.74 (95% CI, 2.67–5.24; reference: <3 years old; Fig. 5).

Risk for mortality

A total of 2219 deaths were observed during the follow-up period and the crude mortality rate was 11 per 1000 patient-years. Information for cause of death was available for 1655 (75%) patients, and cardiovascular disease and infection were the leading causes of both death with functioning graft and after returning to dialysis. The proportion of infection-related deaths was high in those younger than 6 years old for death with functioning graft, whereas the proportion of cardiovascular-related deaths was high in older age for death after returning to dialysis (Table S2). Age of 16 and 17 years was associated with the highest mortality risk, where the fully adjusted HR was 1.62 (95% CI, 1.31–2.00; reference: <3 years old; Fig. S5). The number of deaths after returning to dialysis was approximately two times larger than that of deaths with functioning graft for the first, second, third, and fourth transplant (Fig. 6). While being associated with the highest risk for death after returning to dialysis (fully adjusted HR, 4.01; 95% CI, 2.82–5.71), 16 and 17 years was associated with low risk for death with functioning graft (fully adjusted HR, 0.66; 95% CI, 0.50–0.89; Fig. 7).

Discussion

In a cohort of 20 960 patients, 18% experienced two or more transplants during the median follow-up period of 9.7 years. The graft survival and mortality rate improved over time between 1995 and 2016. Age of 16 and 17 years at the first transplant was associated with the highest risk for the first and subsequent graft failures (1st, 2nd, and 3rd) during the long-term course of ESRD. When examining the first and second transplant events separately, the risks for graft failure associated with age were highest in 16 and 17 years, and 18 and 19 years, respectively. The highest-risk age shifted to even older age in the third transplant. Patients aged 16 and 17 years at the first transplant had a longer time to second transplantation from the first graft failure. Age of 16 and 17 years was also associated with the highest risk for overall mortality. We found that 16 and 17 years old was strongly associated with risk for death after returning to dialysis, whereas the risk for death with functioning graft was low in this age range.

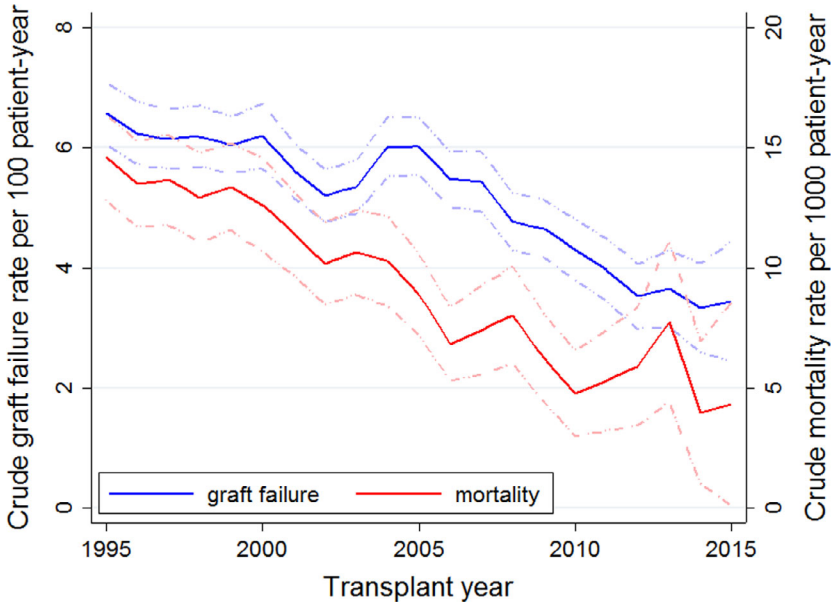

Figure 2 Crude graft failure and mortality rates across transplant year. Blue and red lines represent graft failure and mortality rates with 95% confidence intervals, respectively.

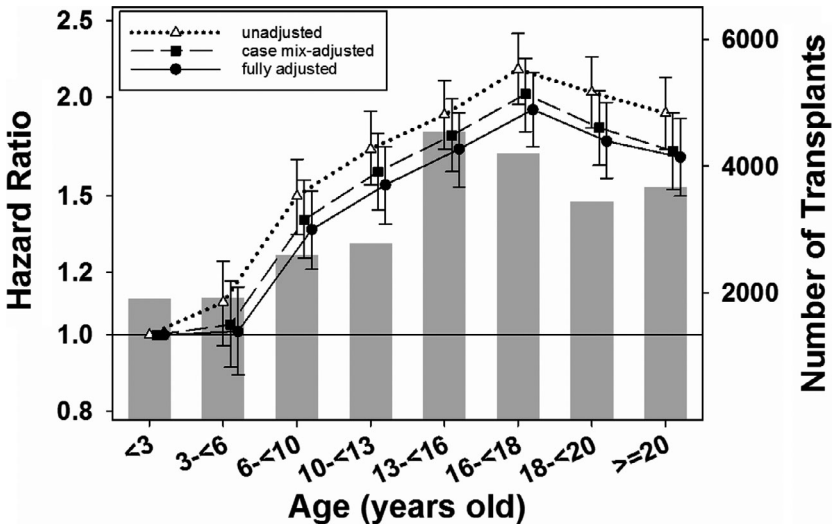

Figure 3 Hazard ratios for recurrent graft failures (reference: <3 years old). The result was obtained from a total of 25 213 transplants which included the first, second, and third transplant.

Our main result showed age at the first transplant with risk for recurrent graft failures, which included time to first graft failure from the first transplant, time to second graft failure from the second transplant, and time to third graft failure from the third transplant, as the long-term association. The risk for graft failure associated with age is often discussed with reference to nonadherence, where adolescence is a time of high risk for nonadherence [21]. Due to many missing data on variables related to nonadherence, we were unable to examine the effect of nonadherence directly. Instead, we examined the association of age with time to second transplantation because patients who lost their graft from nonadherence may have a longer waiting time [22]. The result was similar to the association between age and graft failure risk. This might indirectly indicate involvement of nonadherence even though it does not underpin the theory. Our results also showed that the lowest risk of graft failure was in children younger than 3 years old. Although this finding might encourage transplantation at very young age in terms of

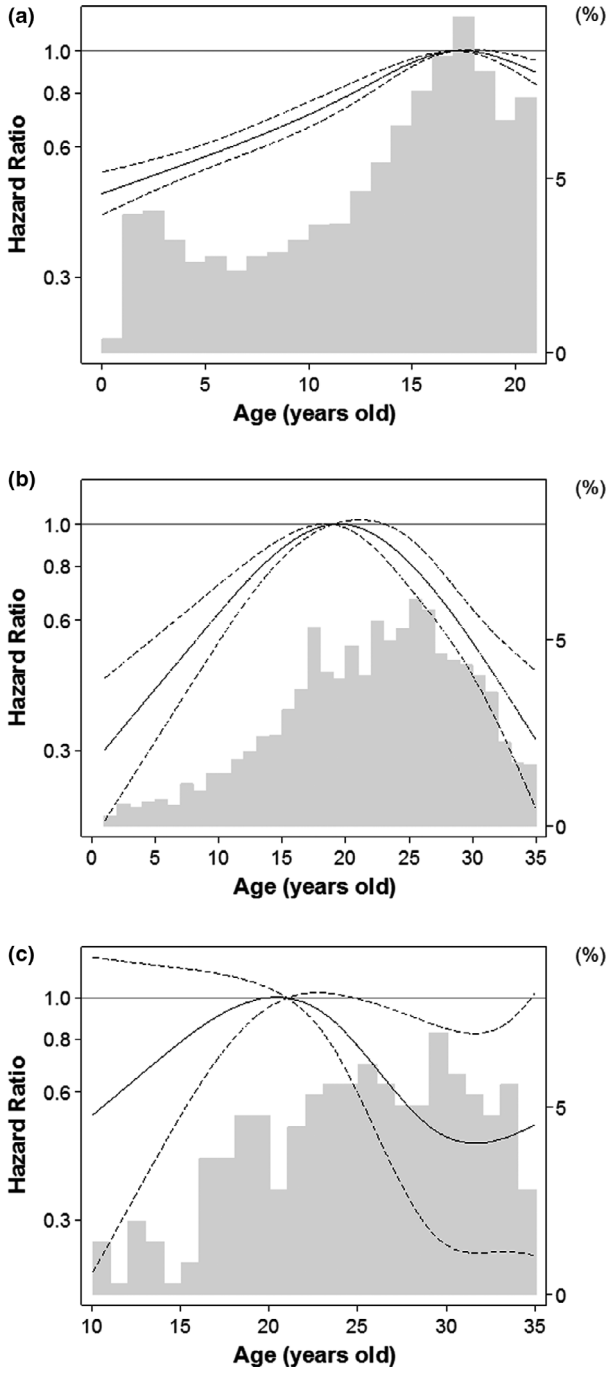

Figure 4 Hazard ratios for graft failure with restricted cubic spline in (a) the first transplant (N = 20 960), (b) the second transplant (N = 3850), and (c) the third transplant (N = 403). Histogram is for age distribution. Solid and dotted lines represent hazard ratio and 95% confidence interval, respectively.

graft failure, careful consideration is needed because the risk for death with functioning graft was also highest in this group.

We found that adolescence is not always the highest-risk age when repeated transplants are separately assessed; that is, the highest-risk age shifted to older age in the second and third transplant. Because a past history of nonadherence is a risk factor for nonadherence in the future [23], patients who lost their first graft due to nonadherence are potentially at risk of nonadherence in subsequent transplants even if they pass through adolescence, which may result in a shift in the highest-risk age. Other factors which are related to repeated transplantation might also explain this shift in age. As examples, repeated operations to previously used sites are complicated [24]; patients with repeated transplants are highly sensitized [24]; patients with focal segmental glomerulosclerosis, which is one of the common causes of ESRD in children, have a high risk for recurrence after the second transplant [25]. Even if patients pass through adolescence and their adherence improves, high graft failure risk might remain owing to the additional effects caused by the factors related to repeated transplant. Thus, age at the first transplant is potentially associated with a long-term graft survival including the first and subsequent transplants. Although patients who received the first kidney transplant during adolescence pass this high-risk age window soon after transplant, they remain at high risk for graft failure for a long time thereafter.

Adolescence at the first transplantation was associated with high mortality risk as well as high risk for graft failure. Because graft failure is strongly associated with mortality among transplant patients [26], graft failure is most likely an intermediate on the causal pathway in the association between age and mortality; that is, adolescence at the first transplantation has a high risk for graft failure which may thereby result in a high risk for mortality. Differences in the cause of death and contrasts between risk for death with functioning graft and after returning to dialysis in our results would underpin this theory. Moreover, the prolonged time to second transplant may aggravate the mortality risk in adolescents. Very young children are more vulnerable to infection than older children which might be one of the reasons for lower risk for death with functioning graft among adolescents and young adults compared to younger children.

Several limitations should be acknowledged. First, because we included patients over 20 years to take into account recurrent graft failure events in the long follow-up period, the cohort was heterogeneous in terms of graft survival rate and number of recurrent graft failures. Pre, post-transplant management and surgical techniques improved over time during the follow-up period, which resulted in the improvement in graft survival rate. Number of recurrent graft failure events was larger in patients receiving transplantation in the early

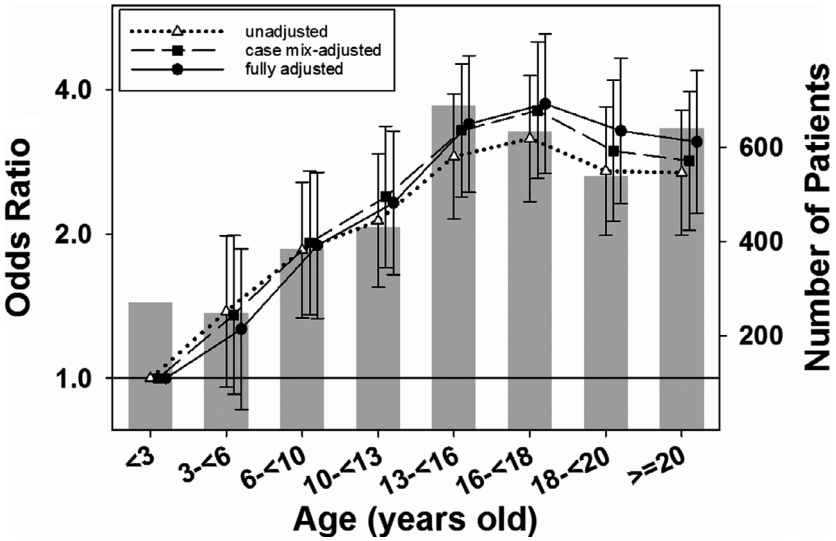

Figure 5 Odds ratios for a prolonged time to second transplantation from the first graft failure among 3850 patients who underwent second transplantation (reference: <3 years old).

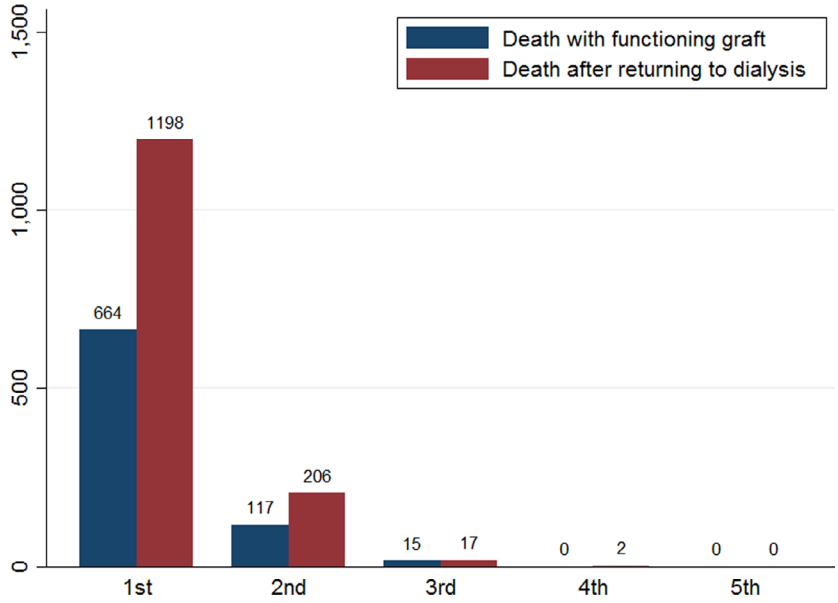

Figure 6 Number of deaths with functioning graft and deaths after returning to dialysis.

study period. This heterogeneity in the outcome might influence our result. Second, we did not evaluate cause of graft failure in our models because of the large amount of missing information, which makes it difficult to clearly discuss the underlying mechanisms between age and graft failure. Yet, our results still indicate the usefulness of age at transplantation as a predictor of future graft failure. Third, due to the observational nature of this study, we were not able to exclude the possibility of residual confounding and the presence of unmeasured confounders.

In conclusion, adolescent age at the first transplant was associated with the highest risk for the first and subsequent graft failures. Health care providers who engage in kidney transplantation should be aware of persistent risk for graft failure in this population even though they pass this high-risk age window soon after the first transplant. In addition, adolescence was associated with the highest risk for death after returning to dialysis in contrast to the low risk for death with a functioning graft. Elucidation of the mechanism of age associated graft failure and improvement in graft survival may lead to improvement

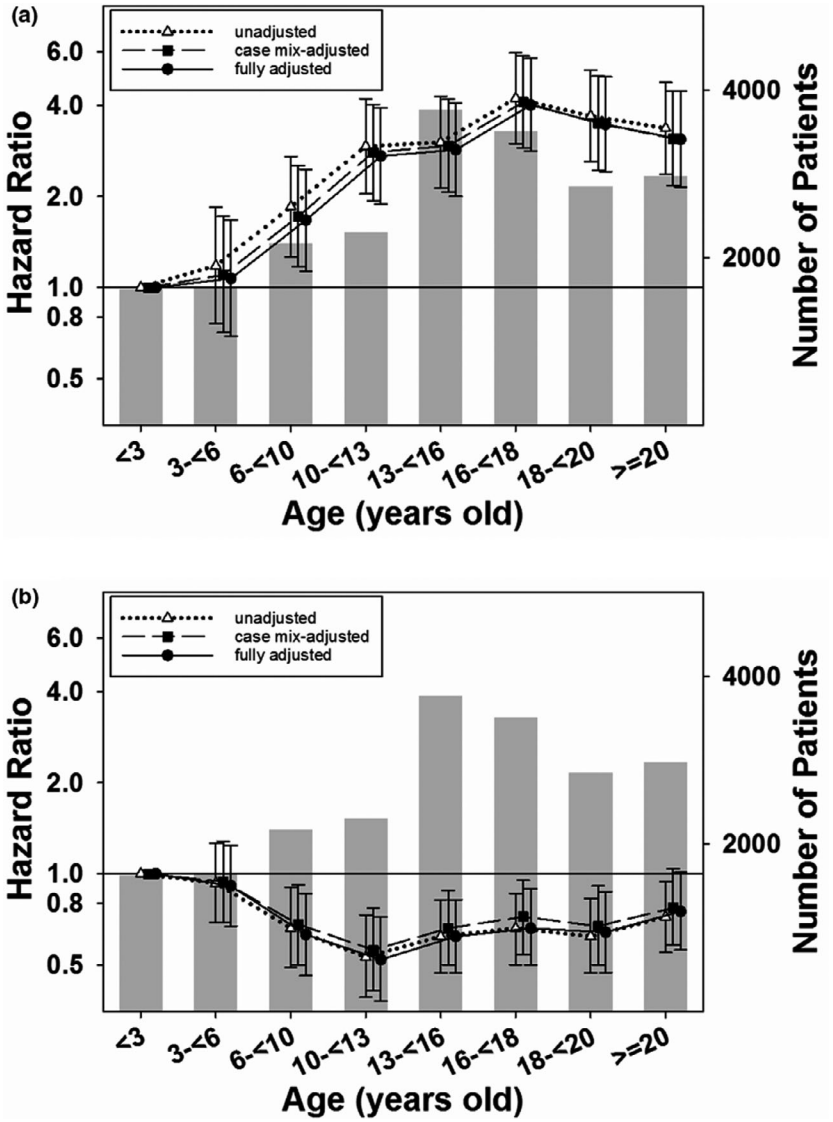

Figure 7 Hazard ratios for risk of (a) death after returning to dialysis and (b) death with functioning graft among 20 960 patients (reference: <3 years old).

in patient survival. Reassessment and update of the association between age and graft failures will be needed in the future due to continuing improvement in the management of pediatric kidney transplantation.

Authorship

Okuda and Kalantar-Zadeh take responsibility for the integrity and the accuracy of the data analysis. Study concept and design: Okuda. Data acquisition: Streja and Kalantar-Zadeh. Data analysis: Okuda and Streja. Data interpretation: Rhee, Tantisattamo, Reddy, Laster, Tang, Rajpoot, Molnar, Ichii, and Obi. Drafting manuscript: Okuda. Study supervision: Kalantar-Zadeh. Approving final version of manuscript: All authors

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Conflict of interest

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. K.K.-Z. has received honoraria and/or

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Data availability statement

Data and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedures, given that data are provided under contract with the United States Renal Data System and are at its disposal. Hence, this center may not override the contractual agreements. Additional details about the analytical methods can be provided on request.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Number of transplants and graft failures during the follow-up period.

Figure S2. Hazard ratios for recurrent graft failures with restricted cubic spline in (A) unadjusted, (B) case mix-adjusted, and (C) fully adjusted models (reference: 2 years old). The result was obtained from a total of 25,213 transplants which included first, second, and third transplant. Histogram is for age distribution. Solid and dotted lines represent hazard ratio and 95% confidence interval, respectively.

Figure S3. Hazard ratios for graft failure in (A) the first transplant (N = 20 960; reference: <3 years old) and (B) the second transplant (N = 3850; reference: <10 years old). Age is that at the timing of the first and the second transplant, respectively.

Figure S4. Hazard ratios for graft failure in living and deceased donor transplant in (A) the first transplant (N = 20 960; reference: <3 years old) and (B) the second transplant (N = 3850; reference: <10 years old). Age is that at the timing of the first and the second transplant, respectively.

Figure S5. Hazard ratios for mortality among 20 960 patients (reference: <3 years old).

REFERENCES

1. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatr Nephrol* 2007; **22**: 1999.
2. Holmberg C, Jalanko H. Long-term effects of paediatric kidney transplantation. *Nat Rev Nephrol* 2016; **12**: 301.
3. Gulati A, Sarwal MM. Pediatric renal transplantation: an overview and update. *Curr Opin Pediatr* 2010; **22**: 189.
4. Foster BJ. Heightened graft failure risk during emerging adulthood and transition to adult care. *Pediatr Nephrol* 2015; **30**: 567.
5. Bertram JF, Goldstein SL, Pape L, *et al.* Kidney disease in children: latest advances and remaining challenges. *Nat Rev Nephrol* 2016; **12**: 182.
6. Smith JM, Martz K, Blydt-Hansen TD. Pediatric kidney transplant practice patterns and outcome benchmarks, 1987–2010: a report of the North American Pediatric Renal Trials and Collaborative Studies. *Pediatr Transplant* 2013; **17**: 149.
7. Smith JM, Ho PL, McDonald RA, *et al.* Renal transplant outcomes in adolescents: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002; **6**: 493.
8. Keith DS, Cantarovich M, Paraskevas S, *et al.* Recipient age and risk of chronic allograft nephropathy in primary deceased donor kidney transplant. *Transpl Int* 2006; **19**: 649.
9. Andreoni KA, Forbes R, Andreoni RM, *et al.* Age-related kidney transplant outcomes: health disparities amplified in adolescence. *JAMA Intern Med* 2013; **173**: 1524.
10. Gupta M, Wood A, Mitra N, *et al.* Repeat kidney transplantation after failed first transplant in childhood: past performance informs future performance. *Transplantation* 2015; **99**: 1700.
11. Foster BJ, Dahhou M, Zhang X, *et al.* Association between age and graft failure rates in young kidney transplant recipients. *Transplantation* 2011; **92**: 1237.
12. Van Arendonk KJ, James NT, Boyarsky BJ, *et al.* Age at graft loss after pediatric kidney transplantation: exploring the high-risk age window. *Clin J Am Soc Nephrol* 2013; **8**: 1019.
13. Kabore R, Couchoud C, Macher MA, *et al.* Age-dependent risk of graft failure in young kidney transplant recipients. *Transplantation* 2017; **101**: 1327.
14. Ritchie AG, Clayton PA, McDonald SP, *et al.* Age-specific risk of renal graft loss from late acute rejection or non-compliance in the adolescent and young adult period. *Nephrology* 2018; **23**: 585.

15. Graves RC, Fine RN. Kidney retransplantation in children following rejection and recurrent disease. *Pediatr Nephrol* 2016; **31**: 2235.
16. Holme I, Fellstrom BC, Jardine AG, *et al*. Model comparisons of competing risk and recurrent events for graft failure in renal transplant recipients. *Clin J Am Soc Nephrol* 2013; **8**: 241.
17. Prentice RL, Williams BJ, Peterson AV. On the regression analysis of multivariate failure time data. *Biometrika* 1981; **68**: 373.
18. Amorim LD, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. *Int J Epidemiol* 2015; **44**: 324.
19. Wei LJ, Glidden DV. An overview of statistical methods for multiple failure time data in clinical trials. *Stat Med* 1997; **16**: 833; discussion 841-851.
20. Lin DY, Wei LJ. The robust inference for the cox proportional hazards model. *J Am Stat Assoc* 1989; **84**: 1074.
21. Nevins TE, Nickerson PW, Dew MA. Understanding medication nonadherence after kidney transplant. *J Am Soc Nephrol* 2017; **28**: 2290.
22. Manickavasagar R, Wong G, Alexander SI, *et al*. Allograft outcome following repeat transplantation of patients with non-adherence-related first kidney allograft failure: a population cohort study. *Transpl Int* 2019; **32**: 1247.
23. Fine RN, Becker Y, De Geest S, *et al*. Nonadherence consensus conference summary report. *Am J Transplant* 2009; **9**: 35.
24. Redfield RR, Gupta M, Rodriguez E, *et al*. Graft and patient survival outcomes of a third kidney transplant. *Transplantation* 2015; **99**: 416.
25. Vinai M, Waber P, Seikaly MG. Recurrence of focal segmental glomerulosclerosis in renal allograft: an in-depth review. *Pediatr Transplant* 2010; **14**: 314.
26. Samuel SM, Tonelli MA, Foster BJ, *et al*. Survival in pediatric dialysis and transplant patients. *Clin J Am Soc Nephrol* 2011; **6**: 1094.