The impact of age at transfer from pediatric to adult-oriented care on renal allograft survival

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Abstract: Immaturity among individuals transferred from pediatric to adult-oriented care at a young age may leave them vulnerable to higher graft failure risks than in individuals transferred older. We sought to determine the impact of age at transfer on renal allograft failure rates. We evaluated graft failure rates among 440 kidney recipients recorded in the UNOS database (1987–2007), who had been transferred from pediatric to adult care. Transfers were identified using the center codes recorded at yearly data collection. Failure rates for those transferred early (< 21 yr old) were compared with rates for those transferred late (≥ 21 yr old); time-dependent Cox models were used to estimate the additional risk of graft failure associated with early vs. late transfer. The age-standardized failure rate was 12.9 per 100 person-years among those transferred early, and 8.7 per 100 person-years among those transferred late. Compared with individuals the same age who had transferred late, graft failure rates were 58% higher ([95% confidence interval: 7%, 134%], p = 0.02) among those who had transferred early. Younger age at transfer to adult care is associated with higher graft failure rates. Transfer to adult-oriented care at < 21 yr of age should be undertaken with caution.

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Success in treating children with chronic kidney disease with dialysis and transplantation has led to a new challenge: how to ensure successful transfer from pediatric to adult-oriented care. Differences between pediatric and adult-oriented care environments (1, 2) may have an impact on the ability of young people to adapt successfully to adult care – particularly if transferred when young. In the adult care context, patient autonomy is expected and the volume of patients is substantially higher than in the pediatric care setting, resulting in less availability of adult care providers (3–6). Despite recommendations that timing of transfer should be determined by a combination of factors including maturity, medical stability, adherence, and patient readiness (5, 7, 8), rather than by chronological age, many institutions still mandate transfer at a specific age (usually 17–21 yr in North America, but as young as 12 in some countries), with variable flexibility in this cutoff (9, 10). Even where timing of transfer is left to the discretion of the treating team, transfer is commonly targeted for 18–21 yr in North America. Because cognitive and social maturation progresses at a relatively predictable rate over time in healthy individuals, age is a widely used, and reasonably accurate, surrogate for maturity level. However, brain development continues well into the third decade, so it is still incomplete even when individuals have attained physical and "legal" definitions of adulthood (3, 11–13). In addition, the experience of chronic disease may interfere with normal development (14, 15), resulting in delayed maturity.

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; SES, socioeconomic status; UNOS, United Network for Organ Sharing; USRDS, United States Renal Data System.

Immaturity may explain common adolescent behaviors such as poor adherence and risk-taking (11, 13) – which may worsen following transfer from pediatric to adult-oriented care (16–18). In kidney transplant recipients, such behavior may have serious consequences. Unexpected graft failure was observed within 36 months of transfer in seven of 20 (35%) kidney transplant patients in one series (17). Whether these graft failures would still have occurred had transfer been delayed until these patients were older is unknown.

Studies that compared the intervals before and after transfer to evaluate the impact of transfer on health outcomes among youth with chronic conditions, including kidney transplant (17, 19) and diabetes (18), drew conflicting conclusions. However, these studies failed to account for potential confounding owing to associations between age and outcomes, making interpretation difficult. There is evidence that graft failure risk varies with age, with adolescents and young adults experiencing higher failure rates than younger or older individuals (20–23). A relation similar to that seen between age and failure risk has been observed between age and adherence (7, 16, 24, 25), supporting the idea that higher failure rates in this age group are caused by poor adherence. No prior studies considered the association between outcomes and age at transfer. If transfer from pediatric to adult-oriented care *does* influence graft failure risk, it is likely that any effect of transfer depends on age at transfer.

Transfer of care must eventually happen for all young people. Mature adults have health care needs distinct from those of children and will be better served in an adult facility. But optimal timing of transfer is unknown (10, 26). We hypothesized that younger age at transfer from pediatric to adult-oriented care would be associated with an increased graft failure rate. Our aim was to determine the impact of age at transfer on the rate of failure, defined as death or loss of graft function.

Methods

This was a retrospective cohort study of individuals recorded in the UNOS database. UNOS collects information on all transplant recipients in the United States at transplant, six months later, and yearly thereafter. Access to organs for transplantation is contingent on reporting to UNOS. No patient identifiers are included in the datasets.

Study subjects

The study included individuals who received a first renal transplant in the US at <21 yr of age, between October 1987 and April 2007, who maintained graft function at least one-yr post-transplant, had a functioning graft on or after their 15th birthday, and who had been transferred from a pediatric to an adult care facility with a functioning graft.

Identification of transfers

The center code recorded by UNOS at each data collection point was used to identify the type of facility (pediatric vs. adult) at which each subject was receiving care. Centers at which >90% of all transplants performed were in individuals ≤21 yr old were coded as pediatric centers by UNOS staff. Other centers were coded as adult centers. This definition was based on the age at transplant distributions across UNOS centers. The date of transfer was recorded as the date half way between the last recorded pediatric visit and the first recorded adult visit. Age at transfer was categorized as either *early* (<21 yr) or *late* (≥21 yr). Graft failure dates and the code identifying the center at which the failure occurred were recorded in the database. The authors had access only to the type of facility at each data collection point, not to specific center codes.

Because the center reporting to UNOS may not always be the location where care is provided, location of care provider was also assessed. Care may be shared with, or provided exclusively by, a non-transplant center physician.

Linkage to USRDS database

UNOS data were linked to USRDS data in an effort to capture all graft failures and deaths. Failures (signaled by new dialysis start records in USRDS, if not reported to UNOS) and deaths may be captured more reliably via the USRDS than via UNOS (27).

Statistical analysis

Time-dependent Cox models with time-varying covariates (28) were used to estimate the additional risk associated with early transfer compared with late transfer. Age at transfer ≥21 yr was chosen as the reference group because 21 yr is commonly used to define adulthood in North America, prior studies suggested improvement in adherence after 21 yr (16, 17), and 21 yr was approximately the median age at transfer in the cohort. A model considering age at transfer as a continuous variable was also fitted. Both age and time since transplant were considered as candidates for the timescale in the Cox models. Prior studies, and preliminary data analyses, indicated a strong relationship between age and rate of graft failure – regardless of age at transplant – with failure rates increasing in adolescence and decreasing during the twenties (20–22). Therefore, age was selected as the timescale, as the hazard as a function of age was more difficult to model parametrically than that for time since transplant (29).

Unadjusted analyses were followed by multivariable analyses, including potential confounders. SES, estimated using median household income by zipcode, was classified by quartile within the US census data (1999) (30). Transplant era categories were based on changes in immunosuppression practices over time (31). We effectively asked: among individuals of the same age, controlling for time since transplant and other potential confounders, were those who failed more likely to have been transferred early than late?

Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA); a p-value <0.05 was considered statistically significant. Owing to the anonymous nature of the

data, the study was considered exempt by the Montreal Children's Hospital Research Ethics Board.

Results

Cohort selection and subject characteristics

There were 2489 individuals who fulfilled age- and graft function-related inclusion criteria and were identified as being followed in a pediatric center. Fig. 1 details the construction of the cohort. The median age at transfer was 20.7 (IQR 19.5–21.7) yr. Analyses focused on the 440 patients in whom transfer to adult care was observed, and who were under observation at 21 yr (223 early and 217 late). The observed experience of the early and late transfer groups was similar (Table 1). Of those in the early transfer group, 75% were over 19.4 yr old at transfer.

Impact of age at transfer on graft survival

Fig. 2 illustrates the observed experience of patients in the study. Comparison between the early and late transfer groups was only possible in the interval between 21 and 30 yr, as those transferred late were not observed after transfer to adult care between 15 and < 21 yr of age (by definition). In the interval of observation between 21 and 30 yr, the early transfer group had an age-standardized failure rate of 12.9 per 100 person-years, compared with 8.7 per 100 person-years in the late transfer group.

Table 2 presents HR for graft failure or death associated with early vs. late transfer, and for each covariate. Compared with patients the same age who had been transferred late, the failure rate was 58% higher among those who had been transferred early (p = 0.02). Black race, female sex, and older donor age were all associated with a significantly higher failure rate. Because the analysis was matched on age and adjusted for time since transplant, the analysis was effectively adjusted for age at transplant. Insurance status was not included in the models because it was missing in half the patients. Results of analyses
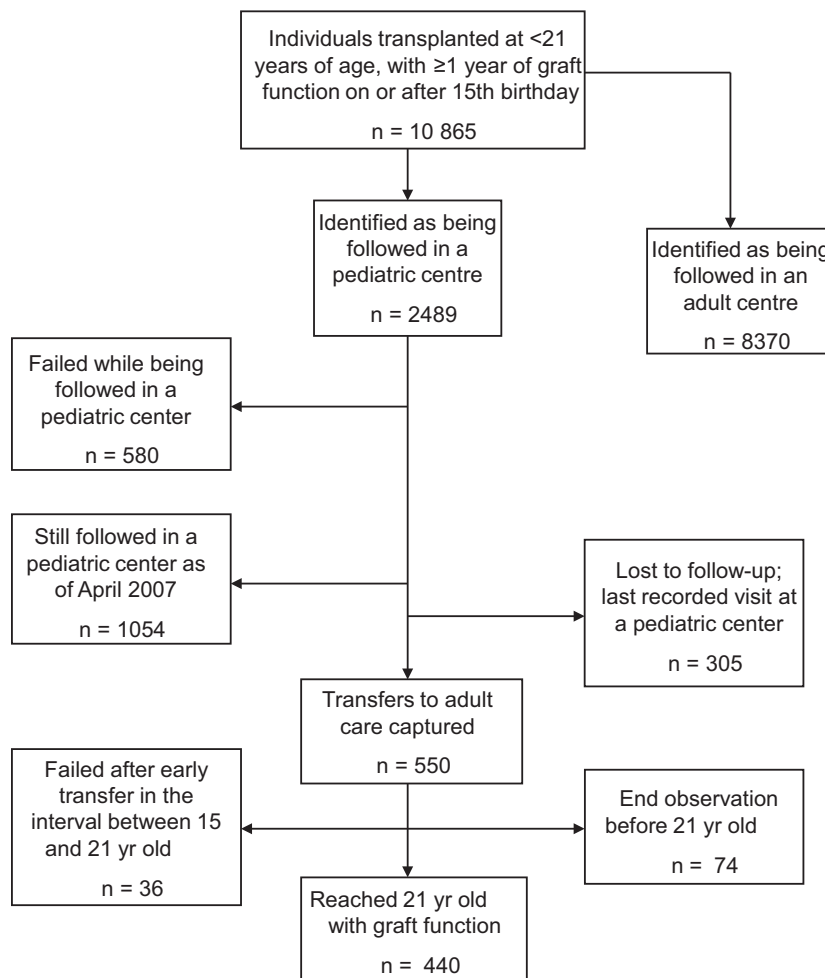

Fig. 1. Transfer to adult care was observed in 550 of the 2489 individuals eligible for study. Analyses focused on the 440 individuals who were available for observation in the interval of interest between 21 and 30 yr of age.

Table 1. Composition of the contrasted experience

	Early transfer (<21 yr)	Late transfer (≥21 yr)	p-Value
n	223	217	–
Person-years	655.4	635.6	–
Median age at transfer	20.1 (19.4, 20.7)	22.2 (21.6, 23.1)	<0.0001
Pretransfer care provided by			
Transplant center (%)	60.1	58.5	0.7
Non-transplant center (%)	1.4	2.3	
Unclear (%)	38.6	39.2	
Mean eGFR at last pediatric visit (mL/min/1.73 m^2)	46 ± 29	51 ± 28	0.07
Male (%)	66.7	59.7	<0.10
Race			
White (%)	60.3	60.2	0.35
Black (%)	26.7	22.9	
Other (%)	13.0	16.9	
Mean age at transplant	13.0 ± 0.3	15.2 ± 0.3	<0.001
Mean donor age	28.6 ± 0.9	30.4 ± 0.9	0.17
Mean years since transplant	8.6 ± 0.2	7.3 ± 0.2	<0.001
Living donor (%)	55.9	50.8	0.24
Transplant era			
1987–1993 (%)	41.5	42.0	0.34
1994–1996 (%)	31.0	24.8	
1997–2000 (%)	19.6	22.8	
2001–2007 (%)	7.9	10.4	
Socioeconomic status quartile			
Lowest (%) ≤ $35 019	21.0	27.2	0.61
Low-mid (%) $35 020–$42 098	16.3	15.0	
High-mid (%) $42 099–$52 363	23.0	16.9	
Highest (%) ≥$52 364	39.7	40.9	
Primary disease			
CAKUT (%)	36.7	30.3	0.27
Glomerulonephritis (%)	23.7	30.0	
Focal segmental glomerulosclerosis (%)	10.8	12.4	
Other (%)	28.8	27.3	
Mean HLA mismatch	2.8 ± 0.09	2.7 ± 0.1	0.56

Because the unit of analysis was person-time, rather than person, the characteristics presented are weighted averages (±standard error), weighted by a factor derived from the contributed experience and number of events. CAKUT, congenital anomalies of the kidneys or urinary tract.

including only those patients for whom insurer was available were unchanged. eGFR at last pediatric visit was not included in the model because it was potentially on the causal pathway of the associations between numerous covariates and the outcome, complicating interpretation of the HR for those covariates. However, the HR associated with early transfer was unchanged in a model including eGFR (estimated using the MDRD equation (32)) at last pediatric visit (1.60 [1.08, 2.36]; p = 0.02); in this model, black race (1.81 [1.24, 2.64]; p = 0.002), lower eGFR (1.03 [1.02, 1.04] per 1 mL/min/1.73 m^2;

p < 0.001), and longer time since transplant (1.09 [1.02, 1.15] per one-yr increment; p = 0.009) were associated with a significantly higher failure rate.

The model in which age at transfer was treated as a continuous variable revealed a 17% higher risk of failure with every one-yr younger age at transfer (HR 1.17 [1.04, 1.31]; p = 0.01). The results of analyses in which the outcome was death-censored graft failure were the same.

Among the 440 patients in whom a transfer was observed, care provider at the last pediatric visit was clearly recorded for 269 (61.1%) – of whom 97% had care provided by the transplant center; care provider was not clearly recorded for the remaining 171 (38.9%). Fig. 3 illustrates the sensitivity analysis performed to account for the possibility that some of these 171 patients may have been followed exclusively by a non-transplant center physician before transfer. Although power was limited with smaller samples, early transfer was consistently associated with a higher failure risk, even when patients who may have been followed exclusively by a non-transplant center physician were excluded. The HR associated with each one-yr younger age at transfer (continuous variable) was 1.16 [1.03, 1.32] in a model including only the 261 for whom care provider was clearly identified as the transplant center.

Impact of inability to capture transfer for some patients

About 305 patients had their last recorded visit at a pediatric center and were then lost to follow-up; neither transfer status nor outcome could be ascertained. These losses likely occurred *because* patients were transferred from a UNOS member center to a non-UNOS center/physician for adult-oriented care. The median age at last follow-up was 20.8 (IQR 19.3–21.8) yr, which mirrors the age at transfer among those for whom transfer was captured. These 305 losses to follow-up had some characteristics that differed slightly from the study population (Table 3). No failures or deaths were found for these 305 patients via the link with USRDS data, suggesting that these patients were truly lost. It is reasonable to conclude that none died, because deaths are reported to USRDS via several mechanisms, ensuring virtually complete capture, but it is unlikely that none would have failed. This highlights the limitations of both the USRDS and UNOS in tracking graft outcomes for all recipients. Nonetheless, when analyses were repeated assuming that all 305 patients were alive, with graft function, as of April 2007, and
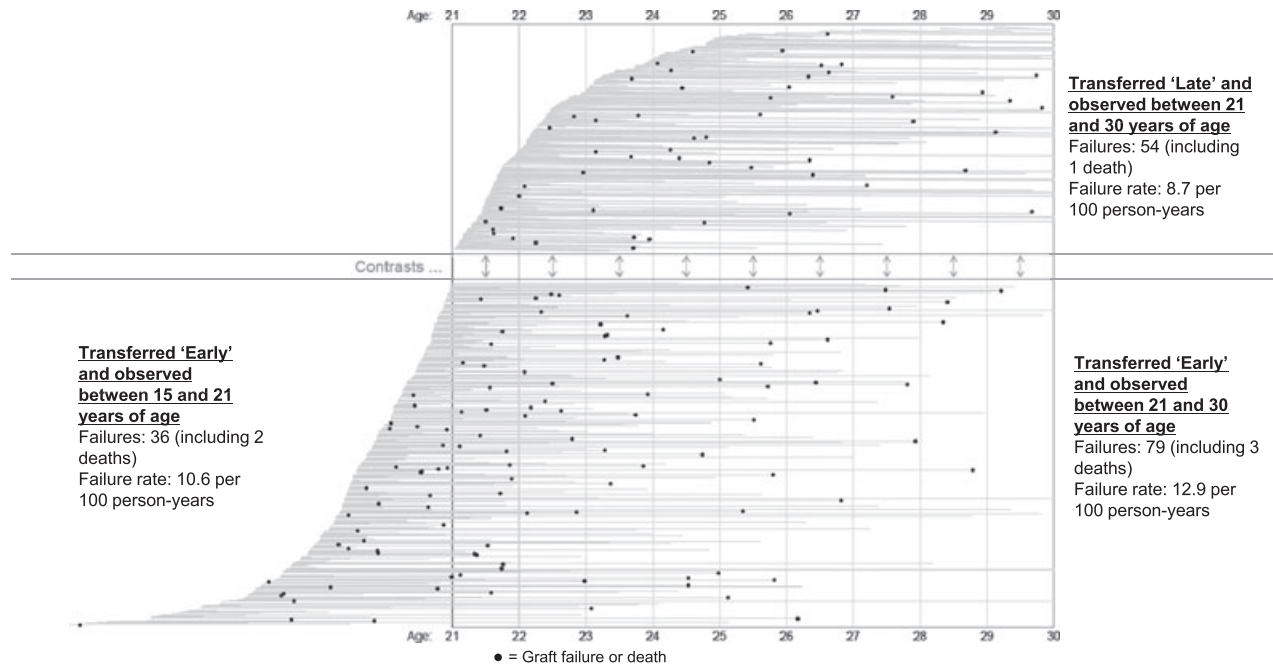
Fig. 2. Each horizontal line represents the experience of a single patient. Patients entered the cohort at transfer to adult-oriented care. The *x*-axis shows patient age at observation (the timescale for the Cox models). Early and late transfer groups were contrasted in the interval between 21 and 30 yr (double-headed arrows). There were 110 patients who were transferred early, but either failed or ended observation in the interval between 15 and 21 yr of age, so were not included in the above contrast, and do not contribute to the HR.

Table 2. Relative hazards of failure

	HR [95% CI]; p-value
Unadjusted model	
Early transfer (vs. late)	1.57 [1.08, 2.27]; 0.02
Adjusted model	
Early transfer (vs. late)	1.58 [1.07, 2.34]; 0.02
Female (vs. male)	1.43 [1.03, 2.00]; 0.04
Race (vs. white)	
Black	1.93 [1.32, 2.84]; <0.001
Other	1.16 [0.70, 1.94]; 0.56
Donor age (per yr)	1.02 [1.00, 1.03]; 0.02
Years since transplant (per 1 yr increment)	1.05 [0.99, 1.12]; 0.12
Living donor (vs. deceased)	0.67 [0.45, 1.00]; 0.05
Transplant era (vs. 1987–1993)	
1994–1996	0.69 [0.44, 1.08]; 0.11
1997–2000	0.76 [0.47, 1.24]; 0.27
2001–2007	1.05 [0.55, 2.03]; 0.88
Socioeconomic status (vs. lowest)	
Mid-low income quartile	1.08 [0.66, 1.74]; 0.77
Mid-high income quartile	1.10 [0.68, 1.78]; 0.70
Highest income quartile	0.87 [0.56, 1.37]; 0.55
Primary disease (vs. CAKUT)	
Glomerulonephritis	1.26 [0.83, 1.90]; 0.28
Focal segmental glomerulosclerosis	1.17 [0.68, 1.99]; 0.57
Other diagnosis	1.18 [0.78, 1.78]; 0.44
HLA mismatch	0.96 [0.84, 1.10]; 0.56

The lack of a substantial difference between the unadjusted and the adjusted HR for early transfer suggests that there was no important confounding by any of the variables included in the model.

CAKUT, congenital anomalies of the kidneys or urinary tract.

that transfer had occurred at the time of loss to follow-up, the HR associated with early transfer was virtually identical (HR 1.60 [1.08, 2.37]; p = 0.02).

Transfer could not be captured for individuals identified as being followed in an adult center at the outset – some (but not all) of whom were likely being followed in a pediatric center unable to be identified as such. Pediatric and adult-oriented transplant programs may be classified under a single center code, even if they are functionally independent; in these cases, transfers could not be captured. Patients identified as being followed in an adult center at the outset were generally similar to the study population but were older (half were >17 yr old at transplant), with a distribution of renal diseases consistent with their older age (Table 3). Many of these were likely older adolescents transplanted and followed in an adult center, who never underwent transfer.

Discussion

Health professionals have long recognized adolescence as a high-risk period, characterized by deterioration in disease control compared with other age groups. Transplant recipients are no
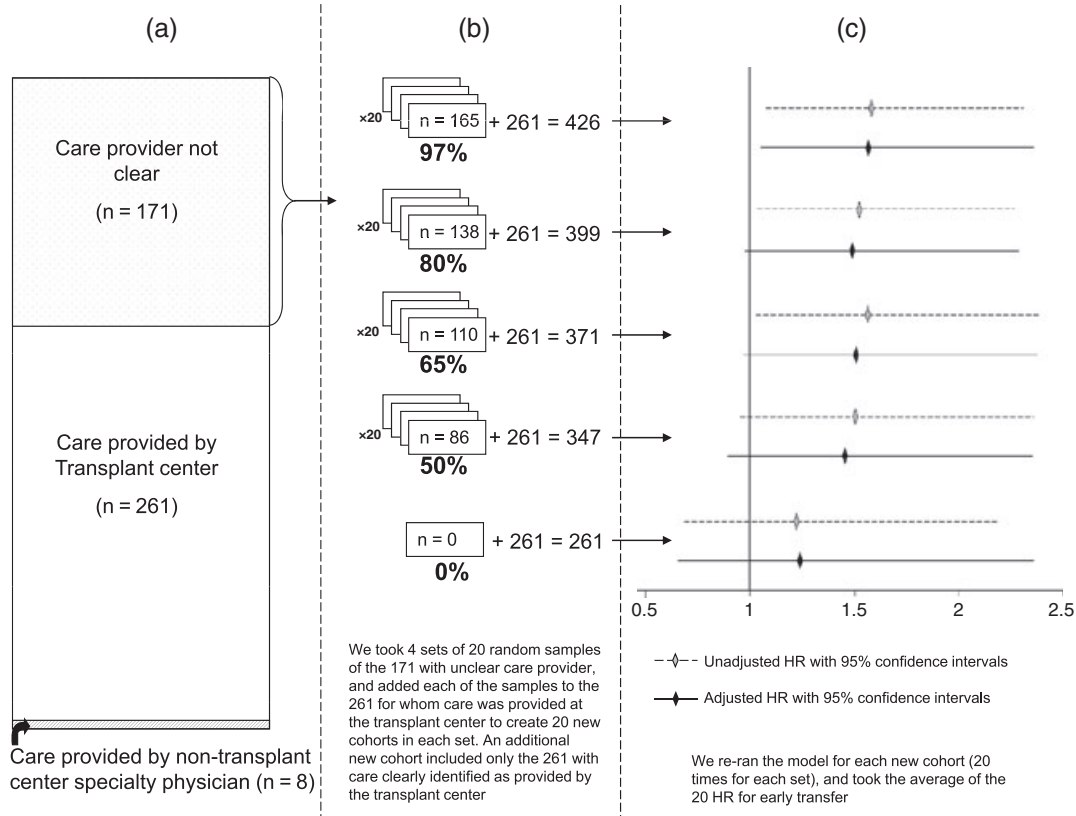
Fig. 3. We performed a sensitivity analysis to account for the possibility that some patients were not followed at the transplant center prior to transfer and therefore may not have actually experienced a change in care team. **Panel a** illustrates the proportions of the 440 patients in the cohort who were identified as still having care provided by the transplant center at the last pediatric visit vs. by a non-transplant center specialty physician (we were unable to distinguish pediatrician from non-pediatrician non-transplant center physicians); none were identified as having care provided by a primary care physician. Care provider was not clearly identified in almost 40%. The proportions in each of the care provider categories were the same in the early and late transfer groups. Among those for whom care provider was not clearly identified, some were likely to have been followed at the transplant center, and others by a non-transplant center physician. Our sensitivity analysis assumed that care had been provided by the transplant center in five different proportions of those for whom care provider was not clearly identified: 97% (same proportion who had care provided by the transplant center among those in whom care provider was clearly identified), 80%, 65%, 50%, and 0%. **Panel b** shows the procedure used to generate new cohorts composed of the 261 for whom care was provided by the transplant center, plus random samples of those for whom care provider was not identified. For each proportion (97%, 80%, 65%, and 50%), 20 random samples were selected, resulting in 20 new cohorts for each sampling frequency; there was only one cohort for the 0% sampling frequency (n = 261). The Cox model was rerun in each of the new cohorts. **Panel c** shows the average of the 20 unadjusted and adjusted HR (with 95% confidence intervals) associated with early (vs. late) transfer. Power was very limited with samples smaller than the full cohort of 440. However, early transfer was consistently associated with a substantially higher risk of failure than late transfer.

exception. Adolescent and young adult kidney transplant recipients have the poorest death-censored graft survival of *all* age groups (33). The present study suggests that younger age at transfer from pediatric to adult-oriented care may contribute to the unacceptably high graft failure rates among youth.

We have shown that compared with individuals of the same age (and therefore the same age-related failure risk), youth who were transferred to adult-oriented care before 21 yr have graft failure rates almost 60% higher than in those transferred after 21 yr. This may reflect a deterioration in adherence following transfer to adult-oriented care among individuals who were relatively immature at the time of transfer.

There is some evidence that adherence may deteriorate after transfer to adult care (16, 34). High patient volumes (resulting in perceived lack of availability of care providers for support), emphasis on the patient's responsibility for her own health, and less frequent routine blood monitoring may hamper adherence in the adult care setting, compared with perceived greater availability of providers, a family-oriented approach (with responsibility shared between the patient and parents), and more frequent monitoring in the pediatric setting (5, 7, 8). While adherence is far from perfect in the pediatric care

Table 3. Characteristics of subjects included in, and excluded from, the cohort

| | Cohort of patients in whom transfer was captured | Patients for whom transfer could not be captured | |
		Patients identified as followed in a pediatric center and lost to follow-up	Patients identified as followed in an adult center
n	550	305	8376
Male (%)	59.1	65.9	56.6
Race			
White (%)	60.6	63.0	60.9
Black (%)	24.0	9.2	18.0
Other (%)	15.4	27.8	21.1
Median age at transplant (IQR)	16.2 (13.7–17.9)	15.7 (13.1–17.5)	17.1 (14.4–19.2)
Median donor age (IQR)	36 (20–43)	32 (19–40)	36 (22–43)
Median years since transplant at last follow-up (IQR)	7.7 (5.0–11.1)	5.0 (3.0–7.3)	6.5 (3.9–10.1)
Living donor (%)	52.7	45.3	56.3
Transplant era			
1987–1993 (%)	31.3	37.4	33.5
1994–1996 (%)	20.0	23.6	17.8
1997–2000 (%)	25.6	25.3	20.9
2001–2007 (%)	23.1	13.8	27.8
Socioeconomic status quartile			
Lowest (%)	20.9	22.6	20.3
Low-mid (%)	16.4	21.6	17.9
High-mid (%)	20.7	18.4	25.9
Highest (%)	42.0	37.4	35.8
Primary disease			
CAKUT (%)	34.1	38.8	24.3
Glomerulonephritis (%)	27.7	24.1	35.0
Focal segmental glomerulosclerosis (%)	12.9	7.7	10.4
Other (%)	25.4	29.6	30.2
Median HLA mismatch (IQR)	3 (2–4)	3 (2–4)	3 (2–4)

The method used to classify centers as pediatric or adult only permitted the identification of freestanding pediatric facilities. Freestanding pediatric facilities with their own UNOS codes include both small and very large pediatric centers. However, we cannot exclude the possibility that there were systematic differences in care practices between centers that we could identify as pediatric and those that provide care to children but were identified as adult centers. Among the 8376 patients identified as being followed in an adult center, many were likely older adolescents followed by adult-oriented care teams and may represent a population distinct from the study population of individuals with childhood-onset kidney disease. However, a substantial number – including 1081 patients who were ≤ 12 yr old at transplant – were likely receiving care in a pediatric center that could not be identified by the center code.

environment, adherence in the adult care setting may demand a level of maturity of which many adolescents are incapable. Poorer outcomes among those transferred to adult-oriented care at a young age should not be interpreted as a failure of adult-oriented care practices, but rather as a "mismatch" between the care environment and the patients' maturity levels.

Consistent with prior studies, black race (35–37), older donor age (38, 39), and female sex (14, 40–43) were also associated with higher failure rates. The reasons for higher graft failure rates among women require further study. Given that brain maturation is generally completed earlier among healthy women than men, it may be reasonable to consider an interaction between sex and age at transfer in future larger studies of the impact of age at transfer on graft failure risk. Caution is advised in interpreting HR associated

with covariates in the analysis; the study was not designed to assess these factors.

The limitations of this registry-based study must be acknowledged. The cohort may have included some patients who received care outside the transplant center and therefore did not truly experience a change in care provider, despite a change in UNOS reporting center. Non-transplant center care providers likely maintain some relationship with the UNOS center that may influence care; care practices may change after ties with the pediatric center have been severed. Furthermore, our sensitivity analysis indicated a consistent association between early transfer and failure, even when varying proportions of patients were assumed to have not experienced a transfer and were excluded.

We cannot exclude the possibility that unmeasured confounders (insurance gaps, education

level, center characteristics), or incomplete adjustment for confounders, may have contributed to the differences in graft failure rates observed between the early and late transfer groups. For example, centers that routinely transfer patients late may better prepare young people for transfer than those transferring patients early, biasing toward better outcomes among those transferred late. However, it should be recognized that later transfer may be *required* for good preparation, insomuch as additional preparation time and further cognitive development are permitted.

Because timing of transfer was not random, bias related to timing of transfer may also have influenced the HR estimate. Transfer is frequently delayed for patients considered to be medically unstable or immature, potentially biasing toward a higher failure rate among those transferred late (if late transfer identified a group at particular risk for medical complications and/or immature behavior [such as poor adherence] which persisted after transfer). Alternatively, early transfer of complicated or poorly adherent patients would bias toward a higher rate of graft failure among those transferred early.

Our inability to capture all transfers was an additional limitation, potentially compromising the generalizability of our findings. We could only observe transfers from freestanding pediatric centers. Measured patient factors known to be associated with graft survival were similar between the study cohort and those excluded because transfer could not be captured (Table 3). Importantly, even if those excluded were at higher or lower risk of graft failure than those studied, bias would only be introduced if the effects of age at transfer were different in those excluded than in the cohort evaluated. However, systematic differences in center characteristics may have existed. For example, centers identifiable as pediatric (allowing capture of transfer) may have had fewer resources available to prepare adolescents for transfer than pediatric centers that could not be identified as such. If this was true – and programs to prepare adolescents for transfer are indeed effective at improving graft survival – then the HR reported here may represent an overestimate of the risk associated with early transfer.

How to optimally support young transplant recipients in the transition from childhood to adulthood is an area of growing interest (14, 40–43). Many centers, including our own, have established, or are developing, "transition programs," in an effort to prepare adolescents with chronic health conditions for the many challenges associated with becoming an adult, including adapting to a new adult-oriented care team (41, 44). The benefits of these programs are not yet proven; timing of transfer remains critical. Even the most effective transition program will not speed the biological process of brain maturation.

It is important to avoid the assumption that physical maturity corresponds with cognitive and social maturity. Our findings emphasize the need for careful assessment of maturity and cognitive skills prior to transfer to adult care. However, accurate judgments regarding transfer "readiness" are difficult to make; we observed progressively better outcomes with increasing age at transfer. Until reliable methods of assessing readiness for transfer are developed, or transition programs are shown to adequately support patients to the extent that graft failure risk is not increased after transfer, these results suggest that transfer of individuals under 21 yr old to adult-oriented care should be undertaken with caution. In addition, this study emphasizes the importance of formally documenting transfer to adult-oriented care, and transition practices, within large databases such as UNOS to allow larger studies to be conducted in the future.

Acknowledgments

Conflict of interest

None of the authors has any competing financial interests to disclose.

Author contributions

manuscript. Mourad Dahhou performed the majority of the statistical analyses, with input and advice from Dr. Zhang. He has no conflicts of interest to report. Xun Zhang performed parts of the statistical analyses and aided with development of the time-dependent Cox models. He has no conflicts of interest to report. Lorraine Bell contributed to the conception of the idea and contributed to editing the manuscript. James Hanley contributed to the application to obtain funding, codirected the analyses, and contributed to editing the manuscript.

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