Age at Graft Loss after Pediatric Kidney Transplantation: Exploring the High-Risk Age Window


Summary
Background and objective The risk of graft loss after pediatric kidney transplantation increases during late adolescence and early adulthood, but the extent to which this phenomenon affects all recipients is unknown. This study explored interactions between recipient factors and this high-risk age window, searching for a recipient phenotype that may be less susceptible during this detrimental age interval.

Design, setting, participants, & measurements With use of Scientific Registry of Transplant Recipients data from 1987 to 2010, risk of graft loss across recipient age was quantified using a multivariable piecewise-constant hazard rate model with time-varying coefficients for recipient risk factors.

Results Among 16,266 recipients, graft loss during ages ≥17 and <24 years was greater than that for both 3–17 years (adjusted hazard ratio [aHR], 1.61; P<0.001) and ≥24 years (aHR, 1.28; P<0.001). This finding was consistent across age at transplantation, sex, race, cause of renal disease, insurance type, pretransplant dialysis history, previous transplant, peak panel-reactive antibody (PRA), and type of induction immunosuppression. The high-risk window was seen in both living-donor and deceased-donor transplant recipients, at all levels of HLA mismatch, regardless of centers’ pediatric transplant volume, and consistently over time. The relationship between graft loss risk and donor type, PRA, transplant history, insurance type, and cause of renal disease was diminished upon entry into the high-risk window.

Conclusions No recipient subgroups are exempt from the dramatic increase in graft loss during late adolescence and early adulthood, a high-risk window that modifies the relationship between typical recipient risk factors and graft loss.


Introduction
Kidney transplants performed during adolescence have excellent 1-year graft survival but paradoxically lower long-term graft survival compared with transplant recipients of other ages (1). Whereas previous studies analyzed static age at transplantation as the marker for this age effect (2–5), a recent study by Foster et al. instead examined graft failure rates across current recipient age and found an increased risk of graft failure among 17- to 24-year-olds regardless of the age at which they received the transplant (6).

The ability of pediatric recipients to successfully traverse these high-risk ages therefore appears to be a more important determinant of graft survival than the specific age at which transplantation was performed. In other words, the period of adolescence and early adulthood, along with any factors during that time that may lead to graft loss, is not specific only to transplantations performed at those ages but rather a high-risk “age window” through which all pediatric kidney transplant recipients must eventually pass. However, the extent to which this age window is equally detrimental to all recipients is unknown.

For example, patients with the highest immunologic risk and those with the greatest barriers to successful transition between pediatric and adult posttransplant care could potentially experience an exaggerated increase in the risk of graft loss during these ages. In addition, this finding could vary dramatically across transplant centers or be biased by changes in graft survival over time.

The objective of this study was to develop a flexible statistical model that would allow us to (1) determine whether any phenotype of recipient is protected against the period of increased graft loss seen during late adolescence and early adulthood and (2) examine potential interactions between the high-risk age window and other risk factors for graft loss after pediatric kidney transplantation.

Materials and Methods
Data Source
This study used data from the Scientific Registry of Transplant Recipients (SRTR), a national registry of all solid organ transplants. The SRTR includes data on all
donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere (7). The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Study Population
All pediatric (recipient <18 years of age) kidney-only transplant recipients between January 1987 and July 2010 were identified in the SRTR. Cause of renal disease was categorized as FSGS, other glomerular diseases, congenital anomalies of the kidney and urinary tract, or other/missing diagnosis on the basis of clinical knowledge and precedent set by the SRTR program-specific regression models (available at www.srtr.org). Induction immunosuppression was categorized as antilymphocyte therapy (antithymocyte globulin [Thymoglobulin], muromonab-CD3 [OKT3], or alemtuzumab [Campath]), IL-2 inhibitors, or no induction.

Outcome Ascertainment
Death-censored graft survival was defined as the time between transplantation and graft loss (marked by retransplantation or a return to dialysis) or last date of follow-up with a functioning graft, with censoring for death and administrative end of study. Death-censored graft failure rates were analyzed within various time intervals; specifically, 7-year graft failure rates were calculated to determine the likelihood of graft survival to age 24 given a functioning graft at age 17. 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 & Medicaid Services.

Hazard Plots
The risk of graft loss across age was graphically explored by plotting hazard functions against current recipient age (rather than the conventional posttransplant follow-up time). Age 0 (rather than date of transplantation) served as the time origin, with late entries into the risk set at each age of transplantation. The hazard function then provided the current graft failure rate at a given age conditional on graft survival up to that age.

Piecewise-constant Hazard Rate Model
A piecewise-constant hazard rate model was used to quantify the hazard of graft loss across posttransplant age. This model is an exponential hazard model that assumes a constant hazard within predefined time segments and then estimates variation in hazard between those time segments (8). Given that the time axis in the analysis was current recipient age, the time segments therefore consisted of periods of age (rather than follow-up time), thus enabling a closer examination of the high-risk age window of ages 17–24 years in comparison to the ages before and after this window. Sensitivity analyses were performed with different comparison age segments, and inferences were unchanged.

A multivariable parameterization of the piecewise-constant hazard rate model allowed us to compare hazard dynamically between posttransplant age categories while adjusting for potential recipient (sex, race, insurance, diagnosis, dialysis history, transplant history, and peak panel-reactive antibody [PRA]), donor (living versus deceased, age, and race), transplant (HLA mismatch and year), and center-level (pediatric transplant volume) confounders.

Subgroup Analyses
By use of the piecewise-constant hazard rate model, the dynamic risk of graft loss across posttransplant age was quantified by strata of recipient (age at transplantation, sex, race, diagnosis, insurance, dialysis history, transplant history, peak PRA, and type of induction immunosuppression), transplant (donor type, HLA mismatch, and year of transplantation), and center (pediatric volume) characteristics. Centers’ pediatric volume was categorized into tertiles according to the number of transplantations performed during the study period in patients <18 years of age.

Effect Modifier Analysis
Time-varying coefficients were added to the piecewise-constant hazard rate model to allow the relationship between risk factors and the hazard of graft loss to vary across various age segments (i.e., the hazard ratio for a given variable could differ across age each category). Specifically, factors associated with a higher risk of graft loss (recipient race, cause of renal disease, insurance status, previous transplant, PRA, donor type, and HLA mismatch) were examined as time-varying coefficients. The addition of these time-varying coefficients enabled the assessment of which characteristics made recipients especially susceptible (or resilient) to the graft loss observed during a particular age period. Through this approach, it was possible to determine, for example, whether repeat transplant recipients, although probably at higher risk of graft loss across all ages, were disproportionately at even higher risk of graft loss during late adolescence and early adulthood.

Statistical Analyses
All tests were two sided, with statistical significance set at α = 0.05. Analyses were performed using Stata software, version 12.0/SE (Stata Corp., College Station, TX).

Results
Graft Loss by Recipient Age
During the study period, 16,266 pediatric kidney transplants were performed (Table 1). Using hazard plots to examine graft loss across current recipient age, the risk of graft loss was most pronounced during late adolescence and early adulthood, as expected. In patients with a functioning graft at age 17 years, 42.4% were in fact expected to lose the graft by age 24. After adjustment for recipient, donor, transplant, and center-level characteristics with a multivariable piecewise-constant hazard
Table 1. Recipient, donor, and transplant characteristics for pediatric (age <18 years) kidney transplantations performed between 1987 and 2010 (n=16,266)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td></td>
</tr>
<tr>
<td>Mean age ± SD (yr)</td>
<td>11.1 ± 5.1</td>
</tr>
<tr>
<td>Female</td>
<td>40.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>58.3</td>
</tr>
<tr>
<td>African American</td>
<td>18.6</td>
</tr>
<tr>
<td>Other</td>
<td>23.1</td>
</tr>
<tr>
<td>Cause of renal disease</td>
<td></td>
</tr>
<tr>
<td>FSGS</td>
<td>10.4</td>
</tr>
<tr>
<td>Other glomerular</td>
<td>14.6</td>
</tr>
<tr>
<td>CAKUT</td>
<td>34.5</td>
</tr>
<tr>
<td>Other/missing</td>
<td>40.5</td>
</tr>
<tr>
<td>Public insurance</td>
<td>64.6</td>
</tr>
<tr>
<td>Preemptive status</td>
<td>17.5</td>
</tr>
<tr>
<td>Previous transplant</td>
<td>11.8</td>
</tr>
<tr>
<td>Peak PRA</td>
<td></td>
</tr>
<tr>
<td>0%-20%</td>
<td>85.6</td>
</tr>
<tr>
<td>21%-80%</td>
<td>10.3</td>
</tr>
<tr>
<td>81%-100%</td>
<td>4.0</td>
</tr>
<tr>
<td>Induction immunosuppression</td>
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<tr>
<td>Antilymphocyte</td>
<td>30.6</td>
</tr>
<tr>
<td>IL-2 inhibitor</td>
<td>25.5</td>
</tr>
<tr>
<td>None</td>
<td>43.9</td>
</tr>
<tr>
<td>Donor</td>
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</tr>
<tr>
<td>Mean age ± SD (yr)</td>
<td>30.0 ± 12.8</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69.0</td>
</tr>
<tr>
<td>African American</td>
<td>12.6</td>
</tr>
<tr>
<td>Other</td>
<td>18.4</td>
</tr>
<tr>
<td>Donor type (% living)</td>
<td>49.3</td>
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<tr>
<td>Transplant</td>
<td></td>
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<tr>
<td>HLA mismatch</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>1–3</td>
<td>53.2</td>
</tr>
<tr>
<td>4–6</td>
<td>41.8</td>
</tr>
</tbody>
</table>

Unless otherwise noted, values are percentages. CAKUT, congenital anomalies of the kidney and urinary tract; PRA, panel-reactive antibody.

Subgroup Analyses: By Recipient Characteristics

This increase in the hazard of graft loss during late adolescence and early adulthood was seen regardless of the age at transplantation (Figure 1A and Table 2). In addition, the increased risk of graft loss during ages 17–24 years was consistent across recipient sex, race, cause of renal disease, insurance type, pretransplant dialysis history, transplant history, peak PRA, and type of induction immunosuppression (Figure 1, B–I and Table 2).

Subgroup Analyses: By Donor, Transplant, and Center Characteristics

The increased risk of graft loss during late adolescence and early adulthood was seen in both living-donor and deceased-donor transplant recipients and at all levels of HLA mismatch (Figure 1, J and K, and Table 2). This finding was not diminished among centers with the highest pediatric volumes (Figure 1L and Table 2) and has not improved over time (Figure 1M and Table 2).

Effect Modifier Analysis

Some recipient risk factors had a similar relationship with the hazard of graft loss before, during, and after the high-risk window of 17–24 years (Table 3). For example, the relative increase in graft loss for African American recipients (versus white recipients) during the 17– to 24-year age window (aHR, 1.58; 95% CI, 1.44–1.74; P < 0.001) was not significantly different than the age interval before (aHR, 1.71; 95% CI, 1.55–1.89; P < 0.001) or after (aHR, 1.59; 95% CI, 1.31–1.92; P < 0.001) that age window. In addition, the relationship between HLA mismatch and the hazard of graft loss was similar before, during, and after the high-risk age window (Table 3).

In contrast, the relationship between several recipient variables and the risk of graft loss was diminished during the high-risk window of 17–24 years (Table 3). The increased hazard associated with a prior kidney transplant (versus patients receiving first transplants) was more dramatic during ages 3–17 years (aHR, 1.53; 95% CI, 1.37–1.71; P < 0.001) than during ages 17–24 years (aHR, 1.15; 95% CI, 1.03–1.28; P = 0.01). Likewise, the increased hazard associated with public insurance (versus patients with private insurance) was lost when advancing from ages 3–17 years (aHR, 1.44; 95% CI, 1.30–1.59; P < 0.001) to ages 17–24 years (aHR, 1.06; 95% CI, 0.97–1.16; P = 0.2). Finally, the increased risk of having FSGS or another glomerular disease, as well as having an elevated peak PRA, was also diminished when moving from ages 3–17 to ages 17–24 years (Table 3).

The graft survival advantage for a living-donor transplant compared with a deceased-donor transplant was also attenuated by the high-risk window of 17–24 years (Table 3). The relative decrease in the risk of graft loss for living-donor transplants (versus deceased-donor transplants) diminished when moving from ages 3–17 (aHR, 0.57; 95% CI, 0.52–0.63; P < 0.001) to ages 17–24 years (aHR, 0.81; 95% CI, 0.75–0.89; P < 0.001) and no longer remained after age 24 (aHR, 1.13; 95% CI, 0.97–1.30; P = 0.1).

Discussion

This national study of more than 16,000 pediatric kidney transplants closely investigated the changing risk of graft loss across recipient age using a flexible statistical model to determine whether susceptibility to the high-risk age window varies and to evaluate how recipient risk factors interact with this age window. The increased risk of graft loss during late adolescence and early adulthood unfortunately appears to be a universal phenomenon, generally consistent across all the recipient, donor, transplant, and center characteristics that were examined. No recipient groups appeared to be unharmed by this high-risk
Figure 1. | Hazard of graft loss across current recipient age among pediatric kidney transplant recipients. The hazard provides the current graft failure rate at a given age conditional on graft survival up to that age. Results are stratified by (A) age at transplantation, (B) sex, (C) race, (D) cause of renal disease, (E) insurance, (F) dialysis history, (G) transplant history, (H) peak panel-reactive antibody, (I) induction immunosuppression, (J) donor type, (K) HLA mismatch, (L) pediatric volume of transplant center, and (M) year of transplantation.
window; in fact, recipients with certain traditionally favorable characteristics (those with diagnoses that are less likely to recur, with private insurance, with low PRA, receiving a first transplant, and receiving a living-donor transplant) seemed to be most vulnerable during this detrimental age interval (relatively speaking, compared with those patients during other age intervals). Essentially the high-risk age window lessened the favorable effect of these variables on graft survival (or alternatively, lessened the unfavorable impact of their alternatives).

Our findings are consistent with and build on the findings of Foster et al., who reported an increased graft failure rate among 17- to 24-year-olds regardless of the age at transplantation (6). Previous studies have reported decreased graft survival among patients receiving transplants in their adolescent years (i.e., age at transplantation) (1–5,9,10). However, graft failure risk appears to be more closely related to current posttransplant age at follow-up rather than age at transplantation, and adolescent age at transplantation may be important only to the degree that it marks imminent entry into the late teens and early twenties (i.e., posttransplant age at follow-up). Of important note, the patients in this study who underwent transplantation between ages 13 and 17 years did not have a more exaggerated risk of graft loss during the high-risk window than patients who had transplantation at younger ages. Patients undergoing transplantation at all ages had a dramatically increased risk of graft loss during the high-risk age window, but adolescent recipients in particular did not experience a more dramatic risk of graft loss during late adolescence and early adulthood.

The increased risk of graft loss during late adolescence and early adulthood may be due to adolescents’ lack of...
adherence to immunosuppression (11–17). Given the extension of the high-risk age window into early adulthood, the effect of this nonadherence on graft survival is probably delayed, or, alternatively, the lack of adherence may also extend into early adulthood. Of note, we found that the use of induction immunosuppression did not appear to lessen the high risk of graft loss during late adolescence and early adulthood. In addition, the high-risk age window was consistent across varying levels of immunologic risk as measured by peak PRA and HLA mismatch.
Nonadherence to immunosuppression during late adolescence and early adulthood may be exacerbated by concurrent alterations in health insurance coverage, which have also been linked to poor outcomes after pediatric kidney transplantation (18–20). The SRTR unfortunately lacks the granularity with respect to insurance status and its changes over time that would allow an in-depth analysis of this factor. However, this study was able to show that recipients with both private and public insurance at the time of transplantation (26) did experience an increased risk of graft loss during the high-risk age window. However, in terms of etiology, the universality of this finding across all recipient subgroups may suggest that an “all-of-the-above” category may be the true cause. In addition, some aspect of this phenomenon may be biologic, with the period of increased growth during adolescence leading to hyperfiltration injury, and thereby subsequent increased rates of graft loss, similar to the hyperfiltration injury thought to occur when kidneys from small donors are transplanted into large recipients (27).

This study is limited by the variables available for analysis with the SRTR. For example, the specific characteristics of the transition process between pediatric and adult posttransplant care is not well captured in the SRTR. Our study therefore could not examine in-depth the role of care transitions in the high-risk age window; it remains possible that a subgroup of recipients experiencing the most ideal transition of care could theoretically be less vulnerable during the high-risk age window. An additional limitation of this study with regard to use of the piecewise-constant hazard rate model is the somewhat arbitrary nature of the choice of age segments. The age window of 17–24 years was chosen empirically and confirmed by the work of Foster...
et al. (6), which identified those particular ages as having an increased risk of graft loss; however, the comparison age segments before and after this risk window could have been narrowed or widened. On the basis of sensitivity analyses, however, such choice of different age segments, although changing the exact point estimates for the hazard comparisons, did not change the inferences from our study. In conclusion, we compared the substantial increase in the risk of graft loss during late adolescence and early adulthood across various patient- and center-level characteristics. No particular recipients appear to be exempt from this high-risk age window, so much so that the favorable effect of some factors (such as having a living donor) on graft survival appears to be dampened or even completely eliminated because of this particular age interval. Because all pediatric recipients must eventually traverse this late adolescence and early adult age window, our study underscores this high-risk window as a prime area for intervention to maximize continuity of care, insurance coverage, and immunosuppression adherence in order to improve long-term pediatric graft survival.

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Disclosures

None.

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