TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Living donor age and kidney transplant outcomes: an assessment of risk across the age continuum

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Keywords
donor age, kidney transplantation, living donor, outcomes.

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Conflicts of interest
The authors of this manuscript have no conflicts of interest to disclose.

Received: 17 August 2012
Revision requested: 12 November 2012
Accepted: 7 January 2013
Published online: 6 February 2013

doi:10.1111/tri.12069

Summary

Detailed data on living donor age, and its interplay with recipient age, in predicting allograft and recipient outcomes are wanting. We used the Scientific Registry of Transplant Recipients (2000–2009, n = 49 589) to assess the effect of living donor age on delayed graft function (DGF), total graft failure, death-censored graft failure, death with graft function, and graft failure with death as a competing risk using logistic and Cox proportional hazards models. Potential nonlinear associations were modeled using fractional polynomial functions. There was a significant 1.87-fold increase in the adjusted odds of DGF in the oldest versus youngest age groups. The 10-year adjusted hazard ratios (HR) for total graft failure, death-censored graft failure, and death with graft function increased in a nonlinear fashion across the range of living donor age studied. Graft failure was most accentuated in the youngest recipient age groups in competing risk models. Adjustment for renal function at 6- and 12-months post-transplant markedly attenuated the association between living donor age and graft/patient outcomes. Our findings confirm the important influence of living donor age on transplant outcomes and provide detailed estimates of risk across the living donor age continuum.

Introduction

With the increasing prevalence of kidney failure, there has been an increased demand for kidney donors. Living donor kidney transplantation (LDKT) not only allows for the expansion of the donor pool but also provides superior short- and long-term graft survival when compared with deceased donor kidney transplantation (DDKT) [1–3]. The improved outcomes associated with LDKT are best explained by a reduction in ischemic injury, shorter waiting time on dialysis, and the transplantation of "healthier" kidney tissue when compared with DDKT.

Older deceased donors have been associated with a higher risk of graft failure [4–7]. This provides a rationale for incorporating broad recipient-donor age matching into kidney allocation algorithms to better align graft quality with life expectancy [8]. Yet, the increasing number of potential candidates for kidney transplantation, and the rising age of both recipients and the general population, has led to a greater acceptance of living donation from older individuals.

In light of the known decrease in glomerular filtration rate with advancing age, several studies have sought to establish the relation between donor age and allograft failure and function following LDKT [9–13]. A recent study by Chang *et al.* [14] showed that, with the exception of recipients aged 18–39 years who had the best outcomes with donors aged 18–39 years, living donor age between 18 and 64 years had minimal effect on the half-life of kidney allografts. This study, however, included a relatively small number of living donors >60 years and the analysis did not account for death as a competing risk.

A recent meta-analysis of 12 clinical studies that assessed patient survival in addition to allograft failure showed inferior 5-year survival in recipients of kidneys from older

living donors compared with younger donors. The studies included in this review were mostly small single-center reports and demonstrated significant between-study heterogeneity [15]. More recent studies have focused on the outcomes of kidney transplants from the oldest living donors (i.e., $\geq$70 years) [9,10] or had insufficient power to detect nonlinear associations [12,13].

The current study seeks to determine the impact of living donor age on short- and long-term outcomes in recipients of LDKT of various age categories in the United States and to better define the spectrum of risk. Our analysis further supplements the current state of knowledge by assessing the impact of living donor age on recipient survival and by accounting for the possibility that death with graft function may act as a competing risk for allograft failure.

Patients and methods

Study population

We conducted a retrospective cohort study using the Standard Analysis Files of the Scientific Registry of Transplant Recipients (SRTR). All U.S. end-stage renal disease (ESRD) patients who underwent LDKT from 1 Jan 2000 to 31 Dec 2009 were eligible for study inclusion. Exclusion criteria included: (i) recipients <18 years, (ii) living donors <18 years at the time of donation; (iii) multi-organ transplant recipients (including kidney-pancreas), (iv) re-transplants, and (v) kidney transplants that never functioned (i.e., primary nonfunction).

Exposure and outcome measurements

The exposure of interest was the age (in years) of the living donor at the time of transplantation. Living donor age was categorized a priori into the following groups: 18–29.9 years, 30–39.9 years, 40–49.9 years, 50–59.9 years, and 60+ years. The relation between living donor age and the outcomes of interest were modeled both as categorical and continuous variables.

The main outcomes of interest included delayed graft function (DGF), total graft failure, death-censored graft failure, and death with graft function. DGF was defined as the need for at least one dialysis session in the first week after kidney transplantation. Total graft failure was a composite of death-censored graft failure and death with graft function. Death-censored graft failure referred to graft losses from all causes other than death with graft function. Death with graft function included all deaths prior to graft loss.

Potential confounders

The following potential confounders were examined in multivariable models: (i) recipient factors (i.e., age, gender, race, cause of ESRD, peak panel reactive antibody level, body mass index, time on dialysis prior to transplant); (ii) donor factors (i.e., gender, race, pre-operative serum creatinine, body mass index); and (iii) transplant factors (i.e., cold ischemia time, number of HLA mismatches, type of induction therapy, and transplant era). Patients with missing data on key variables for analysis were excluded (N = 6938 or 4.4% of the initial cohort).

Statistical analysis

Frequencies within categories of each study variable and their distributions were compared across living donor age groups. The risk of DGF as a function of living donor age was examined in a multivariable logistic regression model, adjusting for potential confounders. Time-to-event outcomes, stratified by living donor age group, were assessed using the Kaplan–Meier product limit method and differences across survival curves were evaluated using the log-rank test. The association between living donor age and the outcomes of interest were assessed in multivariable Cox proportional hazards regression models. Fractional polynomials were used to flexibly capture the relative hazard of each outcome as a continuous function of living donor age [16]. The proportional hazards assumption was assessed using tests based on the Schoenfeld residuals and an examination of log (cumulative hazard) curves. No significant departures from proportionality were detected.

A sensitivity analysis was performed to account for death as a competing event in the analysis of graft failure. Cumulative incidence functions were compared with Kaplan–Meier failure functions. Estimates of the relative hazard for graft loss, while accounting for death as a competing risk, were derived from a Cox proportional subdistribution hazards model [17] and compared with the results from a conventional Cox model. We also conducted secondary analyses to assess the relation between living donor age and the time-to-event outcomes adjusting for eGFR (based on the CKD-EPI formula) at 6- and 12-months post-transplant in subcohorts of patients surviving with a functioning graft to these time points. These follow-up times were chosen as kidney function was most reliably captured at these intervals in the registry.

All statistical analyses were performed using STATA/MP 12.0 (StataCorp, College Station, TX, USA www.stata.com). A two-sided P-value of <0.05 was considered statistically significant. The research ethics board of the University Health Network approved the study.

Results

In total, LDKT was performed in 59 338 patients over the study period. Pediatric recipients and donors (age

<18 years; $n = 3462$ and $n = 7$, respectively), re-transplants ($n = 5257$), recipients of prior nonrenal solid-organ transplants ($n = 881$), and recipients with primary nonfunction of the renal allograft ($n = 142$) were excluded from the analysis. The final study cohort included 49 589 recipients who underwent a first LDKT from 1 Jan 2000 to 31 Dec 2009. The baseline recipient, donor, and transplant characteristics of the study cohort by predefined categories of living donor age at transplantation are presented in Table 1. There was a higher prevalence of recipients who were older, diabetic, White race, and pre-emptively transplanted in the highest age category (i.e., age 60+ years). Older living donors were also more likely to be of White race and female. Renal function and BMI were comparable across living donor age groups.

Delayed graft function occurred in 3.5%, 4.1%, 4.0%, 4.5%, and 5.5% of the patients across increasing living donor age categories. A logistic regression model adjusting for recipient, donor, and transplant characteristics showed an 87% increase in the odds of DGF [OR 1.87 (95% CI: 1.49–2.35)] when comparing the fifth category to the first category of living donor age (Table 2). The risk monotonically increased across ascending categories (P for trend <0.001). The fractional polynomial model showed that a linear relation between living donor age and the log hazard ratio for DGF was a good fit to the data. For every 10-year increase in living donor age, the odds of DGF increased by 15% [OR 1.15 (95% CI: 1.11–1.20)].

Kaplan–Meier curves for total graft survival (a), death-censored graft survival (b), and death with graft function (c), stratified by living donor age categories, are presented in Fig. 1. Ten-year estimates for total graft survival were 61%, 60.5%, 60.8%, 60%, and 52% across ascending living donor age categories. Ten-year estimates for death-censored graft survival and survival with graft function were 73%, 76.1%, 76.3%, 74.4%, 71.5%, and 83.7%, 79.5%, 79.7%, 80.6%, 72.4%, respectively. The overall differences in the survival functions for all three end-points were statistically significant (log-rank test, $P < 0.001$).

Predefined categories of living donor age, and their associations with total graft failure, death-censored graft failure, and death with graft function, were examined in multivariable Cox proportional hazards models (Table 2). A 53% increase in the hazard for total graft failure was seen in the oldest versus youngest living donor age groups [hazard ratio or HR 1.53 (95% CI: 1.37–1.70)]. Similarly, there was a 79% increase in the hazard for death-censored graft failure [HR 1.79 (95% CI: 1.55–2.07)] and a 27% increase in the hazard for death with graft function [HR 1.27 (95% CI: 1.08–1.50)]. A sensitivity analysis that formally addressed death as a competing risk in graft failure analysis (Table 2) showed results that were nearly identical to the analysis that treated death as a censoring event.

The continuous relations between living donor age and total graft failure (a), death-censored graft failure (b), and death with graft function (c) were explored using Cox proportional hazards models adjusted for the recipient, donor, and transplant characteristics shown in Table 1. Living donor age was represented by a fractional polynomial term in the Cox model to flexibly capture nonlinear associations. An increasing curvilinear relation between living donor age and the adjusted log hazard ratio for death-censored graft failure was observed, with a steeper rise beyond 50 years age (Fig. 2). The same cutoff for living donor age was associated with a less pronounced rise in the adjusted log hazard ratio for total graft failure and death with graft function.

The associations of living donor/recipient age subgroup combinations and the risk of total graft failure, death-censored graft failure, and death with graft function are displayed as diamond plots in Fig. 3. The diamond plots depict the effect of two categorical predictors on a continuous outcome [18]. The shaded region in each cell represents the excess risk above a HR of 1 and is standardized to the subgroup that exhibits the lowest HR (i.e., the cell labeled "1*"). The height, width, and area of the shaded region in each cell are proportional to the HR. Figure 3 reveals that the HRs for total graft failure are most pronounced with increasing living donor age in the youngest and oldest recipient age groups. A similar plot constructed for death-censored graft failure revealed that the youngest recipients were the main drivers of the observed association while a plot of death with graft function showed that the oldest recipients took over this role. Of note, however, is a higher HR for death with graft function among the oldest recipients with kidney transplants from living donors >40 years of age, and a twofold increase in the HR of death with graft function in the youngest recipient age with LDKTs from the oldest compared with younger age categories.

The results of our secondary analyses are presented in Table 3. The graded associations of living donor age and total graft failure, death-censored graft failure, or death with graft function were considerably attenuated after adjustment for recipient eGFR at 6- or 12-months post-transplant. In fact, after adjustment for recipient eGFR, a significant increase in the relative hazard for all outcomes persisted only in the oldest living donor age group (i.e., 60+ years) at the 6-month time point post-transplant. At the 12-month time point post-transplant, the association was essentially nullified.

Discussion

In this retrospective cohort study using data from the SRTR, we have shown that living donor age is an important

Table 1. Baseline characteristics by living donor age categories.

Living donor age categories	18.0–29.9 years *N* = 9227	30.0–39.9 years *N* = 13 704	40.0–49.9 years *N* = 15 216	50.0–59.9 years *N* = 9314	60+ years *N* = 2128
Recipient characteristics					
Age in years, mean (SD)	42.6 (13.7)	47.4 (13.3)	47.9 (13.7)	49.1 (13.4)	55.5 (13.4)
Gender (%)					
Male	5511 (59.7)	8043 (58.7)	9228 (61.3)	5713 (61.3)	1315 (61.8)
Female	3716 (40.3)	5661 (41.3)	5988 (39.3)	3601 (38.7)	813 (38.2)
Race (%)					
White	4680 (50.7)	8342 (60.9)	10 795 (70.9)	7230 (77.6)	1756 (82.5)
Black	1975 (21.4)	2544 (18.6)	2028 (13.3)	898 (9.6)	131 (6.2)
Hispanic	1940 (21.0)	2048 (14.9)	1676 (11.0)	699 (7.5)	136 (6.4)
Others	632 (6.9)	770 (5.62)	717 (4.7)	487 (5.2)	105 (4.9)
Cause of ESRD					
Glomerulonephritis	2949 (32.0)	3955 (28.9)	4321 (28.4)	2546 (27.3)	476 (22.4)
Diabetes mellitus	2043 (22.1)	3278 (23.9)	3482 (22.9)	2171 (23.3)	573 (26.9)
Hypertension	1831 (19.8)	2527 (18.4)	2415 (15.8)	1220 (13.1)	320 (15.0)
Polycystic kidney disease	513 (5.6)	1296 (9.5)	2057 (13.5)	1446 (15.5)	289 (13.6)
Others	1891 (20.5)	2648 (19.3)	2941 (19.3)	1931 (20.7)	470 (22.1)
Peak PRA (%)					
0%	5764 (62.5)	8725 (63.7)	9641 (63.4)	5989 (64.3)	1384 (65.0)
0–10%	1729 (18.7)	2512 (18.3)	2920 (19.2)	1773 (19.0)	421 (19.8)
>10%	1734 (18.8)	2467 (18.0)	2655 (17.5)	1552 (16.7)	323 (15.2)
Time on dialysis (%)					
Pre-emptive	2555 (24.4)	3912 (28.5)	4931 (32.4)	3177 (34.1)	766 (36.0)
0–0.5 years	1105 (12.0)	1730 (12.6)	1999 (13.1)	1224 (13.1)	234 (11.0)
0.6–1.0 years	1465 (15.9)	2209 (16.1)	2385 (15.7)	1469 (15.8)	295 (13.9)
1.1–2.0 years	1980 (21.5)	2709 (19.8)	2848 (18.7)	1604 (17.2)	388 (18.2)
2.1–3.0 years	919 (10.0)	1237 (9.0)	1261 (8.3)	782 (8.4)	207 (9.7)
3.1–4.0 years	519 (5.6)	618 (4.5)	651 (4.3)	379 (4.1)	81 (3.8)
>4.0 years	733 (7.9)	886 (6.5)	748 (4.9)	428 (4.6)	95 (4.5)
Missing or unknown	251 (2.7)	403 (2.9)	393 (2.6)	251 (2.7)	62 (2.9)
Body mass index in kg/m^2, median (IQR)	26.4 (7.8)	26.8 (7.5)	26.5 (7.2)	26.5 (7.5)	26.8 (7.4)
Donor characteristics					
Gender (%)					
Male	4557 (49.4)	5952 (43.4)	5564 (36.6)	3323 (35.7)	835 (39.2)
Female	4670 (50.6)	7752 (56.6)	9652 (63.4)	5991 (64.3)	1293 (60.8)
Race (%)					
White	4808 (52.1)	8559 (62.5)	11 153 (73.3)	7531 (80.9)	1816 (85.3)
Black	1871 (20.3)	2345 (17.1)	1767 (11.6)	727 (7.8)	100 (4.7)
Hispanic	1946 (21.1)	2074 (15.1)	1679 (11.0)	694 (7.5)	129 (6.1)
Others	602 (6.5)	726 (5.3)	617 (4.1)	362 (3.9)	83 (3.9)
Pre-op serum creatinine in mg/dl, mean (SD)	0.90 (0.39)	0.91 (0.41)	0.89 (0.42)	0.90 (0.41)	0.90 (0.43)
Body mass index in kg/m^2, median (IQR)	25.8 (6.5)	26.7 (6.3)	26.7 (6.0)	26.6 (5.7)	26.4 (5.4)
Transplant characteristics					
Induction therapy					
Yes	6332 (68.6)	9489 (69.2)	10 592 (69.6)	6612 (71.0)	1531 (71.9)
No	2895 (31.4)	4215 (30.8)	4624 (30.4)	2702 (29.0)	597 (28.1)
Cold ischemia time in hours, median (IQR)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
HLA mismatches, mean (SD)	3.0 (1.6)	3.1 (1.7)	3.2 (1.7)	3.3 (1.7)	3.5 (1.6)
Transplant era (%)					
2000–2003	3517 (38.1)	5548 (40.5)	5895 (38.7)	3204 (34.4)	646 (30.4)
2004–2006	2940 (31.9)	4370 (31.9)	4879 (32.1)	2916 (31.3)	649 (30.5)
2007–2009	2770 (30.0)	3786 (27.6)	4442 (29.2)	3194 (34.3)	833 (39.3)

Table 2. Association of living donor age and the risk of delayed graft function, total graft failure, death-censored graft failure, and death with graft function.

Study end-point*	18.0–29.9 years OR/HR (95% CI)† *N* = 9227	30.0–39.9 years OR/HR (95% CI)† *N* = 13 704	40.0–49.9 years OR/HR (95% CI)† *N* = 15 216	50.0–59.9 years OR/HR (95% CI)† *N* = 9314	60+ years OR/HR (95% CI)† *N* = 2128
Delayed graft function	Referent	1.24 (1.07, 1.43)	1.32 (1.14, 1.52)	1.53 (1.31, 1.79)	1.87 (1.49, 2.35)
Total graft failure	Referent	1.03 (0.97, 1.10)	1.10 (1.03, 1.18)	1.20 (1.12, 1.29)	1.53 (1.37, 1.70)
Death-censored graft failure	Referent	1.00 (0.92, 1.09)	1.13 (1.04, 1.23)	1.25 (1.14, 1.37)	1.79 (1.55, 2.07)
Death with graft function	Referent	1.06 (0.95, 1.18)	1.06 (0.95, 1.18)	1.13 (1.01, 1.28)	1.27 (1.08, 1.50)
Graft failure (competing risk)‡	Referent	1.00 (0.92, 1.09)	1.13 (1.04, 1.09)	1.24 (1.12, 1.36)	1.76 (1.53, 2.03)

*All models adjusted for characteristics listed in Table 1.
†Measure of association for delayed graft function is the odds ratio (OR) while the other endpoints are expressed as hazard ratios (HR).
‡Graft failure accounting for death with graft function as a competing risk; the measure of association for this analysis is the subdistribution HR.

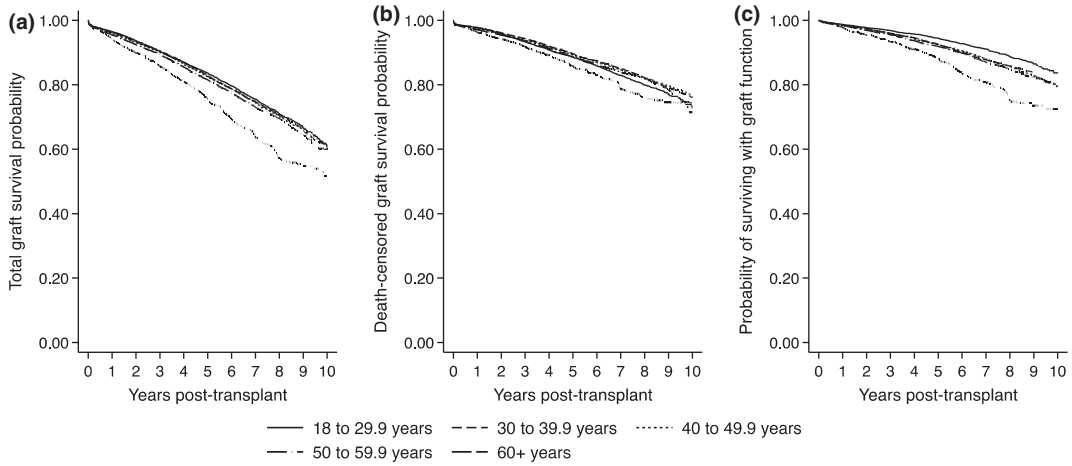

Figure 1 Kaplan–Meier curves for total graft survival (a), death-censored graft survival (b), and patient survival with graft function (c) stratified by living donor age category.

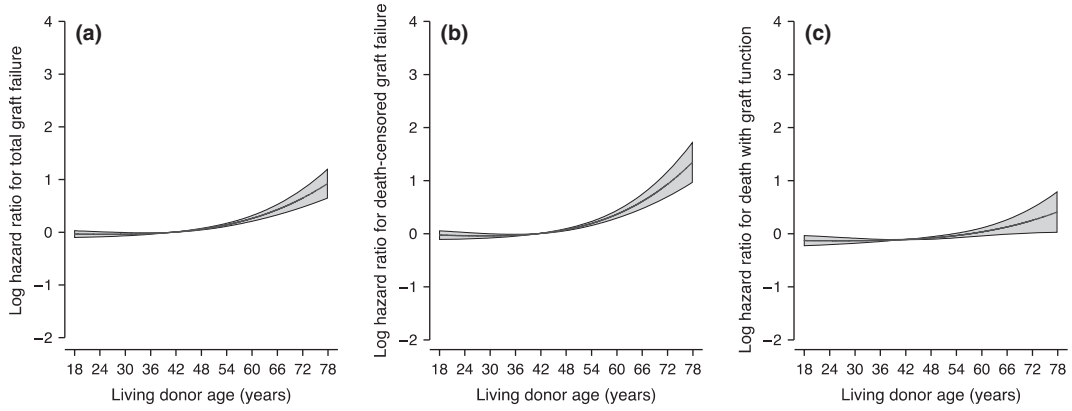

Figure 2 Relative hazard of total graft failure (a), death-censored graft failure (b), and death with graft function (c) as a function of living donor age using the fractional polynomial method.

determinant of short- and long-term outcomes in the contemporary era of kidney transplantation. Furthermore, after accounting for recipient age and other relevant covariates, living donor age is associated with an increased risk of death-censored graft failure, and even death with graft function. This risk is accentuated beyond the donor age of 50 years especially for total graft failure and death-censored graft failure. The associations of living donor age and graft/patient outcomes were markedly attenuated after adjusting for recipient eGFR at 6- or 12-months post-transplant.

The importance of living donor age on allograft survival was recently assessed in a systematic review by Iordanous *et al.* [15]. Similar to our findings, recipients of kidneys from older living donors ($\geq$60 years) were found to have poorer 5-year patient and graft survival than recipients of kidneys from younger donors [72% vs. 80%, unadjusted relative risk 0.89 (95% CI: 0.83–0.95)]. In meta-regression, this association diminished over time [relative risk 0.79 (95% CI: 0.65–0.96) in 1980s vs. 0.91 (95% CI: 0.85–0.99) in 1990s].

When living donor and recipient age categories were cross-classified, it was apparent that the relative hazard for total graft failure was highest in the extremes of recipient age. Separating the outcome of total graft failure into its two components revealed that the risk of death with graft function was most marked in the oldest recipient age group. Of note, however, is a higher HR for death with graft function among the oldest recipients with kidney transplants from living donors >40 years of age and a twofold increase in the HR of death with graft function in the youngest recipient age group using kidneys from the oldest age group. While the increased risk for mortality in the older age group is not unexpected [19,20], these findings re-affirm the importance of adequate kidney allograft function for optimizing patient survival in all recipient age groups, particularly in the youngest recipients.

Schnitzler *et al.* assessed the associations of eGFR at the first transplant anniversary with graft and patient survival up to 9 years post-transplant. Using a multivariate nonlinear regression model, the authors found the likelihood of graft loss and death to increase significantly with lower eGFR. The impact of poor eGFR was most pronounced among living donor recipients [21]. Indeed, when adjusting our analysis for recipient eGFR at 6- or 12-months, the effect of living donor age was considerably attenuated. In fact, the association was essentially nullified after adjustment for eGFR in patients surviving with a functioning graft at 12-months post-transplant. These findings suggest that living donor age does not independently predict graft loss or death beyond the 12-month mark, emphasizing the importance of achieved renal function on the prognosis of kidney transplant recipients. Of note, patients with graft

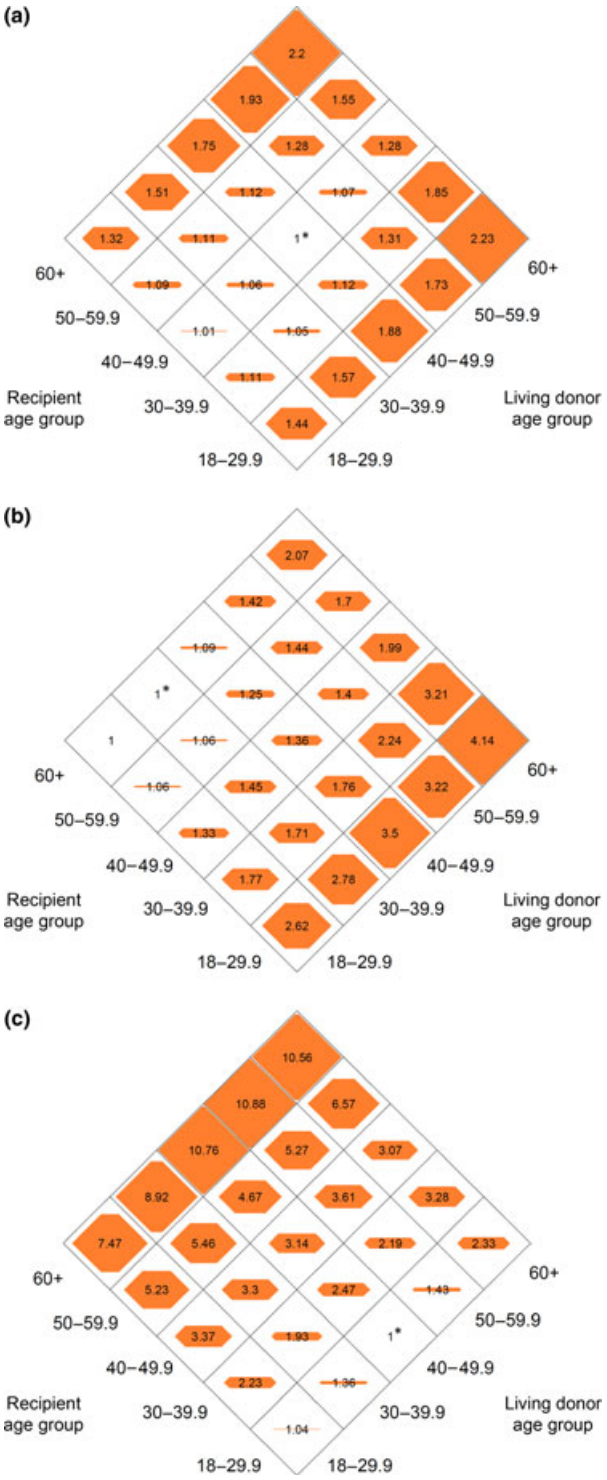

Figure 3 Diamond graphs of adjusted hazard ratios for total graft failure (a), death-censored graft failure (b), and death with graft function (c) across categories of living donor and recipient age (referent standardized to the lowest hazard ratio).

Table 3. Association of living donor age and the risk of total graft failure, death-censored graft failure, or death with graft function adjusting for eGFR at 6- or 12-months post-transplant.

Study end-point*	Adjustment for eGFR	18.0–29.9 years HR (95% CI)	30.0–39.9 years HR (95% CI)	40.0–49.9 years HR (95% CI)	50.0–59.9 years HR (95% CI)	60+ years HR (95% CI)
Conditioning on 6-month survival						
Total graft failure	No	Referent	1.03 (0.96, 1.11)	1.10 (1.03, 1.18)	1.19 (1.10, 1.29)	1.57 (1.40, 1.77)
	Yes	Referent	1.00 (0.94, 1.08)	1.02 (0.95, 1.10)	1.02 (0.94, 1.11)	1.21 (1.08, 1.37)
Death-censored graft failure	No	Referent	1.00 (0.91, 1.09)	1.13 (1.03, 1.24)	1.23 (1.11, 1.36)	1.87 (1.59, 2.19)
	Yes	Referent	0.95 (0.87, 1.04)	1.00 (0.91, 1.10)	0.97 (0.87, 1.08)	1.29 (1.10, 1.51)
Death with graft function	No	Referent	1.08 (0.96, 1.21)	1.06 (0.94, 1.19)	1.14 (1.00, 1.29)	1.32 (1.10, 1.57)
	Yes	Referent	1.07 (0.95, 1.20)	1.04 (0.92, 1.17)	1.09 (0.95, 1.24)	1.20 (1.00, 1.43)
Conditioning on 12-month survival						
Total graft failure	No	Referent	1.03 (0.95, 1.10)	1.09 (1.01, 1.17)	1.16 (1.07, 1.26)	1.50 (1.32, 1.69)
	Yes	Referent	0.98 (0.91, 1.06)	0.99 (0.92, 1.06)	0.94 (0.86, 1.02)	1.06 (0.93, 1.20)
Death-censored graft failure	No	Referent	0.99 (0.90, 1.09)	1.11 (1.01, 1.21)	1.18 (1.06, 1.31)	1.72 (1.45, 2.03)
	Yes	Referent	0.92 (0.84, 1.01)	0.93 (0.85, 1.03)	0.84 (0.75, 0.93)	1.04 (0.87, 1.23)
Death with graft function	No	Referent	1.07 (0.95, 1.21)	1.07 (0.94, 1.21)	1.14 (0.99, 1.30)	1.29 (1.07, 1.56)
	Yes	Referent	1.06 (0.94, 1.12)	1.05 (0.93, 1.18)	1.07 (0.93, 1.23)	1.15 (0.95, 1.39)

*All models adjusted for characteristics listed in Table 1 and eGFR measured at 6- or 12-months post-transplant where specified.

loss or death prior to 6- or 12-months would not be included in these analyses.

Using a cohort of US living donor kidney transplant recipients (1988–2003), Chang *et al.* [14] concluded that, living donor age between 18 and 64 years had a minimal effect on allograft half-life with no graded association. The only exception to this observation was that recipients aged 18–39 years, had the best outcomes with living donors aged 18–39 years. Our analysis assessed allograft outcomes more elaborately, including total graft failure, death-censored graft failure, and death with graft function. We also considered death as a competing risk in the graft failure analysis to ensure that any informative censoring is appropriately addressed. Using a more contemporary U.S. experience over a 10-year period, and including the largest cohort of living donors older than 60 years to date, we find that living donor age remains a significant risk factor for graft outcome despite advances in induction/maintenance immunosuppressive therapies.

A recent Canadian retrospective cohort study reported outcomes in a cohort of kidney recipients who underwent living donor transplantation between January 2000 and March 2008 [13]. The authors of this article report a preferential use of older allografts in older recipients and younger allografts in younger recipients giving rise to a nonstatistically significant increase in the risk for total graft loss in recipients of older ($\geq$60 years) versus younger living donor kidneys [adjusted HR 1.56 (95% CI, 0.98–2.49)]. Since the current study had more patients and events, we were able to confirm a significantly increased adjusted HR for total graft failure, death-censored graft failure, and death with graft function. These findings were confirmed both when living donor age was modeled as a categorical variable and a nonlinear continuous variable.

Similar to data in DDKT [22–24] as well as previous studies in LDKT [12,25,26], our analysis shows an increased risk for DGF as a function of donor age. Unlike DDKT, the cytokine storm associated with the dying process and prolonged cold ischemia is not typically seen in the living donor setting. Instead, the aging kidney may be more susceptible to milder forms of ischemic injury [27]. Since DGF is associated with inferior graft and patient survival [28], the proclivity of older living donor kidneys to reduced early function may partly contribute to their poorer outcomes.

The utilization of living donor kidney allografts from older living donors needs to be evaluated within the context of the critical organ shortage, the survival advantage associated with kidney transplantation compared with dialysis, and the desire to optimize graft survival post-transplant. Our analysis showed a doubling of the risk of total graft failure when recipients in the youngest age group received kidney transplants from living donors 60+ years of age compared with the referent groups of recipients 40–49.9 years receiving kidneys from living donors 40–49.9 years. Our data suggest that the enthusiasm to utilize older living donor kidneys should be tempered with the life expectancy of younger kidney transplant candidates and the anticipated waiting time for a deceased donor kidney transplant. Our analyses provide transplant candidates and physicians with insights into the prognosis of kidney transplants using living donors of various age groups as well as preferable donor-recipient age combinations in the presence of several possible living donors. Our findings by no means discourage the use of organs from older living

donors but rather support a process of risk stratification to precede transplantation from older living donors.

Our study included a large, contemporary, nationally representative cohort of living donor kidney transplant recipients. We used multivariable modeling techniques to provide risk estimates of receiving an older versus younger living donor kidney on clinically important end-points. We also estimated the impact of donor-recipient age category combinations on allograft outcomes as a means to facilitate decision-making and patient counseling. Despite these advantages, our study has limitations. First, our analysis does not take into consideration donors who were not found to be suitable candidates for organ donation. Hence, our results represent the effect of living donor age in the context of current clinical practice in the United States. Second, despite adjustment for an extensive set of covariates, residual confounding cannot be entirely excluded. Finally, this analysis does not answer the question whether a given kidney transplant candidate would fare better should he/she choose to wait for a standard criteria deceased donor kidney over accepting an older living donor kidney. This would be better addressed by a decision analysis incorporating survival data along with valuations of the different treatment strategies and expected impact on quality-of-life.

In summary, our findings confirm the important influence of living donor age on allograft and patient outcomes in the contemporary era of kidney transplantation. Moreover, we have shown that the risk is nonlinear across the range of living donor age studied. To facilitate discussions with potential recipients about the risks and benefits of accepting an older living donor, our study provides detailed estimates of risk across the living donor age continuum and within recipient age categories.

Authorship

SJK: had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RSP, AY, SJK: study concept and design. SJK: acquisition of data. RSP, AY, SJK: analysis and interpretation of data. RSP, AY, SJK: drafting of manuscript. RSP, AY, SJK: critical revision of manuscript. SJK: statistical analyses. SJK: study supervision.

Funding

This project was not supported by any external funding sources.

Acknowledgments

Data contained in this publication have been supplied by the Scientific Registry of Transplant Recipients. The authors alone are responsible for reporting and interpretation. All the data used for this publication were collected pursuant to Contract No. HHSH250201000018C (Department of Health and Human Services, Health Resources and Services Administration, Rockville, Maryland). Dr. Ruth Sapir-Pichhadze is funded by the Eliot Phillipson Clinician Scientist Training Program, Department of Medicine, University of Toronto and the Clinician Investigator Program, Royal College of Physicians and Surgeons of Canada.

References

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; **342**: 605.
2. Cecka JM. Kidney transplantation in the United States. *Clin Transpl* 2008; 1.
3. Gjertson DW, Cecka JM. Living unrelated donor kidney transplantation. *Kidney Int* 2000; **58**: 491.
4. Karatzas T, Gompou A, Bokos J, *et al.* Optimal utilization of expanded criteria deceased donors for kidney transplantation. *Int Urol Nephrol* 2011; **43**: 1211.
5. Moore PS, Farney AC, Hartmann EL, *et al.* Experience with deceased donor kidney transplantation in 114 patients over age 60. *Surgery* 2007; **142**: 514; discussion 523 e511-512.
6. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. *Am J Kidney Dis* 2008; **52**: 553.
7. Woo YM, Gill JS, Johnson N, Pereira BJ, Hariharan S. The advanced age deceased kidney donor: current outcomes and future opportunities. *Kidney Int* 2005; **67**: 2407.
8. Stegall MD. Developing a new kidney allocation policy: the rationale for including life years from transplant. *Am J Transplant* 2009; **9**: 1528.
9. Berger JC, Muzaale AD, James N, *et al.* Living kidney donors ages 70 and older: recipient and donor outcomes. *Clin J Am Soc Nephrol* 2011; **6**: 2887.
10. Gill J, Bunnapradist S, Danovitch GM, Gjertson D, Gill JS, Cecka M. Outcomes of kidney transplantation from older living donors to older recipients. *Am J Kidney Dis* 2008; **52**: 541.
11. Gill JS, Gill J, Rose C, Zalunardo N, Landsberg D. The older living kidney donor: part of the solution to the organ shortage. *Transplantation* 2006; **82**: 1662.
12. Noppakun K, Cosio FG, Dean PG, Taler SJ, Wauters R, Grande JP. Living donor age and kidney transplant outcomes. *Am J Transplant* 2011; **11**: 1279.
13. Young A, Kim SJ, Speechley MR, *et al.* Accepting kidneys from older living donors: impact on transplant recipient outcomes. *Am J Transplant* 2011; **11**: 743.
14. Chang P, Gill J, Dong J, *et al.* Living donor age and kidney allograft half-life: implications for living donor paired exchange programs. *Clin J Am Soc Nephrol* 2012; **7**: 835.

15. Iordanous Y, Seymour N, Young A, *et al.* Recipient outcomes for expanded criteria living kidney donors: the disconnect between current evidence and practice. *Am J Transplant* 2009; **9**: 1558.
16. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999; **28**: 964.
17. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol* 2009; **170**: 244.
18. Li X, Buechner JM, Tarwater PM, Munoz A. A diamond-shaped equiponderant graphical display of the effects of two categorical predictors on continuous outcomes. *Am Stat* 2003; **57**: 193.
19. Foley DP, Patton PR, Meier-Kriesche HU, *et al.* Long-term outcomes of kidney transplantation in recipients 60 years of age and older at the University of Florida. *Clin Transpl* 2005; 101.
20. Sener A, Schweitzer EJ, Munivenkatappa R, *et al.* Deceased-donor renal transplantation in the geriatric population demonstrates equal graft survival compared with younger recipients. *Transplantation* 2009; **87**: 1549.
21. Schnitzler MA, Lentine KL, Gheorghian A, Axelrod D, Trivedi D, L'Italien G. Renal function following living, standard criteria deceased and expanded criteria deceased donor kidney transplantation: impact on graft failure and death. *Transpl Int* 2012; **25**: 179.
22. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. *Am J Transplant* 2010; **10**: 2279.
23. Quiroga I, McShane P, Koo DD, *et al.* Major effects of delayed graft function and cold ischaemia time on renal allograft survival. *Nephrol Dial Transplant* 2006; **21**: 1689.
24. McLaren AJ, Jassem W, Gray DW, Fuggle SV, Welsh KI, Morris PJ. Delayed graft function: risk factors and the relative effects of early function and acute rejection on long-term survival in cadaveric renal transplantation. *Clin Transplant* 1999; **13**: 266.
25. Senel FM, Karakayali H, Moray G, Haberal M. Delayed graft function: predictive factors and impact on outcome in living-related kidney transplantations. *Ren Fail* 1998; **20**: 589.
26. Ghods AJ, Savaj S, Abbasi M, Heidari H, Rokhsatyazdi H. The incidence and risk factors of delayed graft function in 689 consecutive living unrelated donor renal transplantation. *Transplant Proc* 2007; **39**: 846.
27. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. The aging kidney. *Kidney Int* 2008; **74**: 710.
28. Tapiawala SN, Tinckam KJ, Cardella CJ, *et al.* Delayed graft function and the risk for death with a functioning graft. *J Am Soc Nephrol* 2010; **21**: 153.