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Recipient Outcomes Following Transplantation of Allografts From Live Kidney Donors Who Subsequently Developed End Stage Renal Disease

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Abstract

Live kidney donors have an increased risk of ESRD compared with nondonors; however, it is unknown whether undetected, subclinical kidney disease exists at donation that subsequently contributes to this risk. To indirectly test this hypothesis, we followed the donated kidneys themselves, by comparing outcomes of 257 recipients whose donors subsequently developed ESRD with a matched cohort whose donors remained ESRD-free. The compared recipients were matched on donor (age, sex, race/ethnicity, donor/recipient relationship), transplant (HLA mismatch, peak-PRA, previous transplant, year-of-transplant), and recipient risk factors (age, sex, race/ethnicity, body-mass index, cause of ESRD, and time-on-dialysis). Median recipient follow-up was 12.5 years (interquartile range 7.4–17.9, maximum 20 years). Recipients of allografts from donors who developed ESRD had increased death-censored graft loss (74% vs. 56% at 20 years; adjusted hazard ratio [aHR] 1.7; 95% confidence interval [CI] 1.5–2.0; $p < 0.001$) and mortality (61% vs. 46% at 20 years; aHR 1.5; 95% CI 1.2–1.8; $p < 0.001$) compared with matched recipients of allografts from donors who did not develop ESRD. This association was similar among related, spousal, and unrelated nonspousal donors. These findings support a novel view of the mechanisms underlying donor ESRD: that of pre-donation kidney disease. However, biopsy data may be required to confirm this hypothesis.

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DISCLAIMER

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

INTRODUCTION

Emerging evidence suggests that individuals who donate kidneys have higher incidence of end stage renal disease (ESRD) compared with their healthy nondonor counterparts (1–3). Since donors are rigorously screened for kidney disease prior to nephrectomy (4, 5), the prevailing belief is that *de novo* postdonation disease is a crucial step in the pathway to donor ESRD (6, 7). *De novo* kidney disease may sooner progress to ESRD in donors than in their healthy nondonor counterparts because nephrectomy represents a 50% reduction in nephron number, a 20–30% reduction in glomerular filtration rate (8), and, as such, a step closer to ESRD (9).

What remains unknown is whether undetected, subclinical kidney disease exists at donation and subsequently contributes to donor ESRD. Moderate to severe subclinical abnormalities have been found at implantation biopsy in 4% of donated kidneys (10); however, the direct link to post-donation ESRD has been difficult to study. Protocol biopsies on donors (or allografts after donation) are not routine practice at most centers (4, 11, 12); single-center studies are not sufficiently powered to investigate rare outcomes such as ESRD (10, 13–18); and sufficiently powered national studies lack histological data (2, 19).

To assess the contribution of subclinical kidney disease to post-donation outcomes at a national level, we used recipient outcomes as a surrogate for the quality of the kidney that was donated, i.e. if there were subclinical abnormalities in the kidney that were "transmitted" to the recipient. We compared outcomes of recipients whose donors subsequently developed ESRD to outcomes of matched recipients whose donors did not develop ESRD. Because biologically related donors and their recipients may share genetic risk for kidney disease, and spousal donors and their recipients may share lifestyle risks—risks which may themselves manifest as adverse outcomes for both donor and recipient—we also stratified our analysis across related donors, spousal and lifetime partners, and unrelated non-spousal donors.

METHODS

Data sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, waitlisted 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 (20). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Study population and post-donation ESRD ascertainment

We studied a cohort of recipients of allografts from donors who subsequently developed ESRD. To identify donors who developed ESRD, SRTR data were linked to Centers for Medicare and Medicaid Services data as previously described, and ESRD in donors was defined as the initiation of maintenance dialysis or receipt of a living or deceased donor kidney transplant, whichever was identified first (2).

Matched controls

Recipients with allografts from donors who did not develop ESRD were matched to recipients with allografts from donors who developed ESRD in a 5:1 ratio using iterative expanding radius matching as previously described (2, 21–25). Matching was based on donor (age, sex, race, donor/recipient relationship), transplant (HLA mismatch, peak PRA, previous transplant, year of transplant), and recipient characteristics (age, sex, race, body-mass index, cause of ESRD, and time-on-dialysis). We did not include donor kidney function in our matching algorithm because we thought of it as a possible mediator, rather than a confounder, of the association under study. Having matched on year of transplant, recipients of allografts from donors who did not develop ESRD were followed for as long as recipients whose donors developed ESRD. In a subsequent sensitivity analysis, we rerun the entire matched analysis using the propensity score method (26).

Recipient outcomes

We studied all-cause graft loss, death-censored graft loss, and mortality. Graft loss was defined as the resumption of maintenance dialysis, relisting for kidney transplantation, or retransplantation; all-cause graft loss also included death.

Statistical analysis

We used Kaplan-Meier methods to estimate the absolute risk of recipient graft loss and mortality, and Cox regression to estimate the relative risks for the same outcomes. Since we controlled for confounding in our matched study design, all estimates we report are adjusted. In estimating p-values for the comparison of baseline cohort characteristics, we used robust variance estimators to account for clustering in the 5:1 matching design since the multiple controls per case were not independently sampled. All analyses were performed using Stata 14.0/MP for Linux (Stata Corp, College Station, TX). All hypothesis tests were 2 sided ($\alpha = .05$).

RESULTS

Study population

A total of 257 patients received allografts from donors who subsequently developed ESRD after a median of 12.5 years (interquartile range 7.4–17.9) post-donation. In this recipient population, median age was 39 years, 60.7% were male, 51.4% were Caucasian, median BMI was 25 kg/m², and the reported causes of recipient ESRD were diabetes (17.1%), hypertension (19.8%), GN (32.7%), other (30.0%), and missing or unknown cause (0.4%). There were 15.1% recipients with no HLA DR mismatch, 71.2% with a peak PRA less than 10, 89.9% with no previous transplant, and 97.3% with negative HCV serology. The median recipient time on dialysis prior to transplantation was 1 year. By discharge, median recipient eGFR was 54 ml/min/1.73m² and 5.8% of recipients had experienced delayed graft function. Median donor age was 37 years, 61.5% of donors were male, 53.9% were Caucasian, 90.2% were biologically related to the recipient, and median donor eGFR was 96 ml/min/1.73m². By design, the 1103 matched recipients of allografts from donors who did not develop ESRD were comparable in these characteristics (Table 1). Similarly, the matched recipients

identified in a sensitivity analysis using propensity score matching methods were comparable in these characteristics.

All-cause graft loss

The 257 recipients whose donor developed ESRD were followed for a total of 2,095 person-years, a period during which 154 recipients lost their grafts and 148 died (58 with functioning grafts). By comparison, the 1103 recipients whose donor did not develop ESRD were followed for a total of 11,544 person-years, a period during which 492 recipients lost their grafts and 444 died (222 with functioning grafts). Estimated 1-year, 5-year, 10-year, 15-year, and 20-year cumulative incidence of all-cause graft loss was 10.1%, 36.2%, 63.2%, 82.0%, and 85.8 % in recipients whose donor developed ESRD and 6.1%, 22.0%, 43.0%, 61.7%, and 72.2% in matched recipients whose donor did not develop ESRD, with a 1.7-fold higher adjusted risk of all-cause graft loss among those whose donors developed ESRD (95% CI 1.3–1.8; $p<0.001$) (Figure 1A). This association was observed regardless of donor age (18–39 year-old subgroup: aHR 1.6; 95% CI 1.2–1.8; 40–49 years: aHR 1.7; 95% CI 1.2–2.5; and 50–80 years: aHR 1.7; 95% CI 1.2–2.4; interaction $p=0.9$), donor/recipient relationship (parent or child: aHR 1.6; 95% CI 1.2–2.0; sibling or other biological relative: aHR 1.6; 95% CI 1.2–2.0; spouse or lifetime partner: aHR 2.5; 95% CI 1.0–6.9; and unrelated non-spousal: aHR 2.0; 95% CI 1.0–3.7; interaction $p=0.7$), and year of transplant (1987–1991: aHR 1.8; 95% CI 1.3–2.5; 1992–1999: aHR 1.6; 95% CI 1.2–1.8; and 2000–2014: aHR 1.5; 95% CI 1.1–2.2; $p=0.8$ for interaction) (Figure 2). Similar results were obtained in the sensitivity analysis that identified matched recipients using propensity score methods.

Death-censored graft loss

Estimated 1-year, 5-year, 10-year, 15-year, and 20-year cumulative incidence of death-censored graft loss was 9.0%, 31.3%, 51.7%, 69.3%, and 73.5% if the donor developed ESRD and 5.2%, 16.3%, 32.6%, 48.3%, and 56.4% if the donor did not develop ESRD, with a 1.7-fold higher adjusted risk of death-censored graft loss among those whose donors developed ESRD (95% CI 1.5–2.0; $p<0.001$) (Figure 1B). This association was observed regardless of donor age (18–39 year-old subgroup: aHR 1.8; 95% CI 1.5–2.2; 40–49 years: aHR 1.5; 95% CI 1.0–2.4; 50–80 years: aHR 1.7; 95% CI 1.1–2.5; interaction $p=0.7$), donor/recipient relationship (parent or child: aHR 2.0; 95% CI 1.6–2.7; sibling or other biological relative: aHR 1.5; 95% CI 1.2–2.0; spouse or lifetime partner: aHR 3.0; 95% CI 0.7–12.0; unrelated non-spousal: aHR 1.7; 95% CI 0.7–4.4; interaction $p=0.6$), and year of transplant (1987–1991: aHR 2.0; 95% CI 1.5–2.9; 1992–1999: aHR 1.6; 95% CI 1.2–2.0; 2000–2014: aHR 1.7; 95% CI 1.1–2.5; interaction $p=0.9$) (Figure 3). Similar results were obtained in the sensitivity analysis that identified matched recipients using propensity score methods.

Mortality

Estimated 1-year, 5-year, 10-year, 15-year, and 20-year cumulative incidence of mortality was 2.7%, 14.4%, 35.0%, 49.4%, and 61.4% if the donor developed ESRD and 1.5%, 8.8%, 21.6%, 35.4%, and 46.1% if the donor did not develop ESRD, with a 1.5-fold higher adjusted risk of mortality among those whose donors developed ESRD (95% CI 1.2–1.8; $p<0.001$) (Figure 1C). This association was observed regardless of donor age (18–39 years:

aHR 1.5; 95% CI 1.2–2.0; 40–49 years: aHR 1.6; 95% CI 1.1–2.5; and 50–80 years: aHR 1.5; 95% CI 1.0–2.0; interaction $p=0.8$), donor/recipient relationship (parent or child: aHR, 1.2; 95% CI 0.9–1.7; sibling or other biological relative: aHR 1.7; 95% CI 1.2–2.2; spousal or lifetime partner: aHR 2.2; 95% CI 0.8–6.3; unrelated non-spousal: aHR 2.0 95% CI 1.0–4.4; interaction $p=0.3$), and year of transplant (1987–1991: aHR 1.7; 95% CI 1.2–2.2; 1992–1999: aHR 1.5; 95% CI 1.2–2.0; and 2000–2014: aHR 1.3; 95% CI 0.8–2.2 interaction $p=0.7$) (Figure 4). Similar results were obtained in the sensitivity analysis that identified matched recipients using propensity score methods.

DISCUSSION

In this national study, we discovered that allografts from donors who subsequently developed ESRD were associated with 1.7-fold higher adjusted risk of all-cause graft loss, 1.7-fold higher adjusted risk of death-censored graft loss, and 1.5-fold higher adjusted risk of mortality compared with allografts that came from donors who remained ESRD-free. These adverse recipient outcomes were observed regardless of donor age, donor/recipient relationship, and year of transplant. The finding that kidney disease was "transmitted" to the recipient provides indirect evidence that some degree of existing, but undiagnosed, kidney pathology at the time of donation might have contributed to the risk of ESRD following live kidney donation. So, despite careful clinical screening by widely established standards of donor evaluation (4, 5), nontrivial kidney disease in the donor may remain inadequately characterized.

These findings and inferences are consistent with the well-established notion that recipient outcomes are influenced by the quality of the allograft, whether from a living or deceased donor. Adverse recipient outcomes result from transplantation of allografts from donors with characteristics associated with increased risk of ESRD, including old age, African American race, history of diabetes, and history of hypertension (27). In a recent study, worse recipient outcomes were associated with allografts from donors with the high-risk APOL1 phenotype (28). Our study extends this theme by showing worse outcomes in recipients of allografts from carefully screened, healthy donors who were not excluded as higher-risk for renal anomalies at the time of donation, but nonetheless subsequently developed ESRD. Our findings suggest that, in some instances, factors leading to ESRD may exist in the allograft prior to donation, as may be the case with genetically determined kidney disease. By extension, our findings also suggest that asymptomatic (and subtle), early-stage lesions may exist in the allograft prior to donation, as has been found at implantation biopsy (29–35), and that these lesions might be clinically relevant.

Since our study design accounted for well-established donor, transplant, and recipient characteristics, our inferences are unlikely to be confounded by these factors, which include donor age, sex, race, donor/recipient relationship, HLA mismatch, peak-PRA, year-of-transplant, and recipient age, sex, race, body-mass index, cause of ESRD, and time-on-dialysis. Since we stratified our analyses by donor/recipient relationship, and made very similar inferences in each stratum, undiagnosed kidney disease at donation offers the most parsimonious and plausible explanation for our observations. Also, because we obtained similar results in the sensitivity analysis that identified matched recipients using propensity

score methods, our inferences are not sensitive to the choice of matching method. Regardless of whether the allograft was from a biological relative (thus sharing genetic risks), a spouse or lifetime partner (thus sharing lifestyle risks), or an unrelated nonspousal individual (only sharing a kidney), the magnitude of increase in risk of graft loss and patient mortality was substantial.

However, our study must be interpreted in the context of its limitations. In the absence of donor biopsy data, we cannot definitively rule out the contribution to our findings of genetic, lifestyle, or other unknown clinical factors. Our data at best support, but do not confirm, the view that pre-existing kidney disease might be one of the mechanisms underlying donor ESRD. Longitudinal eGFR measurements in both donors and recipients may have offered the opportunity to explore this hypothesis further using national registry data; however, these data are only available for the most recent cohorts of donors and recipients, a subset representing less than 5% of our study population.

In conclusion, our data indirectly support the view that subclinical abnormalities at the time of donation may be one of the mechanisms underlying donor ESRD. Current methods of risk prediction for live kidney donor candidates could potentially be improved if these mechanisms underlying donor ESRD are confirmed and their phenotypes established.

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Abbreviations

BMI	body mass index
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
OPTN	Organ Procurement and Transplantation Network
PRA	panel-reactive antibody
SRTR	Scientific Registry of Transplant Recipients

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A**All-Cause Graft Loss, %**

Figure 1. All-cause graft loss, death-censored graft loss, and mortality in recipients whose donors developed end stage renal disease (ESRD) vs. recipients whose donors did not develop ESRD
Recipients whose donor developed ESRD had higher risk of all-cause graft loss (aHR 1.7; 95% CI 1.3–1.8, panel A), death-censored graft loss (aHR 1.7; 95% CI 1.5–2.0, panel B), and mortality (aHR 1.5; 95% CI 1.2–1.8, panel C; all $p<0.05$).

Figure 2. Risk of all-cause graft loss in subgroups of live donor kidney transplant recipients according to subsequent donor ESRD status

The solid vertical line represents aHR = 1 (no risk associated with donors who developed ESRD vs donors who remained ESRD-free); the dotted vertical line is the aHR for the overall cohort. The risk associated with donors who developed ESRD was consistent across subgroups of age, donor/recipient relationship, and year of donation.

^bBy design, aHR accounts for donor, transplant, and recipient factors (see methods for details)

^aP-value for interaction; ^{b,d}Missing values are for subgroups with <20-year follow-up; ^c19-year follow-up

Figure 3. Risk of death-censored graft loss in subgroups of live donor kidney transplant recipients according to subsequent donor ESRD status

The solid vertical line represents aHR = 1 (no risk associated with donors who developed ESRD vs donors who remained ESRD-free); the dotted vertical line is the aHR for the overall cohort. The risk associated with donors who developed ESRD was consistent across subgroups of age, donor/recipient relationship, and year of donation.

^bBy design, aHR accounts for donor, transplant, and recipient factors (see methods for details)

^aP-value for interaction; ^{b,c,d}Missing values are for subgroups with <20-year follow-up;

^c19-year follow-up

Figure 4. Risk of death in subgroups of live donor kidney transplant recipients according to subsequent donor ESRD status

The solid vertical line represents aHR = 1 (no risk associated with donors who developed ESRD vs donors who remained ESRD-free); the dotted vertical line is the aHR for the overall cohort. The risk associated with donors who developed ESRD was consistent across subgroups of age, donor/recipient relationship, and year of donation

^aBy design, aHR accounts for donor, transplant, and recipient factors (see methods for details)

^aP-value for interaction; ^c19-year follow-up; ^dMissing values are for subgroups with <20-year follow-up

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Table 1

Characteristics of recipients of allografts from live kidney donors who developed end stage renal disease (ESRD) vs. recipients of allografts from live kidney donors who remained ESRD-free, United States, October 1, 1987 to July 31, 2014^a

	Donor Developed ESRD ^b		
	Yes	No ^c	P-value
Recipients of Allografts	n=257	n=1103	
Donor Characteristics			
Donor Age, median years [IQR]	37 [30–49]	38 [30–45]	0.2
Donor Sex ^d (%):			
Male	61.5	58.1	0.3
Female	38.5	41.9	
Donor Race/Ethnicity (%):			
Caucasian/Other	53.9	55.4	0.4
African American	37.5	38.4	
Hispanic	8.6	6.2	
Donor/Recipient Relationship (%):			
Parent/Child	38.8	38.4	1
Sibling/Other	51.4	52.3	
Spouse or lifetime partner	3.2	3.4	
Unrelated Non-spousal	6.7	5.8	
Donor eGFR, median ml/min [IQR] ^e	96 [82–108]	100 [84–114]	0.02
Transplant Characteristics			
HLA Mismatched (%):			
0 A/B/DR Mismatch	15.1	16.4	0.8
0 DR Mismatch	15.1	15.3	
1 DR Mismatch	55.7	56.5	
2 DR Mismatch	14.1	11.7	
Peak PRA (%):			
0–9	71.2	76.2	0.1
10–79	18.3	16.0	
80–100	3.9	1.6	
Missing	6.6	6.1	
Previous Transplant (%):			
No	89.9	94.1	0.02
Yes	10.1	5.9	
Recipient Characteristics			
Age, median year [IQR]	39 [28–51]	39 [28–50]	0.6
BMI, median kg/m ² [IQR]	25 [21–29]	25 [21–28]	0.4

Donor Developed ESRD ^b			
	Yes	No ^c	P-value
Diagnosis (%):			
Diabetes	17.1	18.8	0.9
Hypertension	19.8	18.4	
Glomerulonephritis (GN)	32.7	32.4	
Other	30.0	30.3	
Missing/Unknown	0.4	0.2	
HCV serology (%):			
Negative	97.3	97.5	0.9
Positive	2.7	2.5	
Race/Ethnicity (%):			
Caucasian/Other	51.4	54.4	0.4
African American	40.1	39.1	
Hispanic	8.6	6.5	
Sex (%):			
Male	60.7	59.2	0.7
Female	39.3	40.8	
Time on Dialysis, median years [IQR]	1 [0–2]	1 [0–1]	0.001
Donor/Recipient Weight Ratio, median [IQR]	1.0 [0.9–1.2)	1.0 [0.9–1.2]	0.4
Delayed Graft Function (%):	5.8	5.9	1
Recipient eGFR, median ml/min [IQR] ^f	54 [37–72]	58 [43–76]	0.03
Year of Transplant (%):			
1987–1999	76.7	68.9	0.1
2000–2006	21.8	26.8	
2007–2014	1.6	4.3	

^aRecipient and donor characteristics were defined at the time of transplant

^bDonor ESRD was ascertained over a 25-year period following donor nephrectomy

^cThe two recipient cohorts were matched without replacement on donor (age, race, donor/recipient relationship); transplant (HLA mismatch, peak-PRA, year-of-transplant); and recipient characteristics (age, sex, race, body-mass index, cause of ESRD, and time-on-dialysis)

^dWe matched on donor sex although sex it is not included in the scientific registry of transplant recipients risk-model for patient and graft survival

^eAvailable for 9% of pre-2000 records and 96% of post-2000 records

^fAvailable for 97% of recipients, recipient eGFR is based on serum creatinine at discharge

eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; IQR, interquartile range; PRA, panel-reactive antibody