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Living Donor Post-Nephrectomy Kidney Function and Recipient Graft Loss: A Dose-Response Relationship

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Abstract

Development of ESRD in living kidney donors is associated with increased graft loss in the recipients of their kidneys. Our goal was to investigate if this relationship was reflected at an earlier stage post-donation, possibly early enough for recipient risk prediction based on donor response to nephrectomy. Using national registry data, we studied 29,464 recipients and their donors from 2008–2016 to determine the association between donor 6-month post-nephrectomy eGFR and recipient death-censored graft failure (DCGF). We explored donor BMI as an effect modifier, given the association between obesity and hyperfiltration. On average, risk of DCGF increased with each 10mL/min decrement in post-donation eGFR (aHR 1.06, 95% CI 1.02–1.10, p=0.007). The association was attenuated with higher donor BMI (interaction p=0.049): recipients from donors with BMI=20 (aHR 1.12, 95% CI 1.04–1.19, p=0.002) and BMI=25 (aHR 1.07, 95% CI 1.03–1.12, p=0.001) had a higher risk of DCGF with each 10 mL/min decrement in post-donation eGFR, while recipients from donors with BMI=30 and BMI=35 did not have a higher risk. The relationship between post-donation eGFR, donor BMI, and recipient graft loss can inform counseling and management of living donor kidney transplant recipients.

INTRODUCTION

In considering recipient outcomes following living donor kidney transplantation (LDKT), pre-donation donor risk factors of lower estimated glomerular filtration rate (eGFR), older age, and higher BMI have been associated with greater risk of recipient graft loss (1–4). Post-donation, development of end-stage renal disease (ESRD) in the donor is associated

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DISCLOSURE

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with increased risk of graft loss in the recipient (5). While this is interesting biologically, it is of less utility for clinical risk prediction because ESRD is a rare post-donation event that generally occurs many years after donation (6–8). More useful might be an earlier donor physiologic response to nephrectomy and its relation to recipient outcomes.

Given that most living donors experience a gradual increase in eGFR following donation as their remaining kidney hypertrophies (9–12), lower donor eGFR at an early interval after donor nephrectomy might serve as an earlier or more subtle predictor of recipient graft loss compared to waiting for ESRD development (13, 14). This must be considered in the context that post-donation eGFR is related not only to intrinsic kidney quality (and hence would also reflect the kidney that was donated), but also to the ability of the remaining kidney to hypertrophy (15). As such, donor obesity must also be investigated as an effect modifier: obese donors are more likely to have already developed obesity-related glomerulomegaly (16), so their donor kidneys might have less physiologic reserve and less ability to hypertrophy in response to donation. Thus, higher post-nephrectomy eGFR in obese donors might indicate hyperfiltration rather than physiologic recovery, and portend a different risk prediction for recipients than the same finding in non-obese donors.

In order to examine if donor post-nephrectomy eGFR can function as a predictor of recipient outcomes, we used national registry data to examine the association between 6-month post-donation eGFR and LDKT recipient graft loss. Additionally, we investigated whether this association varied by donor BMI.

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere (17). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study population and ascertainment of the exposure

We studied 42,053 kidney-only adult LDKT recipients and their donors between 1/1/2008 and 12/31/2016. Donor 6-month post-nephrectomy eGFR was calculated from 6-month OPTN donor follow-up forms using the CKD-EPI equation (18). We considered any eGFR reported between 3 months and 9 months post-donation to be a 6-month post-donation eGFR.

LDKT recipient outcomes

We examined all-cause graft failure (ACGF) and death-censored graft failure (DCGF), defined as resumption of maintenance dialysis, listing for re-transplantation, or living donor re-transplantation without listing. We used Cox proportional hazards models to study the association of post-donation donor eGFR with recipient graft loss, adjusting for donor age,

gender, BMI, and race; recipient age, gender, BMI, race, cause of ESRD, time on dialysis, previous kidney transplant, peak panel reactive antibody (PRA), depleting induction therapy (thymoglobulin or alemtuzumab), non-depleting induction therapy (daclizumab or basiliximab), maintenance therapy of tacrolimus, maintenance therapy of cyclosporine; and donor and recipient relationship, ABO incompatibility, and number of human leukocyte antigen (HLA) mismatches.

In order to select the model with the best fit, we compared three models all adjusted for the above covariates with the outcome of ACGF—one including pre-donation eGFR, one including post-donation eGFR, and one including both pre-donation and post-donation eGFR—using the Akaike information criterion (AIC) as an estimator of relative quality of models. The model with the best fit, selected by the lowest AIC, included only post-donation eGFR, meaning that post-donation eGFR provided more information than pre-donation eGFR. We used the same set of covariates for the outcome of DCGF.

Effect modification by donor BMI

In order to examine whether the association between post-donation eGFR and recipient graft loss varied by donor BMI, we created interaction terms between post-donation eGFR and donor BMI. Because we considered both donor BMI and post-donation eGFR in continuous forms, to illustrate the association between post-donation eGFR and graft loss at various donor BMIs, we provided point estimates of the risk of graft loss per 10mL/min decrement in eGFR at a donor BMI of 20, 25, 30, 35, and 40.

Sensitivity analysis and missing data

There were 12,589 (29.9%) donor-recipient pairs who were missing 6-month post-donation eGFR and thus were excluded from complete-case analysis of outcomes. To examine whether excluding these donors might have introduced a selection bias into our study, we used multiple imputation by chained equations to impute missing post-donation eGFR and repeated the analyses described above with the complete population. Our inferences remained the same, therefore we limited our primary analyses to those that had complete data available (n=29,464). Of the 29,464 subjects, only 344 (1.2%) were missing donor BMI, and these were handled by complete-case analysis. There were no missing data for any other variable used in analysis.

Statistical analysis

For descriptive purposes, post-donation eGFR above or below 60 mL/min per $1.73m^2$ was selected for its clinical relevance. For Kaplan-Meier curves of cumulative incidence of graft loss, we used quartiles of post-donation eGFR to demonstrate trends. For regression analysis, post-donation eGFR was examined as a continuous variable scaled per 10 mL/min. Fractional polynomial regression models were compared to models that included eGFR as a scaled linear variable; for both ACGF and DCGF, the models with eGFR as a linear variable had the better fit by AIC. Confidence intervals are reported as per the method of Louis and Zeger (19). All analyses were performed using Stata 14.2/SE for Windows (College Station, Texas).

RESULTS

Study population: Living donors

Among 29,464 LDKT recipients, 1,781 (6.0%) had a donor with 6-month post-donation eGFR<45 mL/min, 10,152 (34.5%) with eGFR 45–60 mL/min, 10,563 (35.8%) with eGFR 60–75 mL/min, 4,913 (16.7%) with eGFR 75–90 mL/min, and 2,055 (7.0%) with eGFR≥90 mL/min. Donors with post-donation eGFR<60 mL/min were older (median 51 years vs. 38 years, p<0.001), had higher BMI (median 27.0 vs. 26.4, p<0.001), were more likely to be male (38.6% vs. 34.8%, p<0.001) and Caucasian (86.1% vs 69.2%, p<0.001), had lower pre-donation eGFR (median 86 vs. 106 mL/min, p<0.001), were less likely to be a first-degree relative (36.0% vs. 42.6%), and were more likely to be a spouse or partner (16.8% vs. 12.9%, p<0.001) compared to those with higher post-donation eGFR (Table 1). There was only moderate correlation between 6-month post-donation eGFR and pre-donation eGFR (ρ=0.65).

Study population: LDKT recipients

LDKT recipients from donors with post-donation eGFR<60 mL/min were older (median 53 years vs. 48 years), more likely to be Caucasian (82.1% vs. 66.9%, p<0.001), and spent less time on dialysis (median 0.5 vs. 0.6 years, p<0.001) compared to LDKT recipients from donors with higher post-donation eGFR. Early post-transplant, LDKT recipients from donors with post-donation eGFR<60 mL/min had lower eGFR at hospital discharge following transplantation (median 51 vs. 59 mL/min, p<0.001) and higher prevalence of delayed graft function (3.6% vs. 3.1%, p=0.03) compared to LDKT recipients from donors with higher post-donation eGFR (Table 1).

All-cause graft failure

There were 2865 all-cause graft failures during 105980.8 person-years of follow-up. There was higher ACGF in recipients from donors with lower post-donation eGFR (Figure 1). However, after adjusting for donor age, gender, BMI, race, donor-recipient relationship, ABO incompatibility, number of HLA mismatches, and recipient age, gender, BMI, race, cause of ESRD, time on dialysis, previous kidney transplant, peak PRA, induction immunosuppression, and maintenance immunosuppression, there was not a statistically significant association between post-donation eGFR and all-cause graft failure (adjusted hazard ratio [aHR] $_{0.96}0.98_{1.01}$, p=0.3) (Table 2).

Death-censored graft failure

There were 1536 death-censored graft failures during 105980.8 person-years of follow-up. There was higher DCGF in recipients from donors with lower post-donation eGFR (Figure 1). After adjusting for donor age, gender, BMI, race, donor-recipient relationship, ABO incompatibility, number of HLA mismatches, and recipient age, gender, BMI, race, cause of ESRD, time on dialysis, previous kidney transplant, peak PRA, induction immunosuppression, and maintenance immunosuppression, risk of DCGF was 5% higher for every 10mL/min decrement in post-donation eGFR (aHR $_{0.91}0.95_{0.98}$, p=0.007) (Table 2).

Effect modification by donor BMI

There was not modification of the association between post-donation eGFR and ACGF by donor BMI (p=0.09) (Table 3). However, the association of post-donation eGFR and DCGF was attenuated with higher donor BMI (interaction p=0.049). For example, LDKT recipients from donors with BMI=20 had a 10% higher risk of DCGF per 10 mL/min decrement in post-donation eGFR (aHR $_{0.84}0.90_{0.96}$, p=0.002) while recipients from donors with BMI=25 had a 7% higher risk of DCGF (aHR $_{0.89}0.93_{0.97}$, p=0.001). LDKT recipients from donors with BMI 30 or higher had no statistically significant higher risk of DCGF with lower post-donation eGFR (aHR for BMI=30 $_{0.92}0.97_{1.02}$, p=0.2; BMI=35 $_{0.94}1.01_{1.09}$, p=0.8; BMI=40 $_{0.94}1.05_{1.17}$, p=0.4) (Table 3).

DISCUSSION

In this national study of recipients of living donor kidney transplants, we found that, on average, recipients had a 5% higher risk of death-censored graft loss for every 10 mL/min decrement in their donors' post-donation eGFR. The association of graft loss and post-donation eGFR varied by donor BMI: LDKT recipients from donors with BMI 20 and 25 had 10% higher risk and 7% higher risk of DCGF for every 10 mL/min decrement in post-donation eGFR while recipients from obese donors had no association between DCGF and post-donation eGFR.

Our findings identify post-donation eGFR as a novel but intuitive risk factor for graft loss, and reaffirm that older donor age and higher donor BMI are risk factors for graft loss (1–4). Our group previously identified that recipients of allografts from donors who develop ESRD had higher graft loss and mortality, supporting the hypothesis that subclinical kidney disease may exist at the time of donation (5). Our findings that the association of graft loss with post-donation eGFR is seen across the range of post-donation eGFR strengthen this hypothesis by demonstrating a dose-response relationship; that is, donors whose remaining kidney has less physiologic reserve are also donating a kidney that has less physiologic reserve to their recipient.

Interestingly, we found that as donor BMI increased, there was less association between donor post-nephrectomy eGFR and recipient death-censored graft loss. One explanation for this is that obese donors are more likely to have obesity-related glomerulomegaly (16), and might already have some degree of hyperfiltration at the time of donation. Further, obese donors are at higher risk of ESRD post-donation (20). Our finding that higher donor BMI was associated with greater long-term risk of all-cause graft failure reaffirms findings from Massie et al. (21). A potential explanation for the conflicting findings regarding post-donation eGFR and graft loss from obese donors is that transplant providers are selecting obese donors who are otherwise quite healthy in other facets of evaluation. Therefore, some obese donors may be healthier than non-obese donors, despite being overweight. While we did adjust for multiple donor characteristics and comorbidities, it is possible that there is unmeasured confounding that is related to this finding that we are unable to capture. We echo others' recommendation that otherwise healthy donors should receive personalized counseling regarding their risk, which should include discussion of their individual risk factors including BMI (20, 22, 23).

Our findings should be considered in the context of several limitations. First, like all studies using national registry data, we are limited by missing data. Given the ongoing implementation of standard donor follow-up reporting, 29.9% of transplant recipients in this study were missing 6-month post-donation eGFR, consistent with national reports (24). To address any potential bias related to this missingness, we performed both a complete-case analysis and a multiple imputation sensitivity analysis and found no difference in inferences. Our results support the concept that a donor's remaining kidney and donated kidney are associated, but we cannot conclude causative relationships with a registry-based study.

The identification of donor post-donation eGFR as a novel predictor for recipient graft loss strengthens our understanding of physiologic response to nephrectomy. The modification of this effect by donor BMI additionally strengthens our understanding of the impact of donor obesity on recipient outcomes. As recipient graft loss is not a rare occurrence, recipients should be provided ongoing individualized counseling and management. With improved understanding of the link between post-donation kidney function and recipient outcomes, transplant providers can better personalize care and counseling for living kidney donor recipients.

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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.

Abbreviations:

ACGF	all-cause graft failure
aHR	adjusted hazard ratio
AIC	Akaike information criterion
BMI	body mass index
CI	confidence interval
DCGF	death-censored graft failure
ESRD	end-stage renal disease
eGFR	estimated glomerular filtration rate
HLA	human leukocyte antigen

HRSA	Heath Resources and Services Administration
IQR	interquartile range
LDKT	Living donor kidney transplant
MMRF	Minneapolis Medical Research Foundation
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIA	National Institute on Aging
OPTN	Organ Procurement and Transplantation Network
PRA	panel reactive antibody
SRTR	Scientific Registry of Transplant Recipients

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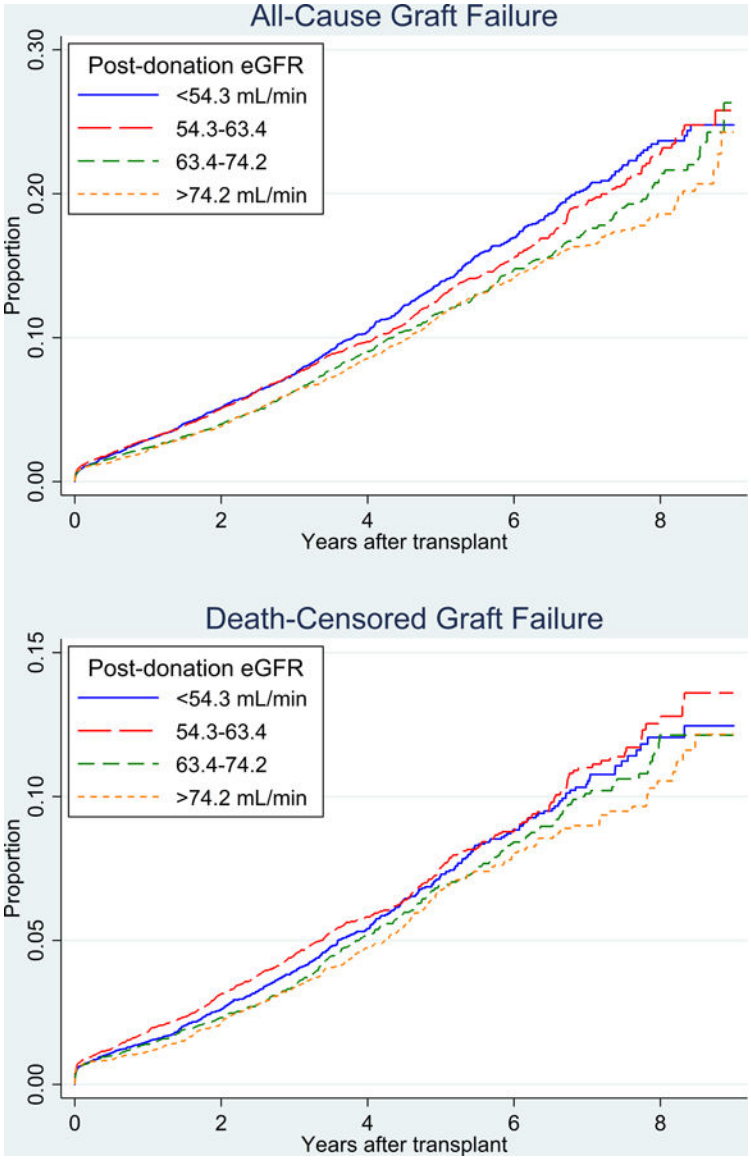

Figure 1.

All-cause graft failure and death-censored graft failure by quartiles of 6-month post-donation eGFR.

Table 1.

Characteristics of living kidney donor recipients and donors by 6-month post-donation estimated glomerular filtration rate (eGFR).

	<60 mL/min (n=11,933)	≥60 mL/min (n=17,531)	p-value
Donor characteristics			
Age, median years (interquartile range [IQR])	51 (44–57)	38 (30–47)	<0.001
BMI, median (IQR)	27.0 (24.3–29.8)	26.4 (23.5–29.5)	<0.001
Male sex (%)	38.6%	34.8%	<0.001
Race/ethnicity (%)			<0.001
Caucasian/other	86.1%	69.2%	
African American	6.4%	13.0%	
Hispanic	7.5%	17.8%	
Pre-donation eGFR, median mL/min per 1.73m^2 (IQR)	86 (77–96)	106 (97–116)	<0.001
Donor-recipient relationship (%)			<0.001
First-degree relative	36.0%	42.6%	
Spouse or partner	16.8%	12.9%	
Unrelated, nonspouse	47.2%	44.6%	
ABO incompatible with recipient (%)	1.6%	1.6%	0.6
Number of HLA mismatches with recipient, median (IQR)	4 (3–5)	3 (2–5)	<0.001
Recipient characteristics			
Age, median years (IQR)	53 (42–62)	48 (36–58)	<0.001
BMI, median (IQR)	27.5 (23.9–31.5)	27.2 (23.5–31.4)	0.03
Male sex (%)	62.4%	62.5%	0.9
Race/ethnicity (%)			<0.001
Caucasian/other	82.1%	66.9%	
African American	9.4%	15.0%	
Hispanic	8.6%	18.0%	
Previous transplant (%)	11.7%	11.3%	0.3
Peak PRA (%)			0.03
0−9	78.7%	77.8%	
10−79	16.3%	17.2%	
80−98	4.0%	3.8%	
99−100	0.9%	1.1%	
Diagnosis (%)			<0.001
Diabetes	22.2%	22.5%	
Hypertension	15.0%	17.1%	
Glomerulonephritis	29.2%	32.0%	
Other	33.6%	28.4%	
Time on dialysis, median years	0.5 (0−1.5)	0.6 (0−1.8)	<0.001

	<60 mL/min (n=11,933)	≥60 mL/min (n=17,531)	p-value
(IQR)			
Delayed graft function (%)	3.6%	3.1%	0.03
Discharge eGFR, median mL/min per 1.73m^2 (IQR)	51 (36−67)	59 (42−77)	<0.001

Table 2.

Adjusted hazard ratios for graft loss from Cox proportional hazards models for all-cause graft failure (ACGF) and death-censored graft failure (DCGF).

	ACGF	DCGF
Donor factors		
Post-donation eGFR (per 10 mL/min)	$_{0.96}0.98_{1.01}$, p=0.3	$_{0.91}0.95_{0.98}$, p=0.007
Age (per 10 years)	$_{1.07}1.11_{1.16}$, p<0.001	$_{1.07}1.13_{1.20}$, p<0.001
Male sex	$_{0.82}0.89_{0.96}$, p=0.004	$_{0.72}0.81_{0.90}$, p<0.001
BMI (per 5 units)	$_{1.00}1.05_{1.10}$, p=0.03	$_{0.92}0.98_{1.04}$, p=0.5
Race		
White	Ref	Ref
African American	$_{0.95}1.14_{1.38}$, p=0.2	$_{1.02}1.29_{1.63}$, p=0.03
Hispanic	$_{0.80}0.96_{1.17}$, p=0.7	$_{0.86}1.10_{1.41}$, p=0.4
Donor-recipient relationship		
Unrelated	Ref	Ref
First degree relative	$_{0.90}1.00_{1.12}$, p=1.0	$_{0.76}0.88_{1.03}$, p=0.1
Spouse/partner	$_{0.76}0.86_{0.97}$, p=0.02	$_{0.74}0.88_{1.04}$, p=0.1
Other, related	$_{1.03}1.19_{1.38}$, p=0.02	$_{0.85}1.03_{1.25}$, p=0.8
ABO incompatibility	$_{1.02}1.33_{1.74}$, p=0.03	$_{1.20}1.67_{2.32}$, p=0.002
HLA mismatches (per 1 mismatch)	$_{1.01}1.04_{1.07}$, p=0.01	$_{1.02}1.06_{1.11}$, p=0.003
Recipient factors		
Age (per 10 years)	$_{1.02}1.05_{1.08}$, p=0.002	$_{0.70}0.73_{0.76}$, p<0.001
Male sex	$_{0.98}1.06_{1.15}$, p=0.2	$_{0.78}0.87_{0.97}$, p=0.01
BMI (per 5 units)	$_{1.04}1.08_{1.12}$, p<0.001	$_{1.10}1.16_{1.21}$, p<0.001
Race		
White	Ref	Ref
African American	$_{0.95}1.13_{1.34}$, p=0.2	$_{1.14}1.40_{1.74}$, p=0.002
Hispanic	$_{0.68}0.82_{0.99}$, p=0.04	$_{0.69}0.88_{1.12}$, p=0.3
Cause of ESRD		
Glomerulonephritis	Ref	Ref
Diabetes	$_{1.26}1.41_{1.56}$, p<0.001	$_{0.90}1.05_{1.22}$, p=0.5
Hypertension	$_{0.92}1.04_{1.17}$, p=0.6	$_{0.82}0.96_{1.13}$, p=0.7
Other	$_{0.79}0.88_{0.98}$, p=0.02	$_{0.72}0.83_{0.95}$, p=0.006
Time on dialysis (per year)	$_{1.05}1.07_{1.08}$, p<0.001	$_{1.03}1.05_{1.08}$, p<0.001
Previous kidney transplant	$_{1.03}1.18_{1.35}$, p=0.01	$_{0.92}1.10_{1.31}$, p=0.3
Peak PRA		
0–9	Ref	Ref
10–79	$_{1.02}1.12_{1.24}$, p=0.02	$_{1.05}1.20_{1.37}$, p=0.008
80–98	$_{1.01}1.23_{1.49}$, p=0.04	$_{1.05}1.34_{1.72}$, p=0.02

	ACGF	DCGF
99–100	$_{0.76}1.08_{1.54}$, p=0.7	$_{0.72}1.13_{1.77}$, p=0.6

*Both models also adjusted for depleting induction, non-depleting induction, cyclosporine maintenance, and tacrolimus maintenance.

Table 3.

Modification of the association between post-donation eGFR and graft loss by donor BMI.

	ACGF Interaction p=0.09	DCGF P=0.049
aHR per 10 mL/min eGFR at BMI 20	$_{0.90}0.95_{1.00}$, p=0.05	$_{0.84}0.90_{0.96}$, p=0.002
aHR per 10 mL/min eGFR at BMI 25	$_{0.94}0.97_{1.01}$, p=0.1	$_{0.89}0.93_{0.97}$, p=0.001
aHR per 10 mL/min eGFR at BMI 30	$_{0.97}1.00_{1.03}$, p=1.0	$_{0.92}0.97_{1.02}$, p=0.2
aHR per 10 mL/min eGFR at BMI 35	$_{0.97}1.02_{1.08}$, p=0.4	$_{0.94}1.01_{1.09}$, p=0.8
aHR per 10 mL/min eGFR at BMI 40	$_{0.97}1.05_{1.14}$, p=0.2	$_{0.94}1.05_{1.17}$, p=0.4

* Both models adjusted for donor age, gender, BMI, and race; recipient age, gender, BMI, race, cause of ESRD, time on dialysis, previous kidney transplant, peak panel reactive antibody (PRA), depleting induction therapy (thymoglobulin or alemtuzumab), non-depleting induction therapy (daclizumab or basiliximab), maintenance therapy of tacrolimus, maintenance therapy of cyclosporine; and donor and recipient relationship, ABO incompatibility, and number of human leukocyte antigen (HLA) mismatches.