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## Long-Term Renal Function in Living Kidney Donors who had Histological Abnormalities at Donation

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### Abstract

**Background**—Recent evidence suggests that living kidney donors are at an increased risk of end-stage renal disease. However, predicting which donors will have renal dysfunction remains challenging, particularly among those with no clinical evidence of disease at the time of donation. Although renal biopsies are not routinely performed as part of the donor evaluation process, they may yield valuable information that improves the ability to predict renal function in donors.

**Methods**—We used implantation protocol biopsies to evaluate the association between histological abnormalities in the donated kidney and postdonation renal function (estimated glomerular filtration rate, eGFR) of the remaining kidney in living kidney donors. Longitudinal analysis using mixed-effects linear regression was used to account for multiple eGFR measures per donor.

**Results**—Among 310 donors between 1997 and 2012, median (IQR) follow-up was 6.2 (2.5–8.7; maximum 14.0) years. In this cohort, the overall prevalence of histological abnormalities was 65.8% (19.7% abnormal glomerulosclerosis, 23.9% abnormal interstitial fibrosis and tubular atrophy (IFTA), 4.8% abnormal mesangial matrix increase, 32.0% abnormal arteriolar hyalinosis,

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#### DISCLOSURE

The authors of this manuscript have no conflicts of interest.

and 32.9% abnormal vascular intimal thickening). IFTA was associated with a 5-mL/min/1.73m<sup>2</sup> decrease of postdonation eGFR after adjusting for donor age at donation, sex, race, preoperative systolic blood pressure, preoperative eGFR, and time since donation (p<0.01).

**Conclusions**—In this single-center study, among healthy individuals cleared for living donation, IFTA was associated with decreased postdonation eGFR, while no other subclinical histological abnormalities provided additional information.

## INTRODUCTION

Despite being rigorously screened for kidney disease,<sup>1</sup> living kidney donors may develop end-stage renal disease (ESRD) as early as 5–10 years postdonation.<sup>2–6</sup> Since it typically takes decades for a healthy, screened individual to develop *de novo* disease, and to progress from chronic kidney disease (CKD) to ESRD,<sup>7</sup> the occurrence of ESRD in the early postdonation period may point to subtle subclinical, undiagnosed kidney disease at donation. Indeed, 4–50% of implantation biopsies have been found to harbor moderate-to-severe histological abnormalities.<sup>8–13</sup> However, there are conflicting reports about the association between these histological abnormalities and postdonation renal function (estimated glomerular filtration rate, eGFR) in living kidney donors.<sup>8–10,12,14</sup>

In studies that found an association between histological abnormalities and postdonation renal function,<sup>12,14</sup> the difference in renal function between donors with and without histological abnormalities (0.2–1.4% difference in the percent of eGFR recovery at 0.5–2 years postdonation) was not clinically significant. The studies that found no association between histological abnormalities and postdonation renal function were notable for insufficient follow-up (<1 year) for the evolution of clinically salient CKD.<sup>8,9</sup> Also, no study to date, to our knowledge, has accounted for the hierarchical structure of eGFR data (repeated measurements of eGFR for an individual); as such, even the significant association found in some studies might represent statistical artifacts.

In order to gain more insight into the relationship between histological abnormalities and postdonation renal function in living kidney donors, we linked implantation biopsy data (ie donor histology) to postdonation medical records. We conducted a retrospective cohort analysis that aimed to characterize the prevalence of histological abnormalities in donated kidneys at time of donation, and the association between these abnormalities and long-term postdonation eGFR trajectories of the remaining kidneys in living kidney donors. To account for multiple eGFR measures per donor, we used longitudinal data analysis (hierarchical) methods.

## METHODS

### Study population

We identified 310 individuals who underwent living donor nephrectomy at our center between February 1997 and June 2012 and had an implantation biopsy of the donated kidney performed at the time of donation as part of a recipient study protocol. Selection for implantation biopsy was related to recipient involvement in research studies, and not based

on any donor characteristics (see Table 1). This study was approved by our institution's Institutional Review Board (NA\_00044282).

### Histological Abnormalities

Core biopsies from the donor kidney were fixed in buffered formalin, embedded in paraffin, and cut sections were stained with hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, and Jones' silver methenamine. Evaluation was performed by light microscopy. Biopsies were reviewed by 1 of 5 experienced nephropathologists at our center at the time of donation, who were blinded to donor demographics, except for donor sex. They were also blinded to the research question, since this is a retrospective analysis of their clinical reads.

Biopsies were evaluated for glomerulosclerosis (gs), interstitial fibrosis and tubular atrophy (IFTA), mesangial matrix increase (mm), arteriolar hyalinosis (ah), and vascular fibrous intimal thickening (cv). gs was quantified as the percentage of observed glomeruli that were globally sclerotic. IFTA was assessed as the observed percentage of cortical area that had IFTA and categorized as minimal (< 5%), mild (6–25%), moderate (26–50%), or severe (>50%); corresponding to Banff IFTA0, IFTA1, IFTA2, and IFTA3, respectively.<sup>15–17</sup> mm was quantified as increase versus no increase; corresponding to Banff mm1–3 and mm0. ah was categorized as no ah, mild-to-moderate, moderate-to-severe, or severe; corresponding to Banff ah0, ah1, ah2, and ah3, respectively. cv was categorized as no cv, mild-to-moderate, moderate-to-severe, or severe; corresponding to Banff cv0, cv1, cv2, and cv3, respectively. If the pathology report did not mention the presence of vasculature, we assumed that there was none observed in the biopsy.

We defined a donor as having any histological abnormalities if he/she had at least 1 of the following types of abnormalities: abnormal gs (< 10%), abnormal IFTA (< IFTA1), abnormal mm (< mm1), abnormal ah (< ah1), and/or abnormal cv (< cv1).

### Postdonation eGFR

We used postdonation medical records to estimate GFR, based on serum creatinine measurements obtained over the course of the donor's postdonation medical care, using the CKD-EPI creatinine equation.<sup>18</sup> We used boxplots to visualize eGFR trajectories over time. We also used multilevel mixed-effects linear regression to perform longitudinal data analysis. Based on the Akaike information criterion and likelihood ratio tests, we selected an optimal hierarchical regression model that allowed for random intercepts (starting eGFR) and slopes (eGFR trajectory). This model was then used to study the unadjusted and adjusted relationships between histological abnormalities and eGFR trajectories, adjusting for time since donation, preoperative donor age at donation, sex, African American race, preoperative systolic blood pressure, and preoperative eGFR.

### Statistical analysis

For continuous variables, the median and interquartile range (IQR) are reported. For categorical variables, the number and percentage are reported. We used t-tests and Fisher exact tests as appropriate to compare our study population (biopsied donors) to the general living kidney donor pool at our center (nonbiopsied donors). We also used t-tests and Fisher

exact tests as appropriate to compare baseline characteristics of donors with and without any histological abnormalities within our study population. Statistical significance was established at a p-value less than 0.05 (2-tailed). All analyses were performed using STATA 13.0 for Mac (College Station, TX). Confidence intervals are reported as per the Louis and Zeger method.<sup>19</sup>

## RESULTS

### Study population

The median (IQR) age at donation of our study population was 47.0 (39.2–54.1) years; 7% were African American and 66% were female (Table 1). The median (IQR) preoperative systolic blood pressure was 120 (110–131) mmHg, and the median (IQR) preoperative eGFR was 97.0 (86.1–107.0) mL/min/1.73m<sup>2</sup> (Table 1). Our study population (biopsied donors) did not differ from the general living kidney donor pool (nonbiopsied donors) at our center, in terms of donor age at donation (p=0.2), sex (p=0.6), African American race (p=0.4), preoperative systolic blood pressure (p=0.3), and preoperative eGFR (p=0.9) (Table 1).

### Histological abnormalities

The prevalence of donors with any histological abnormalities was 65.8% (Table 2). Specifically, 19.7% had abnormal gs, 23.9% had abnormal IFTA, 4.8% had abnormal mm, 32.0% had abnormal ah, and 32.9% had abnormal cv (Table 2). Among 204 donors with any histological abnormalities, 105 (51.5%) had only 1 type of abnormality; 63 (30.9%) had a combination of 2 types of histological abnormality; 25 (12.3%) had a combination of 3 types of histological abnormality; 10 (4.9%) had a combination of 4 types of histological abnormality; and 1 (0.5%) donor had histological abnormalities in all 5 categories.

Donors with any histological abnormalities were slightly older than donors without any histological abnormalities (median (IQR) 48.1 (40.4–55.2) versus 45.9 (37.4–53.1) years, p=0.04). Preoperative systolic blood pressure (p=0.1), preoperative eGFR (p=0.1), percent African American (p=0.7), percent female (p=0.5), and follow-up time (p=0.8) did not differ between donors with versus without any histological abnormalities (Table 3).

### Postdonation eGFR

Donors had a median of 5 postdonation eGFR measurements (IQR 3–8, range 1–30). The median (IQR) postdonation eGFR was 60.5 (53.7–70.1) mL/min/1.73m<sup>2</sup> over a median follow-up time of 6.2 (IQR 2.5–8.7; maximum 14.0) years. The percent of donors who had a post-donation mean eGFR below 60 mL/min/1.73m<sup>2</sup> was 46.5%. The median (IQR) postdonation eGFR was similar among donors with and without any histological abnormalities (58.6 (50.8–69.0) versus 59.8 (52.5–69.4) mL/min/1.73m<sup>2</sup>, p=0.1) (Table 3).

In an adjusted hierarchical regression model, postdonation eGFR increased with time (0.180.41<sub>0.65</sub> mL/min/1.73m<sup>2</sup> per year, p<0.001), decreased with donor age (–4.55–3.10<sub>–1.65</sub> mL/min/1.73m<sup>2</sup> per 10 years, p<0.001), and increased with preoperative eGFR (3.023.96<sub>4.90</sub> mL/min/1.73m<sup>2</sup> per 10 mL/min/1.73m<sup>2</sup>, p<0.001) (Table 4). Moreover, abnormal IFTA was

associated with decreased postdonation eGFR ( $-8.13-4.77_{-1.41}$  mL/min/1.73m<sup>2</sup> per year,  $p<0.01$ ) (Table 4, Figure 1). However, there was no statistically significant association between the other types of histological abnormalities (gs, mm, ah, and cv) and post-donation eGFR. There was also no evidence of interaction between IFTA and time since donation ( $p=0.4$ ).

## DISCUSSION

In this retrospective single-center study of 310 living kidney donors, the prevalence of donors with any histological abnormalities was 65.8%. After adjusting for donor clinical characteristics and time since donation, we found that subclinical IFTA was associated with a 5-mL/min/1.73m<sup>2</sup> decrease of postdonation eGFR.

Our findings are consistent with the findings of Ohashi et al<sup>12</sup> that study found that the presence of chronic histological changes (defined as having at least 2 of the following: >5% gs, any IFTA, and any arteriosclerosis) was associated with a 0.23% decrease in the percent eGFR recovery from immediate post-donation to 2-year postdonation, after adjusting for donor age and change of eGFR from baseline to immediate postdonation ( $n=110$ ).<sup>12</sup> However, our findings are in contrast with the findings of Chauhan et al,<sup>8</sup> Choi et al,<sup>9</sup> and Elsherbiny et al.<sup>14</sup> This difference could arise due to several reasons, including our longer follow-up time, differences in patient casemix, covariate adjustment, our robust statistical methods to account for the correlated nature of the longitudinal data (multiple eGFR measurements per donor), and/or the types of histological abnormalities studied and their cut-offs.

Chauhan et al ( $n=1600$ ) reported that 4-month postdonation eGFR was similar in donors with and without moderate-to-severe histological changes (a composite score of interstitial fibrosis, ah, cv, tubular atrophy, and allograft glomerulopathy), after adjusting for donor clinical characteristics;<sup>8</sup> given the very low prevalence (4%) of moderate-to-severe histological changes in living kidney donors in their study, their study may have lacked statistical power to identify the association seen in our study.<sup>8</sup> Choi et al ( $n=121$ ) reported that 12-month postdonation eGFR was not affected by tubular atrophy, gs, or ah at time of donation, after adjusting for clinical characteristics;<sup>9</sup> they do not include interstitial fibrosis in their analysis that could again explain the discrepancy in our findings.<sup>9</sup> Elsherbiny et al ( $n=1,395$ ) reported a 1.4% decrease in the percent of GFR recovery, from baseline to a mean follow-up of 6.2 months postdonation, per 1 mm<sup>3</sup> of globally sclerotic density, after adjusting for other renal morphometric measures at donation;<sup>14</sup> differences in our findings could be due to the differences in casemix and covariate adjustment.

We also found that, after adjusting for other donor clinical characteristics, postdonation eGFR increased with time (0.4 mL/min/1.73m<sup>2</sup> per year), indicating that the remaining donor kidney might be hyperfiltrating as a compensation mechanism for the insult sustained during donation. Postdonation eGFR also increased with preoperative eGFR (4 mL/min/1.73m<sup>2</sup> per 10 mL/min/1.73m<sup>2</sup>), and decreased with donor age at donation (-3 mL/min/1.73m<sup>2</sup> per 10 years), suggesting that preoperative eGFR and age are 2 important clinical characteristics in quantifying donor healthiness and ability to recover postdonation.

Our study is limited by sample size, the retrospective nature of the data, and the use of eGFR to quantify renal function.<sup>20</sup> Nevertheless, our study has longitudinal follow-up (multiple measures over time for many patients), with relatively longer postdonation follow-up time compared to previous studies; our median postdonation follow-up was 6.2 years, whereas other studies reported mean follow-up times of 0.3–2 years.<sup>8,9,12,14</sup> Another strength of our study is that we accounted for the hierarchical structure (repeated measurements of eGFR for an individual) of postdonation eGFR data. Moreover, in our study we separately investigated each type of histological abnormality. This allowed us to investigate how each type of abnormality is associated with postdonation eGFR.

Our study was conducted on healthy individuals who have undergone rigorous living donor evaluation and were cleared for donation. Most abnormalities observed in our study were mild. Therefore, our results may not generalize to abnormalities more serious than those observed in our study, or observed in individuals with poorer baseline health. While our study shows decreased eGFR in donors with mild to moderate IFTA, biopsies are invasive processes. Even if a biopsy may yield increased information about postdonation eGFR in a potential donor, any benefit from this information may be outweighed by the harm of the biopsy. Moreover, the decline in postdonation eGFR among donors with IFTA is modest; the human kidney is redundant by design and may compensate for minor damage. Therefore, we do not recommend incorporating biopsies into the donor screening process. However, if biopsy data are available, they may be useful in counseling donors postdonation.

In conclusion, in our single-center study, among healthy individuals cleared for living kidney donation, subclinical IFTA was associated with decreased postdonation eGFR, after adjusting for other donor characteristics. These results may help guide the direction of future research of postdonation renal function in living kidney donors.

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## ABBREVIATIONS

<b>ah</b>	arteriolar hyalinosis
<b>CKD</b>	chronic kidney disease
<b>cv</b>	vascular fibrous intimal thickening
<b>eGFR</b>	estimated glomerular filtration rate
<b>ESRD</b>	end-stage renal disease
<b>gs</b>	glomerular sclerosis



<b>IFTA</b>	interstitial fibrosis and tubular atrophy
<b>IQR</b>	interquartile range
<b>mm</b>	mesangial matrix increase

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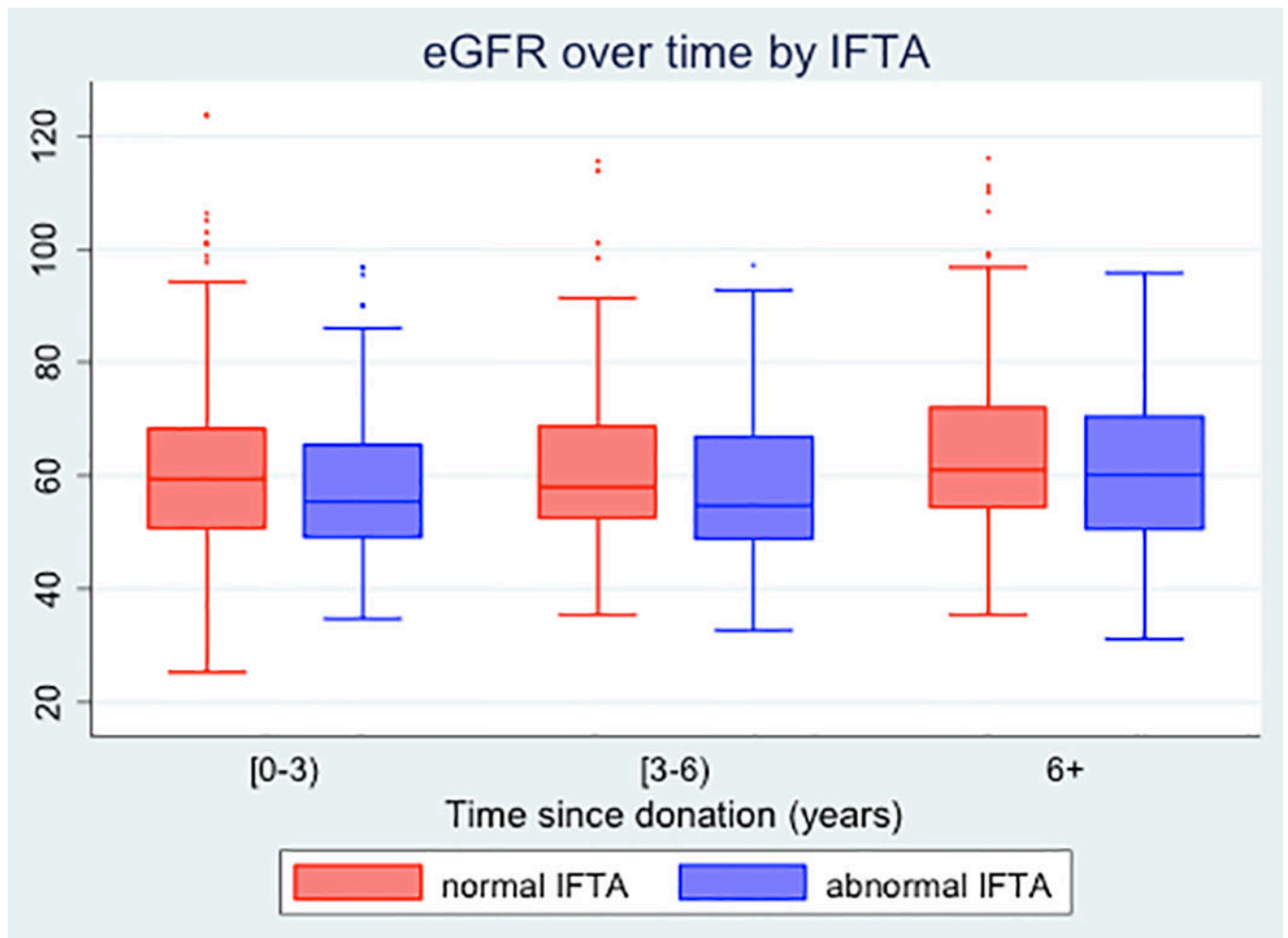
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**Figure 1.** Boxplots of post-donation eGFR of living kidney donors over time, by status of interstitial fibrosis and tubular atrophy (IFTA). Time since donation is categorized into three bins: (0–3) years, (3–6) years, and 6+ years. IFTA is categorized as abnormal (IFTA = 1) vs normal (IFTA < 1)

**Table 1**  
**Donor characteristics stratified by biopsy availability**

This table compares the donor characteristics of our study population (biopsied donors) and the general living donor pool (nonbiopsied donors) at our center

Characteristics	Biopsied donors (n=310)	Non-biopsied donors (n=522)	p-value
Age at donation (y), median (IQR)	47.0 (39.2–54.1)	46.4 (37.3–54.3)	0.2
African American, n(%)	23 (7.4%)	54 (10.3%)	0.4
Female, n(%)	203 (65.5%)	332 (63.6%)	0.6
Preoperative systolic blood pressure (mmHg), median (IQR)	120 (110–131)	124 (112–133)	0.3
Preoperative eGFR (mL/min/1.73m <sup>2</sup> ), median (IQR)	97.0 (86.1–107.0)	97.3 (84.8–107.6)	0.9

**Table 2**  
**Prevalence of histological abnormalities detected at time of kidney donation among living kidney donors**

Five types of histological abnormalities were identified at time of kidney donation: glomerulosclerosis (gs), interstitial fibrosis and tubular atrophy (IFTA), mesangial matrix increase (mm), arteriolar hyalinosis (ah), and vascular fibrous intimal thickening (cv).

<b>Histological Abnormalities (n=310)</b>	<b>n (%)</b>
glomerulosclerosis (gs)	
<10%	200 (64.5)
10%	61 (19.7)
missing	49 (15.8)
interstitial fibrosis and tubular atrophy (IFTA)	
IFTA0 - Minimal	234 (75.5)
IFTA1 - Mild	70 (22.6)
IFTA2 - Moderate	4 (1.3)
IFTA3 - Severe	0 (0.0)
missing	2 (0.7)
mesangial matrix increase (mm)	
mm0 - No increase	280 (90.3)
mm1-3 - Increase	15 (4.8)
missing	15 (4.8)
arteriolar hyalinosis (ah)	
ah0 - No ah	188 (60.7)
ah1 - Mild-to-moderate	96 (31.0)
ah2 - Moderate-to-severe	2 (0.7)
ah3 - Severe	1 (0.3)
missing	23 (7.4)
vascular fibrous intimal thickening (cv)	
cv0 - No cv	185 (59.7)
cv1 - Mild-to-moderate	92 (29.7)
cv2 - Moderate-to-severe	9 (2.9)
cv3 - Severe	1 (0.3)
missing	23 (7.4)
any histological abnormalities	
present	204 (65.8)
absent	106 (34.2)

**Table 3**  
**Study population characteristics stratified by any histological abnormalities**

A donor was considered to have any histological abnormalities if he/she had at least 1 abnormality in any of: glomerular sclerosis, interstitial fibrosis and tubular atrophy, mesangial matrix increase, arteriolar hyalinosis, and/or vascular fibrous intimal thickening.

Characteristics	Donors with any histological abnormalities (n=204)	Donors without any histological abnormalities (n=106)	p-value
Age at donation (y), median (IQR)	48.1 (40.4–55.2)	45.9 (37.4–53.1)	0.04
African American, n(%)	16 (7.8)	7 (6.6)	0.7
Female, n(%)	131 (64.2)	72 (67.9)	0.5
Preoperative systolic blood pressure (mmHg), median (IQR)	124 (110–132)	118 (110–130)	0.1
Preoperative eGFR (mL/min/1.73m <sup>2</sup> ), median (IQR)	96.3 (85.7–107.6)	99.0 (87.5–105.1)	0.5
Follow-up time (y), median (IQR)	6.3 (2.5–8.7)	6.1 (2.6–8.7)	0.8
Post-donation eGFR, (mL/min/1.73m <sup>2</sup> ), median (IQR)	58.6 (50.8–69.0)	59.8 (52.5–69.4)	0.1
Number of post-donation eGFR measurements per donor, median (IQR)	5 (3–8)	5 (3–9)	0.2

**Table 4**  
**Multilevel mixed-effects linear regression models of postdonation eGFR trajectory using individual histological abnormalities**

The unadjusted model included time since donation (per 1-year increase), glomerulosclerosis (gs per 10% increase in globally sclerotic glomeruli), interstitial fibrosis and tubular atrophy (abnormal IFTA 1 vs normal IFTA<1), mesangial matrix increase (abnormal mm 1 vs normal mm<1), arteriolar hyalinosis (abnormal ah 1 vs normal ah<1), and vascular fibrous intimal thickening (abnormal cv 1 vs normal <1). The adjusted model includes all of the above plus age at donation (per 10 years increase), sex (females vs males), race (African American vs other), preoperative systolic blood pressure (per 10 mmHg increase), and preoperative eGFR (per 10 mL/min/1.73m<sup>2</sup>).

	Difference in eGFR (mL/min/1.73m <sup>2</sup> ) <sup>C</sup>	
	Unadjusted Model	Adjusted Model <sup>A</sup>
Per year	0.28 <b>0.50</b> <sub>0.72</sub>	0.18 <b>0.41</b> <sub>0.65</sub>
gs (per 10%)	-3.63-1.29 <sub>1.05</sub>	-0.03 <b>1.84</b> <sub>3.70</sub>
Abnormal IFTA (vs normal)	-8.96 <b>-4.74</b> <sub>-0.53</sub>	-8.13 <b>-4.77</b> <sub>-1.41</sub>
Abnormal mm (vs normal)	-7.55-0.43 <sub>6.70</sub>	-5.82-0.01 <sub>5.81</sub>
Abnormal ah (vs normal)	-0.69 <b>2.76</b> <sub>6.20</sub>	-1.54 <b>1.22</b> <sub>3.99</sub>
Abnormal cv (vs normal)	-2.08 <b>1.51</b> <sub>5.10</sub>	-1.39 <b>1.46</b> <sub>4.31</sub>
Age at donation (per 10y)	-	<b>-4.55-3.10</b> <sub>-1.65</sub>
Female (vs. male)	-	-2.44 <b>0.23</b> <sub>2.90</sub>
African American (vs. other)	-	-5.23 <b>0.66</b> <sub>6.54</sub>
Preoperative systolic blood pressure (per 10 mmHg)	-	-1.62-0.77 <sub>0.07</sub>
Preoperative eGFR (per 10 mL/min/1.73m <sup>2</sup> )	-	<b>3.023.96</b> <sub>4.90</sub>

Notes: Bolded p-value statistically significant at  $\alpha = 0.05$ .

<sup>A</sup> Adjusted for time since donation, donor age at donation, sex, race, preoperative systolic blood pressure, and preoperative eGFR.

<sup>C</sup> 95% confidence intervals are reported as per the Louis and Zeger method.<sup>19</sup>