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The Role of Artificial Intelligence Measured Preoperative Kidney Volume in Predicting Kidney Function Loss in Elderly Kidney Donors: a Multicenter Cohort Study

Authors

Eun-Ah Jo[1,6], Juhan Lee[2], Seonggong Moon[3], Jin Sung Kim[3,4,5], Ahram Han[1], Jongwon Ha[1], Yong Chul Kim[7], Sangil Min[1*]

Affiliations

[1]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

[2]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

[3]OncoSoft Inc., Seoul, Korea

[4]Department of Radiation Oncology, Yonsei Cancer Center Severance Hospital, Seoul, Korea

[5]Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Korea

[6]Department of Surgery, Chung-Ang University Hospital, Seoul, Korea

[7]Department of Nephrology, Seoul National University College of Medicine, Seoul, Korea

***Corresponding author**

Sangil Min, MD, PhD

Department of Surgery, Seoul National University College of Medicine, Seoul, Korea

Address: 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea

Tel: +82-2-2072-2330

Fax: +82-2-766-3975

Email: surgeonmsi@gmail.com

ORCID

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Eun-Ah Jo 0000-0002-9324-4877
Juhan Lee 0000-0003-4910-2596
Seonggong Moon 0000-0002-4957-7308
Jin Sung Kim 0000-0003-1415-6471
Ahram Han 0000-0002-3866-5214
Jongwon Ha 0000-0003-2285-3517
Yong Chul Kim 0000-0003-3215-8681
Sangil Min 0000-0002-0688-0278

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Highlights

- Nephrectomy in elderly donors may not leave sufficient reserve and ultimately lead to more rapid declines in kidney function post-donation.
- A fully automated model for measuring kidney cortex volume using preoperative computer tomographic images was developed and validated.
- Larger preoperative kidney cortex volume was significantly associated with less functional decline post-donation.
- The study underscores the significance of preoperative assessment of kidney cortex volume as a prognostic indicator for kidney function change post-donation.

Abstract

Background

The increasing use of kidneys from elderly donors raises concerns due to age-related nephron loss. Combined with nephrectomy, this loss of nephrons markedly increases the risk of developing chronic kidney disease (CKD). This study aimed to investigate the prognostic value of preoperative kidney cortex volume in predicting the loss of kidney function in

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elderly donors, by developing an artificial intelligence (AI)-based model for precise kidney volume measurement and applying it to living kidney donors.

Materials & Methods

A multicenter retrospective cohort study using data from living donors who underwent donor nephrectomy between January 2010 and December 2020 was conducted. An AI segmentation model was developed and validated to measure kidney cortex volume from pre-donation computer tomographic (CT) images. The association between measured preoperative kidney volumes and post-nephrectomy renal function was analyzed through a generalized additive model.

Results

A total of 1074 living kidney donors were included in the study. Validation of the developed kidney cortex volume model showed a Dice similarity coefficient of 0.97 and a Hausdorff distance of 0.76 mm. The measured cortex volumes exhibited an age-related decrease, which correlated with declining kidney function. Elderly donors showed greater decreases in estimated glomerular filtration rates (eGFR) post-donation compared to young donors (p = 0.041). Larger preoperative remnant kidney cortex volume was associated with significantly less decline of eGFR post-donation than those with smaller preoperative remnant kidney cortex volume (p<0.001).

Conclusion

This study highlights the critical role of preoperative kidney cortex volume in the donor assessment process, particularly for elderly donors. The fully automated model for measuring kidney cortex volume provides a valuable tool for predicting post-donation renal function and holds promise for enhancing donor evaluation and safety.

Keywords: kidney transplantation, living donor, nephrectomy, chronic kidney disease, kidney cortex

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Introduction

Increased life expectancy has led to a growing elderly population and higher utilization of kidneys from elderly donors for transplantation[1,2]. Aging primarily causes functional nephron loss due to an increased number of sclerotic glomeruli[3-5]. This loss results in age-related declines in glomerular filtration rates (GFR) and higher incidences of chronic kidney disease (CKD)[2,4]. Nephrectomy in these individuals may not leave sufficient reserve, potentially leading to a more rapid decline in kidney function[6,7].

Studies using computed tomography (CT) have also shown age-related declines in kidney volume with age [8,9]. In a study of 1344 kidney donors, a particularly accelerated loss of total kidney volume after the age of 50 years was noted [10]. The combination of senescent nephrosclerosis and nephrectomy in these elderly donors could significantly diminish total functional reserve to maintain adequate GFR post-donation [3,10,11]. Previous research has correlated preoperative morphometric markers of kidney size and volume with post-donation renal outcomes [11-14]. Especially, cortical volume helped predict post-donation eGFR[13,15,16]. We hypothesize that preoperatively measured kidney cortex volume obtained through CT images can help stratify elderly patients at risks for greater declines in kidney function post-nephrectomy.

However, no fully automated methods to auto-segment the kidney cortex and measure its volume have been applied in previous studies. Manual or semi-automated measurements are time-consuming, prone to error, and lack standardization[17]. To address this issue, we first developed and validated an artificial intelligence (AI) segmentation model for precise and reproducible measurement of kidney cortical volume. Then we applied it to living kidney donors to assess its prognostic value as a marker for post-donation kidney function.

Materials and Methods

Study Design & Data Collection

A multicenter retrospective cohort data was undertaken. First, an artificial intelligence (AI) segmentation model was developed and validated. Sequentially, the preoperative kidney volumes measured through this model were used to analyze its association with post-donation kidney function in living donors. The study is reported in line with the STROCSS, Supplemental Digital Content 1, http://links.lww.com/JS9/D266 criteria, a reporting guideline for surgical cohort studies[18].

Data from living donors who underwent donor nephrectomy between January 2010 and

December 2020 from two tertiary hospitals was used. The participating tertiary hospitals performed an annual volume of 100–150 living donor kidney transplantations during the study period. All donors aged > 18 years were included in the study. Donors without preoperative contrast-enhanced computer tomographic (CT) kidney images or a minimum postoperative follow-up of 1-year were excluded.

The pre-donation arterial phase CT digital imaging and communications in medicine (DICOM) images covering bilateral kidneys of each patient were downloaded. Electronic medical records were comprehensively reviewed to extract data for various preoperative clinical variables. Baseline characteristics such as age, sex, medical history, weight, and height were extracted. Hypertension was defined as a pre-existing diagnosis or preoperative use of antihypertensive medication to lower blood pressure. Cardiovascular disease was defined as any history of myocardial infarction, arrhythmia requiring medication, peripheral vascular disease with significant stenosis or occlusion, or cerebrovascular stroke. A family history of CKD was defined as the presence of a family member diagnosed with CKD within the second degree of kinship. The body surface area was calculated using the Du Bois and Du Bois formula [19]. Preoperative laboratory results such as white blood cell (WBC) count, hemoglobin levels, neutrophil-to-leukocyte ratio (NLR), serum protein, and albumin levels were collected. Surgical records were reviewed to determine donor nephrectomy laterality (right or left). Postoperative serum creatinine values were collected up to postoperative 5-year period.

The kidney function was assessed using the estimated glomerular filtration rate (eGFR), which was calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 equation [20]. The primary outcome assessed was change in kidney function post-donation at time (t) in years. This was defined as Δ (t), a percent change from baseline eGFR (eGFR(0)).

$$\Delta\,(\mathrm{t}) = \frac{\mathrm{eGFR}\,(\mathrm{t}) - \mathrm{eGFR}\,(0)}{\mathrm{eGFR}(0)}\ \mathrm{x}100$$

A negative percent change indicates a decline from baseline eGFR and positive percent change indicates an increase from baseline eGFR.

Donors were analyzed based on age group. Donors greater than the age of 60 were defined as elderly donors and donors less than or equal to 60 were defined as young donors.

Cortex Volume Auto-segmentation Model Development

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The DICOM images from the living kidney donors were processed using 'OncoStudio' (OncoSoft Inc., Seoul, Korea), an AI-based auto-segmentation tool. OncoStudio has been approved by the Korean Food and Drug Administration and is currently in clinical use. The AI model in OncoStudio utilizes a modified 3D DenseNet for CT site detection and segmentation [21]. The program has various tools to contour and segment various anatomical lesions. Once a region of interest is modelled and trained in the program, it automatically proceeds to CT site detection and segmentation and delivers volume measurement within seconds. Volumes are measured in voxel units based on segmentation and the resolution data. Simple addition and multiplication calculations using voxel count and resolution information yielded the final volume in cubic centimeters (cc).

For the measurement of kidney cortex volume, we initially performed semi-manual segmentation using contrast detection and labeling of the bilateral kidney cortex in 5% of the total dataset. Through OncoStudio, the regions pertaining to bilateral kidneys were manually selected and an automated contrast detection tool was used to further segment the kidney cortex. Final labelling of the kidney cortex was performed by manual editing and labelling of the contrast detected contours. The final labeled dataset was then divided into an 8:1:1 ratio for training, independent testing, and validation to develop a fully auto-segmentation model using deep learning. The Segmentation, modeling, and validation were all performed using OncoStudio.

The Dice similarity coefficient (DSC) and Hausdorff distance (HD) metrics were used to compare the AI model with the manually segmented data [22,23]. DSC is quantitative manner to express the degree of association between two different species and a coefficient of 1.0 shows that the two species occur together in exactly number of sample units expected by chance[21]. HD measures the extent to which each point of a model set lies near some point of an image set and vice versa[22]. The smaller the values are the closer the two sets align.

After developing the AI model, we measured the cortex volumes of both the left and right kidneys of all donors using preoperative CT images. The workflow diagram is shown in Figure 1. The volume of the kidney cortex on the side that remained after donation was collected for further analysis and denoted as the remnant kidney volume (RKV).

To adjust for differences in body size, the remnant kidney cortex volume was divided by donor weight. This was labeled as the remnant kidney volume-to-weight ratio (RKVW, cc/kg) and was used in the risk analysis for decreases in kidney function post-donation.

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Post-donation Kidney Function Analysis and Statistics

Continuous variables were presented as mean with standard deviation (±SD) and n (%) for categorical variables. The univariable differences between groups were compared using the Student's t-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables.

To include both linear and nonlinear relationships between baseline factors and change in kidney function post-donation, a generalized additive model (GAM) was applied to factors listed in Table 1. The model included both smooth and parametric components. Interactions between age and RKVW were specifically examined. Analysis was performed using age groups (young vs. old) and RKVW quartiles. The RKVW quartiles were defined as the following: first quartile, ≤25th percentile; second quartile, 25~50th percentile; third quartile, 50th~75th percentile; and fourth quartile. >75th percentile. The model was fitted using a Gaussian family with an identity link function.

All tests were two-tailed, and statistical significance was determined for differences with p values < 0.05. Statistical analyses were conducted using R software, and RStudio (R version 4.3.1).

Registration and ethics

The study was approved by the institutional review board at each hospital (IRB no. H-2205-051-1322 and no.4-2022-357). The need for informed consent was waived owing to the retrospective nature of the study. The research is registered through clinicaltrials.gov.

Results

Study population

During the study period, 2326 living-donor nephrectomies were performed. After excluding donors without preoperative contrast-enhanced CT, missing laboratory data, or less than postoperative 1-year follow-up, 1074 patients were included in the analysis (Figure 2). The baseline characteristics and preoperative laboratory results are presented in Table 1. The cohort was divided into young donors (n=996; mean age = 44.0 ± 10.4 years) and elderly donors (n=78; mean age = 63.6 ± 2.6 years). The baseline eGFR was significantly lower in elderly donors compared to young donors (95.6 ± 9.6 vs. 104.5 ± 14.4; p < .001). Age-associated decline in baseline eGFR was observed (Figure S1, Supplemental Digital Content

2, http://links.lww.com/JS9/D267).

Cortex Auto-segmentation Model

From the total dataset of 1074 donor CT images, 50 were randomly selected for model development. Forty of the selected data were used for training, and five of them were further used to perform independent tests. The developed model was validated in the remaining 10, which were not used for the training. The DSC and HD of the right kidney cortex was 0.95 and 0.69 mm for the independent test and 0.97 and 0.77 mm for the validation test. The DSC and HD of the left kidney cortex was 0.97 and 0.75 mm for the independent test and 0.97 and 0.77 mm for the validation test.

Remnant Kidney Volume

The developed cortex auto-segmentation model was applied to all preoperative CT images of the study cohort to measure remnant kidney cortex volume. The measured mean RKV was lower in elderly donors than young donors (110.5 ± 20.0 cc vs. 116.3 ± 20.6 cc; $p = 0.016$). However, there was no significant difference in RKVW between young and elderly donors (1.8 ± 0.3 vs. 1.8 ± 0.2; $p = 0.065$, Figure S2A, Supplemental Digital Content 3, http://links.lww.com/JS9/D268). The RKVW declined with increasing age in both sexes, whereas a significantly steeper curve was noted in females than males (Figure S2B, Supplemental Digital Content 3, http://links.lww.com/JS9/D268).

Kidney function post-donation

None of the patients developed end-stage renal disease that required dialysis during the cumulative 5-year follow-up period. The trajectory of eGFR in both young and elderly donors show post-donation decrease with the greatest decline occurring within the first year of donation (Figure 3). Although not statistically significant, elderly donors presented lower eGFR values than younger donors (p=0.249).

Elderly donors showed greater declines in Δ (t) than young donors up to three years post-donation (Figure 4). The coefficient estimates presented significant negative correlations with age group (p=0.041), which suggests a greater decline in eGFR post-donation in the elderly (Table 2).

Effects of Cortex Volume Quartiles on Kidney Function

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The analysis demonstrated significant effects of RKVW quartiles on Δ (t), with higher RKVW quartiles showing increasingly positive impacts (Table 2). This positive coefficient indicates that higher cortex volumes are associated with a more positive change in kidney function post-donation, suggesting that larger cortex volume might be protective against GFR decline. Up to post-donation 3 years, the largest 4th quartile RKVW group in both young (Figure 5A) and old (Figure 5B) show significantly less change in eGFR from baseline than the other quartile groups. The Δ (t) between quartiles appear more pronounced in elderly donors. The interaction terms between age and RKVW were significant in the highest quartile group (Table 3). This supports the idea that larger RKVW might indeed have a protective effect on kidney functional decline post-donation and counteract the negative effects associated with older age.

Discussion

Our study demonstrated that elderly donors had significantly greater declines in post-donation kidney function than young donors. Furthermore, we developed a fully automated model for measuring kidney cortex volume, which enables a standardized and reproducible assessment of kidney volume, reducing interobserver variability. Donors with larger preoperative cortex volume were associated with less changes in post-donation kidney function than those with smaller remnant kidney volume-to-weight ratio. This protective effect is even more pronounced in the largest quartile group and counteracts some of the negative effects associated with older age.

The key finding that donors with a higher preoperative kidney volume-to-weight ratio exhibit lower changes in post-donation eGFR underscores the importance of morphometric markers for predicting functional outcomes. Kidney function in the larger RKVW quartile groups exhibited less declines compared to smaller 1st or 2nd quartile groups (Figure 5). Moreover, the interaction effect of age and RKVW Q4 to Δ (t) offset the negative effect of old age in declining renal function post-donation (p = 0.018). As part of the normal senescence process, structural changes in the kidney occur independently of the age-related decline in whole kidney GFR [3,24] Nephrosclerosis, loss of nephrons, and cortical volume decrease with age, leading to significant alterations in the rate of renal functional decline, exhaustion of functional reserve, and predisposition to acute kidney injury [4,10,25-27] Nephrectomy may further expedite the progression of *de novo* kidney disease and accelerate functional decline through adaptive changes that occur in the remnant kidney [28] Congruently, our data showed

that elderly donors showed greater declines in renal function. However, the positive association of Δ (t) and RKVW suggests that a greater reservoir of functional nephrons may be preserved in elderly individuals with larger preoperative kidney cortex volumes. A study by Fanapazir et al. also found that post-donation renal function was independently associated with remnant cortical volume [13] This suggests that kidney cortex volume can additionally capture kidney functional declines from the structural changes that occur. Considering these findings, it is imperative to incorporate preoperative morphometric markers into the donor evaluation process to improve donor outcomes and safety.

Many transplant centers routinely perform CT scans for living-donor evaluation, as they can be used to map renal vasculatures, identify other anomalies, and identify solid organ diseases [17,29] Recently, multiple studies have shown that kidney volume measured from CT scans estimates split renal function more accurately than does nuclear renography [15-17] In particular, remnant cortical volume showed stronger correlations with post-donation eGFR than whole kidney volume or split renal function measured using nuclear scans [13,16] However, a systematic review and meta-analysis by Habbous *et al* showed that the calculation of volume differs significantly across studies [17] Manual or semi-manual (ie.3D reconstruction) labeling and calculation methods were used. No fully automated methods to auto-segment the kidney and measure its volume have been applied. This is not only laborious and time-consuming but also results in interobserver variability and errors. Consequently, the fully automatic program developed for kidney cortex segmentation and volume measurement, as described in this study, holds promise. It demonstrated high performance and reproducibility, even in the validation set with a high DSC score of 0.97 and HD of less than 1mm. According to studies on automated segmentation of medical images using deep learning a DSC above 0.90 is generally considered excellent performance and a HD value below 1 mm are indicative of accurate boundary detection in medical imaging[30,31]. This program not only saves time and ensures reproducibility but also has the potential to revolutionize the donor selection process by incorporating a potentially critical preoperative measurement. With further large-scale

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prospective studies, the accuracy and reproducibility of this renal volume measurement may replace nuclear studies to predict and measure split renal function.

Furthermore, previous studies have shown associations between donor kidney volume and recipient outcomes [32] The findings of this study raise further questions regarding recipient outcomes. Do larger donor kidney volumes also correlate with improved recipient outcomes? This is an avenue for future investigation, as optimizing recipient outcomes is equally important in transplantation.

While both sexes exhibit a decrease in kidney volume with age, a steeper curve among women was noted (Figure S2B, Supplemental Digital Content 3, http://links.lww.com/JS9/D268). Higher changes in lean body mass in females, especially those in perimenopausal age, may attribute to this change[33,34]. Despite larger remnant kidney volumes, males were negatively correlated with Δ (t), suggesting that males were prone to greater declines in kidney function post-donation. This finding correlates with the "CKD paradox" found in various sex-based studies on CKD outcomes. Despite a higher prevalence of CKD in females, males progress more rapidly to kidney failure [35-38]. Especially in older age, steeper declines in kidney function are noted in males compared to females [36,37] . The direct effects of sex hormones and other unhealthy lifestyle factors have been suggested as potential causes [37,38]. Based on these findings, it is important to carefully consider age and sex in the donor selection process.

The retrospective nature of the study has certain inherent biases. The number of follow-up patients markedly decreased with time, which may have resulted in the loss of statical power especially in the 4th and 5th year post-donation. Nevertheless, the observed changes in eGFR and kidney volume with age are in accordance with those of previous studies [4,15,16,32] With further research in a larger population, it could be even possible to calculate a cut-off RKVW value that is safe for donation in both young and elderly donors.

Conclusion

This study underscores the significance of kidney cortex volume in assessing the risk of post-donation renal function among elderly living donors. It suggests that a larger preoperative kidney cortex volume may offer a protective effect on post-donation kidney function, likely due to a greater reserve of functioning nephrons. Moreover, the development of an automated

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program for kidney volume measurement not only saves time but also serves as a surrogate marker for donor outcome post-donation. This tool could prove invaluable in donor evaluation, aiding healthcare professionals in making informed decisions regarding donation suitability.

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Data Statement

The retrospective data was collected after approval of Institutional Review Board of each hospital. The need for informed consent was waived due to the retrospective nature of the study.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure 1. Work flow diagram of auto-segmentation model development for kidney cortex volume measurement

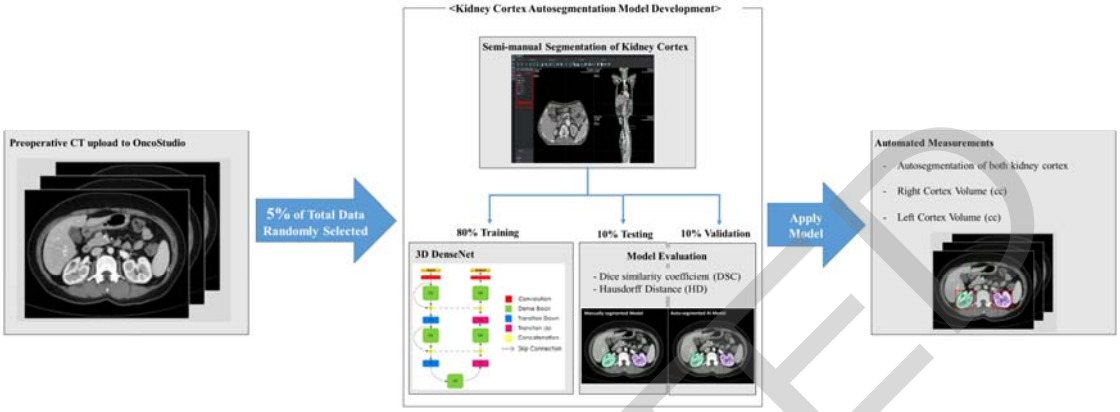

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Figure 2. Flow chart of the study cohort included for analysis

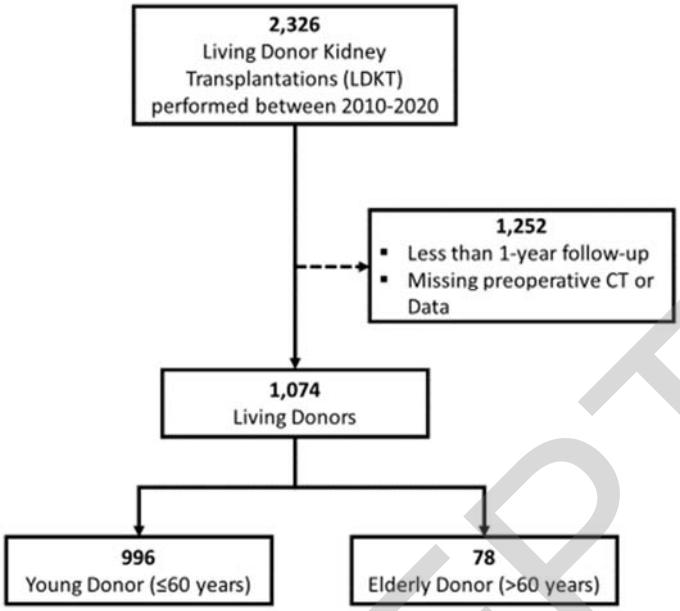

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Figure 3. The post-donation serum eGFR trajectories in young vs. elderly kidney donors

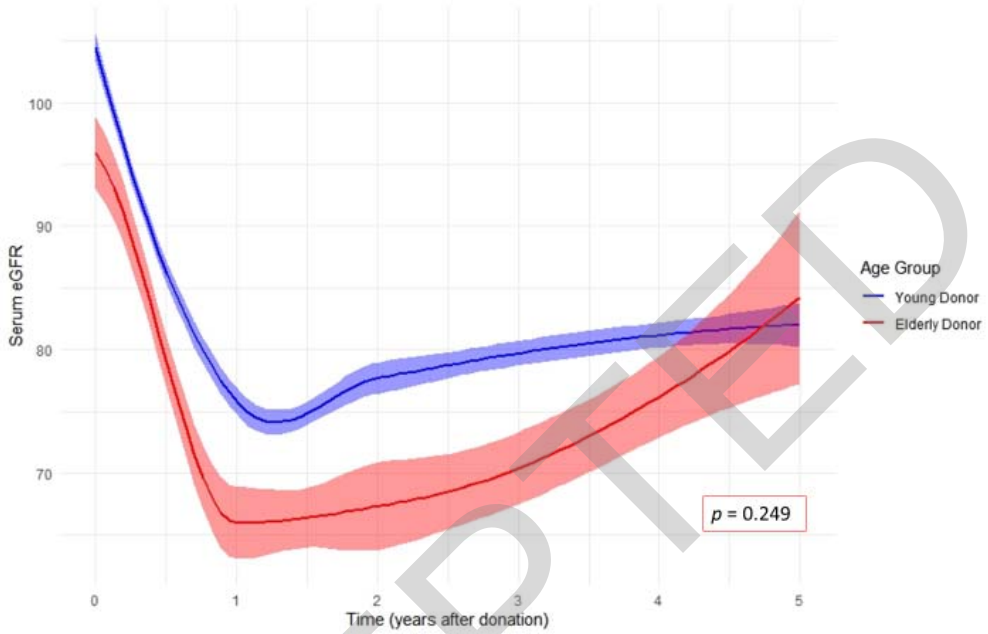

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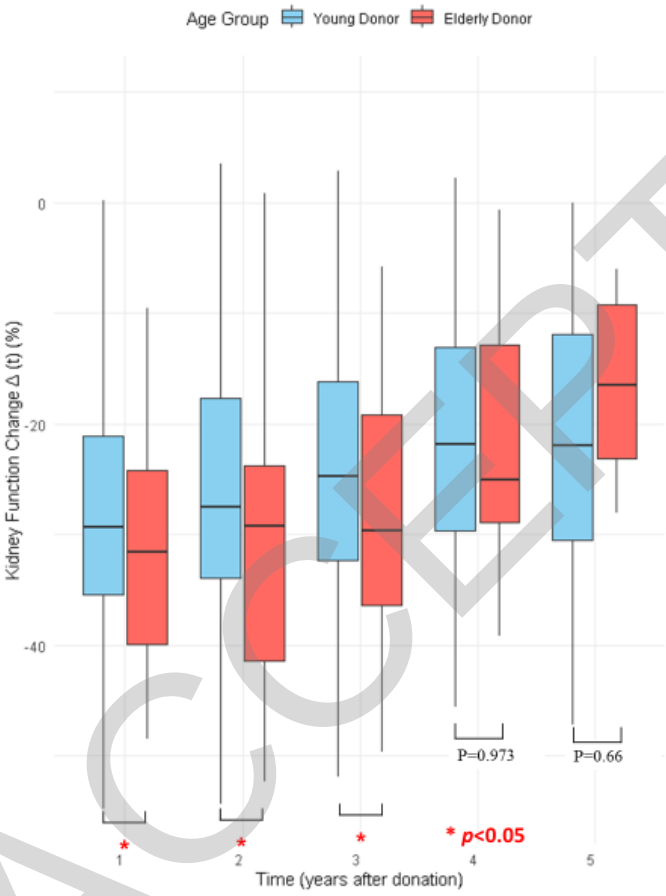
Figure 4. The kidney function change Δ (t) post-donation in young vs. elderly kidney donors. Δ (t) is the percent change in eGFR from baseline eGFR at time (t). Negative percent change indicates a decline from baseline eGFR and positive percent change indicates an increase from baseline eGFR. Statistically significant interactions between two variables are shown with '*'.



Numbers at risk

Young Donor	996	776	639	422	326
Elderly Donor	78	53	36	25	10
	1	2	3	4	5

Time (years after donation)

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Figure 5. The kidney function change Δ (t) post-donation stratified by remnant cortex volume to weight ratio (RKVW, cc/kg) quartiles in young donors (A) and elderly donors (B). The quartiles are divided as follows: first quartile Q1, ≤25th percentile; second quartile Q2, 25~50th percentile; third quartile Q3, 50th~75th percentile; and fourth quartile Q4. >75th percentile. Statistically significant interactions between two variables are shown with '*'.

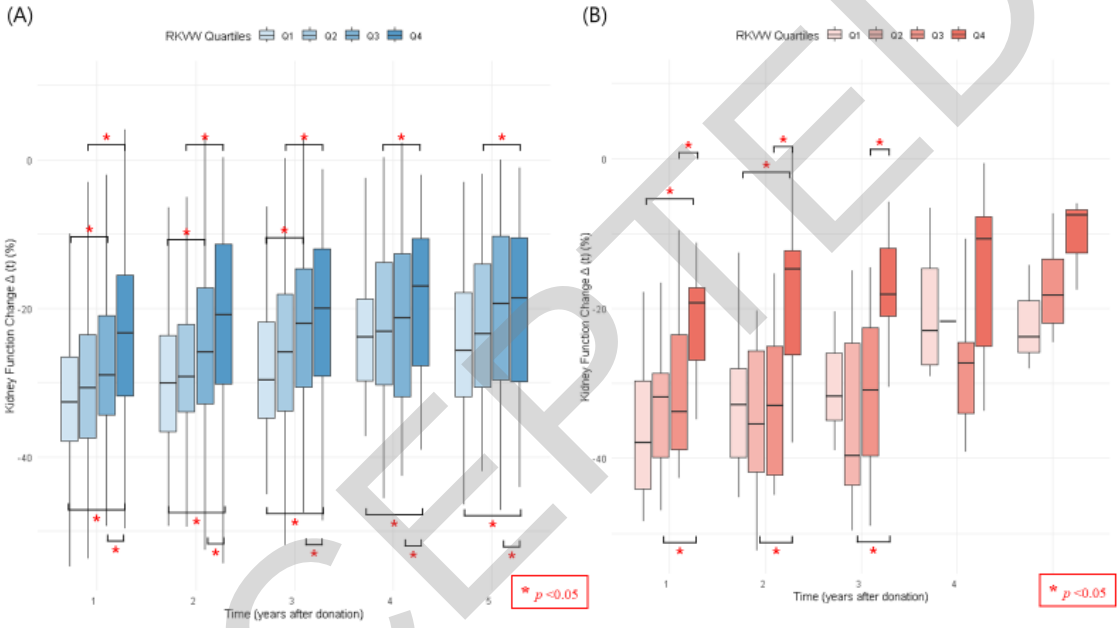

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Table 1. Baseline characteristics and preoperative lab

	Young (N=996)	Elderly (N=78)	P-value
Age	44.0 ± 10.40	63.6 ± 2.58	< 0.001
Sex, Male	435 (43.7%)	39 (50.0%)	0.335
BMI	23.60 ± 2.85	24.30 ± 2.77	0.030
BSA	1.70 ± 0.18	1.65 ± 0.16	0.049
HTN	33 (3.3%)	2 (2.6%)	0.999
DM	9 (0.9%)	0 (0.0%)	0.999
DL	218 (21.9%)	18 (23.1%)	0.919
CVD	2 (0.2%)	2 (2.6%)	0.028
Malignancy	4 (0.4%)	0 (0.0%)	0.999
Family history of CKD	619 (62.1%)	39 (50.0%)	0.045
SBP, mmHg	121.3 ± 13.32	121.9 ± 16.43	0.763
Hb, g/dL	13.7 ± 1.56	13.3 ± 1.33	0.015
WBC, x10³μL	6.16 ± 1.55	5.74 ± 1.56	0.039
NLR	1.66 ± 0.77	1.51 ± 0.62	0.044
Serum total protein, g/dL	7.29 ± 0.42	7.25 ± 0.55	0.665
Serum albumin, g/dL	4.43 ± 0.27	4.35 ± 0.31	0.015
$eGFR_0$, mg/min/1.73m²	104.5 ± 14.40	95.60 ± 9.54	< 0.001

Abbreviations: BMI, body mass index; BSA, body surface area; HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CVD, cardiovascular disease; CKD, chronic kidney disease; SBP, systolic blood pressure; $eGFR_0$, baseline estimated glomerular filtration rate; Hb, hemoglobin; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio.

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Table 2. Coefficient estimates from the generalized additive model for longitudinal measures of change in kidney function post-donation.

Effect	Estimate	Std. Error	p value
Age group (>60 years)	-2.69	1.31	0.041
Male	-9.13	0.50	<0.001
BMI	0.04	0.07	0.52
HTN	2.44	0.86	0.004
DM	-2.01	1.62	0.22
DL	-2.82	0.44	<0.001
CVD	2.13	2.60	0.41
Family history of CKD	-1.52	0.36	<0.001
Hb, g/dL	0.81	0.16	<0.001
WBC, x10³µL	0.21	0.12	0.08
NLR	-0.06	0.22	0.79
Serum total protein, g/dL	0.41	0.50	0.41
Serum albumin, g/dL	0.54	0.87	0.54
RKVW Q1	1.0		
RKVW Q2	1.95	0.52	<0.001
RKVW Q3	3.75	0.52	<0.001
RKVW Q4	6.34	0.54	<0.001

Abbreviations: BMI, body mass index; BSA, body surface area; HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia; CVD, cardiovascular disease; CKD, chronic kidney disease; Hb, hemoglobin; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; RKVW, Remnant kidney volume to weight ratio (cc/kg); Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile

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Table 3. Interaction effects of age group and remnant cortex to volume quartile groups on longitudinal measures of change in kidney function post-donation.

Effect	Estimate	Std. Error	p value
Age x RKVW Q1	1.00		
Age x RKVW Q2	-1.83	2.04	0.368
Age x RKVW Q3	-0.58	1.81	0.748
Age x RKVW Q4	4.72	1.99	0.018

RKVW, Remnant kidney volume to weight ratio (cc/kg); Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile

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