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Supplemental methods

Biopsy Morphometry

The following measurements were obtained from the scanned images of PAS-stained wedge sections and used for stereological analyses:

1. The area of cortex.
2. The number and total area of complete non-sclerotic glomerular (NSG) tufts.
3. The number and total area of globally sclerotic glomeruli (GSG).
5. Area of non-tubular regions within 5 consecutive circles (totaling 1,000,000 μm^2) placed in the middle portion of cortex, approximately equidistant between capsule and corticomedullary junction.
6. The number of complete tubular profiles within these 5 circles.
7. The number of partial tubular profiles within these 5 circles.
8. The area of interstitial fibrosis and tubular atrophy (IF/TA).
9. The luminal boundary and intimal-media boundary of the three most orthogonal arteries.

A) Measures of nephron size:

We used stereological models by Weibel and Gomez(1) to characterize three-dimensional structures from these two-dimensional measurements to calculate Mean NSG volume (**Eq.1**), NSG volumetric density (**Eq. 2 and 3**) which was inverted into cortex volume per glomerulus (**Eq. 4 and 5**). The mean profile tubular area estimates the average cross-sectional area of a tubule by counting the number of tubules in 1,000,000 μm^2 defined area of cortex after excluding all non-tubular structures (**Eq. 6**).(2)

$$\text{(Eq. 1) NSG volume (mm}^3\text{)} = \frac{1.382 \times (\text{Mean area of NSG})^{\frac{3}{2}}}{1.01}$$

$$\text{(Eq. 2) NSG volumetric density (NSG per mm}^3\text{ of cortex)} = \frac{1}{1.382} \times \sqrt[2]{\frac{\left(\frac{\text{Total number of NSG}}{\text{Area of cortex}}\right)^3}{\frac{\text{Total area of NSG}}{\text{Area of cortex}}}}$$

$$\text{(Eq. 3) NSG volumetric density in non-fibrotic cortex} = \frac{1}{1.382} \times \sqrt[2]{\frac{\left(\frac{\text{Total number of NSG}}{\text{Area of non-IFTA cortex}}\right)^3}{\frac{\text{Total area of NSG}}{\text{Area of non-IFTA cortex}}}}$$

$$\text{(Eq. 4) Cortex per glomerulus (mm}^3\text{)} = \frac{1}{\text{NSG volumetric density}}$$

$$\text{(Eq. 5) Non-fibrotic cortex per glomerulus (mm}^3\text{)} = \frac{1}{\text{NSG volumetric density in non-fibrotic cortex}}$$

$$\text{(Eq. 6) Tubular cross-sectional area (}\mu\text{m}^2\text{)} =$$

$$\frac{1,000,000 - \text{area of nontubular structures}}{\text{Number of complete tubules} + 0.5 \times \text{Number of partial tubules}}$$

B) Measures of nephrosclerosis:

The GSG number was used to estimate % globally sclerotic glomeruli (**Eq. 7**). % Artery luminal stenosis was the area of intima relative to the area of intima and lumen (**Eq. 8**). % interstitial fibrosis with tubular atrophy (%IFTA) was calculated by dividing all areas of IFTA by the cortex area (**Eq. 9**).

$$\text{(Eq. 7) \% GSG} = \frac{\text{Number of GSG}}{\text{Total number of NSG} + \text{Number of GSG}}$$

$$\text{(Eq. 8) \% Artery luminal stenosis} =$$

$$\text{Mean of 3 arteries} \left[\frac{\text{Intima to media boundary area} - \text{intimal to luminal boundary area}}{\text{Intima to media boundary area}} \right]$$

$$\text{(Eq. 9) \% IF/TA} = 100 \times \frac{\text{Area of interstitial fibrosis and tubular atrophy}}{\text{Area of Cortex}}$$

Supplemental Tables

Supplemental Table 1. The summary of specific kidney diseases obtained from the medical record among 28 patients excluded from the study.

Specific disease	Number of patients
Severe and diffuse tubulointerstitial inflammation	10
End stage kidney histology (thinned and nearly completely scarred cortex)	4
Severe ischemic changes with interstitial fibrosis/tubular atrophy (>90%)	3
Concurrent lymphoma	2
Diffuse cystic disease	2
Glomerulonephritis	2
Severe vascular sclerosis with onion skinning	2
Severe diabetic nephropathy	1
Large focal scar	1
Diffuse nodular and mesangial sclerosis (smoking related)	1

Supplemental Table 2. Structural predictors of chronic kidney disease (CKD) progression from 4 months after a radical nephrectomy with censoring for cancer recurrence.

Predictor	Unadjusted HR (95% CI)	P-value	Adjusted for age, sex, BMI, HTN, DM and smoking HR (95% CI)	P-value	Further adjusted for eGFR HR (95% CI)	P-value	Further adjusted for eGFR and proteinuria* HR (95% CI)	P-value
Nephron size								
Non-sclerotic glomerular volume	2.44 (1.63, 3.63)	<0.0001	2.63 (1.68, 4.13)	<0.0001	2.51 (1.61, 3.91)	<0.0001	2.36 (1.44, 3.89)	0.0007
Cortex per glomerulus	2.64 (1.87, 3.72)	<0.0001	2.48 (1.70, 3.61)	<0.0001	2.30 (1.58, 3.36)	<0.0001	2.09 (1.37, 3.20)	0.0006
Non-fibrotic cortex per glomerulus	2.37 (1.66, 3.39)	<0.0001	2.20 (1.49, 3.23)	<0.0001	2.06 (1.40, 3.02)	0.0002	1.88 (1.23, 2.86)	0.003
Tubular cross-sectional area	1.76 (0.95, 3.25)	0.07	1.69 (0.90, 3.20)	0.10	1.60 (0.85, 3.02)	0.15	1.55 (0.78, 3.06)	0.21
Nephrosclerosis								
% IF/TA	1.32 (1.19, 1.46)	<0.0001	1.25 (1.11, 1.40)	0.0001	1.22 (1.09, 1.38)	0.0007	1.22 (1.07, 1.39)	0.003
% Globally sclerotic glomeruli	1.66 (1.40, 1.96)	<0.0001	1.51 (1.24, 1.84)	<0.0001	1.45 (1.18, 1.78)	0.0004	1.41 (1.12, 1.78)	0.003
% Artery luminal stenosis	1.94 (1.17, 3.24)	0.01	1.48 (0.87, 2.50)	0.15	1.39 (0.82, 2.35)	0.22	1.08 (0.61, 0.90)	0.80

CKD progression defined as eGFR reduction by $\geq 40\%$, need for dialysis or kidney transplantation. Sample size 936 with 91 events after censoring for cancer recurrence. BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; IF/TA, interstitial fibrosis /tubular atrophy.

*proteinuria subgroup analysis had 816 patients with 74 events.

Supplemental Table 3. Structural predictors of chronic kidney disease progression from 4 months after a radical nephrectomy in patients dichotomized at a BMI of 30kg/m²

	BMI<30 (n=489)	BMI≥30 (n=447)	
Predictor	HR (95% CI)	HR (95% CI)	Interaction P-value
Nephron size			
Non-sclerotic glomerular volume	2.02 (1.14-3.58)	2.87 (1.77-4.64)	0.36
Cortex per glomerulus	2.59 (1.57-4.29)	2.71 (1.80-4.07)	0.90
Non-fibrotic cortex per glomerulus	2.28 (1.37-3.79)	2.45 (1.58-3.78)	0.83
Tubular cross-sectional area	1.27 (0.61-2.63)	2.51 (1.13-5.55)	0.22
Nephrosclerosis			
% IF/TA	1.28 (1.13-1.45)	1.28 (1.14-1.45)	0.98
% Globally sclerotic glomeruli	1.39 (1.15-1.68)	1.73 (1.40-2.15)	0.13
% Artery luminal stenosis	1.92 (1.01-3.65)	2.20 (1.15-4.21)	0.77

Supplemental Table 4. Prediction of chronic kidney disease (CKD) progression in three separate models: clinical predictors only, structural predictors only, and clinical and structure predictors

Predictor	Clinical model		Structural model		Clinical and structural model	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at surgery, per 10 years	1.33 (1.06-1.68)	0.01	-	-	1.26 (0.98-1.63)	0.07
Male	0.81 (0.53-1.25)	0.34	-	-	0.64 (0.41-1.01)	0.05
Body mass index, per 5kg/m ²	1.20 (1.03-1.39)	0.02	-	-	1.07 (1.92-1.26)	0.37
Hypertension	1.53 (0.89-2.64)	0.12	-	-	1.32 (0.76, 2.28)	0.32
Diabetes	1.30 (0.76-2.23)	0.34	-	-	1.12 (0.65-1.92)	0.69
Current smoker	0.83 (0.41-1.68)	0.61	-	-	0.79 (0.39-1.60)	0.51
Baseline eGFR, per 10 ml/min/1.73 m ²	0.83 (0.69-1.01)	0.07	-	-	0.96 (0.78-1.18)	0.70
Baseline proteinuria, per doubling	1.24 (1.10-1.41)	<0.001	-	-	1.15 (1.01-1.31)	0.03
Tumor stage 3 or 4	1.03 (0.66-1.61)	0.88	-	-	1.04 (0.67-1.62)	0.86
Tumor volume, per doubling	1.07 (0.96-1.18)	0.22	-	-	1.04 (0.94-1.16)	0.43
Non-sclerotic glomerular volume	-	-	1.68 (0.83-3.43)	0.15	1.75 (0.77-3.98)	0.18
Cortex per glomerulus	-	-	1.67 (0.80-3.45)	0.17	1.59 (0.68-3.68)	0.28
Tubular cross-sectional area	-	-	0.50 (0.24-1.03)	0.06	0.52 (0.23-1.19)	0.12
% IF/TA	-	-	1.12 (1.00-1.26)	0.05	1.11 (0.97-1.27)	0.14
% Globally sclerotic glomeruli	-	-	1.26 (1.05-1.52)	0.02	1.13 (0.89-1.43)	0.33
% Artery luminal stenosis	-	-	1.28 (0.79-2.09)	0.31	1.06 (0.62-1.81)	0.84
C-statistic*	0.687/0.660		0.695/0.689		0.724/0.699	

CKD progression defined as eGFR reduction by $\geq 40\%$, need for dialysis, or kidney transplantation. *Second value is C-statistic after 10-fold cross-validation.

Supplemental Table 5. Prediction of non-cancer mortality in three separate models: clinical predictors only, structural predictors only, and clinical and structure predictors

Predictor	Clinical model		Structural model		Clinical and structural model	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at surgery, per 10 years	2.63 (2.14-3.25)	<0.001	-	-	2.63 (2.11-3.29)	<0.001
Male	1.61 (1.13-2.28)	0.008	-	-	1.45 (1.01-2.08)	0.05
Body mass index, per 5kg/m ²	1.21 (1.08-1.37)	0.001	-	-	1.17 (1.03-1.32)	0.01
Hypertension	1.51 (0.99-2.30)	0.06	-	-	1.34 (0.87-2.06)	0.19
Diabetes	0.95 (0.58-1.57)	0.84	-	-	0.87 (0.53-1.44)	0.59
Current smoker	1.39 (0.84-2.32)	0.20	-	-	1.33 (0.79-2.22)	0.29
Baseline eGFR, per 10 ml/min/1.73 m ²	0.93 (0.80-1.09)	0.40	-	-	0.96 (0.82-1.14)	0.66
Baseline proteinuria, per doubling	1.15 (1.04-1.27)	0.006	-	-	1.10 (0.99-1.23)	0.07
Tumor stage 3 or 4	1.11 (0.78-1.56)	0.57	-	-	1.05 (0.74-1.49)	0.77
Tumor volume, per doubling	1.03 (0.96-1.11)	0.40	-	-	1.03 (0.95-1.11)	0.51
Non-sclerotic glomerular volume	-	-	1.10 (0.62-1.95)	0.75	1.58 (0.82-3.02)	0.17
Cortex per glomerulus	-	-	1.00 (0.56-1.81)	0.99	0.82 (0.42-1.62)	0.58
Tubular cross-sectional area	-	-	1.11 (0.63-1.97)	0.72	1.07 (0.56-2.04)	0.84
% IF/TA	-	-	1.16 (1.06-1.26)	0.001	1.14 (1.03-1.25)	0.01
% Globally sclerotic glomeruli	-	-	1.26 (1.09-1.45)	0.002	0.99 (0.82-1.20)	0.93
% Artery luminal stenosis	-	-	1.53 (1.02-2.29)	0.04	1.20 (0.77-1.87)	0.42
C-statistic*	0.779/0.654		0.701/0.668		0.792/0.664	

*Second value is C-statistic after 10-fold cross-validation

Supplemental Table 6. Structural predictors of cancer mortality starting at 4 months after a radical nephrectomy.

Predictor	Unadjusted HR (95% CI)	P-value	Adjusted for age, sex, BMI, HTN, DM and smoking HR (95% CI)	P-value	Further adjusted for eGFR HR (95% CI)	P-value	Further adjusted for eGFR and proteinuria* HR (95% CI)	P-value
Nephron size								
Non-sclerotic glomerular volume	1.26 (0.88, 1.80)	0.22	1.34 (0.90, 1.99)	0.15	1.31 (0.88, 1.95)	0.18	1.17 (0.76, 1.79)	0.47
Cortex per glomerulus	1.36 (0.99, 1.88)	0.06	1.37 (0.97, 1.96)	0.08	1.34 (0.94, 1.91)	0.11	1.20 (0.82, 1.76)	0.35
Non-fibrotic cortex per glomerulus	1.25 (0.94, 1.73)	0.15	1.25 (0.88, 1.77)	0.21	1.22 (0.86, 1.73)	0.27	1.13 (0.78, 1.63)	0.53
Tubular cross-sectional area	1.21 (0.72, 2.03)	0.46	1.20 (0.70, 2.06)	0.50	1.18 (0.69, 2.01)	0.55	1.19 (0.68, 2.09)	0.53
Nephrosclerosis								
% Interstitial fibrosis	1.09 (1.00, 1.18)	0.05	1.03 (0.94, 1.14)	0.49	1.03 (0.93, 1.13)	0.60	0.98 (0.89, 1.09)	0.76
% Globally sclerotic glomeruli	1.10 (0.97, 1.25)	0.12	1.01 (0.86, 1.19)	0.91	0.98 (0.83, 1.16)	0.83	0.90 (0.75, 1.08)	0.27
% Artery luminal stenosis	1.20 (0.80, 1.79)	0.37	1.00 (0.65, 1.53)	0.99	0.99 (0.65, 1.52)	0.97	1.12 (0.70, 1.80)	0.64

Sample size 936 with 116 events. BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; IF/TA, interstitial fibrosis /tubular atrophy.

*proteinuria subgroup analysis had 816 patients with 103 events.

Supplemental Table 7. Structural predictors of cancer recurrence starting at 4 months after a radical nephrectomy.

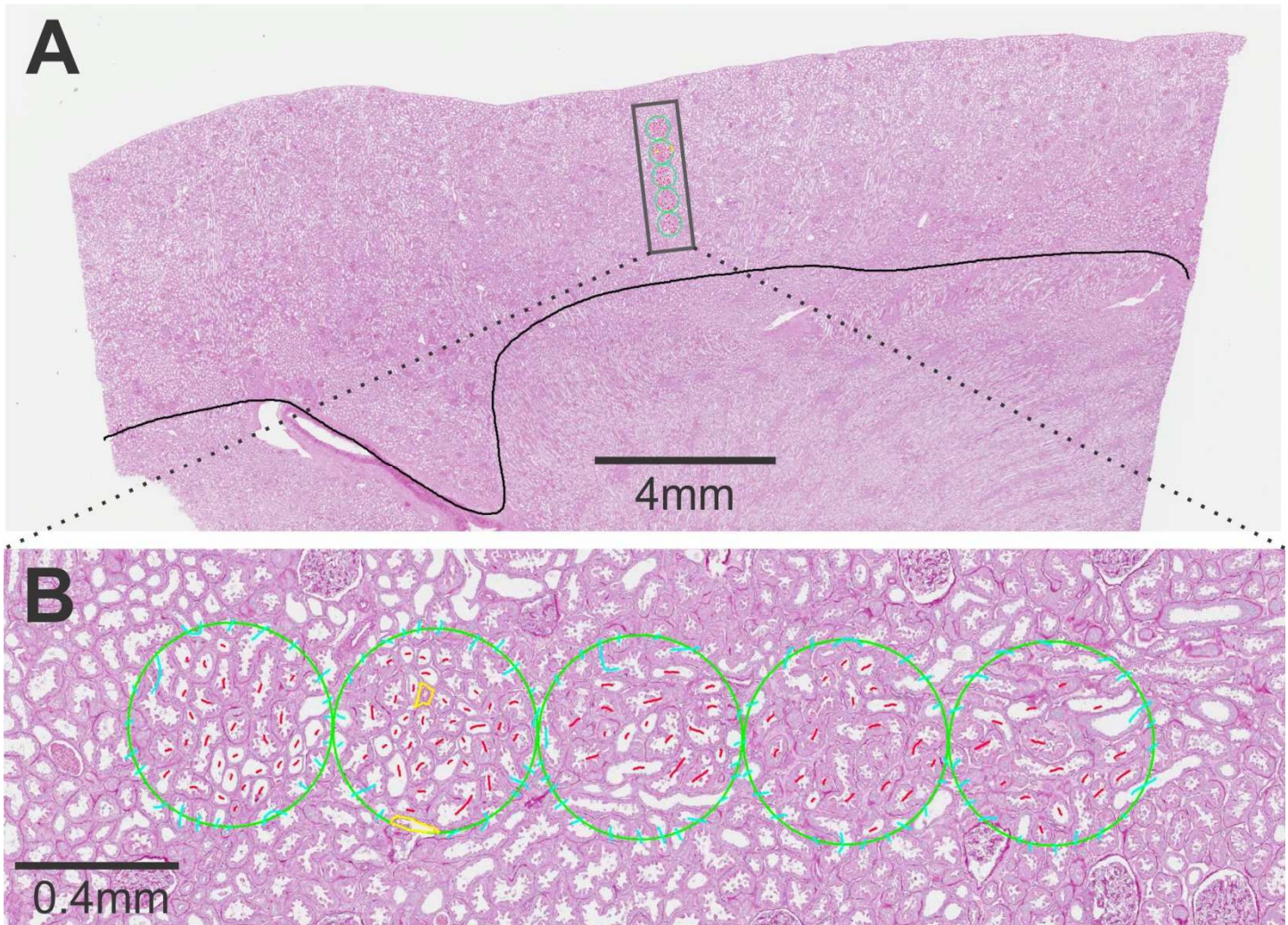
Predictor	Unadjusted HR (95% CI)	P-value	Adjusted for age, sex, BMI, HTN, DM and smoking HR (95% CI)	P-value	Further adjusted for eGFR HR (95% CI)	P-value	Further adjusted for eGFR and proteinuria* HR (95% CI)	P-value
Nephron size								
Non-sclerotic glomerular volume	0.93 (0.72, 1.20)	0.57	0.98 (0.73, 1.30)	0.88	0.96 (0.72, 1.28)	0.79	1.00 (0.73, 1.38)	0.98
Cortex per glomerulus	0.94 (0.76, 1.17)	0.58	0.94 (0.75, 1.19)	0.62	0.93 (0.74, 1.18)	0.57	1.00 (0.77, 1.29)	0.99
Non-fibrotic cortex per glomerulus	0.86 (0.70, 1.06)	0.17	0.87 (0.70, 1.08)	0.22	0.87 (0.70, 1.08)	0.20	0.92 (0.73, 1.17)	0.50
Tubular cross-sectional area	0.85 (0.60, 1.21)	0.37	0.88 (0.60, 1.28)	0.50	0.87 (0.60, 1.27)	0.48	0.95 (0.62, 1.44)	0.80
Nephrosclerosis								
% Interstitial fibrosis	1.08 (1.02, 1.15)	0.01	1.07 (1.00, 1.15)	0.07	1.07 (0.99, 1.15)	0.09	1.04 (0.96, 1.12)	0.35
% Globally sclerotic glomeruli	1.09 (1.00, 1.20)	0.06	1.06 (0.95, 1.19)	0.28	1.05 (0.94, 1.18)	0.36	1.00 (0.89, 1.13)	0.97
% Artery luminal stenosis	1.02 (0.76, 1.36)	0.92	0.89 (0.65, 1.22)	0.47	0.88 (0.65, 1.21)	0.44	0.95 (0.68, 1.32)	0.76

Sample size 936 with 236 events. BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; IF/TA, interstitial fibrosis /tubular atrophy.

*proteinuria subgroup analysis had 816 patients with 212 events.

Supplemental Figures

Supplemental Figure 1. **A)** An example of middle portion from a wedge section where 5 consecutive 0.2 mm^2 circles (light green trace) were placed to calculate mean cross-sectional tubular area. **B)** Magnified view shows how each tubule within the green circle (red trace) or partial tubule that crosses the green circle (cyan trace), and all non-tubular structures within the circles (yellow trace) were also labeled.



References

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2. Elsherbiny HE, Alexander MP, Kremers WK, Park WD, Poggio ED, Prieto M, et al. Nephron hypertrophy and glomerulosclerosis and their association with kidney function and risk factors among living kidney donors. *Clinical journal of the American Society of Nephrology : CJASN.* 2014;9(11):1892-902.