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Supplemental methods

Biopsy Morphometry

The following measurements were obtained from the consecutive PAS- and TRI-stained slides that were scanned into high-resolution digital images:

A) PAS stained section

1. The area of PAS cortex.
2. The number and total area of complete non-sclerotic glomerular (NSG) tufts.
3. The number and total area of partial non-ischemic non-sclerotic glomerular (NSG) tufts. These are the glomeruli at the biopsy edges transected by a biopsy needle, and on average counted as 0.5 complete NSG.
4. The number of globally sclerotic glomeruli (PAS-GSG).
5. The number of segmentally sclerotic glomeruli (SegSG).
6. The number of ischemic-appearing glomeruli.
7. The area of distinct inflammatory foci.
8. The number of arterioles with any arteriolar hyalinosis (circumferential or partial/nodular). If two or more arterioles with hyalinosis were found within a distance of 500 μm of each other, only one was counted.

B) Mason Trichrome (TRI) stained section

9. The area of TRI cortex.
10. The number of globally sclerotic glomeruli (TRI-GSG).
11. The areas of distinct interstitial fibrosis and tubular atrophy (IFTA) foci.
12. The luminal boundary and intimal-media boundary of the most orthogonal small-medium artery.

A) Measures of sclerosis:

The total number of non-globally sclerosed glomeruli was obtained by summing the numbers of complete NSG, partial NSG, segmentally sclerosed glomeruli and ischemic-appearing glomeruli. The GSG number was first averaged between PAS and TRI sections (Mean number of GSG),(1) and then used to calculate % GSG (**Eq. 1**). Likewise, the sum of ischemic-appearing, segmentally sclerosed, and globally-sclerosed glomeruli were divided by the total number of all glomeruli to calculate % glomerulosclerosis (**Eq.2**). The %interstitial fibrosis with tubular atrophy (%IFTA) was calculated by dividing all areas of IFTA by the cortex area (**Eq. 3**). The IFTA density was calculated by dividing the number of distinct IFTA foci by the cortex area (number of IFTA foci per mm^2) (**Eq. 4**). % Artery luminal stenosis was the area of intima divided by the area of intima and lumen of the most orthogonal artery (**Eq. 5**). We grouped the total count of AH lesions into 4 categories: 1) No AH, 2) 1 AH lesion, 3) 2 AH lesions, and 3) 3 or more AH lesions.

(Eq. 1) % GSG = $$\frac{\text{Mean number of GSG}}{\text{Total number of all glomeruli}}$$

(Eq. 2) % Glomerulosclerosis = $$\frac{\text{Mean number of GSG+Number of SegSG+Number of ischemic-appearing glomeruli}}{\text{Total number of all glomeruli}}$$

(Eq. 3) % IFTA = $$100 \times \frac{\text{Sum of all areas of interstitial fibrosis and tubular atrophy}}{\text{Area of Cortex}}$$

(Eq. 4) IFTA density (per mm²) = $\frac{\text{Number of IFTA foci}}{\text{Area of Cortex } (mm^2)}$

(Eq. 5) % Artery luminal stenosis = $\frac{\text{Intima to media boundary area – intimal to luminal boundary area}}{\text{Intima to media boundary area}}$

B) Measures of nephron size:

We used stereological models by Weibel and Gomez(2) to characterize three-dimensional properties from the two-dimensional measurements of non-sclerosed glomeruli on PAS-stained section in order to calculate mean glomerular volume (**Eq.6**) and glomerular volumetric density (**Eq. 7 and 8**) which was inverted into cortex volume per glomerulus (**Eq. 9 and 10**).

(Eq. 6) Glomerular volume (mm³) = $\frac{1.382\ X\ (\text{Mean NSG area})^{\frac{3}{2}}}{1.01}$

(Eq. 7) Glomerular volumetric density (glomeruli per mm³ of cortex) = $\frac{1}{1.382} \times \sqrt[2]{\frac{(\frac{\text{Total number of NSG}}{\text{Area of cortex}})^3}{\frac{\text{Total area of NSG}}{\text{Area of cortex}}}}$

(Eq. 8) Glomerular volumetric density in non-IFTA cortex = $\frac{1}{1.382} \times \sqrt[2]{\frac{(\frac{\text{Total number of NSG}}{\text{Area of non-IFTA cortex}})^3}{\frac{\text{Total area of NSG}}{\text{Area of non-IFTA cortex}}}}$

(Eq. 9) Cortex per glomerulus (mm³) = $\frac{1}{\text{Glomerular volumetric density}}$

(Eq. 10) Non-IFTA cortex per glomerulus (mm³) = $\frac{1}{\text{Glomerular volumetric density in non-IFTA cortex}}$

C) Inflammation:

The percent of cortical involvement with inflammation was calculated by dividing the sum of all areas of inflammation foci by the PAS-cortex area (**Eq. 11**).

(Eq. 11) % Inflammation = $100 \times \frac{\text{Sum of all areas with inflammatory foci}}{\text{Area of Cortex}}$

Supplemental Table 1. Classification of primary clinicopathologic diagnoses among 353 patients with native kidney biopsies. When two numbers are listed in parentheses, the first is the count for the ESKD outcome and the second is the count for the Progressive CKD outcome.

Diabetic kidney disease (N=25)	Nonproliferative glomerulopathies (N=89)	Proliferative GN (N=131)	Paraprotein (N=14)	Vascular (N=21)	Tubulointerstitial (N=53)	Other (N=20)
Diabetic nephropathy (25/23)	FSGS (59/57)	IgA Nephropathy (61/56)	Amyloidosis (5)	Arteriosclerosis (9/8)	ATN (26/15)	Non-specific changes (6)
	Membranous nephropathy (23/22)	Lupus nephritis (20)	Cast nephropathy (3/2)	Cholesterol emboli (2/1)	Interstitial nephritis (23/16)	Focal mild IFTA (2/1)
	Minimal change disease (6)	Immune complex GN (22/20)	MGRS (6)	CNI toxicity (1)	Nephrocalcinosis (2)	Mitochondrial cytopathy (1)
	Familial glomerulopathy (1)	Pauci-immune GN (23/19)		Fibrinoid vasculopathy (1)	Oxalate nephropathy (2)	FGGS (2)
		Fibrillary GN (3)		Hypertensive nephrosclerosis (3)		Thin basement membrane disease (8)
		MPGN-C3 (1)		Thrombotic microangiopathy (5)		Fabry's disease (1)
		Necrotizing GN-anti GBM (1)				

FSGS: focal segmental glomerulosclerosis; GN: glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; MGRS: monocloal gammopathy of renal significance; CNI: calcineurin inhibitors; ATN: acute tubular necrosis; FGGS: focal global glomerulosclerosis.

Supplemental Table 2. Spearman's correlation of measures of sclerosis and nephron size with each other among 353 Olmsted County patients with a diagnostic kidney biopsy.

	Sclerosis							Nephron size		
	%GSG	**% Glomerulosclerosis**	**%IFTA**	**IFTA density**	**%Luminal stenosis**	**Arteriolar hyalinosis**	**% Interstitial inflammation**	**Glomerular volume**	**Cortex per glomerulus**	**Non-IFTA cortex per glomerulus**
	r_s (p-value)	r_s (p-value)	r_s (p-value)	r_s (p-value)	r_s (p-value)		r_s (p-value)	r_s (p-value)	r_s (p-value)	r_s (p-value)
%GSG	---	**0.87 (<0.001)**	**0.57 (<0.001)**	**0.44 (<0.001)**	**0.27 (<0.001)**	**0.37 (<0.001)**	**0.48 (<0.001)**	0.04 (0.48)	**0.39 (<0.001)**	**0.20 (<0.001)**
%Glomerulosclerosis	**0.87 (<0.001)**	---	**-0.66 (<0.001)**	**0.51 (<0.001)**	**0.28 (<0.001)**	**0.40 (<0.001)**	**0.57 (<0.001)**	0.00 (0.97)	**0.34 (<0.001)**	**0.12 (0.02)**
%IFTA	**0.57 (<0.001)**	**0.66 (<0.001)**	---	**0.70 (<0.001)**	**0.30 (<0.001)**	**0.48 (<0.001)**	**0.72 (<0.001)**	**-0.11 (0.05)**	**0.23 (<0.001)**	-0.08 (0.12)
IFTA density	**0.44 (<0.001)**	**0.51 (<0.001)**	**0.70 (<0.001)**	---	**0.24 (<0.001)**	**0.49 (<0.001)**	**0.41 (<0.001)**	0.02 (0.73)	**0.20 (<0.001)**	0.03 (0.52)
%Luminal stenosis	**0.27 (<0.001)**	**0.28 (<0.001)**	**0.30 (<0.001)**	**0.24 (<0.001)**	---	**0.25 (<0.001)**	**0.25 (<0.001)**	-0.01 (0.1)	0.10 (0.05)	0.00 (0.93)
Arteriolar hyalinosis	**0.37 (<0.001)**	**0.40 (<0.001)**	**0.48 (<0.001)**	**0.49 (<0.001)**	**0.25 (<0.001)**	---	**0.31 (<0.001)**	0.07 (0.22)	**0.19 (<0.001)**	0.04 (0.44)
%Interstitial inflammation	**0.48 (<0.001)**	**0.57 (<0.001)**	**0.72 (<0.001)**	**0.41 (<0.001)**	**0.25 (<0.001)**	**0.31 (<0.001)**	---	**-0.10 (0.05)**	**0.22 (<0.001)**	-0.02 (0.75)
Glomerular volume	0.04 (0.48)	0.00 (0.97)	**-0.11 (0.05)**	0.02 (0.73)	-0.01 (0.81)	0.06 (0.22)	**-0.10 (0.05)**	---	**0.55 (<0.001)**	**0.60 (<0.001)**
Cortex per glomerulus	**0.39 (<0.001)**	**0.34 (<0.001)**	**0.23 (<0.001)**	**0.20 (<0.001)**	0.10 (0.05)	**0.19 (<0.001)**	**0.22 (<0.001)**	**0.55 (<0.001)**	---	**0.92 (<0.001)**
Non-IFTA cortex per glomerulus	**0.20 (<0.001)**	**0.12 (0.02)**	-0.08 (0.12)	0.03 (0.52)	0.00 (0.93)	0.04 (0.44)	-0.02 (0.75)	**0.60 (<0.001)**	**0.92 (<0.001)**	---

Supplemental Table 3. Spearman's correlation between the four sclerosis measures that parallel between pathologist report and morphometry.

		By Morphometry			
		%GSG	**%IFTA**	**%Luminal stenosis**	**Arteriolar hyalinosis**
		r_s (p-value)	r_s (p-value)	r_s (p-value)	r_s (p-value)
By Pathology	**%GSG**	**0.82 (<0.001)**	**0.56 (<0.001)**	**0.26 (<0.001)**	**0.39 (<0.001)**
	%IFTA	**0.56 (<0.001)**	**0.84 (<0.001)**	**0.33 (<0.001)**	**0.45 (<0.001)**
	%Luminal stenosis	**0.37 (<0.001)**	**0.43 (<0.001)**	**0.44 (<0.001)**	**0.32 (<0.001)**
	Arteriolar hyalinosis	**0.27 (<0.001)**	**0.34 (<0.001)**	**0.25 (<0.001)**	**0.62 (<0.001)**

Supplemental Table 4. Risk of ESKD per 1-point increase (0-10) in renal chronicity scores.

	Unadjusted		Adjusted for clinical characteristics*	
	HR	P-Value	HR	P-Value
Pathologist Renal Chronicity score[a] [%GSG score (0-3) + 2× (%IFTA score (0-3)) + arteriosclerosis score (0-1)]	**1.33 (1.23-1.44)**	**<0.001**	**1.29 (1.18-1.40)**	**<0.001**
C-statistic †	0.750/0.733		0.776/0.768	
Morphometric Renal Chronicity score[b] [%GSG score (0-3) + 2x (%IFTA score (0-3)) + arteriosclerosis score (0-1)]	**1.34 (1.24-1.44)**	**<0.001**	**1.31 (1.20-1.42)**	**<0.001**
C-statistic †	0.771/0.751		0.789/0.771	
Modified Morphometric Renal Chronicity score[c] [%Glomerulosclerosis score (0-3) + %IFTA score (0-3) + IFTA foci density score (0-3) + arteriolar hyalinosis score (0-1)]	**1.64 (1.48-1.82)**	**<0.001**	**1.58 (1.42-1.76)**	**<0.001**
C-statistic †	0.837/0.827		0.845/0.835	

Shown are HRs (95% CIs) per one-point increase in the score (range from 0-10). HR, hazard ratio; 95% CI, 95% confidence interval.
* adjusted for age, hypertension, diabetes, BMI, eGFR and proteinuria.
† Second value is C-statistic after 10-fold cross-validation. The Modified Morphometric Renal Chronicity score better discriminated outcomes than the Morphometric Renal Chronicity score ($p<0.001$ with or without adjustment for clinical characteristics).
[a] Pathologist renal chronicity score was generated by sum of the GSG score (0-3), two time the IFTA score (0-3), and AS score (0-1). IFTA score was counted twice, because IF and TA were scored separately in the study by Sethi et al.(3)
[b] All morphometric measures were first converted into scores. Morphometric renal chronicity score was generated by sum of the %GSG score (0-3), two times the morphometric %IFTA score (0-3), and morphometric AS score (0-1).
[c] Modified morphometric renal chronicity score was generated by sum of the %Glomerulosclerosis score (0-3), morphometric %IFTA score (0-3), IFTA foci density score (0-3) and morphometric AH score (0-1).

Supplemental Table 5. Risk of progressive CKD per 1-point increase (0-10) in renal chronicity scores.

	Unadjusted		**Adjusted for clinical characteristics***	
	HR	P-Value	HR	P-Value
Pathologist Renal Chronicity score[a] [%GSG score (0-3) + 2× (%IFTA score (0-3)) + arteriosclerosis score (0-1)]	**1.26 (1.19-1.33)**	**<0.001**	**1.23 (1.14-1.31)**	**<0.001**
C-statistic †	0.692/0.685		0.714/0.703	
Morphometric Renal Chronicity score[b] [%GSG score (0-3) + 2x (%IFTA score (0-3)) + arteriosclerosis score (0-1)]	**1.26 (1.19-1.33)**	**<0.001**	**1.26 (1.18-1.35)**	**<0.001**
C-statistic †	0.699/0.689		0.717/0.706	
Modified Morphometric Renal Chronicity score[c] [%Glomerulosclerosis score (0-3) + %IFTA score (0-3) + IFTA foci density score (0-3) + arteriolar hyalinosis score (0-1)]	**1.44 (1.35-1.54)**	**<0.001**	**1.49 (1.37-1.61)**	**<0.001**
C-statistic †	0.763/0.748		0.774/0.762	

Shown are HRs (95% CIs) per one-point increase in the score (range from 0-10). HR, hazard ratio; 95% CI, 95% confidence interval.
* adjusted for age, hypertension, diabetes, BMI, eGFR and proteinuria.
† Second value is C-statistic after 10-fold cross-validation. The Modified Morphometric Renal Chronicity score better discriminated outcomes than the Morphometric Renal Chronicity score ($p<0.001$ with or without adjustment for clinical characteristics).
[a] Pathologist renal chronicity score was generated by sum of the GSG score (0-3), two time the IFTA score (0-3), and AS score (0-1). IFTA score was counted twice, because IF and TA were scored separately in the study by Sethi et al.(3)
[b] All morphometric measures were first converted into scores. Morphometric renal chronicity score was generated by sum of the %GSG score (0-3), two times the morphometric %IFTA score (0-3), and morphometric AS score (0-1).
[c] Modified morphometric renal chronicity score was generated by sum of the %Glomerulosclerosis score (0-3), morphometric %IFTA score (0-3), IFTA foci density score (0-3) and morphometric AH score (0-1).

Supplemental Table 6. Risk of ESKD and progressive CKD at 2 or 5 years after baseline (90 days after biopsy) at each level of the Modified Morphometric Renal Chronicity Score.

Modified Renal Chronicity Score	2-year ESKD risk*	2-year progressive CKD risk*	5-year ESKD risk*	5-year progressive CKD risk*
0	0.0% (48)	2.3% (43)	0.0% (42)	7.0% (38)
1	0.0% (41)	13.6% (31)	0.0% (38)	13.6% (29)
2	2.6% (36)	6.1% (32)	5.7% (31)	6.1% (29)
3	3.0% (33)	6.3% (30)	3.0% (29)	20.1% (23)
4	3.2% (26)	8.0% (22)	3.2% (20)	27.0% (14)
5	0.0% (30)	11.3% (24)	10.9% (22)	31.3% (16)
6	3.7% (27)	19.7% (21)	12.3% (20)	35.8% (15)
7	18.7% (21)	21.3% (17)	27.8% (16)	46.7% (11)
8	31.5% (20)	59.4% (12)	50.6% (13)	74.2% (8)
9	46.7% (9)	66.7% (6)	54.3% (7)	80.0% (4)
10	50.0% (2)	0.0% (1)	100.0% (1)	100.0% (1)

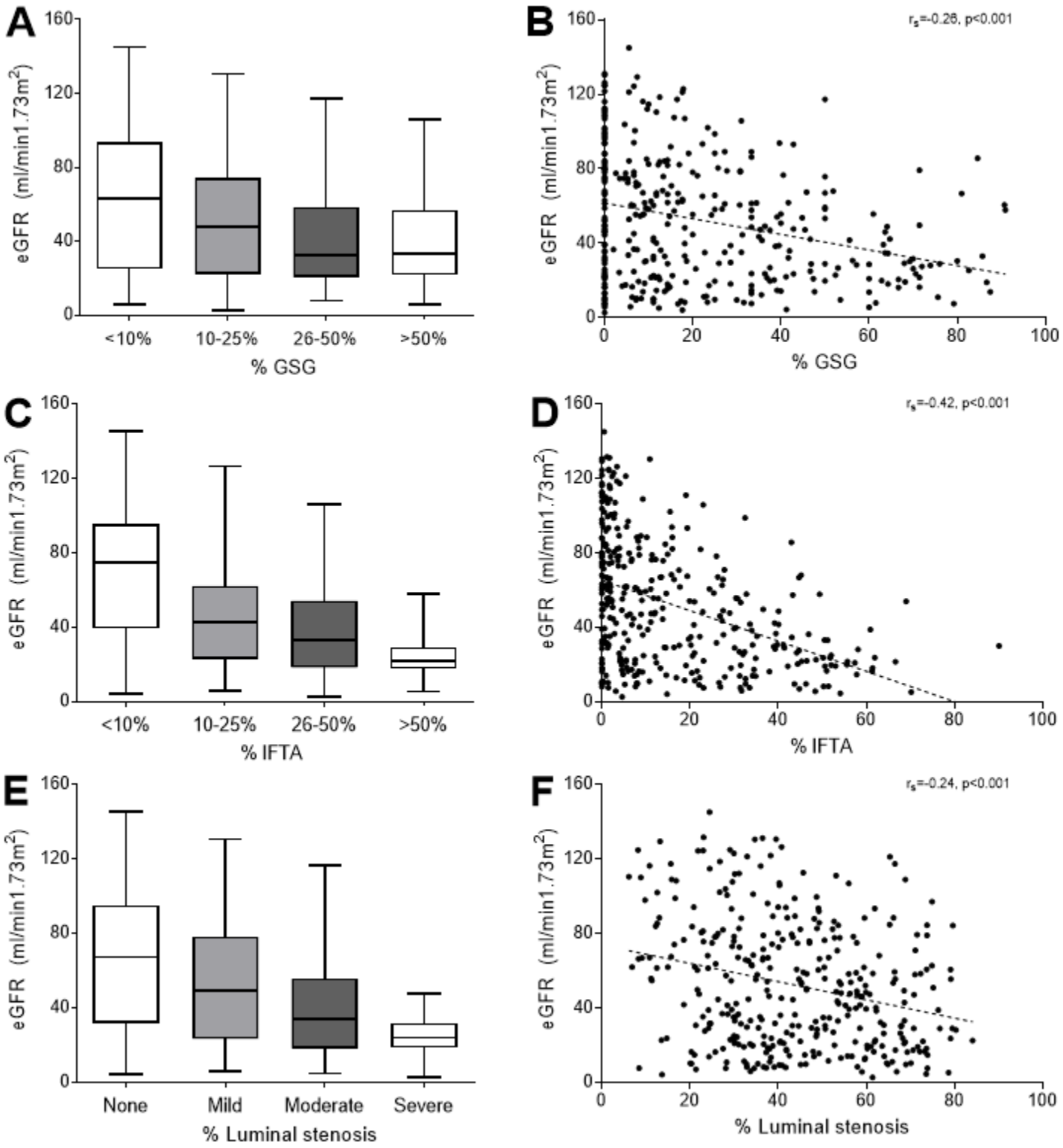
*Percentages based on Kaplan-Meier risk estimates with number at risk at 2 and 5 years is given in parentheses.

Supplemental Table 7. Risk of ESKD and CKD per 1-point increase (0-10) in modified morphometric renal chronicity scores in patients with FSGS or patients with IgA nephropathy versus patients without these primary clinicopathologic diagnoses.

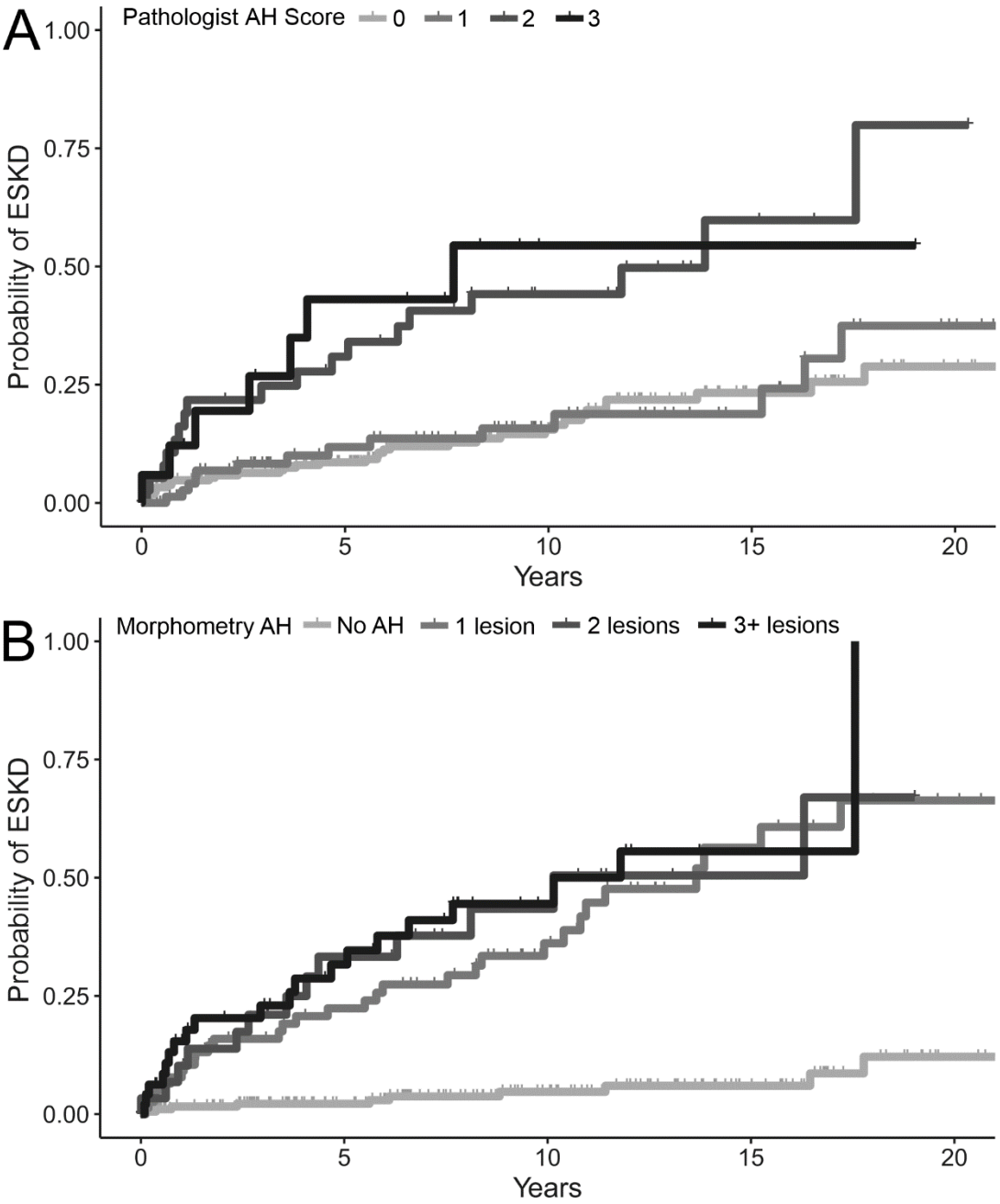
Primary diagnosis	Risk of ESKD			Risk of progressive CKD		
	HR	P-Value	C-statistic	HR	P-Value	C-statistic
FSGS*	**1.53 (1.23-1.91)**	**<0.001**	0.843	**1.40 (1.20-1.62)**	**<0.001**	0.732
Not FSGS	**1.66 (1.48-1.87)**	**<0.001**	0.838	**1.45 (1.34-1.56)**	**<0.001**	0.766
IgA Nephropathy*	**1.89 (1.35-1.64)**	**<0.001**	0.893	**1.59 (1.32-1.90)**	**<0.001**	0.856
Not IgA Nephropathy	**1.61 (1.44-1.80)**	**<0.001**	0.824	**1.41 (1.31-1.52)**	**<0.001**	0.744

*The tests of interaction showed no differential performance of the score between those with or without FSGS (ESKD p=0.34, CKD p=0.43) or between those with or without IgA Nephropathy (ESKD p=0.52, CKD p=0.21).

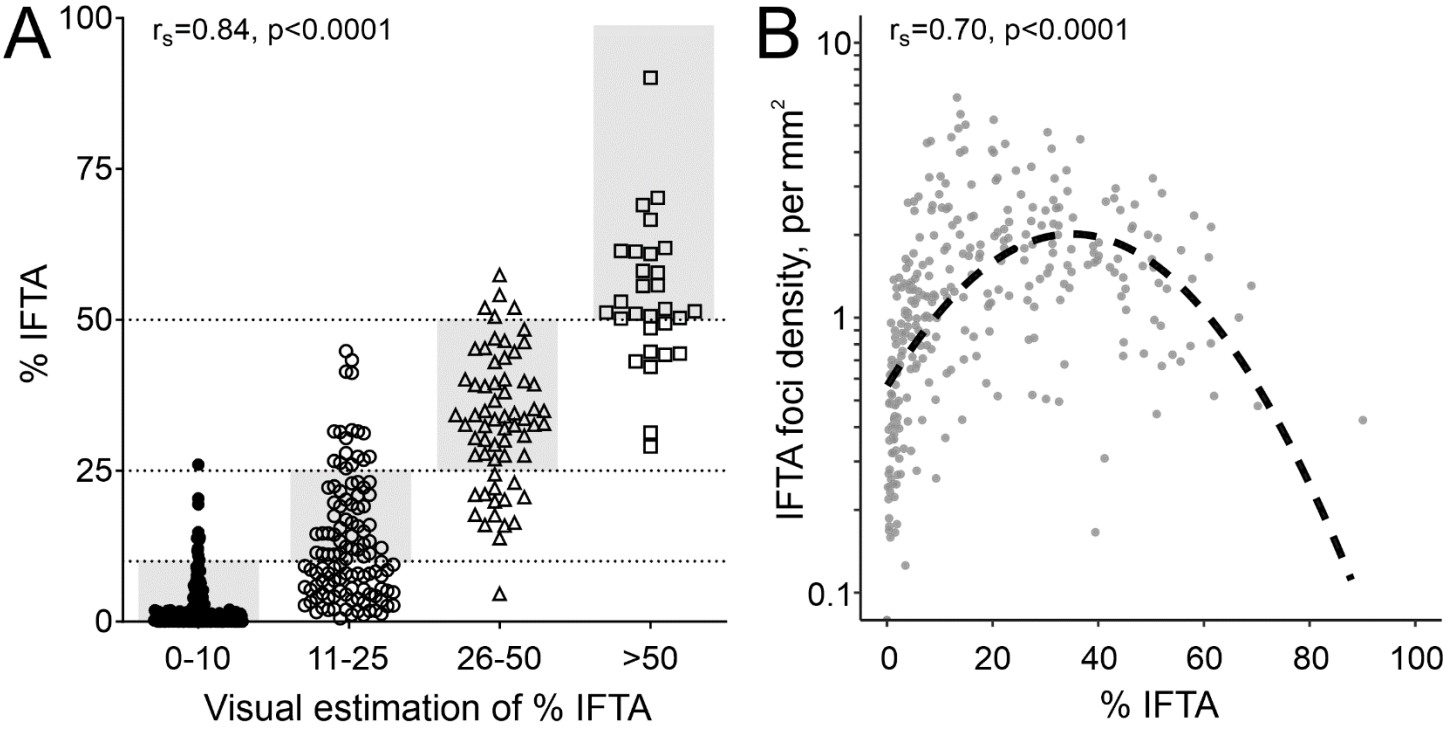
Supplemental Figures



Supplemental Figure 1. Both pathologist scores (**A-C-E**) and morphometry measures (**B-D-F**) for %GSG, %IFTA, and %luminal stenosis significantly associate with lower eGFR**.**



Supplemental Figure 2. Risk of ESKD by **A**) pathologist AH score and **B)** morphometric AH score.



Supplemental Figure 3. Correlation of morphometry %IFTA, pathologist's visually estimated %IFTA score, and IFTA foci density. **A)** Morphometric measures of %IFTA shows correlation with pathologist's visually estimated IFTA score (r_s=0.84, p <0.0001). Gray shaded area and dotted lines represent the ranges for pathologist scores. **B**) Overall, morphometric measure of IFTA foci density increases with morphometric %IFTA (r_s=0.70, p <0.0001), but for %IFTA >20% the IFTA foci density declines with further increases in %IFTA. Dashed line shows the nonlinear trend is approximated by a quadratic regression.

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1. Denic A, Alexander MP, Kaushik V, Lerman LO, Lieske JC, Stegall MD, et al.: Detection and Clinical Patterns of Nephron Hypertrophy and Nephrosclerosis Among Apparently Healthy Adults. *Am J Kidney Dis,* 68**:** 58-67, 2016 10.1053/j.ajkd.2015.12.029
2. Weibel ER, Gomez DM: A principle for counting tissue structures on random sections. *J Appl Physiol,* 17**:** 343-348, 1962 10.1152/jappl.1962.17.2.343
3. Sethi S, D'Agati VD, Nast CC, Fogo AB, De Vriese AS, Markowitz GS, et al.: A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int,* 91**:** 787-789, 2017 10.1016/j.kint.2017.01.002