Supplemental Data

The Prognostic Value of Histopathologic Lesions in Native Kidney Biopsy Specimens: Results from the Boston Kidney Biopsy Cohort Study

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Tables:

Figures:

Supplemental Table 1. Histopathologic Scoring System for Light Microscopy

Histologic Feature	Scoring
Mesangial Matrix Expansion	0 (none), 1 (mild,), 2 (moderate), 3 (severe)
Global Glomerulosclerosis	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Segmental Glomerulosclerosis	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Endocapillary Glomerular Inflammation	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Extracapillary Cellular Crescents	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Focal Glomerular Necrosis	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Fibrocellular Crescents	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Interstitial Fibrosis and Tubular Atrophy	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Inflammation, Non-Fibrosed Interstitium	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Inflammation, Fibrosed Interstitium	0 (≤10%), 1 (11-25%), 2 (26-50%), 3 (>50%)
Acute Tubular Injury	0 (none), 1 (mild,), 2 (moderate), 3 (severe)
Arterial Sclerosis	0 (none), 1 (mild,), 2 (moderate), 3 (severe)
Arteriolar Sclerosis	0 (none), 1 (mild,), 2 (moderate), 3 (severe)

Percentages were calculated by assessing affected areas over total cortical volume or glomeruli affected.

References used to develop scoring system:

Mauer, S, Steffes, M, Ellis, E, Sutherland, D, Brown, D, Goetz, F: Structural-Functional Relationships in Diabetic Nephropathy. *J Clin Invest,* 74**:** 1143-1155, 1984.

Bajema, I, ECH, H, Hansen, B, Hermans, J, Noel, L, Waldherr, R, et al.: The renal histopathology in systemic vasculitis: an international survey study of inter- and intra-observer agreement. *Nephrol Dial Transplant,* 11**:** 1989-1995, 1996.

Racusen, LC, Solez, K, Colvin, RB, Bonsib, SM, Castro, MC, Cavallo, T, et al.: The Banff 97 working classification of renal allograft pathology. *Kidney Int,* 55**:** 713-723, 1999.

Weening, J, D'Agati, V, Schwartz, M, Seshan, S, Alpers, C, Appel, G, et al.: The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited. *Journal of the American Society of Nephrology,* 15**:** 241-250, 2004

D'Agati, VD, Fogo, AB, Bruijn, JA, Jennette, JC: Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *American Journal of Kidney Diseases,* 43**:** 368-382, 2004.

Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Roberts, IS, Cook, HT, Troyanov, S, Alpers, CE, Amore, A, Barratt, J, et al.: The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int,* 76**:** 546-556, 2009.

Tervaert, TW, Mooyaart, AL, Amann, K, Cohen, AH, Cook, HT, Drachenberg, CB, et al.: Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol,* 21**:** 556-563, 2010.

Berden, AE, Ferrario, F, Hagen, EC, Jayne, DR, Jennette, JC, Joh, K, et al.: Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol,* 21**:** 1628-1636, 2010.

Farris, AB, Adams, CD, Brousaides, N, Della Pelle, PA, Collins, AB, Moradi, E, et al.: Morphometric and visual evaluation of fibrosis in renal biopsies. *J Am Soc Nephrol,* 22**:** 176-186, 2011.

Supplemental Table 2. Correlation of eGFR and Proteinuria with Histopathologic Lesions

	Mesangial Expansion	Global Glomerulosclerosis	Segmental Glomerulosclerosis	Endocapillary Glomerular Inflammation	Cellular Crescents	Fibrinoid Necrosis	Fibrocellular Crescents	IFTA	Inflammation, Non-Fibrosed Interstitium	Inflammation Fibrosed Interstitium	ATI	Arterial Sclerosis	Arteriolar Sclerosis
eGFR	-0.16	-0.46	-0.01	-0.14	0.05	0.07	0.01	-0.62	-0.18	-0.47	-0.40	-0.44	-0.48
Proteinuria	0.29	0.06	0.11	0.11	0.05	-0.01	0.03	0.13	0.04	0.09	0.08	0.08	0.09

Correlation matrix using Spearman correlation coefficients. Color shading corresponds to level of significance:
P < 0.05
P < 0.001

Supplemental Table 3. Correlation Matrix between Histopathologic Lesions in the Boston Kidney Biopsy Cohort

	Mesangial Expansion	Global Glomerulosclerosis	Segmental Glomerulosclerosis	Endocapillary Glomerular Inflamation	Cellular Crescents	Fibrinoid Necrosis	Fibrocellular Crescents	IFTA	Inflammation, Non-Fibrosed Interstitium	Inflammation, Fibrosed Interstitium	ATI	Arterial Sclerosis
Global Glomerulosclerosis	0.17											
Segmental Glomerulosclerosis	0.08	0.16										
Endocapillary Glomerular Inflammation	0.24	-0.13	-0.03									
Cellular Crescents	0.04	-0.09	0.10	0.45								
Fibrinoid Necrosis	0.03	-0.08	0.04	0.37	0.69							
Fibrocellular Crescents	0.03	-0.03	0.12	0.28	0.60	0.42						
IFTA	0.28	0.64	0.13	-0.09	-0.03	-0.05	0.04					
Inflammation, Non-Fibrosed Interstitiium	0.03	-0.01	-0.05	0.15	0.25	0.21	0.20	0.10				
Inflammation, Fibrosed Interstitium	0.19	0.43	0.07	0.03	0.11	0.03	0.11	0.61	0.31			
ATI	0.02	-0.01	-0.07	0.04	0.13	0.10	0.12	0.19	0.28	0.25		
Arterial Sclerosis	0.24	0.45	0.01	-0.14	-0.13	-0.10	-0.11	0.52	-0.06	0.32	0.08	
Arteriolar Sclerosis	0.32	0.50	0.03	-0.16	-0.18	-0.14	-0.13	0.59	-0.07	0.38	0.08	0.68

Correlation matrix using Spearman correlation coefficients. Color shading corresponds to level of significance:
P < 0.05
P < 0.001

Supplemental Table 4. Individual Histopathologic Lesions and the Risk of Renal Replacement Therapy

Histopathological Lesion	N	Events per 100 person-years	Model 1 HR [95% CI]	Model 2 HR [95 % CI]	Model 3 HR [95 % CI]
Glomerular Compartment					
Endocapillary Glomerular Inflammation					
Absent	569	6.4	--	--	--
Present	101	3.7	0.62 [0.34 – 1.14]	0.93 [0.44 – 1.95]	1.19 [0.57 – 2.46]
Cellular Crescents					
Absent	586	6.3	--	--	--
Present	85	3.8	0.61 [0.31 – 1.22]	1.34 [0.55 – 3.29]	1.29 [0.54 – 3.07]
Fibrinoid Necrosis					
Absent	611	6.3	--	--	--
Present	60	2.3	0.38 [0.14 – 1.03]	0.52 [0.18 – 1.51]	0.58 [0.20 – 1.68]
Fibrocellular Crescents					
Absent	602	6.1	--	--	--
Present	68	4.3	0.74 [0.38 – 1.47]	1.32 [0.60 – 2.89]	1.04 [0.48 – 2.26]
Mesangial Expansion					
None or Mild	438	4.1	--	--	--
Moderate	155	7.3	1.69 [1.07 – 2.66]	1.38 [0.81 – 2.34]	1.18 [0.68 – 2.04]
Severe	69	15.4	3.42 [2.09 – 5.58]	1.23 [0.58 – 2.62]	0.85 [0.39 – 1.83]
Segmental Sclerosis					
Absent	532	5.5	--	--	--
Present	138	7.5	1.32 [0.86 – 2.03]	1.22 [0.77 – 1.94]	1.14 [0.72 – 1.82]
Global Glomerulosclerosis					
Minimal (<10%)	255	2.0	--	--	--
Mild (11-25%)	164	3.3	1.53 [0.74 – 3.13]	1.44 [0.68 – 3.04]	1.12 [0.52 – 2.39]
Moderate (26-50%)	149	6.5	3.13 [1.68 – 5.83]	2.51 [1.27 – 4.93]	1.58 [0.79 – 3.19]
Severe (>50%)	104	25.0	11.1 [6.31 – 19.3]	8.10 [4.31 – 15.2]	3.66 [1.90 – 7.03]
Tubulointerstitial Compartment					
Acute Tubular Injury					
Absent	412	4.1	--	--	--
Present	254	9.6	2.20 [1.51 – 3.20]	1.90 [1.26 – 2.87]	1.05 [0.67 – 1.66]
Inflammation, Non-Fibrosed Interstitium					
Absent	560	6.1	--	--	--
Present	104	5.6	0.86 [0.50 – 1.49]	0.71 [0.38 – 1.33]	0.45 [0.24 – 0.86]
Inflammation, Fibrosed Interstitium					
None or Mild	436	3.5	--	--	--
Moderate	187	10.2	2.77 [1.85 – 4.15]	2.12 [1.37 – 3.27]	1.27 [0.82 – 1.97]
Severe	45	19.3	4.78 [2.70 – 8.46]	4.71 [2.57 – 8.65]	2.04 [1.09 – 3.83]
Interstitial Fibrosis/Tubular Atrophy					
Minimal (<10%)	249	1.3	--	--	--
Mild (11-25%)	142	2.6	1.89 [0.82 – 4.37]	1.68 [0.69 – 4.08]	0.83 [0.33 – 2.11]

Moderate (26-50%)	118	6.2	4.38 [2.08 – 9.22]	3.96 [1.81 – 8.69]	1.36 [0.59 – 3.12]
Severe (>50%)	158	23.4	15.3 [8.06 – 29.2]	11.6 [5.71 – 23.5]	3.08 [1.45 – 6.57]
Vascular Compartment					
Arterial Sclerosis					
None or Mild	287	2.5	--	--	--
Moderate	204	4.5	1.79 [1.01 – 3.19]	1.63 [0.86 – 3.08]	1.35 [0.72 – 2.53]
Severe	194	14.0	5.08 [3.05 – 8.47]	3.49 [1.88 – 6.48]	2.11 [1.14 – 3.92]
Arteriolar Sclerosis					
None or Mild	331	1.7	--	--	--
Moderate	204	7.5	4.21 [2.41 – 7.35]	4.47 [2.42 – 8.27]	2.52 [1.34 – 4.73]
Severe	131	20.0	10.3 [5.99 – 17.8]	7.77 [3.92 – 15.4]	4.24 [2.13 – 8.43]

Model 1 is Unadjusted

Model 2 is stratified by site and adjusted for age, sex, race, log transformed proteinuria, primary clinicopathologic diagnosis, and ACEi or ARB medication use

Model 3 includes model 2 and further adjusts for eGFR

Supplemental Table 5. Risk of Kidney Disease Progression in Pathologic vs No or Age-related Global Glomerulosclerosis

Global Glomerulosclerosis	N	Events	Model 1 HR [95% CI]	Model 2 HR [95% CI]	Model 3 HR [95% CI]
No or age-related	308	53	--	--	--
Pathologic Minimal (≤10%)	29	6	1.11 [0.48 – 2.59]	1.56 [0.64 – 3.77]	1.97 [0.80 – 4.84]
Pathologic Mild (11 – 25%)	90	16	1.02 [0.58 – 1.78]	1.11 [0.63 – 1.98]	1.14 [0.65 – 2.03]
Pathologic Moderate (26 – 50%)	141	56	2.64 [1.81 – 3.85]	2.12 [1.41 – 3.18]	1.82 [1.20 – 2.75]
Pathologic Severe (>50%)	104	66	4.92 [2.35 – 6.54]	3.75 [2.49 – 5.65]	2.76 [1.80 – 4.25]

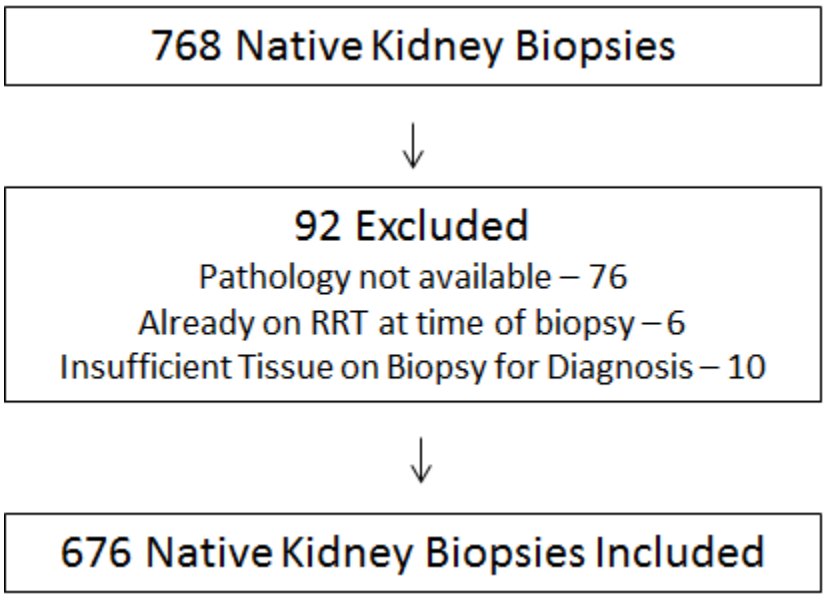
Model 1 is Unadjusted
Model 2 is stratified by site and adjusted for age, sex, race, log transformed proteinuria, primary clinicopathologic diagnosis, and ACEi or ARB medication use
Model 3 includes model 2 and further adjusts for eGFR

Supplemental Table 6. Risk of Renal Replacement Therapy using the Kidney Biopsy Chronicity Score

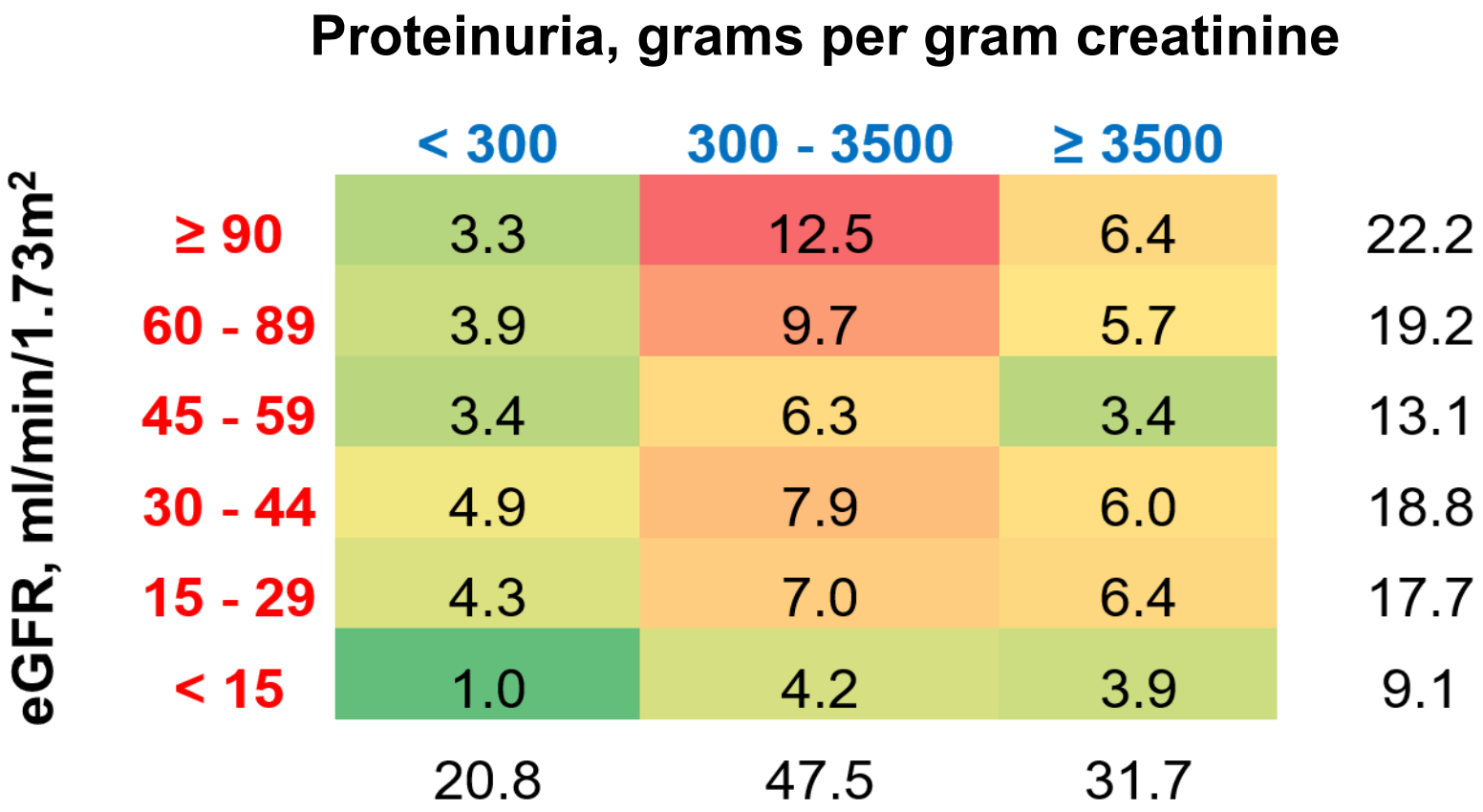
Chronicity Score*	N	Events per 100 person-years	Model 1 HR [95% CI]	Model 2 HR [95 % CI]	Model 3 HR [95 % CI]
Per 1-point change	654	5.6	1.42 [1.33 – 1.52]	1.38 [1.28 – 1.49]	1.24 [1.13 – 1.35]
Minimal chronic changes (0-1)	199	1.1	--	--	--
Mild chronic changes (2-4)	168	2.5	2.22 [0.87 – 5.65]	2.08 [0.77 – 5.59]	1.30 [0.47 – 3.63]
Moderate chronic changes (5-7)	146	6.0	5.38 [2.30 – 12.6]	5.52 [2.23 – 13.7]	2.13 [0.83 – 5.48]
Severe chronic changes (≥8	141	23.9	19.6 [8.94 – 43.1]	15.7 [6.47 – 38.1]	4.67 [1.83 – 11.9]

*Chronicity score is calculated by adding scores of global glomerulosclerosis (0 – 3), IFTA (0 – 3), and arterial sclerosis (0 -1). IFTA is counted twice as interstitial fibrosis and tubular atrophy are scored separately in the Sethi et al proposal. Arterial sclerosis is given a score of 0 for none/mild and 1 for moderate/severe lesions.

Shown are hazard ratios (95% confidence intervals) per one point increase in the score (range 0 to 10).
Model 1 is Unadjusted
Model 2 is Model 1 stratified by site and adjusted for age, sex, race, log transformed proteinuria, primary clinicopathologic diagnosis, and ACEi or ARB medication use
Model 3 is Model 2 and adjusts for eGFR



Supplemental Figure 1. Flow Diagram for Inclusion/Exclusion of Individuals Enrolled in Boston Kidney Biopsy Cohort



Supplemental Figure 2. Individuals Enrolled in the Boston Kidney Biopsy Cohort by eGFR and Proteinuria Categories

Percent of total individuals in each category.