Supplemental Data

The Associations of Plasma Biomarkers of Inflammation with Histopathologic Lesions, Kidney Disease Progression, and Mortality – The Boston Kidney Biopsy Cohort Study

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Tables:

Supplemental Table 1. Histopathologic scoring system for light microscopy

Supplemental Table 2. Absolute plasma biomarker concentrations by primary clinicopathologic diagnosis

Supplemental Table 3. Associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with adverse clinical outcomes by primary clinicopathologic diagnosis

Supplemental Table 4. Competing risk analyses for the associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with ESKD

Supplemental Table 5. Associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with adverse clinical outcomes after adjustment for immunosuppressive medications

Figures:

Supplemental Figure 1. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with tubulointerstitial lesions

Supplemental Figure 2. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with glomerular lesions

Supplemental Figure 3. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with microvascular lesions

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.

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Supplemental Table 2. Absolute plasma biomarker concentrations by primary clinicopathologic diagnosis

	Proliferative glomerulonephritis	Non-proliferative glomerulopathy	Paraprotein disease	Diabetic nephropathy	Vascular disease	Tubulointerstitial disease	Advanced glomerulosclerosis	Other
eGFR, ml/min/1.73m²	66.9 ± 38.3	74.1 ± 36.3	56.1 ± 30.4	37.1 ± 20.6	44.5 ± 28.3	25.5 ± 16.5	42.9 ± 27.0	79.0 ± 35.2
Proteinuria, g/g creatinine	1.5 [0.7 – 3.3]	3.7 [1.8 – 7.2]	2.4 [0.7 – 5.6]	3.5 [0.8 – 6.7]	0.6 [0.2 – 2.1]	0.4 [0.2 – 1.4]	1.0 [0.2 – 3.6]	0.1 [0.0 – 0.4]
sTNFR-1, pg/ml	864 [404 – 1835]	772 [484 – 1654]	778 [448 – 1826]	1921 [1046 – 2806]	900 [578 – 2178]	1494 [688 – 3297]	1254 [531 – 2351]	298 [239 – 1237]
sTNFR-2, pg/ml	5446 [2973 – 9587]	6904 [3745 – 10809]	4238 [2762 – 6761]	8352 [5351 – 14463]	6083 [3431 – 16421]	8034 [4841 – 13922]	6567 [3929 – 11897]	2017 [1495 – 8858]
YKL-40, ng/ml	36.1 [22 – 73]	53.2 [26 – 101]	59.6 [21 – 124]	69.5 [50 – 117]	65.5 [30 – 92]	73.3 [37 – 157]	53.7 [36 – 107]	23.5 [15 – 59]
MCP-1, pg/ml	122.2 [84 – 189]	134.2 [99 – 206]	138.7 [100 – 198]	160.9 [114 – 206]	157.3 [99 – 197]	136.5 [96 – 182]	129.8 [102 – 175]	103.1 [69 – 167]
suPAR, pg/ml	2730.3 [1553 – 5833]	2644.8 [1646 – 4994]	2480 [1878 – 5520]	4913.4 [1991 – 7220]	3156.2 [1747 – 6305]	5223.7 [2293 – 11693]	3698.8 [2112 – 6725]	2300.8 [1613 – 6278]

Data presented as mean ± standard deviation, median [interquartile range]

Supplemental Table 3. Associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with adverse clinical outcomes by primary clinicopathologic diagnosis

	Events	HR (95% CI)	P-interaction
Kidney disease progression*			
sTNFR1			
Glomerulopathy	78	1.36 (1.09 – 1.71)	0.51
Other diagnoses	103	1.23 (0.98 – 1.54)	
sTNFR2			
Glomerulopathy	78	1.52 (1.18 – 1.94)	0.93
Other diagnoses	103	1.25 (0.98 – 1.60)	
YKL-40			
Glomerulopathy	75	1.31 (1.06 – 1.62)	0.99
Other diagnoses	95	1.01 (0.82 – 1.24)	
MCP-1			
Glomerulopathy	78	1.34 (1.04 – 1.72)	0.50
Other diagnoses	103	1.33 (0.97 – 1.82)	
suPAR			
Glomerulopathy	74	1.06 (0.93 – 1.21)	0.13
Other diagnoses	101	1.19 (1.03 – 1.38)	
ESKD			
sTNFR1			
Glomerulopathy	50	1.31 (0.96 – 1.80)	0.64
Other diagnoses	73	1.25 (0.98 – 1.60)	
sTNFR2			
Glomerulopathy	50	1.43 (1.01 – 2.01)	0.77
Other diagnoses	73	1.33 (0.99 – 1.79)	
YKL-40			
Glomerulopathy	49	1.18 (0.90 – 1.54)	0.34
Other diagnoses	67	1.13 (0.87 – 1.46)	
MCP-1			
Glomerulopathy	50	1.53 (1.08 – 2.16)	0.80
Other diagnoses	73	1.41 (0.99 – 2.02)	
suPAR			
Glomerulopathy	48	1.02 (0.86 – 1.21)	0.06
Other diagnoses	73	1.30 (1.10 – 1.52)	
Mortality			
sTNFR1			
Glomerulopathy	35	1.27 (0.90 – 1.79)	0.53
Other diagnoses	48	0.96 (0.76 – 1.21)	
sTNFR2			
Glomerulopathy	35	1.57 (1.09 – 2.26)	0.86
Other diagnoses	48	1.06 (0.82 – 1.36)	
YKL-40			
Glomerulopathy	35	1.35 (0.98 – 1.86)	0.16
Other diagnoses	40	1.58 (1.11 – 2.24)	
MCP-1			
Glomerulopathy	35	1.26 (0.88 – 1.81)	0.39
Other diagnoses	47	1.59 (1.03 – 2.47)	
suPAR			
Glomerulopathy	34	0.99 (0.81 – 1.19)	0.29
Other diagnoses	46	1.15 (0.93 – 1.43)	

Model is stratified by site and adjusted for age, sex, race, natural log transformed proteinuria, and baseline eGFR

HR per doubling of biomarker

Glomerulopathy is defined as proliferative glomerulonephritis, non-proliferative glomerulopathy, or paraprotein-related disease

*Kidney disease progression defined as ≥40% eGFR decline or ESKD

Supplemental Table 4. Competing risk analyses for the associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with ESKD

	Events	Model 1 HR (95%CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
sTNFR-1				
ESKD	124	1.81 (1.57 – 2.09)	1.78 (1.53 – 2.08)	1.25 (1.03 – 1.51)
sTNFR-2				
ESKD	124	1.93 (1.65 – 2.25)	1.91 (1.59 – 2.30)	1.34 (1.06 – 1.70)
YKL-40				
ESKD	117	1.52 (1.34 – 1.74)	1.54 (1.32 – 1.81)	1.16 (0.97 – 1.39)
MCP-1				
ESKD	124	1.27 (1.07 – 1.50)	1.25 (1.00 – 1.55)	1.46 (1.15 – 1.87)
suPAR				
ESKD	122	1.27 (1.15 – 1.39)	1.25 (1.13 – 1.38)	1.12 (1.01 – 1.24)

Death is treated as the competing risk.

Model 1 is unadjusted

Model 2 is adjusted for age, sex, race, natural log transformed proteinuria, and primary clinicopathologic diagnosis

Model 3 is Model 2 and further adjusted for baseline eGFR

HR per doubling of biomarker

Supplemental Table 5. Associations of sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR with adverse clinical outcomes after adjustment for immunosuppressive medications

	Events	Model 3 HR (95% CI)	Model 3 + IS or CS HR (95% CI)
sTNFR-1			
Kidney disease progression*	182	1.33 (1.13 – 1.56)	1.32 (1.12 – 1.55)
ESKD	124	1.31 (1.07 – 1.60)	1.28 (1.04 – 1.57)
Mortality	85	1.17 (0.94 – 1.46)	1.16 (0.93 – 1.44)
sTNFR-2			
Kidney disease progression*	182	1.47 (1.24 – 1.75)	1.45 (1.21 – 1.72)
ESKD	124	1.50 (1.18 – 1.90)	1.44 (1.14 – 1.83)
Mortality	85	1.33 (1.04 – 1.71)	1.28 (1.01 – 1.64)
YKL-40			
Kidney disease progression*	171	1.21 (1.04 – 1.40)	1.19 (1.03 – 1.38)
ESKD	117	1.19 (0.99 – 1.44)	1.17 (0.97 – 1.41)
Mortality	77	1.45 (1.15 – 1.82)	1.40 (1.11 – 1.77)
MCP-1			
Kidney disease progression*	182	1.33 (1.09 – 1.61)	1.31 (1.08 – 1.59)
ESKD	124	1.47 (1.16 – 1.88)	1.43 (1.12 – 1.82)
Mortality	84	1.36 (1.03 – 1.79)	1.28 (0.97 – 1.69)
suPAR			
Kidney disease progression*	176	1.08 (0.99 – 1.19)	1.09 (0.99 – 1.19)
ESKD	122	1.11 (0.99 – 1.25)	1.13 (1.01 – 1.26)
Mortality	82	1.08 (0.94 – 1.24)	1.08 (0.94 – 1.23)

Model 3 is stratified by site and adjusted for age, sex, race, natural log transformed proteinuria, primary clinicopathologic diagnosis, and eGFR

HR per doubling of biomarker

*Kidney disease progression defined as ≥40% eGFR decline or ESKD

Abbreviations: IS, immunosuppression medications; CS, corticosteroids
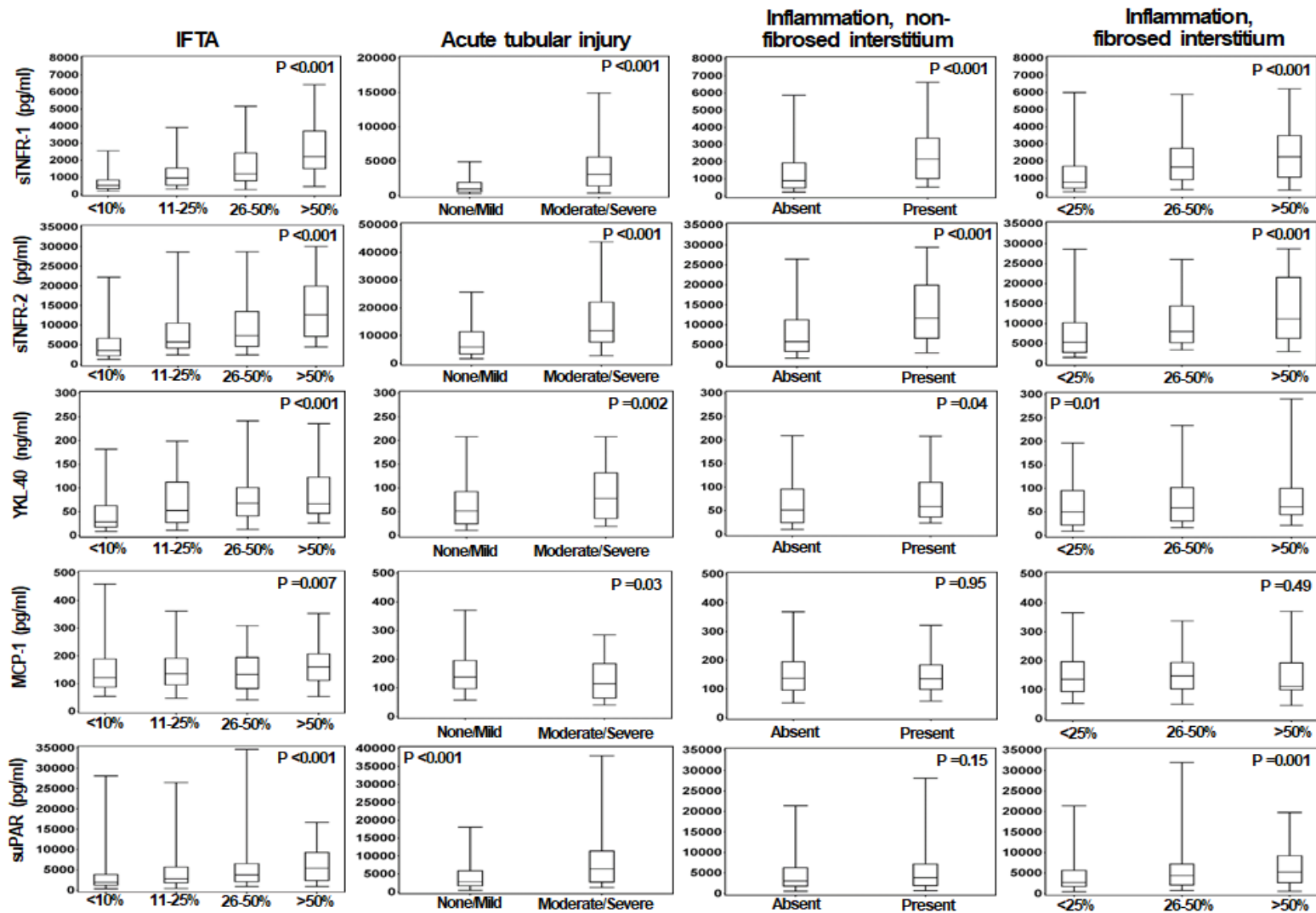
Supplemental Figure 1. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with tubulointerstitial lesions
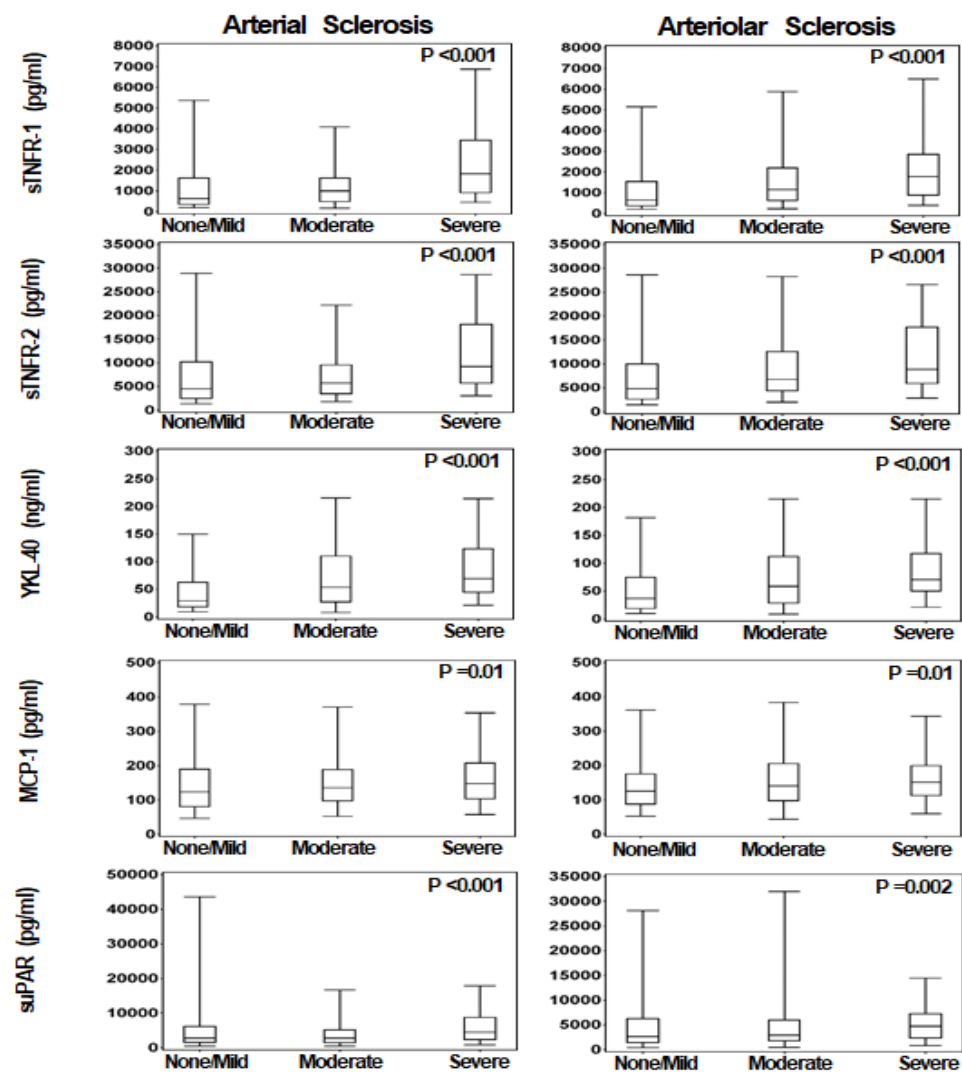Boxplots show differences between grades of adjudicated glomerular lesions and plasma inflammatory biomarkers. Boxes show median with interquartile range and whiskers represent 5% lower bound and 95% upper bound for each plasma inflammatory biomarker.
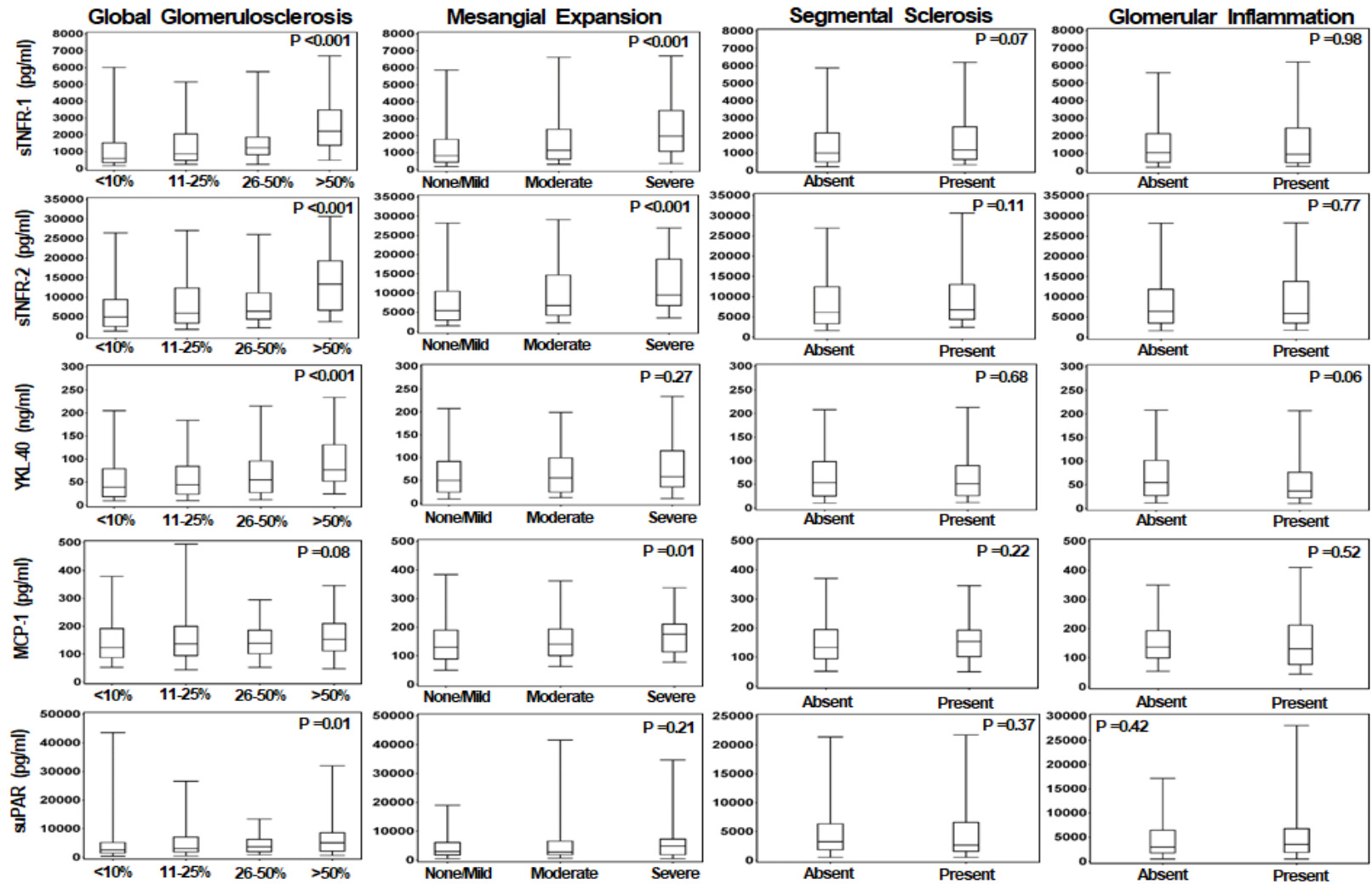
Supplemental Figure 2. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with glomerular lesions
Boxplots show differences between grades of adjudicated glomerular lesions and plasma inflammatory biomarkers. Boxes show median with interquartile range and whiskers represent 5% lower bound and 95% upper bound for each plasma inflammatory biomarker.

Supplemental Figure 3. sTNFR-1, sTNFR-2, YKL-40, MCP-1, and suPAR associate with microvascular lesions
Boxplots show differences between grades of adjudicated microvascular lesions and plasma inflammatory biomarkers. Boxes show median with interquartile range and whiskers represent 5% lower bound and 95% upper bound for each plasma inflammatory biomarker.