Clinical Characteristics and Histopathology in Adults With Focal Segmental Glomerulosclerosis

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Rationale & Objective: Few data are available regarding histological features at the time of focal segmental glomerulosclerosis (FSGS) diagnosis among diverse real-world populations. This study describes clinical and histological characteristics and correlates of histological disease severity in adults with FSGS who underwent a clinical kidney biopsy.

Study Design: Real-world cohort study with data derived from health records.

Setting & Participants: Adults with FSGS by kidney biopsies from Arkana Laboratories from January 1, 2016 to May 31, 2020.

Exposure: Race, chronic kidney disease stage, nephrotic proteinuria, age, sex, and hypertension.

Outcomes: Severe histological disease, defined as global glomerulosclerosis in >50% of glomeruli and >25% interstitial fibrosis and tubular atrophy (IFTA).

Analytical Approach: Demographic, clinical, and histological characteristics were compared between race groups. Correlates of severe disease were analyzed using multiple logistic regression.

Results: Among 2,011 patients with FSGS, 40.6% were White, and 23.6% Black. White patients were older (52.8 vs 45.5 years, $P < 0.001$) with a higher estimated glomerular filtration rate (eGFR) than Black patients (53.5 vs 43.1 mL/min/1.73 m^2, $P < 0.001$). A higher proportion of Black patients had global glomerulosclerosis ≥50% (32.1% vs 14.6%, $P < 0.001$) or IFTA >50% (34.6% vs 14.7%, $P < 0.001$). Severe histological disease was more likely in Black patients (OR, 2.46; 95% CI, 1.59-3.79; $P < 0.001$). A higher proportion of patients with nephrotic than non-nephrotic proteinuria exhibited diffuse foot process effacement.

Limitations: Unequal representation across United States regions, missing demographic and clinical data, and lack of data on primary versus secondary FSGS, treatments, or outcomes.

Conclusions: Black patients were more frequently diagnosed at younger age with lower eGFR and more severe histological disease compared with White patients. Timelier identification of FSGS could increase the opportunity for therapeutic intervention, especially for high-risk patients, to mitigate disease progression and complications.

Complete author and article information provided before references.

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Focal segmental glomerulosclerosis (FSGS) is a histologic lesion of glomerular scarring that causes proteinuria and may lead to kidney failure.[1] Studies in the United States demonstrate that FSGS accounts for 20%-25% of diagnoses derived from clinical kidney biopsies and up to 40% of patients with glomerular diseases that progress to kidney failure.[2-5] FSGS incidence has increased across all races, but it is found in up to 80% of Black patients with nephrotic syndrome, making FSGS the leading nephrotic syndrome diagnosis in this population.[6-8] The incidence of FSGS in the Black population is considerably higher than for other races. Notably, APOL1 gene variants in individuals of African ancestry substantially increase the risk of progression to kidney failure and are relatively common in Black patients diagnosed with FSGS.[9-11]

FSGS is heterogeneous with glomerular lesions categorized into 5 histological classes including collapsing, tip, cellular, perihilar, and not otherwise specified (NOS).[12-14] These classes are associated with different clinical characteristics and outcomes, indicating that they are prognostically important.[10] Kidney biopsy is required to diagnose and classify FSGS at a point when therapeutic interventions may be beneficial. A 24-hour urinary protein level of >3.5 g/d and serum albumin level of <3.0 g/dL suggest a primary form of FSGS, especially in the presence of diffuse foot process effacement.[15] Clinical practice guidelines recommend that treatment of primary FSGS includes an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker plus glucocorticoids as initial therapy.[15] Calcineurin inhibitors are recommended as an alternative for patients who are resistant or intolerant to glucocorticoid therapy.[15]

Limited data are available regarding the classes and distribution of histological features at the time of FSGS diagnosis among diverse real-world populations. The aim of this study was to describe clinical and histological characteristics as well as correlates of histological disease severity in adults with FSGS who underwent clinical kidney biopsy.

METHODS

Study Design and Data Source

This real-world data study comprises patients diagnosed with FSGS in the United States from January 1, 2016 to May 31, 2020, based on health records of those with clinical kidney biopsies analyzed by Arkana Laboratories (Little Rock, AR). Arkana Laboratories provides kidney pathology services to US health care institutions across 43 states. The deidentified dataset provided by Arkana

PLAIN-LANGUAGE SUMMARY

Focal segmental glomerulosclerosis (FSGS) accounts for around one-quarter of diagnoses derived from clinical kidney biopsies in the United States. Limited data are available regarding the classes and distribution of histological features at FSGS diagnosis among diverse real-world populations. Analyzing data from US patients who underwent kidney biopsy and were diagnosed with FSGS, we showed that up to half of patients had features of severe histological disease. Of this overall population, Black patients were more frequently diagnosed at a younger age but with more severe histological disease than White patients. The work highlights the need for timelier diagnosis of FSGS to enable intervention at an earlier disease stage.

Laboratories for these analyses included demographic and clinical information collected at the time of biopsy and histological information from adults with FSGS. To be included in this study, patients had to be ≥18 years old, have had at least 1 kidney biopsy with FSGS during the study period, and must not have received a kidney transplant. The biopsy must not have had any immunoglobulins, complement components, or light chains consistent with a primary glomerulopathy or paraprotein-mediated kidney disease. Only the first biopsy was used for analysis in this study. Solutions Institutional Review Board reviewed and approved the study with an exemption from the requirement for informed consent (protocol number 2022/08/26).

Study Measures

The baseline demographic characteristics included age, sex, and race and ethnicity. Baseline clinical characteristics included hypertension status, serum creatinine level, and proteinuria as either urinary protein-to-creatinine ratio (UPCR; g/g) or 24-hour urinary protein excretion (g/d). Estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine level based Chronic Kidney Disease-Epidemiological (CKD-EPI) 2021 Calculation.[16] Patients were categorized into CKD stage at time of biopsy using the calculated eGFR values as follows: stage 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2), stage 3A (eGFR = 45-59 mL/min/1.73 m^2), stage 3B (eGFR = 30-44 mL/min/1.73 m^2), stage 4 (eGFR = 15-29 mL/min/1.73 m^2), and stage 5 (eGFR < 15 mL/min/1.73 m^2). Nephrotic range proteinuria was defined as UPCR ≥3.0 g/g or 3.5 g/d.[15] Demographic and clinical characteristics were assessed in the overall cohort and stratified by race and ethnicity as White, Black, or Other. Sex was defined as a biological variable, although birth assignment was not verified.

Histological characteristics were assessed as glomerulosclerosis (GS), interstitial fibrosis and tubular atrophy (IFTA), and foot process effacement, which were assigned grading scores, and FSGS lesion type (tip, perihilar, cellular, collapsing, or NOS). Grading scores were assigned based on the proportion of biopsy tissue displaying each histological characteristic, and lesion type was determined using the Columbia classification.[17] Severe histological disease was defined by a composite measure combining global GS in >50% of kidney tissue and >25% IFTA.[10,18,19] Non-severe disease was defined as lower levels of global GS and/or IFTA.

Histology

All kidney biopsy samples were processed by Arkana Laboratories using standard techniques.[20] Light microscopy samples were fixed in formalin, embedded in paraffin, and serially sectioned at 3 μm before being stained with hematoxylin and eosin, Jones methenamine silver, Masson trichrome, or periodic acid–Schiff reagent. For electron microscopy, 1-mm cubes were removed from the ends of the biopsy sample, dehydrated with graded alcohols, and embedded in Epon-Araldite resin. Sections of 1 μm were cut with an ultramicrotome, stained with toluidine blue, and examined with a light microscope for glomerular evaluation. Thin sections were cut at 60 nm and examined in a Jeol JEM 1011 electron microscope (Jeol, Tokyo, Japan), and photomicrographs were taken at 4,000, 12,000 and 20,000× magnification.

Statistical Analyses

Descriptive analyses were performed, with categorical variables summarized using frequencies and percentages, and continuous variables summarized using means, standard deviations (SDs), medians, and interquartile ranges (IQRs). Here, χ^2 tests were used to compare categorical variable outcomes between racial and ethnic groups. In the event of frequencies less than 5 participants or 0 cells, Fisher exact test was used to assess significance. For comparison of a continuous variable outcome between 2 groups, a normality assumption was assessed using Shapiro-Wilk test. If the normality assumption held, Welch t-test was used to estimate association between the continuous variable and groups. If the normality assumption was violated, a Kruskal-Wallis test was conducted.

CKD stage, proteinuria, age, sex, race and ethnicity, and hypertension status at the time of biopsy were assessed as correlates of histological disease severity. Multivariable logistic regression analyses were used to assess the associations of these covariates with histological disease severity. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Sensitivity analyses were conducted using a different race and ethnicity variable in which patients of an unknown racial group were included in the Other category. All statistical tests were 2 sided with a significance level of $P < 0.05$. Analyses were performed using SAS Studio 3.81 (SAS Institute, Cary, NC).

RESULTS

Baseline Demographics and Clinical Characteristics

A total of 2,011 patients were included in this study (Table 1). The majority of patients were male (56.4%),

Table 1. Demographics and Clinical Characteristics at Time of Kidney Biopsy Overall and by Race

		Race				
	Overall	White	Black	Other[a]	Unknown[b]	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Category	**2,011 (100.0)**	**817 (40.6)**	**474 (23.6)**	**191 (9.5)**	**529 (26.3)**	***P* Value[c]**
Age (y)						
Mean (SD)	49.1 (17.2)	52.8 (17.3)	45.5 (15.5)	41.6 (16.6)	49.4 (17.2)	<0.001
Median (Q1, Q3)	49 (35, 63)	56 (38, 66)	46 (33, 57)	38 (29, 52)	50 (35, 63)	
Sex						
Female	877 (43.6)	355 (43.5)	214 (45.2)	80 (41.9)	228 (43.1)	0.86
Male	1,134 (56.4)	462 (56.6)	260 (54.9)	111 (58.1)	301 (56.9)	
Race and/or Ethnicity						
White	817 (40.6)	817 (100.0)				
Black	474 (23.6)		474 (100.0)			
Hispanic	114 (5.7)			114 (59.7)		
Asian	51 (2.5)			51 (26.7)		
Other	26 (1.3)			26 (13.6)		
Unknown	529 (26.3)				529 (100.0)	
Hypertension						
Patients with available hypertension data (N, %)	1,487 (73.9)	633 (77.5)	354 (74.7)	135 (70.7)	365 (69.0)	0.35
Yes	1,407 (94.6)	593 (93.7)	340 (96.0)	126 (93.3)	348 (95.3)	
No	80 (5.4)	40 (6.3)	14 (4.0)	9 (6.7)	17 (4.7)	
Unknown	524 (26.1)	184 (22.5)	120 (25.3)	56 (29.3)	164 (31.0)	
Creatinine (mg/dL)						
Patients with available creatinine measurements (N, %)	1,684 (83.7)	710 (86.9)	403 (85.0)	164 (85.9)	407 (76.9)	<0.001
Mean (SD)	2.2 (2.5)	2.0 (1.5)	2.7 (2.2)	2.8 (5.8)	2.0 (1.7)	
Median (Q1, Q3)	1.7 (1.1, 2.6)	1.6 (1.1, 2.3)	2.1 (1.4, 3.3)	1.8 (1.2, 2.6)	1.6 (1.1, 2.4)	
Unknown	327 (16.3)	107 (13.1)	71 (15.0)	27 (14.1)	122 (24.1)	
eGFR (mL/min/1.73m^2) [d]						
Patients with available creatinine measurements (N, %)	1,684 (83.7)	710 (86.9)	403 (85.0)	164 (85.9)	407 (76.9)	
Mean (SD)	50.9 (32.7)	53.5 (31.9)	43.1 (32.0)	51.7 (32.8)	53.7 (33.6)	<0.001
Median (Q1, Q3)	42.2 (25.3, 72.0)	45.9 (28.7, 74.9)	32.3 (19.8, 57.7)	44.2 (28.0, 72.0)	43.6 (27.7, 76.0)	
CKD stage 1 or 2	539 (32.0)	251 (35.4)	96 (23.8)	53 (32.3)	139 (34.2)	<0.001
CKD stage 3	599 (35.6)	261 (36.8)	126 (31.3)	58 (35.4)	154 (37.8)	
CKD stage 3A	247 (14.7)	115 (16.2)	47 (11.7)	27 (16.5)	58 (14.3)	
CKD stage 3B	352 (20.9)	146 (20.6)	79 (19.6)	31 (18.9)	96 (23.6)	
CKD stage 4	383 (22.7)	146 (20.6)	111 (27.5)	36 (22.0)	90 (22.1)	
CKD stage 5	163 (9.7)	52 (7.3)	70 (17.4)	17 (10.4)	24 (5.9)	
Unknown	327 (16.3)	107 (13.1)	71 (15.0)	27 (14.1)	122 (24.1)	

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Table 1 (Cont'd). Demographics and Clinical Characteristics at Time of Kidney Biopsy Overall and by Race

		Race				
	Overall	White	Black	Other[a]	Unknown[b]	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Category	**2,011 (100.0)**	**817 (40.6)**	**474 (23.6)**	**191 (9.5)**	**529 (26.3)**	***P* Value[c]**
Proteinuria						
Patients with available proteinuria measurements (N, %)	1,326 (65.9)	592 (72.5)	299 (63.1)	127 (66.5)	308 (58.2)	
Urinary protein-to-creatinine ratio	557 (42.0)	234 (39.5)	126 (42.1)	59 (46.5)	138 (44.8)	
Mean (SD) (g/g)	5.1 (4.4)	5.2 (4.6)	5.1 (4.2)	5.0 (4.2)	5.1 (4.2)	0.95
Median (Q1, Q3)	3.8 (2, 7)	4 (2, 7)	4 (2, 7)	4 (2, 6)	4 (2, 7)	
24-hour urine protein output	769 (58.0)	358 (60.5)	173 (57.9)	68 (53.5)	170 (55.2)	
Mean (SD) (g/d)	6.3 (5.6)	6.6 (5.0)	5.9 (5.8)	5.2 (3.9)	6.8 (7.0)	0.01
Median (Q1, Q3)	4.7 (3, 9)	5 (3, 10)	4 (2, 7)	4 (2, 7)	5 (3, 10)	
Nephrotic (≥3.0 g/g or ≥3.5 g/d)	824 (62.1)	376 (63.5)	176 (58.9)	78 (61.4)	194 (63.0)	0.58
Nonnephrotic	502 (37.9)	216 (36.5)	123 (41.1)	49 (38.6)	114 (37.0)	
Unknown	685 (34.1)	225 (27.5)	175 (36.9)	64 (33.5)	221 (41.8)	

Abbreviations: ANOVA, analysis of variance; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.
[a]Inclusive of patients from Hispanic and Asian racial groups.
[b]Patients of Unknown race were not included in the statistical analysis.
[c]ANOVA and/or Kruskal-Wallis test and χ^2 test were used for continuous and categorical variables, respectively.
[d]Without race and/or ethnicity modifier. Calculated for patients with available creatinine data using CKD-EPI 2021 creatinine calculation.

Table 2. Demographics and Clinical Characteristics at Time of Kidney Biopsy Overall and by Nephrotic versus Nonnephrotic Range Proteinuria[a]

		Proteinuria			
	Overall	Nephrotic	Nonnephrotic	Unknown[b]	
	N (%)	N (%)	N (%)	N (%)	
Category	**2,011 (100.0)**	**824 (41.0)**	**502 (25.0)**	**685 (34.0)**	***P* Value[c]**
Age (y)					
Mean (SD)	49.1 (17.2)	51.9 (17.5)	45.5 (16.0)	48.3 (17.2)	<0.001
Median (Q1, Q3)	49 (35, 63)	54 (37, 66)	45 (33, 58)	48 (34, 62)	
Sex					
Female	877 (43.6)	348 (42.2)	242 (48.2)	287 (41.9)	0.03
Male	1,134 (56.4)	476 (57.8)	260 (51.8)	398 (58.1)	
Race and/or ethnicity					
White	817 (40.6)	376 (45.6)	216 (43.0)	225 (32.9)	0.69
Black	474 (23.6)	176 (21.4)	123 (24.5)	175 (25.6)	
Hispanic	114 (5.7)	41 (5.0)	26 (5.2)	47 (6.9)	
Asian	51 (2.5)	27 (3.3)	15 (3.0)	9 (1.3)	
Other	26 (1.3)	10 (1.2)	8 (1.6)	8 (1.2)	
Unknown	529 (26.3)	194 (23.5)	114 (22.7)	221 (32.3)	
Hypertension					
Patients with available hypertension data (N, %)	1,487 (73.9)	651 (79.0)	404 (80.5)	432 (63.1)	0.001
Yes	1,407 (94.6)	623 (95.7)	365 (90.3)	419 (97.0)	
No	80 (5.4)	28 (4.3)	39 (9.7)	13 (3.0)	
Unknown	524 (26.1)	173 (21.0)	98 (19.5)	253 (36.9)	
Creatinine (mg/dL)					
Patients with available creatinine measurements (N, %)	1,684 (83.7)	770 (93.5)	457 (91.0)	457 (66.7)	0.03
Mean (SD)	2.2 (2.5)	2.1 (1.4)	1.8 (1.1)	2.8 (4.1)	
Median (Q1, Q3)	1.7 (1.1, 2.6)	1.7 (1.1, 2.6)	1.6 (1.1, 2.3)	2.0 (1.3, 2.9)	
Unknown	327 (16.3)	54 (6.5)	45 (9.0)	228 (33.3)	
eGFR (mL/min/1.73m²)[d]					
Patients with available creatinine measurements (N, %)	1,684 (83.7)	770 (93.5)	457 (91.0)	457 (66.7)	
Mean (SD)	50.9 (32.7)	51.3 (32.6)	56.5 (33.1)	44.7 (31.6)	0.003
Median (Q1, Q3)	42.2 (25.3, 72.0)	42.8 (25.2, 74.9)	48.0 (29.6, 78.7)	36.3 (22.0, 58.3)	
CKD stage 1 or 2	539 (32.0)	253 (32.9)	178 (38.9)	108 (23.6)	0.02
CKD stage 3	599 (35.6)	267 (34.7)	160 (35.0)	172 (37.6)	
CKD stage 3A	247 (14.7)	110 (14.3)	72 (15.8)	65 (14.2)	
CKD stage 3B	352 (20.9)	157 (20.4)	88 (19.3)	107 (23.4)	
CKD stage 4	383 (22.7)	178 (23.1)	98 (21.4)	107 (23.4)	
CKD stage 5	163 (9.7)	72 (9.4)	21 (4.6)	70 (15.3)	
Unknown	327 (16.3)	54 (6.5)	45 (9.0)	228 (33.3)	

(Continued)

Table 2 (Cont'd). Demographics and Clinical Characteristics at Time of Kidney Biopsy Overall and by Nephrotic versus Nonnephrotic Range Proteinuria[a]

		Proteinuria			
	Overall	Nephrotic	Nonnephrotic	Unknown[b]	
	N (%)	N (%)	N (%)	N (%)	
Category	**2,011 (100.0)**	**824 (41.0)**	**502 (25.0)**	**685 (34.0)**	***P* Value[c]**
Proteinuria					
Patients with available proteinuria measurements (N, %)	1,326 (65.9)	824 (100.0)	502 (100.0)		
Urinary protein-to-creatinine ratio	557 (42.0)	334 (40.5)	223 (44.4)		
Mean (SD) (g/g)	5.1 (4.4)	7.4 (4.2)	1.7 (0.8)		<0.001
Median (Q1, Q3)	3.8 (2, 7)	6 (4,9)	2 (1, 2)		
24-hour urine protein output	769 (58.0)	490 (59.5)	279 (55.6)		
Mean (SD) (g/d)	6.3 (5.6)	8.8 (5.7)	2.0 (0.9)		<0.001
Median (Q1, Q3)	4.7 (3, 9)	7 (5, 11)	2 (1, 3)		
Nephrotic (≥3.0 g/g or ≥3.5 g/d)	824 (62.1)	824 (100.0)			
Nonnephrotic	502 (37.9)		502 (100.0)		
Unknown	685 (34.1)				

Abbreviations: ANOVA, analysis of variance; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.
[a]Nephrotic range proteinuria was defined as urinary protein-to-creatinine ratio ≥3.0 g/g or 3.5 g/d.
[b]Patients of Unknown proteinuria were not included in the statistical analysis.
[c]ANOVA and/or Kruskal-Wallis test and χ^2 test were used for continuous and categorical variables, respectively.
[d]Without race and/or ethnicity modifier. Calculated for patients with available creatinine data using CKD-EPI 2021 creatinine calculation.

and the overall mean age at biopsy was 49.1 ± 17.2 years. Most patients were White (40.6%) or Black (23.6%). The proportions of patients reporting Hispanic ethnicity and Asian race were small (5.7% and 2.5%, respectively), so these were grouped with the Other group of patients who comprised 1.3% of the study population. Information on race was not available for 26.3% of patients (termed "Unknown" race). Mean (SD) eGFR in the overall cohort was 50.9 ml/min/1.73 m^2 (32.7) and 68.0% had CKD stage 3 or higher at time of biopsy (Table 1). Proteinuria data were available for 1,326 of 2,011 patients (65.9%) in the overall cohort with a UPCR available for 42.0% (mean [SD], 5.1 [4.4] g/g) and 24-hour measurements available for 58.0% (mean [SD], 6.3 [5.6] g/d). Nephrotic range proteinuria was observed in 62.1% of patients with proteinuria data in the overall cohort (Table 1).

The White group was directly compared with the Black and Other groups (Table 1). The mean (SD) age of the White group was higher than that of the Black or Other groups (52.8 [17.3] vs 45.5 [15.5] and 41.6 [16.6], respectively; $P < 0.001$) (Table 1). The mean eGFR was significantly higher (53.5 mL/min/1.73 m^2 vs 43.1 mL/min/1.73 m^2, $P < 0.001$) and a lower proportion of patients were diagnosed with CKD stage ≥4 at biopsy (27.9% vs 44.9%; $P < 0.001$) in the White group compared with the Black group (Table 1). Nephrotic range proteinuria was observed in 63.5% of the White group, 58.9% of the Black group, and 61.4% of Other group ($P = 0.58$) (Table 1).

Demographics and clinical characteristics by nephrotic and nonnephrotic range proteinuria are presented in Table 2 and by age group in Table S1.

Features and Correlates of Histological Disease Severity in FSGS

In the overall population, global GS ≥ 50% and IFTA ≥ 50% were each observed in the biopsies of 1 in 5 patients, while diffuse foot process effacement (≥80%) was seen in almost half of patient biopsies (47.3%) (Fig S1). The odds of severe histological disease were progressively greater for CKD stages 3-5 relative to CKD stages 1 or 2, and the OR (95% CI) was highest for CKD stage 5 (OR, 22.59; 95% CI, 9.36-54.49; $P < 0.001$) ($n = 774$; Fig 1). The odds of severe histological disease were significantly lower in patients aged 65+ years (OR, 0.51; 95% CI, 0.29-0.89; $P = 0.02$) compared with age 18-44 years ($n = 774$; Fig 1).

Histopathological Features of FSGS at Diagnosis and Clinical Correlates of Histological Disease Severity in Different Racial Groups

GS ≥ 50% and IFTA > 50% were observed in a significantly higher proportion of biopsies in the Black and Other groups compared with the White group (32.1% and 28.3% vs 14.6%; 34.6% and 24.6% vs 14.7%, respectively; $P < 0.001$) (Fig 2). Diffuse foot process effacement (≥80%) was observed in a significantly higher proportion of participants in the White group compared with the Black and Other groups (51.9% vs 39.7% and 36.1%, $P = 0.03$) (Fig 2). NOS and collapsing lesions were observed more frequently in the Black and Other groups compared with the White group (74.9% and 70.2% vs 63.9%; 12.2% and 6.8% vs 2.8%, respectively; $P < 0.001$), while tip lesions were observed more frequently in the White group than the Black and Other groups (22.2% vs 7.8% and 12.0%; $P < 0.001$) (Fig 2). Black patients were more likely to have severe histological disease at biopsy compared with White patients (OR, 2.46; 95% CI, 1.59-3.79; $P < 0.001$), as were those patients in the Other group (OR, 3.99; 95% CI, 2.19-7.27; $P < 0.001$) ($n = 774$; Fig 1). A sensitivity analysis was conducted in which patients with unknown race were included in the Other group. Patients in the Other/Unknown group still had higher odds of severe histological disease relative to the patients in the White group with overall model stability ($P < 0.001$) ($n = 982$; Fig S2).

Overall, a greater proportion of patients with nephrotic range proteinuria had diffuse foot process effacement compared with those with nonnephrotic proteinuria (60.1% vs 23.7%; $P < 0.001$) (Table 3). Other histological characteristics were similar between proteinuria groups. There was a significant difference in the overall distribution of lesion types between the 2 groups. NOS lesions were predominant in both groups but occurred in a significantly higher proportion of patients in the nephrotic group compared with the nonnephrotic group (80.3% vs 64.0%, $P < 0.001$). A significantly greater proportion of patients in the nephrotic range proteinuria group had tip lesions (22.1% vs 3.4%, $P < 0.001$) and collapsing lesions (7.0% vs 3.6%, $P = 0.01$) compared with the nonnephrotic group, while a greater proportion of patients in the nonnephrotic group than nephrotic group had perihilar lesions (12.6% vs 6.6%, $P < 0.001$). Nephrotic range proteinuria was not significantly associated with higher odds of severe histological disease compared with proteinuria below the nephrotic range (OR, 0.99 [0.66-1.50]; $P = 0.98$) ($n = 774$; Fig 1).

DISCUSSION

This large real-world data study from the United States found that two-thirds of patients with FSGS had CKD stage ≥3 and nearly one-third of them had CKD stages 4-5 at kidney biopsy. The proportion of patients with advanced CKD (stages 4-5) at biopsy was significantly higher in Black patients compared with White patients and in the nephrotic range proteinuria group compared with the nonnephrotic range group. Compared with those with nonnephrotic proteinuria, more than twice as many patients with nephrotic range proteinuria also had diffuse foot process effacement.

The risk of severe histological disease in FSGS increased progressively as CKD stage increased, with a nearly 5-fold

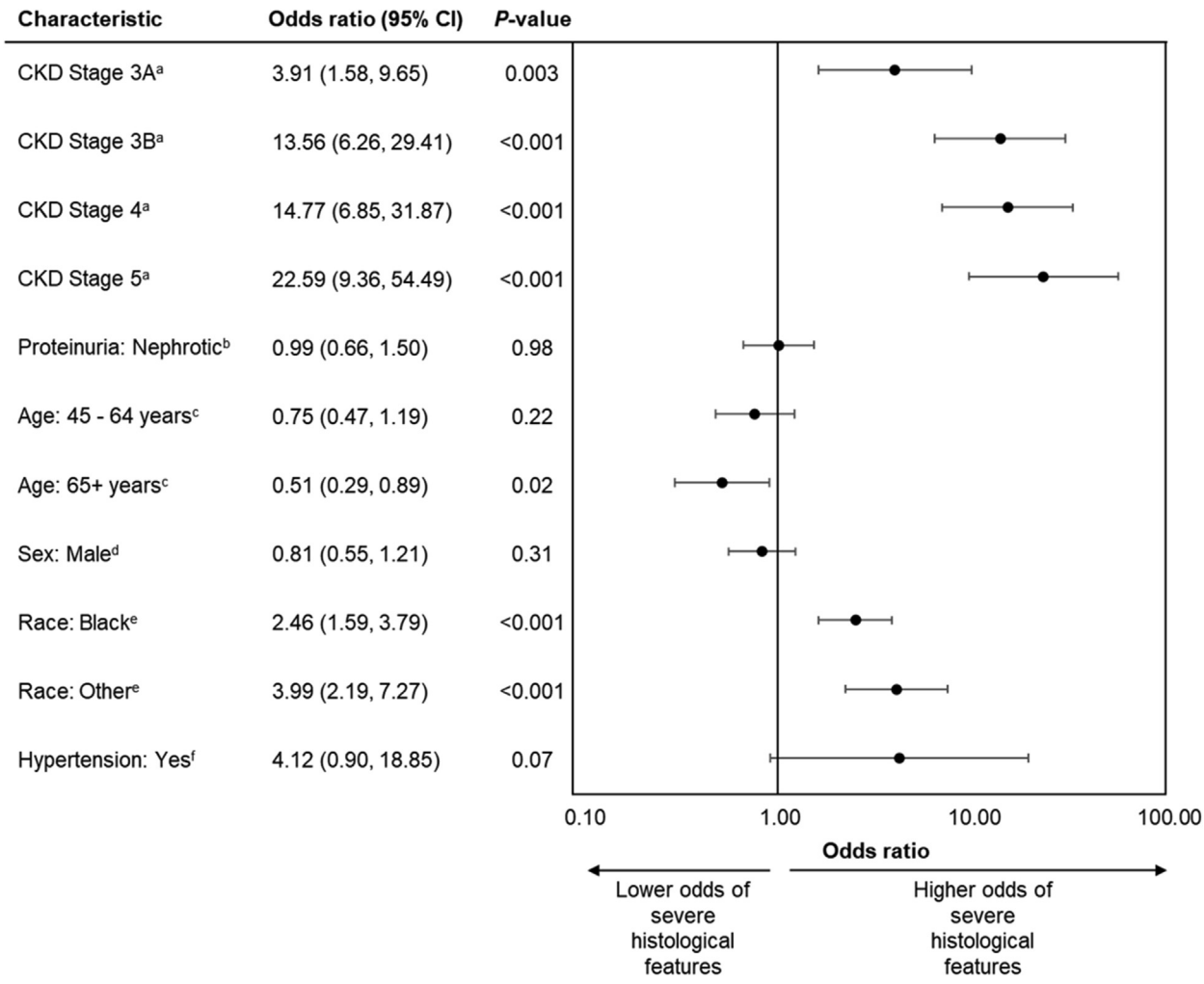

Figure 1. Clinical correlates of severe histological features of FSGS (N = 774). Abbreviations: CI, confidence interval; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis. [a]Reference group: CKD stages 1 and 2. [b]Reference group: Nonnephrotic proteinuria. [c]Reference group: 18-44 years. [d]Reference group: Female. [e]Reference group: White. [f]Unknown racial group was excluded from this analysis. [g]Reference group: No.

higher OR at stage 5 than stage 3a. Younger age (<45 years) and Black race also increased risk of severe histological disease. Although nephrotic range proteinuria did not predict risk of severe histological disease by the study definition, diffuse foot process effacement suggestive of primary FSGS was observed in a much larger proportion of patients with nephrotic range proteinuria compared with those with lesser degrees of proteinuria.

Given the clear associations between late CKD stage and severe histological disease, and the observation that Black patients, although biopsied at a younger age, still had higher odds of having severe histological disease than White patients, our data suggest that FSGS is being diagnosed late. Earlier diagnosis could enable therapeutic intervention when there is greater likelihood of reducing histological disease severity and progression. In our current real-world cohort, almost 70% of patients had NOS lesions, making this the predominant type of FSGS lesion. Together with prior reports, the present data support the observation that NOS is the predominant FSGS type in the United States and elsewhere.[21-24] NOS lesions were predominant across race and proteinuria subgroups in this cohort. However, there were significant differences in the distribution of other lesion types. Tip and collapsing lesions were observed in a higher proportion of patients with nephrotic range proteinuria while perihilar lesions were observed in a higher proportion of patients with proteinuria below the nephrotic range. Tip and perihilar lesions were observed in a greater proportion of White patients, while collapsing lesions were observed in a greater proportion of Black patients.

More than a fifth of patients exhibited global GS and/or IFTA in ≥50% of their kidney biopsy. In the overall patient population, almost half had diffuse foot process effacement. These strikingly high proportions of patients with advanced FSGS lesions show that high-risk patients are being diagnosed late in the course of their disease. When stratified by race, Black patients exhibited more severe

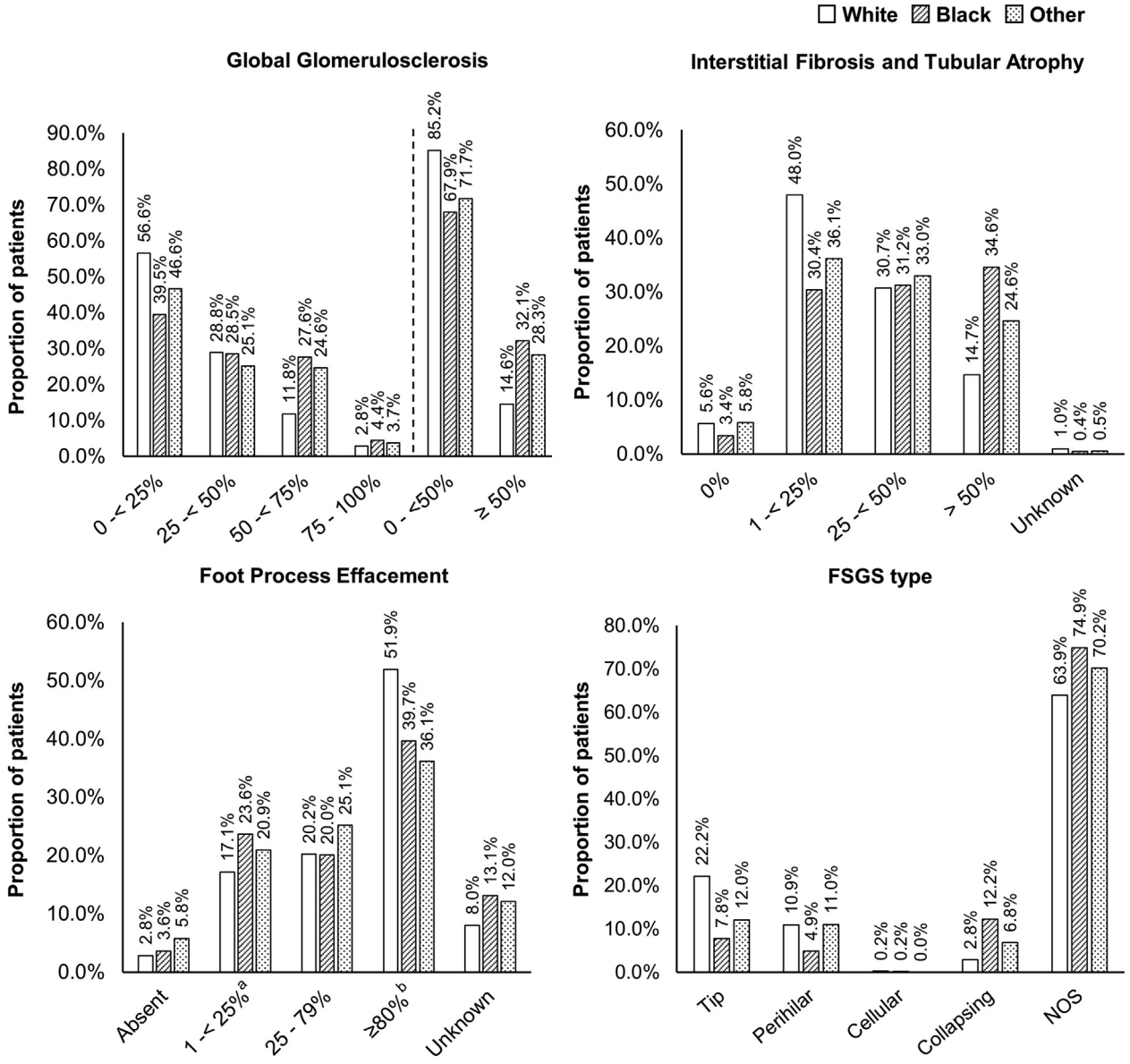

Figure 2. Distribution of histological characteristics in patients with FSGS at time of kidney biopsy and stratified by race. Note: All *P* values were <0.001. Other racial group is inclusive of Hispanic and Asian patients. Unknown groups were not included in χ^2 tests. Abbreviations: FSGS, focal segmental glomerulosclerosis; NOS, not otherwise specified. [a]Focal. [b]Diffuse.

global GS and IFTA compared with the White group. Over double the proportion of Black patients had >50% global GS or >50% IFTA compared with the White group. A possible explanation for these findings may be the presence of APOL1 gene variants, which increases the risk of progression to kidney failure in people with African ancestry.[11,25-27] However, it should be noted that APOL1 genotyping data were not available for this study. Nonetheless, more severe histological disease in Black patients at the time of FSGS diagnosis likely contributes to higher rates of progression to kidney failure.

When using real-world data sources for comparative analyses a number of limitations exist. Although this study represents a large sample of US adult patients with FSGS, Arkana Laboratories only provides services to institutions in 43 US states, and even these regions may not be equally represented. Thus, the ability to generalize the findings to the broader US or non-US populations may be limited. The analysis also used a race-free equation to estimate eGFR. Results could differ if calculated using equations that include race. These analyses were also somewhat hindered by limited availability of demographic and clinical data in the Arkana database. For example, the sample size was not sufficient to compare risks of histologically severe FSGS by specific racial or ethnic groups or geographic location. In some cases, information such as serum creatinine level or proteinuria were not provided (missing for 16.3% and 34.1% of patients, respectively). Additionally, data were

Table 3. Histological Characteristics by Proteinuria Status at Time of Kidney Biopsy Stratified by Nephrotic and Nonnephrotic Proteinuria Levels[a]

	Nephrotic	Nonnephrotic	
	N (%)	N (%)	
Category	**824 (100.0)**	**502 (100.0)**	***P* Value[b]**
% **Global GS**			
N (%)	823 (99.9)	502 (100.0)	
Mean (SD)	27.1 (23.5)	28.3 (21.1)	0.07
Median (Q1, Q3)	22 (7, 44)	25 (11, 43)	
0 to <25%	438 (53.2)	246 (49.0)	0.01
25 to <50%	209 (25.4)	153 (30.5)	
50 to <75%	140 (17.0)	95 1(8.9)	
75 to 100%	36 (4.4)	8 (1.6)	
0 to <50%	647 (78.6)	399 (79.5)	0.83
≥50%	176 (21.4)	103 (20.5)	
IFTA			
N (%)	824 (100.0)	502 (100.0)	
0%	49 (6.0)	24 (4.8)	0.06
1 to <25%	314 (38.1)	224 (44.6)	
25 to <50%	262 (31.8)	161 (32.1)	
>50%	190 (23.1)	91 1(8.1)	
Unknown	9 (1.1)	2 (0.4)	
Foot process effacement			
N (%)	824 (100.0)	502 (100.0)	
Absent	14 (1.7)	33 (6.6)	<0.001
1 to <25% (focal)	86 (10.4)	168 (33.5)	<0.001
25 to 79%	146 (17.7)	133 (26.5)	<0.001
≥80% (diffuse)	495 (60.1)	119 (23.7)	<0.001
Unknown	83 (10.1)	49 (9.8)	0.85
FSGS type			
N (%)	824 (100.0)	502 (100.0)	
Tip	182 (22.1)	17 (3.4)	<0.001
Perihilar	54 (6.6)	63 (12.6)	<0.001
Cellular	3 (0.4)	1 (0.2)	0.60
Collapsing	58 (7.0)	18 (3.6)	0.01
NOS	527 (64.0)	403 (80.3)	<0.001

Abbreviations: FSGS, focal segmental glomerulosclerosis; IFTA, interstitial fibrosis and tubular atrophy; NOS, not otherwise specified; SD, standard deviation.
[a]Nephrotic range proteinuria was defined as urinary protein-to-creatinine ratio of ≥3.0 g/g or 3.5 g/d.
[b]χ^2 test and Fisher exact test were conducted for categorical variables.

not available for medication use, blood pressure, body weight, APOL1 genotype, or social determinants of health and comorbid conditions, which could influence FSGS type. Therefore, this cohort likely represents a mix of different forms of FSGS. In addition, the proportion with primary FSGS is unclear, although diffuse foot process effacement is consistent with this type.[15] Moreover, the data in this study represent a snapshot in each patient's disease journey, with only the information at time of biopsy available. As such, it was not possible to assess patient characteristics in the months preceding or following biopsy.

In conclusion, we found that at time of biopsy, advanced CKD (stages 4-5) is common in patients with FSGS. Patients of Black race were more frequently diagnosed with FSGS at younger ages, lower eGFR, and more severe histological disease compared with White patients. Diffuse foot process effacement was much more common in those with nephrotic range proteinuria, suggestive of a primary form of FSGS, compared with those with lesser proteinuria. Timelier identification of FSGS could increase the opportunity for therapeutic intervention, especially for high-risk patients, to mitigate disease progression and complications.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Distribution of Histological Characteristics in Patients With FSGS at Time of Kidney Biopsy.

Figure S2: Clinical Correlates of Severe Histological Features of FSGS Following Sensitivity Analysis to Include Patients With Unknown Race (N = 982).

Item S1: Renal Biopsy Requisition Form.

Table S1: Demographics and Clinical Characteristics at Time of Kidney Biopsy Overall and By Age.

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