PO1531

Clinicopathological Characteristics of Adult Patients in the United States with Focal Segmental Glomerulosclerosis (FSGS)

Katherine R. Tuttle[1], Clint W. Abner[2], Kerime Ararat[2], Patrick D. Walker[2], Amin Yakubu[3], Martin Bunke[4]

[1]University of Washington, Spokane, WA, USA; [2]Arkana Laboratories, Little Rock, AR, USA; [3]Genesis Research, Hoboken, NJ, USA; [4]Travere Therapeutics, Inc., San Diego, CA, USA

Background

- Focal segmental glomerulosclerosis (FSGS) often follows a progressive course to end-stage kidney disease (ESKD)[1] making FSGS a significant glomerular cause of kidney failure in the United States (US)[2]
- It has been hypothesized that FSGS in black patients is different than in other racial/ethnic groups due to higher rates of kidney failure[3-6]
- Limited information is available to describe the histological differences among adult patients with FSGS across various racial/ethnic groups at time of kidney biopsy

Objective

- To examine differences in demographic, clinical, and kidney biopsy histological characteristics among adult patients with FSGS across race/ethnicity groups at time of kidney biopsy

Methods

Study design and data source

- This is a retrospective cohort study of data collected from patients with biopsy-confirmed FSGS in the US from the Arkana Biopsy database from January 1, 2016 to May 31, 2020

Inclusion criteria, exclusion criteria, index dates

- Patients who: (1) were ≥18 years of age, (2) had at least 1 FSGS-positive kidney biopsy during study period (January 1, 2016 – May 31, 2020), (3) had available data on race/ethnicity, and (4) had no prior kidney transplant

Arkana Laboratories

- Arkana Laboratories provides renal pathology, serology, molecular pathology, and neuropathology services from healthcare institutions across 40 states in the US. Patient clinical characteristics are retrospectively collected at time of biopsy.

Histology

- Kidney biopsy examination techniques were used, including light, immunofluorescence, and electron microscopy[7]
- Light microscopy samples were fixed in formalin, embedded in paraffin and serially cut at 3 microns and stained with hematoxylin and eosin, Jones methenamine silver, Masson trichrome, and periodic acid–Schiff reagent
- Tissue for immunofluorescence was snap frozen, embedded in OCT and sections were cut at 4 mm and stained with fluorescein-tagged polyclonal rabbit anti-human antibodies to IgG, IgA, IgM, C3, C1q, fibrinogen, and k- and l-light chains (Dako, Carpenteria, CA) for 1 hour, and rinsed; a coverslip was applied using aqueous mounting media
- 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. 1-micron sections were cut with an ultramicrotome and 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 taken at 4 000, 12 000 and 20 000 x magnification.

Measures and statistical analyses

- Categorical variables were summarized using frequencies and percentages and continuous variables were summarized using means, standard deviations, medians, and interquartile ranges
- Analysis of variance (ANOVA), Kruskal-Wallis, Chi-square, and Fisher's exact tests, were conducted to determine pairwise differences between race/ethnicity groups on continuous and categorical variables as appropriate

Results

Table 1. Demographics and Patient Characteristics of Adult Patients with FSGS at Time of Kidney Biopsy

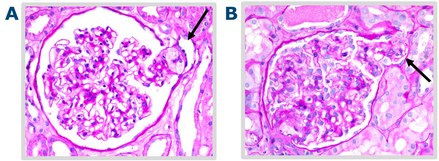
	Overall (n=1,482)	White (n=817)	Black (n=474)	LatinX (n=114)	Asian (n=51)	Other** (n=26)	p-value
Age (yrs.), mean ± SD	49.0±17.2	52.8±17.3	45.5±15.5*	39.4±15.8*	47.8±18.2	39.2±13.5	<0.001
Male, n (%)	833 (56.2)	462 (56.6)	260 (54.9)	69 (60.5)	30 (58.8)	12 (46.2)	0.651
Year of biopsy							
2016	276 (18.6)	138 (16.9)	98 (20.7)	26 (22.8)	6 (11.8)	8 (30.8)	0.260
2017	334 (22.5)	192 (23.5)	100 (21.1)	22 (19.3)	13 (25.5)	7 (26.9)	
2018	356 (24.0)	210 (25.7)	106 (22.4)	30 (26.3)	8 (15.7)	2 (7.7)	
2019	392 (26.4)	210 (25.7)	132 (27.9)	25 (21.9)	19 (37.3)	6 (23.1)	
2020 (up to May 31)	124 (8.4)	67 (8.2)	38 (8.0)	11 (9.7)	5 (9.8)	3 (11.5)	
Hypertension, n (%)	1059 (71.5)	593 (72.6)	340 (71.7)	67 (58.8)	40 (78.4)	19 (73.1)	0.241
Serum Creatinine (mg/dL) (n=1,277), median (IQR)	1.8 (1.1-2.6)	1.6 (1.1-2.3)	2.1 (1.4-3.3)*	1.8 (1.2-2.8)*	1.8 (1.2-2.5)	1.4 (1.0-2.2)	<0.001
eGFR with race modifier (n=1,277), median (IQR)	41.1 (24.6-69.2)	43.3 (26.8-71.1)	35.8 (21.6-64.7)*	40.9 (23.8-69.2)	42.3 (26.2-67.6)	49.7 (34.2-81.3)	0.011
CKD stage with race modifier (n, %)							
Stage 1 or Stage 2	391 (30.6)	235 (33.1)	107 (26.5)	27 (29.7)	13 (16.5)	9 (37.5)	0.001
Stage 3	440 (34.5)	254 (35.8)	124 (30.8)	33 (36.3)	18 (36.7)	11 (45.8)	
Stage 3A	182 (14.3)	107 (15.1)	51 (12.7)	9 (9.9)	9 (18.4)	6 (25.0)	
Stage 3B	258 (20.2)	147 (20.7)	73 (18.1)	24 (26.4)	9 (18.4)	5 (20.8)	
Stage 4	313 (24.5)	164 (23.1)	113 (28.0)	17 (18.7)	16 (32.7)	3 (12.5)	
Stage 5	133 (10.4)	57 (8.0)	59 (14.6)	14 (15.4)	2 (4.1)	1 (4.2)	
eGFR without race modifier (n=1,277), median (IQR)	39.5 (23.4-67.6)	43.3 (26.8-71.1)	30.9* (18.7-55.8)	40.9 (23.8-69.2)	42.3 (26.2-67.6)	49.7 (34.2-81.3)	<0.001
CKD stage without race modifier (n, %)							
Stage 1	170 (13.3)	102 (14.4)	44 (10.9)	12 (13.2)	7 (14.3)	5 (20.8)	<0.001
Stage 2	203 (15.9)	133 (18.7)	45 (11.2)	15 (16.5)	6 (12.2)	4 (16.7)	
Stage 3	436 (34.1)	254 (35.8)	120 (29.8)	33 (36.3)	18 (36.7)	11 (45.8)	
Stage 3A	173 (13.5)	107 (15.1)	42 (10.4)	9 (9.9)	9 (18.4)	6 (25.0)	
Stage 3B	263 (20.6)	147 (20.7)	78 (19.4)	24 (26.4)	9 (18.4)	5 (20.8)	
Stage 4	317 (24.8)	164 (23.1)	117 (29.0)	17 (18.7)	16 (32.7)	3 (12.5)	
Stage 5	151 (11.8)	57 (8.0)	77 (19.1)	14 (15.4)	2 (4.1)	1 (4.2)	
Proteinuria (g/g) (n=1,018), median (IQR)* **	4.0 (2.0-8.0)	4.0 (2.0-9.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-8.0)	5.0 (3.0-6.0)	0.350
Nephrotic (≥3.0 g/g)	674 (66.2)	398 (67.2)	190 (63.5)	46 (68.7)	28 (66.7)	12 (66.7)	0.555
Non-nephrotic (<3.0 g/g)	344 (33.8)	194 (32.8)	109 (36.5)	21 (31.3)	14 (33.3)	6 (33.3)	
Arteriosclerosis (n, %) (n=1,430)							
Absent or no comment	314 (22.0)	170 (21.5)	95 (20.7)	31 (29.2)	12 (24.0)	6 (24.0)	0.070
Minimal or mild	358 (25.0)	192 (24.3)	107 (23.3)	39 (36.3)	14 (28.0)	6 (24.0)	
Moderate	329 (23.0)	192 (24.3)	107 (23.3)	13 (12.3)	11 (22.0)	6 (24.0)	
Marked or severe	429 (30.0)	235 (29.8)	151 (32.8)	23 (21.7)	13 (26.0)	7 (28.0)	
Arteriolosclerosis (n, %) (n=1,480)							
Absent or no comment	694 (46.9)	386 (47.5)	204 (43.1)	68 (59.7)	25 (49.0)	11 (42.3)	0.192
Minimal or mild	421 (28.4)	238 (29.3)	139 (29.4)	25 (21.9)	13 (25.5)	6 (23.1)	
Moderate	193 (13.0)	108 (13.3)	62 (13.1)	11 (9.7)	8 (15.7)	4 (15.4)	
Marked or severe	172 (11.6)	84 (10.3)	68 (14.4)	10 (8.8)	5 (9.8)	5 (19.2)	

Abbreviations: CKD, chronic kidney disease; **eGFR**, estimated glomerular filtration rate; **IQR**, interquartile range; **UPC**, urine protein creatinine ratio. The ANOVA / Kruskal-Wallis test, Chi-square test, Fisher's exact test, and Shapiro-Wilk test (normality test) were conducted for continuous and categorical variables, as appropriate. For categorical variables, Fisher's exact test was used when 25% of the cells had expected counts less than 5.

eGFR calculated using the CKD-EPI equation.[7]

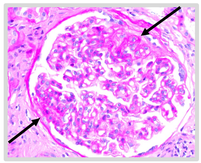
*Significantly different than White patients, p<0.017 for pairwise testing (Bonferroni correction); **Excluded from statistical testing; ***Based on UPC measurements.

Figure 1. Examples of Tip Lesion



FSGS tip lesions are located at the take off point of the proximal convoluted tubule. (A) Foamy cells accompany an area of loop collapse and sclerosis located at the junction of Bowman's capsule with the proximal convoluted tubule (PAS stain, original magnification 400 x, arrow points to the proximal convoluted tubule). (B) Segmental sclerosis extruding into the proximal convoluted tubule (PAS stain, original magnification 400 x, arrow points to area of sclerosis in the proximal convoluted tubule).

Figure 2. Example of NOS Lesion



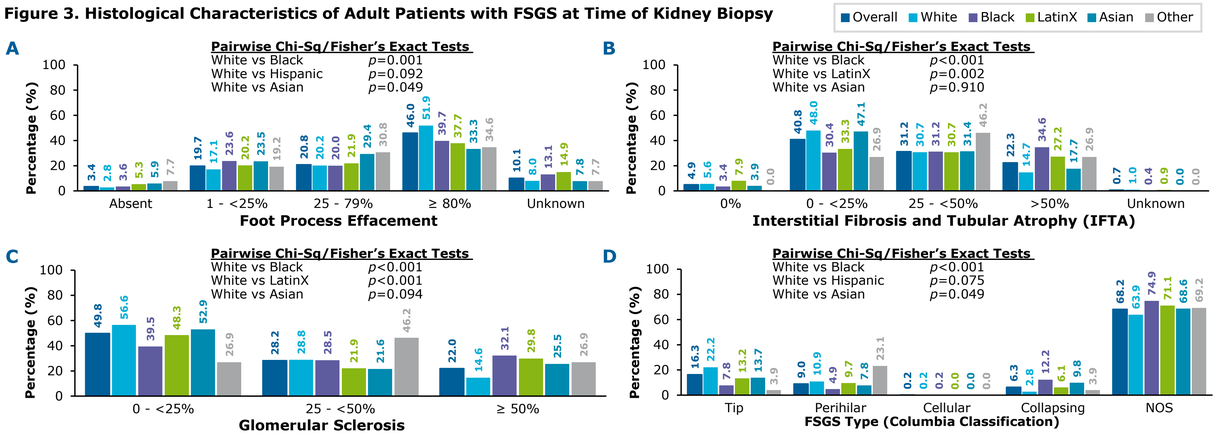
FSGS, Not Otherwise Specified (NOS) lesions are randomly distributed. Areas of segmental loop collapse and sclerosis in one glomerulus (PAS stain, original magnification 400 x, arrows points to areas of sclerosis).

Table 2. Frequency of FSGS Study Population Risk by eGFR and Albuminuria Category

Prognosis of CKD by GFR and Albuminuria Categories			Albuminuria* Categories Description and Range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol N	A1 %	A2 Moderately increased 30-299 mg/g 3-29mg/mmol N	A2 %	A3 Severely increased ≥300 mg/g ≥30 mg/mmol N	A3 %
eGFR Categories** (ml/min/1.73m²) Description and Range	G1	Normal or high	≥90	.	.	3	0.2%	188	15.3%
	G2	Mildly decreased	60-90	.	.	3	0.2%	203	16.5%
	G3a	Mildly to moderately decreased	45-59	.	.	3	0.2%	178	14.5%
	G3b	Moderately to severely decreased	30-44	.	.	8	0.7%	239	19.5%
	G4	Severely decreased	15-29	1	0.1%	4	0.3%	294	24.0%
	G5	Kidney failure	<15	.	.	1	0.1%	102	8.3%

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. (Kidney Disease: Improving Global Outcomes (KDIGO) 2012); *Albuminuria measured by converting UPC (urine protein to creatine ratio) by applying a factor of 1.43 (KDIGO, 2012); **Calculated using CKD-EPI equation without race modifier.

Figure 3. Histological Characteristics of Adult Patients with FSGS at Time of Kidney Biopsy



Discussion

- Black patients were diagnosed with FSGS at younger ages and presented with lower levels of eGFR and more advanced glomerulosclerosis and interstitial fibrosis and tubular atrophy compared to White patients
- Two thirds of patients with FSGS had very high risk for chronic kidney disease (CKD) progression and kidney failure based on KDIGO risk classification at the time of their kidney biopsy
- For patients suspected of having FSGS, conducting a kidney biopsy earlier in their course of CKD could lead to timelier detection and opportunity for therapeutic intervention

Limitations

- Retrospective cohort study design using lab data are hypothesis generating
- Some groups had a very small sample size (n<5)

Conclusions

- In this sample of patients with biopsy-confirmed FSGS, Black patients were more frequently diagnosed with FSGS at lower levels of eGFR and more advanced GS and IFTA compared to White patients
- Results were similar between comparisons made using eGFR estimates with and without the race modifier
- Strategies for earlier awareness and detection of FSGS are needed to facilitate therapeutic intervention in high-risk patients, thereby preventing progression to ESKD and attendant consequences

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