Poster# TH-PO478

Evaluating the Predictors of Structural Features in Kidney Biopsies from Adults with Focal Segmental Glomerulosclerosis

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Disclosures

- **KT** has received research grant support and consultancy fees from Travere Therapeutics, Inc.
- **CA** and **PW** received consultancy fees from Travere Therapeutics, Inc.
- **MB** is a consultant for Travere Therapeutics, Inc.
- **KW** is an employee and stockholder of Travere Therapeutics, Inc.
- **JH** and **AR** are employees of Genesis Research which received compensation from Travere Therapeutics, Inc. for conducting this study

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- Focal segmental glomerulosclerosis (FSGS) is a lesion of glomerular injury in patients with nephrotic syndrome
- FSGS often follows a progressive course to kidney failure (KF), and FSGS is a leading glomerular cause of KF in the US[1-3]
- Persistent podocyte injury leads to proteinuria and a progressive decline in eGFR[3-6]

Objectives

- To assess histopathological characteristics of FSGS at diagnosis
- To assess clinical predictors of the histological severity of FSGS among adults undergoing kidney biopsy

Abbreviations: FSGS, focal segmental glomerulosclerosis; **KF,** kidney failure; **eGFR,** estimated glomerular filtration rate

1. Rosenberg AZ, Kopp JB. *Clin J Am Soc Nephrol.* 2017;12(3):502-517. **2.** Levey AS, et al. *Nephrol Dial Transplant.* 2020;35:1077-1084. **3.** Korbet SM. *J Am Soc Nephrol.* 2012;23(11):1769-1776. **4.** Abbate M, et al. *J Am Soc Nephrol.* 2006;17(11):2974-2984. **5.** De Vriese AS, et al. *J Am Soc Nephrol.* 2018;29(3):759-774. **6.** Levey AS, et al. *Ann Intern Med.* 2009; 150(9):604-612.

METHODS

Study design, data source and inclusion criteria

- This is a study of real-world data collected from patients with biopsy-confirmed FSGS in the US from the Arkana Biopsy database from January 1, 2016 to May 31, 2020
- Included patients: (1) were ≥18 years of age, (2) had at least 1 FSGS-positive kidney biopsy during the study period (January 1, 2016 – May 31, 2020), (3) had no prior kidney transplant

Measures and statistical analyses

- Histological characteristics were assessed in the overall cohort and stratified by race as White vs. Non-White (Black, Asian, other, unknown). Chi-squared tests were used to compare categorical variables between race groups
- Severe histological disease was defined by a composite measure combining GS in ≥50% of glomeruli and IFTA in ≥25% the tubulointerstitium
- Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using means, SD, medians, and interquartile ranges
- A multiple logistic regression model was used to assess the associations of CKD stage and proteinuria with severe histological disease, adjusting for age, sex, race, and hypertension

Abbreviations: FSGS, focal segmental glomerulosclerosis; **GS,** global glomerulosclerosis; **IFTA,** interstitial fibrosis/tubular atrophy; **SD,** standard deviations; **CKD,** chronic kidney disease

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- 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 and electron microscopy[7]
- Light microscopy samples were fixed in formalin; embedded in paraffin and serially cut at 3 µm; and stained with hematoxylin & 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 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 were taken at 4,000, 12,000 and 20,000 x magnification

7. Walker PD. *Arch Pathol Lab Med.* 2009;133(2):181-188.

RESULTS

Demographic and clinical characteristics

- The cohort consisted of 2,011 adult patients (age ≥18 years). Mean age was 49.1 years, 43.6% were female
- 40.6% were White. Race information was not available for 26.3% of the cohort
- Proteinuria data were available for 65.9% of patients. Median urinary protein-creatinine ratio (UP/C) was 3.8 g/g, median 24-hour urinary protein was 4.7 g/day
- Nephrotic range proteinuria was observed in 62.1% of patients with available proteinuria data
- Median eGFR was 42.2 mL/min/1.73 m^2 and among patients with available eGFR (83.7%), the majority were CKD stages 3–5 at diagnosis (68.0%)

Table 1. Demographic and clinical characteristics

	N=2,011
Age, Mean (SD), years	49.1 (17.2)
Gender, n (%), Female	877 (43.6)
Race, n (%)	
White	817 (40.6)
Non-White	1,194 (59.4)
Black	417 (23.6)
Hispanic	114 (5.7)
Asian	51 (2.5)
Other	26 (1.3)
Unknown	529 (26.3)
Proteinuria data available, n (%)	1,326 (65.9)
UP/C available, n (%)	557 (42.0)
Median (Q1,Q3), g/g	3.8 (2.0,7.0)
24-hour urinary protein available, n (%)	769 (58.0)
Median (Q1,Q3), g/day	4.7 (3.0,9.0)
Nephrotic range proteinuria,* n (%)	824 (62.1)†
eGFR,‡ median (Q1,Q3), mL/min/1.73 m^2	42.2 (25.3,72.0)
CKD stage available, n (%)	1,684 (83.7)
Stage 1	257 (15.3)
Stage 2	282 (17.8)
Stage 3	599 (35.6)
Stage 4	383 (22.7)
Stage 5	163 (9.7)

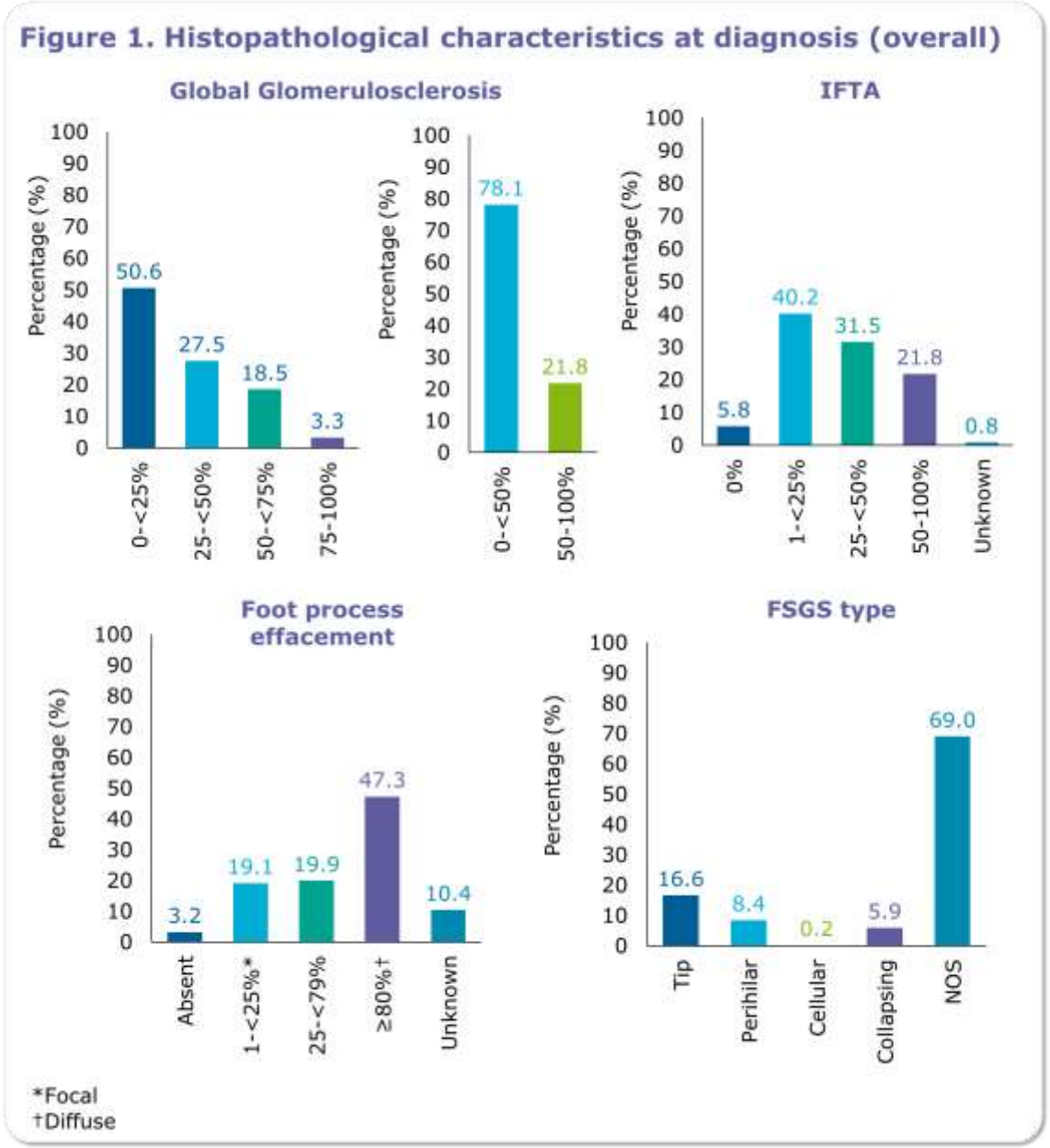
*Defined as proteinuria ≥3 g/g or ≥3.5 g/day; †Percentage of patients with available proteinuria data; ‡Based on CKD-EPI 2021 equation

Abbreviations: CKD, chronic kidney disease; **eGFR,** estimated glomerular filtration rate; **UP/C,** urinary protein-creatinine ratio

RESULTS

Histopathological features of FSGS at diagnosis

- Global GS of ≥50% of glomeruli was observed in the biopsies of 21.8% of patients
- IFTA ≥50% in the tubulointerstitial compartment was present in 21.8% of patients
- Diffuse foot process effacement (FPE) (≥80% of glomeruli) was seen in almost half of patients
- More than two thirds of patients had FSGS with NOS (not otherwise specified) type lesions

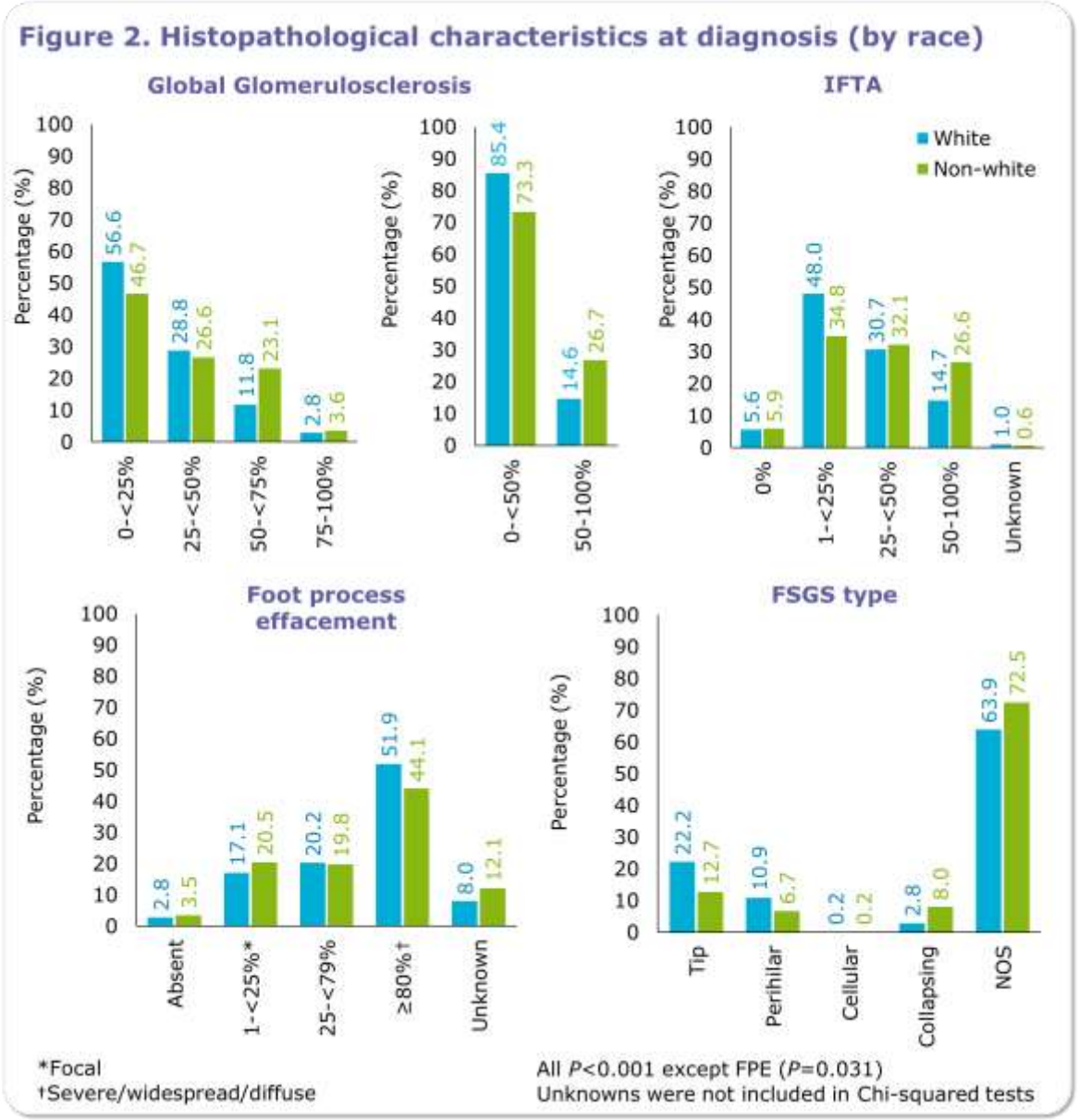


Abbreviations: FPE, foot process effacement; **FSGS,** focal segmental glomerulosclerosis; **GS,** glomerulosclerosis; **IFTA,** interstitial fibrosis/tubular atrophy; **NOS,** not otherwise specified

RESULTS

Histopathological features of FSGS at diagnosis by race/ethnicity

- Significant differences in histopathological characteristics and FSGS subtypes were observed between White and Non-White groups
- GS ≥50% and IFTA ≥50% were observed more frequently in the Non-White group compared with the White group while severe FPE was observed more frequently in the White group
- NOS and collapsing lesions both occurred in a significantly higher proportion of patients in the Non-White group



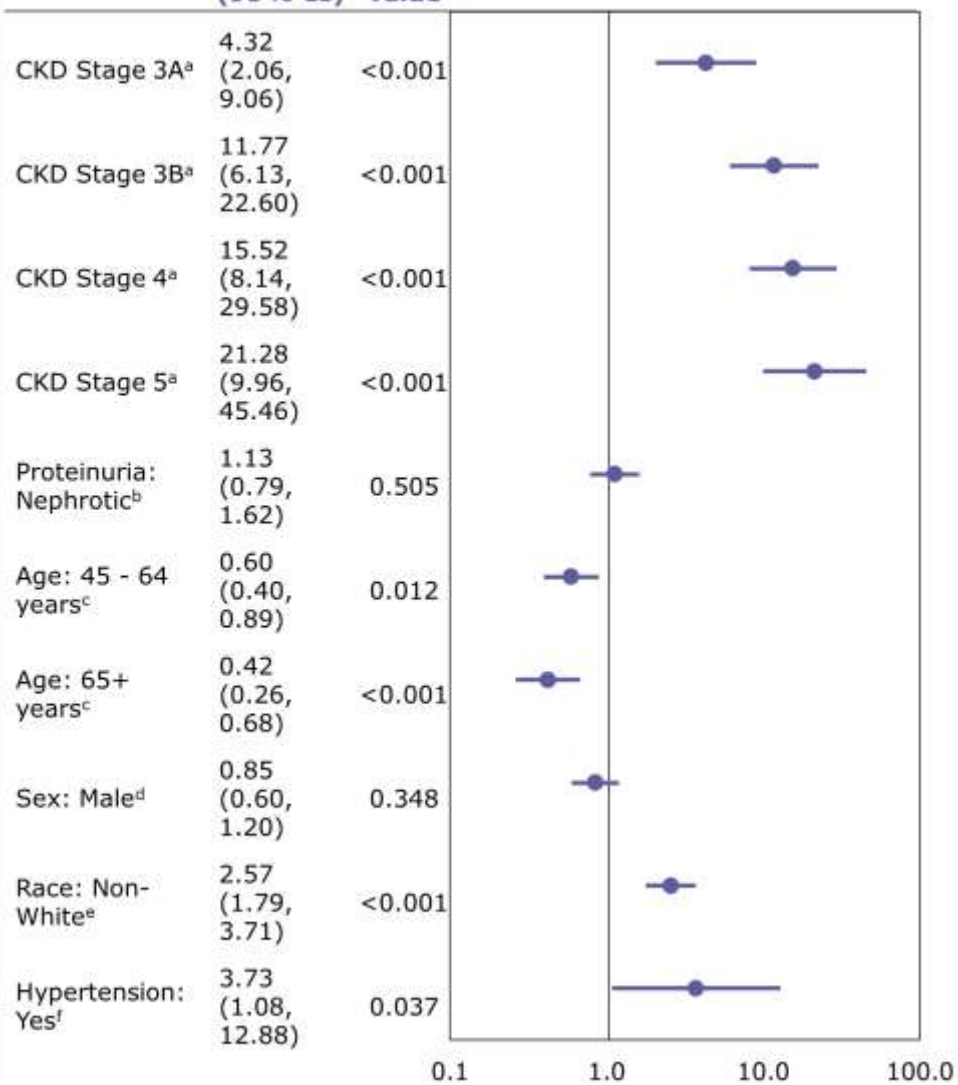
Abbreviations: FPE, foot process effacement; **FSGS,** focal segmental glomerulosclerosis; **GS,** glomerulosclerosis; **IFTA,** interstitial fibrosis/tubular atrophy; **NOS,** not otherwise specified

RESULTS

Clinical predictors of histological disease severity

- CKD stages 3-5 were associated with significantly higher odds of severe histological disease than stages 1-2
- Non-White race and hypertension were also associated with severe histological disease
- Older age was associated with significantly lower odds of severe histological disease
- Neither nephrotic-range proteinuria nor sex were significantly associated with histological disease severity

Figure 3. Clinical predictors of histologically severe FSGS



Reference groups: [a]CKD stages 1 and 2; [b]Non-nephrotic proteinuria; [c]18 – 44 years; [d]Female; [e]White; [f]No

Abbreviations: CKD, chronic kidney disease; **FSGS,** focal segmental glomerulosclerosis

DISCUSSION AND CONCLUSIONS

- Most patients (68%) had CKD stage ≥3 and over a fifth (23%) had ≥50% GS or IFTA. Non-White race was associated with a significantly higher frequency of advanced GS or IFTA
- ~70% of patients had NOS lesions. Non-White race was associated with a higher frequency of NOS or collapsing lesions and fewer tip or perihilar lesions
- The risk of severe histological disease was significantly greater with later CKD stages. Nephrotic-range proteinuria was not significantly associated with severe histological disease, but further analysis may show association with more severe FPE
- Younger age, Non-White race, and hypertension were associated with increased risk of severe histological disease

Limitations

- Generalizability may be limited by unequal distribution of patients across the 40 states serviced by Arkana within the database. Reasons for missing demographic/clinical data could not be assessed. The number of patients in Non-White race/ethnicity groups was small. Unknown race was included in the Non-White group which could have led to undetected bias

Conclusions

- Severe histologic features of FSGS are predicted by later CKD stage, but not nephrotic range proteinuria, at the time of kidney biopsy
- Younger, Non-White, and hypertensive patients are at greater risk of severe histologic FSGS
- Strategies for earlier diagnosis before onset of eGFR decline and severe structural injury are needed, especially in high-risk groups, to improve kidney disease outcomes in patients with FSGS

Abbreviations: CKD, chronic kidney disease; **eGFR,** estimated glomerular filtration rate; **FSGS,** focal segmental glomerulosclerosis; **GS,** global glomerulosclerosis; **IFTA,** interstitial fibrosis/tubular atrophy; **NOS,** not otherwise specified;