Article published online: 2023-02-24

A Study of Focal and Segmental Glomerulosclerosis according to the Columbia Classification and Its Correlation with the Clinical Outcome

Swapna Nuguri[1] Meenakshi Swain[2] Michelle de Padua[2] Swarnalata Gowrishankar[2]

[1] Department of Pathology, ESIC Medical College, Hyderabad, Telangana, India
[2] Department of Histopathology, Apollo Hospitals, Hyderabad, Telangana, India

Address for correspondence Meenakshi Swain, MD, Senior Consultant Pathologist, Department of Histopathology, Apollo Hospitals, Jubilee Hills, Hyderabad, 500033, Telangana, India (e-mail: swainmeenakshi1@gmail.com).

J Lab Physicians 2023;15:431–436.

Abstract

Introduction Focal and segmental glomerulosclerosis (FSGS) is a leading cause of nephrotic syndrome in both adults and children. The "Columbia classification of FSGS" includes five variants; not otherwise specified (NOS), tip, perihilar, cellular, and collapsing variants that may have different prognostic and therapeutic implications.

Materials and Methods This is a retrospective study and was carried out in the Department of Histopathology, Apollo Hospitals, Hyderabad. Of a total of 11,691 kidney biopsies over a 7-year period, from 2006 to 2012, 824 cases were diagnosed as FSGS, of which 610 cases in which detailed clinical findings were available were included in this study. FSGS was then categorized according to the Columbia classification.

Results FSGS, NOS was the predominant histomorphological variant. Serum creatinine was significantly high in the collapsing variant, followed by NOS. Follow-up data was available for 103 cases,72.8% had complete remission, 10.6% had partial remission, and in 16.5 % there was no remission. Relapses were observed in 6.7% cases, two patients (1.9%) succumbed, and 4.8% cases progressed to chronic kidney disease.

Conclusion This study showed that perihilar variant was less prevalent, with tip and cellular variants being more prevalent in Indian subcontinent compared to Western literature. Collapsing variant was also less common.

Keywords
- FSGS
- Columbia classification
- focal and segmental glomerulosclerosis

Introduction

Focal and segmental glomerulosclerosis (FSGS) is one of the causes of nephrotic syndrome with an incidence of 7 per million.[1] About 20% of children and 40% of adults have FSGS as the cause for nephrotic syndrome. Histopathological features of FSGS are characterized by FSGS of glomerular capillaries, with the underlying pathogenesis being podocyte injury.[1]

The working "Columbia classification of FSGS" has categorized FSGS into five variants: not otherwise specified

received
October 1, 2022
accepted after revision
December 16, 2022
article published online
February 24, 2023

DOI https://doi.org/10.1055/s-0043-1761930.
ISSN 0974-2727.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

(NOS), tip, perihilar, cellular, and collapsing types that may have different prognostic and therapeutic implications.[1,2]

The main objective of the study is to stratify biopsy-proven cases of FSGS into the Columbia classification subtypes and correlate the subtypes with the laboratory profile and clinical outcome in a subset of the Indian population.

Materials and Methods

This is a retrospective study and was carried out in the Department of Histopathology, Apollo Hospitals, Hyderabad. Out of a total of 11,691 kidney biopsies received over a 7-year period from 2006 to 2012, 824 cases were diagnosed as FSGS. Six-hundred ten cases in which detailed clinical findings were available were included in the study.

Patient Selection

All the renal biopsies received in the laboratory were processed and analyzed.

The cases diagnosed as FSGS were included in the study.

Clinical Parameters

The clinical information was collected from the electronic database of Apollo Hospitals. Request forms received with samples from other hospitals were also used for collecting data. The data included age, sex, clinical presentation, and duration of symptoms. Biochemical data included serum creatinine, proteinuria, and findings of urine analysis.

Histology

The renal biopsies were processed according to standard protocols for light microscopy. Hematoxylin and eosin, periodic acid Schiff, Masson trichrome, and periodic acid silver methenamine stains were done. Direct immunofluorescence study was done using antibodies to immunoglobulin G (IgG), IgA, IgM, C3c, C1q, kappa, and lambda.

The diagnosed cases of FSGS were categorized according to Columbia classification into five types, that is, FSGS NOS, tip, perihilar, cellular, and collapsing variant.[1]

Histological features included percentage of segmental sclerosis, global sclerosis, quantification of interstitial fibrosis and tubular atrophy, and vascular remodeling that were analyzed and correlated with clinical parameters. The treatment response details were available in 103 cases where the patients were treated with steroids, immunosuppressants, and angiotensin-converting enzyme inhibitors.

Clinical Definitions Based on the KDIGO Guidelines[3]

Complete remission: proteinuria less than 0.3 g/day with a stable serum creatinine (<50% increase from baseline).

Partial remission: proteinuria between 0.3 and 3.5 g/day, with at least 50% reduction in proteinuria from the baseline and a stable serum creatinine.

Relapse: proteinuria more than 3.5 g/day after complete remission has been achieved or increase in the proteinuria by more than 50% during partial remission.[3]

Statistical Analysis

Statistical analysis of the data was done with appropriate tests, that is, the chi-squared test, Fisher's exact test *p*-value, Mann–Whitney U tests, and Kruskal–Wallis test *p*-value, post-hoc analysis by Mann–Whitney U test, Bonferroni method. A *p*-value of less than 0.05 was considered to be significant.

Results

The incidence of FSGS was 7% of the total kidney biopsies in this study. FSGS was seen in pediatric and adult age groups (►**Table 1**). The ages ranged from 1 year to 84 years, with a median age of 30.3 ± 16.8 years. FSGS in the first decade was observed predominantly in the second decade (21.1%) and third decade (24.6%). The male-to-female ratio was 1.4:1. The distribution of morphological variants of FSGS was as follows: 523 cases were NOS variant (85.7%), 32 were tip variant (5.2%), 29 were cellular (4.8%), 17 were perihilar (2.8%), and 9 were collapsing variant (1.5%; ►**Fig. 1**). The clinical and histological presentation of these variants has been depicted in ►**Tables 1** and **2**. There was no statistical significance among the variants with regard to age, gender, proteinuria, or microscopic hematuria. The correlation of high serum creatinine and rapid worsening in collapsing variant was statistically significant. Proteinuria was maximum in

Table 1 Clinicopathological correlation of variants of FSGS

	NOS	TIP	PH	CEL	COL	*p*-Value[a]
n = 610	523	32	17	29	9	
Age range (y) Mean ± SD	1–84 30.2 ± 16.9	6–69 26.1 ± 11.5	5–54 36.2 ± 20.1	11–60 33 ± 15.6	11–58 28.7 ± 14.5	0.04
M:F	1.4:1	2.2:1	2.4:1	1.6:1	3.5:1	0.45
Proteinuria	65%	72%	58.8%	72.4	88.9	0.27
Microscopic RBCS	32.1%	29.6%	35.7%	30.8%	62.5%	0.47
Serum[a] creatinine	1.7 ± 1.6	1.2 ± 0.6	1.2 ± 0.8	1.4 ± 1.2	2.9 ± 1.2	<0.05
Duration of symptoms (mo)	6.8 ± 17.1	8.6 ± 10.1	11.3 ± 10	11.5 ± 14.3	3.8 ± 2.6	

Abbreviations: CEL, cellular; COL, collapsing; FSGS, focal and segmental glomerulosclerosis; NOS, not otherwise specified; PH, perihilar; SD, standard deviation.
[a]Chi-squared/Fisher's exact test.

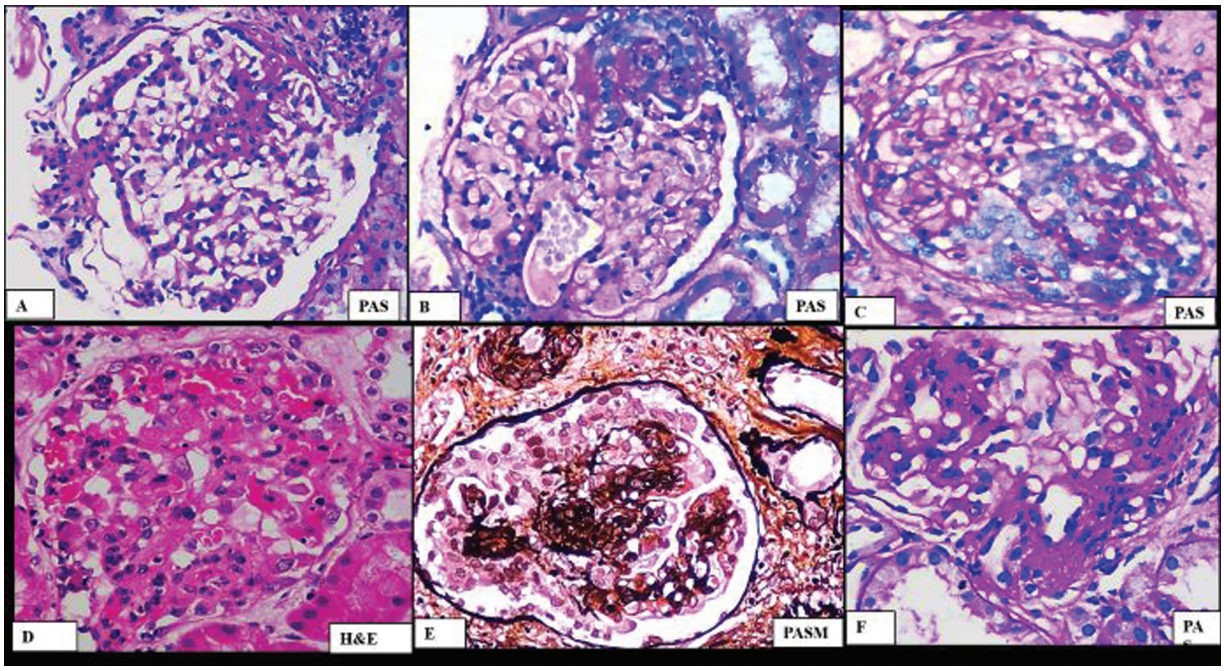

Fig. 1 (**A**) FSGS, NOS, PAS stain; (**B**) FSGS, TIP variant PAS stain; (**C**) FSGS cellular, PAS stain; (**D**) FSGS Cellular hematoxylin and eosin (H&E); (**E**) collapsing variant Jones methenamine silver. (**F**) Perihilar PAS X 400. FSGS, focal and segmental glomerulosclerosis; NOS, not otherwise specified; PAS stain, periodic acid Schiff.

collapsing variant (88%), followed by cellular and tip, both at 72%. There was no association of human immunodeficiency virus (HIV) in the collapsing variant. The renal biopsy findings showed significant correlation with degree of global sclerosis in collapsing variant followed by perihilar variant. Interstitial fibrosis and vascular remodeling among these variants had a statistically significant *p*-value (►**Table 2**).

Treatment response details were retrieved for 103 cases. Of these, 90 cases were NOS (87%), 5 were tip (4.8%), 5 cellular (4.8%), and 1 collapsing variants (0.97%). Among the 103 cases, 72.8% had complete remission, 10.6% had partial remission, and in 16.5 % there was no remission. Relapses were observed in 6.7% cases, two patients (1.9%) succumbed, 4.8% cases developed chronic kidney disease (CKD) including

Table 2 Comparison of histopathological features of FSGS variants

	NOS	TIP	PH	CEL	COL	*p*-Value
$n = 610$	523	32	17	29	9	
Morphological findings						
Segmental sclerosis (%) Mean ± SD	18.8 ± 15.8	17.1 ± 13.3	12.8 ± 6.1	21.8 ± 13.3	28.8 ± 28.1	0.303[a]
Global sclerosis (%) Mean ± SD	18.7 ± 24.8	3.8 ± 11.12	21.8 ± 18.6	7.4 ± 13.8	27.3 ± 35.2	<0.05[a]
IFTA (%)						
U/R	18.9	40.6	17.6	37.9	33.3	0.008[b]
Mild	64.2	59.4	76.5	62	33.3	
Moderate	12.8	0	5.9	0	22.2	
Severe	4.0	0	0.0	0.0	11.1	
Blood vessel changes (%)						
AH	11.5	0.0	35	17.2	11.1	0.006[b]
IF	7.6	3.1	11.8	6.9	0.0	
MH, AH, IF	11.7	0.0	0.0.	0.0	11.1	
U/R	69.2	96.9	52.9	75.9	77.8	

Abbreviations: AH, arteriolar hyalinosis; CEL, cellular; COL, collapsing; FSGS, focal and segmental glomerulosclerosis; IF, intimal fibrosis; IFTA, interstitial fibrosis, and tubular atrophy; MH, medial hyperplasia; NOS, not otherwise specified; PH, perihilar; U/R, unremarkable.
[a]Kruskal–Wallis test, [b]Chi-squared/Fisher's exact test.

4.4% of NOS, and 100% of collapsing variants. Complete remission was seen in 85% cases of NOS, 5.3% of cellular, 2.5% perihilar, and 6.6% of tip variant. Partial remission was observed in 11% of NOS and 11% of cellular variant. There was no remission in a single case of collapsing (100%) and 17% cases of NOS variants.

Immunofluorescence showed nonspecific immune deposits for IgM and C3c in 354 cases. Electron microscopy was not done in view of cost constraints.

Discussion

FSGS is a histopathological pattern of injury and one of the leading causes of proteinuria and end-stage renal disease (ESRD)in children and adults. This is associated with various etiological factors depending on the underlying mechanisms of injury of the podocyte and podocyte substructures.[4] Many published articles have categorized FSGS based on underlying diseases and aetiology.[4,5] Few articles propose new typing of FSGS into primary and secondary. Primary being due to a presumed permeability factor-related FSGS, with circulating permeability factors causing injury to podocytes. Secondary FSGS is presumed to be due to multiple factors and further divided as maladaptive FSGS, drug-induced FSGS, virus-induced FSGS, FSGS lesions superimposed on other glomerular diseases, genetic FSGS due to defects in podocytes and GBM (Glomerular basement membrane) proteins, and unclassifiable FSGS of unknown cause.[4,5] The Columbia classification categorized FSGS lesions into five types: NOS, tip, cellular, perihilar collapsing on light microscopy. The Columbia classification has potential prognostic value.[1,2,5]

This study analyzed the clinicopathological features of cases diagnosed as FSGS and classified them according to the Columbia classification.[1] The frequency of FSGS variants has been compared with various studies that also included multiethnic groups (►**Table 3**). NOS variant was the predominant one, similar to other studies.[2,6–20] The prevalence of collapsing in multiethnic group studies, which included African Americans, was more (54 to 91%) compared to other study cohorts, which did not have this ethnic group, ranging from 2 to 6.9%. This observation showed that collapsing variant was more frequent in Afro-American population.[7] The prevalence of collapsing variant was low in this Indian cohort.

The published literature showed that collapsing glomerulopathy (also referred collapsing FSGS) was associated with recent African ancestry individuals where it was attributed to high risk G1 and G2 gain-of-function polymorphisms in the APOL1 gene.[5,21,22] The APOL 1 gene was found to be protective against the trypanosomiasis. The data published showed that these G1 and G2 variants of APOL 1 gene increased the risk of kidney diseases. These variants of APOL1 gene were associated with podocyte injury that resulted in increased rates of FSGS, focal global glomerulosclerosis, and various other nondiabetic kidney disease such as hypertension-associated end-stage kidney disease (H-ESKD), severe lupus nephritis HIV-associated nephropathy, and sickle cell nephropathy.[5,21,22] There was a difference in prevalence of tip and cellular variants in Indian

Table 3 Comparative data of FSGS variants in literature (across different populations and ethnicity in%)

FSGS variants	Present study	Thomas et al [2]	Deegens et al[6]	Nada et al[7]	Das et al[8]	D'Agati et al[9]	Testagrossa and Malheiros [13]	Arias et al[10]	Sethi et al[14]	Kwon et al[15]	Swarna latha et al[16]	Dhana priya et al[17]	Trivedi et al[18]	Fatehi et al[19]	Tsuchimoto et al[20]
NOS	85	42	32	72.5	44.6	68	38.2	77	53.6	63.1	62.2	56	74.5	42.9	60.1
TIP	5.2	17	37	13.5	12.3	10	14.5	3.7	7.3	18	7.7	24	13.3	32.5	85
PH	2.8	26	26	4	24.6	7	6.9	4.8	2.43	15.3	11.2	10	6.25	23.1	15.4
Cel	4.8	3	0	8	4.6	3	3.8	1	9.7	2.7	9.4	9	3.57	0.5	9.5
Col	1.5	11	11	2	13.9	12	36.6	3.4	7.3	0.9	4.6	1	2.23	0.9	6.5

Abbreviations: CEL, cellular; COL, collapsing; FSGS, focal and segmental glomerulosclerosis; NOS, not otherwise specified; PH, perihilar.

subcontinent that varied from 7.7 [16] to 24%[17] and 3.5[18] to 9.4%.[16] The cellular variant was uncommon in majority of the studies (►**Table 3**). The perihilar variant was less common, varying from 4[7] to 11%[16] compared to studies by Thomas et al and Deegens et al, where it was 26% each.[2,6]

The median age of presentation was seen in third and fourth decade similar to the other studies[7,16,18,19] with younger population being affected in tip and collapsing variants.[7] This was discordant with other studies that had a predominance in fifth and sixth decade[2,6,15,20] and was variable in few other studies.[10]

The degree of proteinuria was high in collapsing variant, similar to other series.[7,8,10,18] In few other studies, proteinuria was higher in tip, collapsing,[6,15,20] and cellular variants[2] and lowest in perihilar variant.[7] Microscopic hematuria was observed in collapsing and perihilar types in this cohort in contrast to the cellular variant as seen in one other series.[7] This was of no statistical significance compared with other variants of FSGS (p-value =s 0.47). The microscopic hematuria could have been the cause for early presentation in the collapsing variant. There was a significant correlation of a shorter duration of disease course and higher levels of serum creatinine observed in collapsing variant, as seen in other cohorts.[2,6–8,10,16,18]

Various studies have shown correlation of FSGS variants with hypertension, glomerular filtration rate, and serum albumin, but this was not documented in this study, in the absence of adequate clinical details.

The extent of segmental sclerosis was higher in the collapsing and cellular variants in this study unlike other studies that showed greater segmental changes in perihilar type,[7] followed by NOS,[8] and then the tip variant.[18] These differences were probably due to larger number of cases and the ethnicity of population included. In this study, the extent of global sclerosis was statistically significant among the variants and showed corresponding changes of interstitial fibrosis and tubular atrophy. The greater extent of chronicity observed in collapsing and perihilar variants in this study were similar to Tsuchimoto et al.[20] This varied from other cohorts in which NOS,[7] and perihilar had a greater extent of global glomerulosclerosis.[10,18] This may have been due to difference in the etiologies of FSGS.

There was a varied distribution of remission rates in the five variants of FSGS documented in various studies (►**Table 4**), which indicated that tip variant had complete remission and better prognosis than other variants.[2]

The cases with partial remission had higher degree of global sclerosis (p-value = 0.01) which correlated statistically with higher serum creatinine values (p-value = 0.01). The percentage of segmental sclerosis was higher in cases with no remission (p-value = is 0.001), possibly indicating different underlying etiopathogenetic mechanisms.

In the study by Chun et al, it was observed that there was no remission in 47% of treated cases of NOS, 36% of cellular, and 22% of tip variants. ESRD developed in 25% of NOS, 43% of cellular, and 27% of tip variants.[23] In the study by Kwon et al, relapses were seen in 11.4% cases of NOS, 15% of tip, and 5.9% of perihilar variants. ESRD was seen in 11.4% of NOS and 5% of tip variant.[15] Arias et al showed CKD in 53.9% of NOS, 30.8% in tip, 87.5% in perihilar, and 55.6% in collapsing variant.[10] CKD was observed in 4.4% of NOS and 100% ($n = 1$) collapsing variants in this study.

These differences in the clinical outcome can be attributable to various factors such as different therapeutic approaches, advanced renal disease at presentation in the absence of regular health checks, with increasing degree of tubular atrophy and interstitial fibrosis along with varying underlying etiologies.[23]

Limitations of the Study

The number of cases of FSGS variants other than NOS was small and the treatment response and follow-up details were not available for all the cases. There was a lack of history of other associated diseases and absence of electron microscopic evaluation, which was a major limitation.

Table 4 Status of remission in various studies

FSGS variant	Present study	Deegens et al[6]	Thomas et al[2]	Chun et al[23]	Kwon et al[15]	Arias et al[10]
NOS—CR	64	6 ($n = 30$)	10 ($n = 83$)	6 ($n = 36$)	16 ($n = 70$)	12 ($n = 105$)
NOS—PR	10	6	2	3	22	12
TIP—CR	5	15 ($n = 34$)	17 ($n = 34$)	5	10 ($n = 20$)	15 ($n = 26$)
TIP—PR	0	3	1	2 (n =11)	6	8
PH—CR	2	3 ($n = 24$)	5.2 ($n = 52$)	NA	3 ($n = 17$)	0 ($n = 8$)
PH—PR	0	2	5	NA	4	0
CEL—CR	4	0	2 ($n = 6$)	6 ($n = 40$)	NA	NA
CEL—PR	1	0	2 (CR/PR)	10	NA	NA
COL—CR	0	2 ($n = 5$)	3 ($n = 22$)	NA	NA	1 ($n = 9$)
COL—PR	0	0	1	NA	NA	1

Abbreviations: CEL, cellular; COL, collapsing; CR, complete remission; NA, nonavailability of cases; NOS, not otherwise specified; PH, perihilar; PR, partial remission.

Conclusion

In this study, FSGS, NOS variant was the commonest subtype. The tip and cellular variant were more prevalent compared to perihilar and collapsing variants that were less common in Indian subcontinent in contrast to western data. The poor response to treatment could be attributable to advanced disease at presentation, as evidenced by global sclerosis and IFTA. The clinicopathological features in the subtypes of FSGS vary among diverse ethnic populations.

Authors Contributions
All the authors contributed equally to the manuscript.

Funding
None.

Conflict of Interest
None declared.

References

1 D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med 2011;365(25):2398–2411
2 Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int 2006;69(05):920–926
3 KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney International 2021;100:S1–S276
4 Shabaka A, Tato Ribera A, Fernández-Juárez G. Focal segmental glomerulosclerosis: state-of-the-art and clinical perspective. Nephron 2020;144(09):413–427
5 De Vriese AS, Wetzels JF, Glassock RJ, Sethi S, Fervenza FC. Therapeutic trials in adult FSGS: lessons learned and the road forward. Nat Rev Nephrol 2021;17(09):619–630
6 Deegens JK, Steenbergen EJ, Borm GF, Wetzels JF. Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population–epidemiology and outcome. Nephrol Dial Transplant 2008;23(01):186–192
7 Nada R, Kharbanda JK, Bhatti A, Minz RW, Sakhuja V, Joshi K. Primary focal segmental glomerulosclerosis in adults: is the Indian cohort different? Nephrol Dial Transplant 2009;24(12):3701–3707
8 Das P, Sharma A, Gupta R, Agarwal SK, Bagga A, Dinda AK. Histomorphological classification of focal segmental glomerulosclerosis: a critical evaluation of clinical, histologic and morphometric features. Saudi J Kidney Dis Transpl 2012;23(05):1008–1016
9 D'Agati VD, Alster JM, Jennette JC, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. Clin J Am Soc Nephrol 2013;8(03):399–406
10 Arias LF, Jiménez CA, Arroyave MJ. Histologic variants of primary focal segmental glomerulosclerosis: presentation and outcome. J Bras Nefrol 2013;35(02):112–119
11 Shi SF, Wang SX, Zhang YK, Zhao MH, Zou WZ. [Clinicopathologic study of different variants of focal segmental glomerulosclerosis]. Zhonghua Bing Li Xue Za Zhi 2007;36(01):11–14
12 Roja JR, Pérez M, Hurtado A, Asato C. [Factors predicting for renal survival in primary focal segmental glomerulosclerosis]. Nefrologia 2008;28(04):439–446
13 Testagrossa LA, Malheiros DM. Study of the morphologic variants of focal segmental glomerulosclerosis: a Brazilian report. J Bras Patol Med Lab 2012;48:211–215
14 Sethi S, Zand L, Nasr SH, Glassock RJ, Fervenza FC. Focal and segmental glomerulosclerosis: clinical and kidney biopsy correlations. Clin Kidney J 2014;7(06):531–537
15 Kwon YE, Han SH, Kie JH, et al. Clinical features and outcomes of focal segmental glomerulosclerosis pathologic variants in Korean adult patients. BMC Nephrol 2014;15:52
16 Swarnalatha G, Ram R, Ismal KM, Vali S, Sahay M, Dakshinamurty KV. Focal and segmental glomerulosclerosis: does prognosis vary with the variants? Saudi J Kidney Dis Transpl 2015;26(01):173–181
17 Dhanapriya J, Dineshkumar T, Gopalakrishnan N, Sakthirajan R, Balasubramaniyan T. Clinicopathological correlation and treatment response of primary focal segmental glomerulosclerosis in adults and adolescents. Indian J Nephrol 2016;26(05):347–351
18 Trivedi M, Pasari A, Chowdhury AR, Abraham-Kurien A, Pandey R. The spectrum of focal segmental glomerulosclerosis from Eastern India: is it different? Indian J Nephrol 2018;28(03):215–219
19 Fatehi F, Hosaini SM, Nasri H. A study on variants of focal segmental glomerulosclerosis and their relationship with various biochemical and demographic parameters in kidney biopsies; a single center study. J Nephropharmacol 2019;8(02):1–5
20 Tsuchimoto A, Matsukuma Y, Ueki K, et al. Utility of Columbia classification in focal segmental glomerulosclerosis: renal prognosis and treatment response among the pathological variants. Nephrol Dial Transplant 2020;35(07):1219–1227
21 Nicholas Cossey L, Larsen CP, Liapis H. Collapsing glomerulopathy: a 30-year perspective and single, large center experience. Clin Kidney J 2017;10(04):443–449
22 Friedman DJ, Pollak MR. APOL1 nephropathy: from genetics to clinical applications. Clin J Am Soc Nephrol 2021;16(02):294–303
23 Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol 2004;15(08):2169–2177

