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The prevalence and clinicopathological characteristics of morphologic variants of focal segmental glomerulosclerosis in Iran

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Abstract

Introduction: Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of primary glomerular disease and its incidence is increasing worldwide. According to the morphological features, a group of nephropathologists proposed a standardized classification system, called the Columbia classification of FSGS in 2003.

Objectives: This study was carried out to define the frequency of FSGS variants, and their relationship with demographic and clinicopathological factors.

Patients and Methods: This cross-sectional study was conducted on renal biopsy reports at a nephropathology laboratory between 2009 to 2022. Out of 2100 patients, 345 renal biopsies had primary FSGS diagnosed by light and immunofluorescence microscopies, and classified according to the Columbia classification. The pathological, para-clinical, and demographic characteristics including gender and age were assessed.

Results: The mean age of 345 patients was 40.05±14.98 years. Regarding gender, 60.9% (n=210) of the patients were males. The mean serum creatinine and proteinuria in all patients were 1.54±0.91 mg/dL and 2267.94±1501.22 mg/d, respectively. The classic or not otherwise specified (NOS) variant was the most frequent variant. In this study, serum creatinine was significantly different among the five variants in which collapsing variant had higher serum creatinine 2.83±1.12 mg/dL. Similarly, proteinuria was higher in the collapsing variant, 2666.67±568.03 mg/d. A comparison of the mean age, serum creatinine, and proteinuria among genders showed a significant difference between male and female patients with males having higher mean age, 42.28±15.71 years, serum creatinine, 1.6822±1.02 mg/dL and proteinuria, 2434.67±1735.60 mg/d. In this study, the NOS variant was more prevalent in males, followed by the perihilar variant (n=57) and tip variant (n=56). Interstitial fibrosis was compared among different variants. It was significantly different among the variants, in which collapsing variant had higher interstitial fibrosis at 58.50±25.24%. On comparing the variants frequency, serum creatinine, proteinuria, and interstitial fibrosis among the age groups (40 years and less versus above 40 years) of patients with FSGS, the results showed no significant difference.

Conclusion: The results of this study showed that overall, the FSGS, NOS variant, was the most common morphological variant. However, the collapsing variant was more severe as compared to other variants. The disease was severe in males as compared with females. No significant difference was found in the frequency of variants or disease severity between elderly versus young FSGS patients.

Keywords: Focal segmental glomerulosclerosis, Serum creatinine, Proteinuria, Interstitial fibrosis, Columbia classification

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Introduction

Focal segmental glomerulosclerosis (FSGS) is currently recognized as one of the most common causes of primary glomerular disease in adults and its incidence has recently been increasing (1). Furthermore, it accounts for about 20%-25% of patients who undergo renal biopsy for the diagnosis of glomerulonephritis. This disease is also one of the most common glomerular diseases, which leads to end-stage renal disease (2). This lesion is a histological pattern of glomerular injury, rather than a single disease, that is caused by diverse clinicopathological entities with different mechanisms of injury to the podocyte, which is the principal target of the lesion, leading to the characteristic sclerotic lesions in parts (i.e., segmental) of some (i.e., focal) but not all of the glomeruli (3).

According to the etiology, FSGS has been classified into primary and secondary forms which include maladaptive, genetic, virus-associated, and medication-induced FSGS.

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Implication for health policy/practice/research/ medical education

In a cross-sectional study on 345 focal segmental glomerulosclerosis (FSGS) patients, we found that serum creatinine was 1.54±0.91 mg/dL, along with proteinuria of 2267.94±1501.22 mg/d. We also found, the classic or not otherwise specified (NOS) variant was the most frequent variant, however, the collapsing variant was more severe as compared to other variants. The disease was severe in males as compared with females. No significant difference was found in the frequency of variants or disease severity between elderly versus young FSGS patients.

The primary disease results in nephrotic syndrome (NS) while secondary forms may be associated with systemic disease (4). Distinguishing between the different forms is crucial since management must be tailored according to the underlying etiology. Primary FSGS is presumably an immunological disease caused by an unknown circulating factor that leads to nephrotic syndrome (4,5).

According to the morphological features, a group of nephropathologists proposed a standardized classification system, named the Columbia classification in 2003. Based on this classification, five histologic variants have been defined for FSGS as follows (6-9);

- Not otherwise specified (NOS) or classic variant
- Tip variant
- Collapsing variant
- Perihilar variant
- Cellular variant

Objectives

This study was carried out to determine the frequency of each variant of FSGS among a group of adult primary FSGS patients at a single nephropathology laboratory in, Isfahan, Iran. We also aimed to evaluate the relationship among various demographic and clinical factors with the morphological features of FSGS.

Patients and Methods

Study method

This is a cross-sectional, descriptive analytical study conducted on the referral renal biopsies from hospitalized patients at Al-Zahra and Khurshid hospitals of Isfahan university of medical sciences or from private clinics as well as from the nephrology department of Shahrekord university of medical sciences from 2009 to 2022. This study is an update of our previous investigation of 212 patients with primary forms of FSGS (10), in which was continued to date. Along with new renal biopsies, we set out to re-assess the data of renal biopsies of 345 biopsy-proven FSGS after eight years of the publication of the first study. In this study, we additionally focused on the presentation of FSGS in elderly versus young patients. All biopsies were examined using both light and immunofluorescence (IF) microscopies. The diagnosis was made by the absence of IgA, IgG, and C1q deposits and/or with few deposits of C3 and/or IgM on the IF microscopy along with morphologic lesions on light microscopy (LM). The relevant demographic and laboratory information, including age, gender, and serum creatinine levels and also 24-hour proteinuria was collected and recorded.

To evaluate the morphologic lesions by LM, specimens were processed in formalin to stain with H&E, Jones, periodic acid–Schiff (PAS), and Masson's trichrome staining. The exclusion criterion was biopsies below eight glomeruli on LM. The description of glomerular morphologic lesions and variants of FSGS were determined, according to previous studies (8,9). Briefly, the tip variant of FSGS required the exclusion of collapsing variant along with the presence of at least one glomerulus with segmental lesion involving the tip domain of the glomerular capillary tuft (Figure 1). Regarding the perihilar variant, the segmental sclerotic lesion was situated at the vascular pole and required the exclusion of collapsing, tip, or cellular lesions (Figure 2). The cellular variant necessitated the exclusion of collapsing and tip lesions and was described by segmental endocapillary hypercellularity occluding

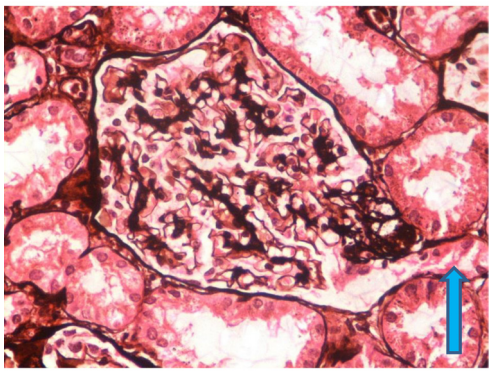

Figure 1. A glomerulus showing segmental sclerosis involving the tip domain of the glomerulus (blue arrow). There is also adhesion formation and intracapillary foam cells. The vascular pole is located at the opposite side of the lesion (JMS, ×400).

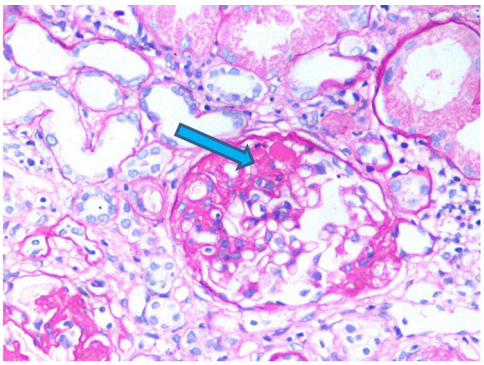

Figure 2. A glomerulus at high-power magnification showing segmental sclerosis involving the vascular pole (blue arrow). There is also marked hyalinosis in the areas of scarring (PAS, ×400).

lumina in at least one glomerulus. The collapsing variant was identified by the collapse of at least one capillary loop along with hypertrophy and hyperplasia of overlying visceral epithelial cells, regardless of the presence of other variants of FSGS (Figure 3). In cases where none of these definitions were satisfied, the term NOS was used (Figure 4). Thus, FSGS of the NOS type is a histologic diagnosis of exclusion (9).

In addition, the percent of interstitial fibrosis and tubular atrophy was also determined. Moreover, deposits of C3 and IgM by the IF microscopy were indicated using intensity values ranging from 0 to +3. The diagnosis of the FSGS variant was made according to previous studies (8,10).

Statistical analysis

The quantitative variables were described using the mean and standard deviation (SD), while the qualitative variables were described using the frequency and percentage. The comparisons were performed using Pearson's correlation, independent t-test, and one-way ANOVA for quantitative variables, and chi-square and Fisher's exact tests for qualitative variables. Data analysis was conducted by SPSS version 22 with a significance level of $P<0.05$ for all tests.

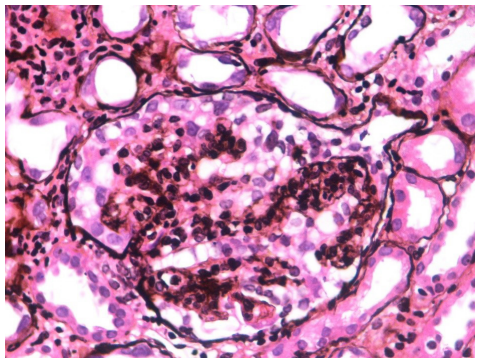

Figure 3. A glomerulus at high magnification shows the global collapse of capillary tufts associated with podocyte hypertrophy and hyperplasia. The later are filling the Bowman's space (JMS, ×400).

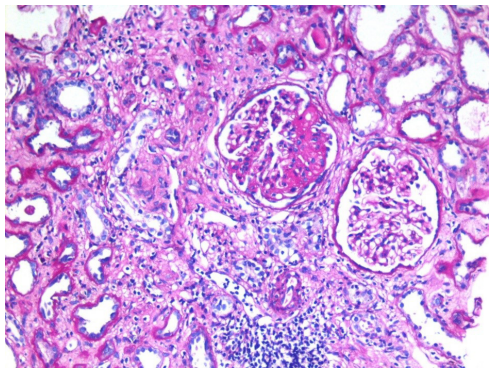

Figure 4. A medium-power view shows two glomeruli, one of which is normal. The other glomerulus is showing segmental sclerosis involving the periphery of the capillary tuft and focal adhesion formation with Bowman's capsule. The vascular pole is at the upper part of the glomerulus. There is marked tubular atrophy and interstitial inflammation in the background (PAS, ×200).

Results

The mean age of all patients was 40.05±14.98 years (range; 3-86 years). Regarding gender, 60.9% (n=210) of the patients were males and 39.1% (n=135) females. Figure 5 shows the frequency distribution of the variants of FSGS in this study. This figure shows that the classic or NOS variant was the common variant, followed by tip and perihilar variants, respectively.

The mean serum creatinine and 24-hour proteinuria levels in all patients were 1.54±0.91 mg/dL and 2267.94±1501.22 mg/d, respectively. In this study, serum creatinine was significantly different among the five variants ($P<0.001$); the collapsing variant had higher serum creatinine, 2.83±1.12 mg/dL. The 24-hour proteinuria was also higher in the collapsing variant, 2666.67±568.03 mg/d (Table 1).

A comparison of the mean age, serum creatinine, and proteinuria of FSGS between genders is illustrated in Table 2. All variables had significant differences between male and female patients in which male patients had high levels of serum creatinine and proteinuria and were older.

Table 3 shows the frequency distribution of variants of FSGS according to the patients' gender. This table shows that the NOS variant (n=91) was more common in the male gender. The collapsing variant was found exclusively in male patients.

Interstitial fibrosis was compared among different FSGS variants using one-way ANOVA. Interstitial fibrosis was significantly different in different variants ($P=0.015$), in which, collapsing variant had higher interstitial fibrosis, 58.50±25.24 % (Table 4).

The mean percent of glomerulosclerosis was 25.22±21.10 % without significant difference among variants ($P=0.130$) and genders ($P=0.721$; Table 5).

There was no significant correlation between glomerulosclerosis and age (r=0.011, $P=0.868$), serum

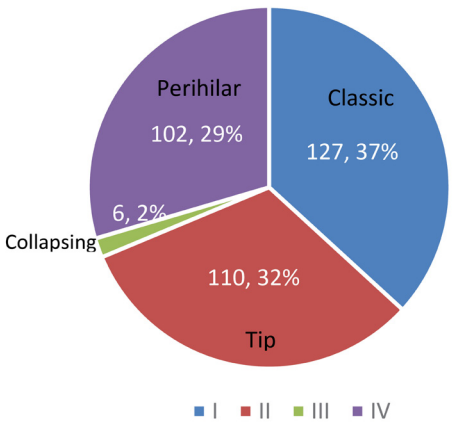

Figure 5. Frequency of FSGS variants in the studied patients (n=345).

Table 1. Comparison of serum creatinine and proteinuria across different variants using one-way ANOVA

Variables	FSGS variants	Number	Mean	Standard deviation	*P* value
Serum creatinine (mg/dL)	NOS	127	1.66	0.93	<0.001
	Tip	110	1.26	0.53	
	Collapsing	6	2.83	1.12	
	Perihilar	102	1.64	1.09	
Proteinuria (mg/d)	NOS	127	2097.35	1388.21	0.021
	Tip	110	2617.78	1854.07	
	Collapsing	6	2666.67	568.03	
	Perihilar	101	2077.75	1149.41	

creatinine (r=-0.037, $P=0.577$), and proteinuria (r=-0.050, $P=0.450$) of the patients; however, interstitial fibrosis (r=0.327, $P<0.001$) had a weak positive correlation with glomerulosclerosis (Table 6).

On applying the chi-square test to compare variants across age groups (40 and less versus above 40 years), the results showed no significant difference ($P=0.370$; Table 7).

According to the independent T-test comparing serum creatinine, proteinuria, and interstitial fibrosis in different age groups (40 and less versus above 40 years), the results showed no significant difference regarding serum creatinine ($P=0.122$), proteinuria ($P=0.406$) and interstitial fibrosis ($P=0.440$; Table 8).

Table 2. Comparison of age, serum creatinine, and proteinuria among genders using independent T-test

Variable		Mean	SD	*P* value
Age (years)	Male	42.28	15.71	0.001
	Female	36.71	13.018	
Serum creatinine (mg/dL)	Male	1.6822	1.02	0.001
	Female	1.3411	0.67	
Proteinuria (mg/d)	Male	2434.67	1735.60	0.009
	Female	2002.43	991.13	

Table 3. Comparison of different variants of FSGS across gender using chi-square test

Variable	Variant				*P* value
	NOS	Tip	Collapsing	Perihilar	
Male	91	56	6	57	0.001
Female	36	54	0	45	

Table 4. Comparison of interstitial fibrosis among different variants of FSGS using one-way ANOVA test

Variable		Mean	Standard deviation	*P* value
Interstitial fibrosis (%)	NOS	24.26	21.74	0.015
	Tip	28.01	30.36	
	Collapsing	58.50	25.24	
	Perihilar	26.06	25.23	

Discussion

FSGS is one of the most common causes of NS in adults and children, and its prevalence is increasing worldwide. FSGS is a rare and complex kidney disease that can lead to significant morbidity and mortality. The prevalence and characteristics of FSGS vary in different populations and geographic regions, so studying this disease in specific populations is important to better understand its pathogenesis and clinical outcomes.

The findings of this study provide valuable insights into the prevalence and characteristics of different variants of FSGS in Iran. This study investigated the prevalence of variants of FSGS, and the clinicopathologic and demographic characteristics of each of the variants in Iran and focused on differences in the frequency of FSGS variants in the young versus old population.

We found that the NOS variant was the most frequent variant among all variants (36.8%), which is consistent with the previous studies (11-14). It was followed by tip (31.88%) and perihilar (29.5%) variants. The mean age of all patients was 40.05±14.98 years (range: 3-86 years) which shows a lower average than a previous study (15). The lower mean age of patients in this study as compared to the study by Nada et al (15) may indicate a higher incidence of FSGS in younger populations in Iran.

Regarding gender, 60.9% of the patients were male and 39.1% female as in a previous study from the United States (12). Not only the NOS variant was more prevalent in all

Table 5. Comparison of glomerulosclerosis by FSGS variants and gender using independent T-test and one-way ANOVA

Glomerulosclerosis (%)		Mean	Standard deviation	*P* value
Variant	NOS	26.37	19.01	0.130*
	Tip	23.48	22.22	
	Collapsing	43.78	30.85	
	Perihilar	23.81	21.59	
Gender	Male	25.61	21.48	0.721**
	Female	24.58	20.54	

Table 6. Pearson's correlation of glomerulosclerosis with age, serum creatinine, proteinuria, and interstitial fibrosis

Variable		Age (year)	Serum creatinine (mg/dL)	Proteinuria (mg/dL)	Interstitial fibrosis (%)
Glomerulosclerosis	Pearson's correlation coefficient	0.011	-0.037	-0.050	0.327
	P value	0.868	0.577	0.450	<0.001

Table 7. Frequency of variants across the age groups using chi-square

Variants	Age group		*P* value
	≤40 years	>40 years	
NOS	72	55	0.370
Tip	75	35	
Collapsing	3	3	
Perihilar	54	48	

Table 8. Comparison of serum creatinine, proteinuria, and interstitial fibrosis across age groups using independent T-test

Variable	Age (y)	Mean	SD	*P* value
Serum creatinine (mg/dL)	≤40	1.48	0.95	0.122
	>40	1.63	0.84	
Interstitial fibrosis (%)	≤40	28.11	26.16	0.406
	>40	25.09	24.79	
Proteinuria (mg/d)	≤40	2216.04	1556.93	0.440
	>40	2343.58	1418.21	

patients, it was also more frequent in male gender. The gender distribution of FSGS patients in this study is also consistent with previous studies, and the ratio of male patients was greater than female patients. Interestingly, the NOS variant was more frequently detected in male patients, which may indicate a gender-specific predisposition to this variant. More research is needed to better understand the underlying mechanisms and risk factors associated with this gender bias.

Males had greater mean age, mean serum creatinine and mean 24-hr proteinuria than females. The interstitial fibrosis was considerably different among the variants in which collapsing variant had the highest amount of interstitial fibrosis. The relationship between interstitial fibrosis and the collapsing variant of FSGS is an important finding that shows the importance of early diagnosis and treatment of FSGS to prevent the progression of the disease and the development of interstitial fibrosis. This finding also suggests that the collapsing variant may have a more aggressive course than other variants of FSGS, which may require more aggressive treatment.

The mean percent of glomerulosclerosis was one quarter of all cases. In this study, no significant difference among variants, genders, age, serum creatinine, and proteinuria of the patients was seen with regard to glomerulosclerosis. However, interstitial fibrosis had a positive association with glomerulosclerosis.

In this study, we compared serum creatinine, proteinuria and interstitial fibrosis across age groups (40 years old and less versus above 40 years); the results presented no significant difference regarding serum creatinine, proteinuria and interstitial fibrosis. The lack of significant differences in serum creatinine, proteinuria, and interstitial fibrosis across age groups suggests that FSGS may have similar clinical features and outcomes regardless of age.

A comparison of the results of the present study with previous similar studies reveals various similarities and differences. This comparison is a suitable method to check the course of changes related to the investigated disorders over time, which helps to more accurately check the disease and its appropriate treatment.

In Table 9, a summary of the frequency of variants in 10 countries is presented as literature review.

According to the results of this comparative study, in relation to gender, in all studies in which the gender of the patients, males outnumbered women. In addition, in terms of the type of lesions, in the vast majority of studies, the NOS variant was the predominant variant. Of note, the collapsing variant of FSGS was more common in Brazil compared to other centers worldwide, possibly related to environmental and socioeconomic factors. In the current study, the collapsing variant had higher serum creatinine, which was in accordance with the results of the most recent study in this field by Nuguri et al (20). Furthermore, in our study, higher proteinuria was noted in the collapsing variety, which was different from other studies. For instance, in a study by Thomas et al (12), in addition to the collapsing variant, proteinuria was also high in the tip variety. In the study of Shi et al (13), proteinuria was higher in tip and cellular variants. In a study by Nada et al (15), this quantity was also higher in the tip variant. The result of our study is in accordance with the study by Nuguri et al (20) in terms of both serum creatinine and proteinuria.

Overall, this study provides important information about the prevalence, demographic and clinicopathological characteristics of different variants of FSGS in Iran. More research is needed to better understand the underlying mechanisms and risk factors associated with FSGS and to develop more effective treatments for this debilitating disease. The findings of this study may have important implications for the management of FSGS in Iran and other populations with similar characteristics.

Conclusion

Columbia classification of idiopathic FSGS into five histologic variants provides insight into the distinct clinicopathologic features of these variants in different populations and should be further elucidated by detailed

Table 9. A comparison of the frequency of FSGS variants across different countries

Variants	NOS	Tip	Collapsing	Prehilar	Cellular	Total
Huang et al (11) (China, 2004)	-	7	-	17	14	38
Thomas et al (12) (USA, 2006)	83	34	22	52	6	197
Shi et al (13) (China, 2007)	57	5	7	7	26	102
Deegens et al (14) (The Netherlands, 2008)	30	34	5	24	-	93
Nada et al (15) (India, 2009)	12	28	4	8	17	69
El-Refaey et al (16) (Egypt, 2010)	61	2	4	5	-	72
Testagrossa et al (17) (Brazil, 2012)	50	19	48	9	5	131
Shakeel et al (18) (Pakistan, 2013)	92	12	14	2	1	121
Kwon et al (19) (South Korea, 2014)	70	20	1	17	3	111
Nuguri et al (20) (India, 2023)	523	32	9	17	29	610
Nasri et al (Iran,2023)	127	102	6	102	-	345

long-term follow-up studies in the future. This study investigated the frequency of variants and compared serum creatinine, proteinuria and interstitial fibrosis in age groups in patients with FSGS. The results showed that there is no significant difference in the frequency of variants or these biomarkers between older and younger patients. These findings suggest that age may not be an important factor in the development of FSGS or its associated biomarkers. However, more research is needed to confirm these results and explore other potential factors that may contribute to this condition. Overall, this study highlights the importance of continued research into FSGS and its underlying mechanisms to improve diagnosis, treatment, and patient outcomes. The findings of this study show the need for timely diagnosis and treatment of FSGS in Iran to prevent disease progression and interstitial fibrosis.

Limitations of the study

This study was single center-based and cross-sectional in nature. No treatment or follow-up data was analyzed. We suggest larger multi-centric investigations on this subject.

Authors' contribution

Conceptualization: Hamid Nasri and Raha Manouchehrian.
Data curation: Raha Manouchehrian .
Formal analysis: Raha Manouchehrian.
Investigation: Hamid Nasri.
Methodology: Hamid Nasri.
Project administration: Hamid Nasri.
Resources: Hamid Nasri.
Software: Hamid Nasri.
Supervision: Hamid Nasri.
Validation: Hamid Nasri.
Visualization: Hamid Nasri.
Writing–original draft: Raha Manouchehrian.
Writing–review & editing: Hossein Mardanparvar, Yassamin Rabiei, Muhammed Mubarak, Rahma Rashid

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This investigation adhered to the Declaration of Helsinki. Additionally, the study received approval from the Ethics Committee of Isfahan University of Medical Sciences (Ethical code: IR.MUI.MED.REC.1399.1053). Written informed consent was obtained from all participants prior to renal biopsy or upon hospitalization. The study protocol also was registered on the Research Registry website with the unique identification number (UIN) researchregistry9615). The authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

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