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Original Article

Clinical pathological characteristics and initial treatment of primary focal segmental glomerulosclerosis in Chinese patients

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Abstract: Background: Few studies have focused on the clinical pathological features and initial treatment of focal segmental glomerulosclerosis (FSGS) in Asian populations. There is a lack of large-sample-size retrospective studies of primary FSGS in Chinese patients. Methods: This retrospective study included 808 patients diagnosed with primary FSGS, between January 2003 until December 2017. This study aimed to explore the prevalence of pathological and clinical features of primary FSGS over the past 15 years, as well as characteristics of each variant under the Columbia classification, a recognized pathological classification. A total of 361 patients were classified by the Columbia classification, of which 277 underwent regular follow-ups (6 months - 60 months). According to follow-up data, the current study summed up the best initial treatment based on proteinuria and Columbia classification. Results: As the years have progressed, the proportion of pFSGS patients, among all renal biopsy patients, has decreased gradually. Detection rates of 2003-2007, 2008-2012, and 2013-2017 were, respectively, 14.7%, 9.7%, and 7.9%. The proportion of pFSGS patients, among primary glomerular disease (PGD), has also decreased, respectively 22.5%, 14.5%, and 11.1%. Over time, the proportion of glomerular segmental sclerosis has gradually decreased, while the proportion of glomerular global sclerosis has gradually increased. In the current study, NOS showed the highest prevalence of (73.6%), followed by perihilar (14.1%), tip (9.2%), and collapsing variants (2.5%). Cellular variants had the lowest prevalence (0.6%). Present results showed that, in Perihilar with moderate proteinuria, simple ACEI/ARB, as an initial treatment, can bring satisfactory remission rates. Regarding NOS and tip, ACEI/ARB combined with steroids can lead to better remission rates. For Tip with severe proteinuria, steroids alone are able to obtain satisfactory remission rates. With NOS, remission rates of steroids + CTX are better than those of steroids alone or steroids + CNIs. Conclusion: Over the past 15 years, FSGS detection rates of renal biopsies and PGD have shown a downward trend. Over time, the proportion of glomerular segmental sclerosis has gradually decreased, while the proportion of glomerular global sclerosis has gradually increased, with aging as an independent factor in this trend. In choosing an initial treatment, the combination of both proteinuria and Columbia classification may bring higher remission rates.

Keywords: Focal segmental glomerulosclerosis, epidemiology, Columbia classification, initial treatment, remission rate

Background

Focal segmental glomerulosclerosis (FSGS) is a common clinical pathology syndrome, with proteinuria or nephrotic syndrome (NS) as the main manifestation. Characteristic pathological features include focal, segmental, non-proliferative capillary loop sclerosis, and podocyte injuries. FSGS is divided into primary and secondary FSGS. A variety of known causes may lead to focal segmental glomerulosclerosis lesions, described as secondary FSGS, including viral infections, drug toxicity, reflux nephropathy, glomerular capillary high pressure or high perfusion, and a variety of chronic glomerulonephritis cases turning into FSGS later. Diagnosis of primary FSGS requires ruling out various secondary factors. Many patients eventually progress to end-stage renal disease (ESRD), posing a financial burden and resulting in a decline in the quality of life. Patients with FSGS tend to have a poor prognosis, with 50% of patients

with proteinuria over 3 g/24 hours progressing to ESRD within 10 years [1].

Based on the Columbia pathological classification, FSGS is divided into 5 histologic variants, including not-otherwise specified (NOS), tip, perihilar, collapsing, and cellular [2]. According to previous studies, NOS is most common in Asian countries, with the collapsing variant showing the highest proportion of glomerulosclerosis by light microscopy, accounting for 60%. The tip variant shows the best prognosis [3]. Few studies have focused on pathological and clinical features of FSGS in Asian populations. Large-sample-size retrospective studies of primary FSGS are lacking. Therefore, the current retrospective study aimed to explore changes in pathological and clinical features of primary FSGS over the past 15 years, examining characteristics and the best initial treatment of each variant of the Columbia classification.

Methods

Ethics

This study was approved by the Ethics Committee of Ruijin Hospital [Clinical Ethics Approval No.154] and is in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Inclusion and exclusion criteria

Inclusion criteria: 1) Underwent renal biopsy from 2003-2017; 2) Renal biopsy confirmed as FSGS; and 3) Age > 14 years (**Figure 1**).

Exclusion criteria: 1) Secondary FSGS; 2) Number of glomeruli < 10; 3) Complicated by tumors or serious infections; and 4) Obese patients with a body mass index (BMI) > 28 kg/m^2.

Pathologic and clinical data

Ultrasound was used to perform percutaneous renal biopsies. The lower pole of the right kidney was marked on the skin. Biopsy specimens were made into 25 sections, each containing more than ten glomeruli. They were stained by Masson's staining, H&E staining, PAS staining, and Jones staining. All specimens were analyzed by light microscopy, immunofluorescence, and electron microscopy. During the observation period, unified diagnostic criteria were maintained. The Columbia classification was proposed in 2004 and gradually adopted widely. The present research department formally adopted the Columbia classification in 2009. From 2009-2017, 361 patients were classified into NOS, perihilar, tip, collapsing, and cellular variants by the Columbia classification. Demographic and clinical data included age of onset, gender, blood pressure, presence of hematuria and NS, serum creatinine (Scr), estimated glomerular filtration (eGFR), chronic kidney disease (CKD) staging, 24-h proteinuria, serum albumin (Alb), hemoglobin (Hb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen (BUN), uric acid (UA), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), and low density lipoprotein (LDL). Moreover, in this study, e-GFR was calculated by the CKD-EPI equation. Hematuria is defined as ≥ 3 red blood cells under high magnification. NS is defined as 24-h proteinuria > 3.5 g/d, Alb < 30 g/L, with or without generalized edema and hypercholesterolemia. Nephrotic proteinuria is defined as 24-hours of proteinuria > 3.5 g. CKD staging was divided into eGFR, stage 1 CKD: eGFR ≥ 90 mL/min/1.73 m^2, stage 2 CKD: 60 ≤ eGFR < 90 ml/min/1.73 m^2, stage 3 CKD: 30 ≤ eGFR < 60 ml/min/1.73 m^2, stage 4 CKD: 15 ≤ eGFR < 30 ml/min/1.73 m^2, and stage 5 CKD: eGFR < 15/min/1.73 m^2. Also, eGFR was calculated by the EPI formula. Tubulointerstitial lesion (TIL) index: 0-no lesions found, 1-lesion range < 25%, 2-lesion range 25-50%, and 3-lesion range > 50% [4].

Evaluation of outcomes

Observing clinical and pathological data of 808 pFSGS patients from 2003-2017, the current study sought to determine if there was a variation in pFSGS prevalence over the previous 15 years. With 361 patients classified by the Columbia classification, this study summed the characteristics of each variant under the Columbia classification. Of the 361 patients, 277 were regularly followed-up. The composite endpoint event is defined as a doubling of baseline serum creatinine or entering the ESRD phase, with ESRD defined as eGFR < 15/min/1.73 m^2. Complete remission (CR) is defined as < 0.3 g/24 hours of proteinuria. Partial remission

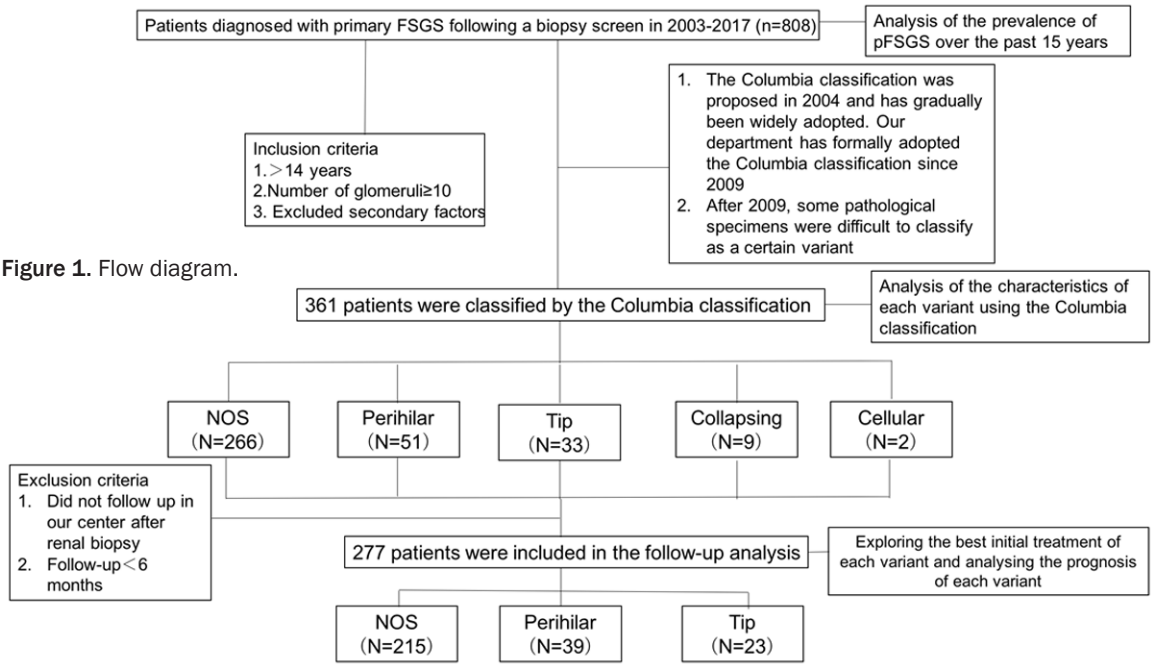

Figure 1. Flow diagram.

(PR) is defined as > 50% reduction in proteinuria from baseline. Baseline data was collected at the time of the renal biopsy.

Statistical analyses

Statistical analyses were performed using IBM SPSS statistic 24. Normal distribution measurement data are expressed as means ± standard deviation and differences between groups were tested by one-way ANOVA. Non-normal distribution data are expressed as medians (interquartile range) and differences between groups were tested by the Kruskal-Wallis test. Enumeration data are expressed in terms of frequency and differences between groups were tested by Chi-squared test. Pairwise comparisons of multiple groups were conducted with Bonferroni's test. Multiple linear regression was used to test independent factors. In this study, $p < 0.05$ indicates statistical significance.

Results

Characteristics of FSGS patients

From 2003 until 2017, 808 patients underwent renal biopsies and were diagnosed as primary FSGS. Of these, 459 were males (56.8%) and 349 were females (43.2%). Age of onset ranged from 14 to 82 years and the median age was 39 years. Regarding clinical manifestations, 372 patients presented with simple proteinuria (46%) and 436 patients presented with hematuria complicated with proteinuria (54%). For baseline 24-hour proteinuria, the most common range was 1.0-3.5 g (325 patients, 40%). This was followed by nephrotic range proteinuria (233, 29%), 0.5-1 g (108, 14%), 0.15-0.5 g (99, 12%), and ≤ 0.15 g (42, 5%). Overall, 224 patients presented with NS before the renal biopsy, accounting for 28% of all pFSGS patients. According to CKD staging, 305 patients in this retrospective study belonged to stage 1 CKD (37.67%), 153 patients to stage 2 (18.9%), 190 patients to stage 3 (23.5%), 110 patients to stage 4 (13.6%), and 50 patients to stage 5 (6.2%). Patients that were in CKD stage 5 when they underwent the renal biopsy were accompanied with acute kidney injuries or acute exacerbation of chronic kidney disease. Of the 808 patients with primary FSGS, 361 were classified into NOS (266, 73.6%), perihilar (51, 14.1%), tip (33, 9.2%), collapsing (9, 2.5%) and cellular (2, 0.6%) variants, according to Columbia classification.

Variation tendency of pFSGS over the past 15 years

Patients were divided into three groups according to the year of renal biopsy, including 2003-2007, 2008-2012, and 2013-2017. The num-

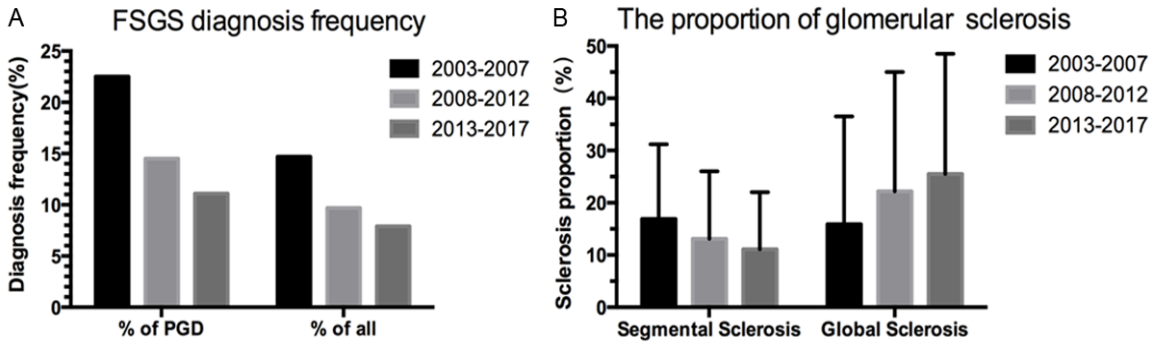

Figure 2. A. FSGS diagnosis frequency of all renal biopsies and primary glomerular disease (PGD) patients decreased during the 15-year period. In 2003-2007, 2008-2012, and 2013-2017, the FSGS detection rate of PGD was 22.5%, 14.5%, and 11.1%, respectively. The detection rate of renal biopsy was 14.7%, 9.7%, and 7.9%, respectively. Detection rates of both renal biopsy and PGD showed gradual downward trends. B. The proportion of glomerular segmental sclerosis gradually decreased (16.9% vs 13.1% vs 11.1%), while the proportion of glomerular global sclerosis gradually increased (15.9% vs 22.2% vs 25.5%) during the 15-year period.

bers of patients in each group were 339, 250, and 219, respectively. There were no significant differences in gender between the groups. In 2003-2007, 2008-2012, and 2013-2017, the pFSGS detection rate of renal biopsy was 14.7%, 9.7%, and 7.9%, respectively. Detection rate of PGD was 22.5%, 14.5%, and 11.1%, respectively. Detection rates of both renal biopsy and PGD showed gradual downward trends (**Figure 2A**). Clinical and pathological data are listed in **Table 1**. According to statistical analysis, FSGS patients show an aging trend in recent years (45.4 vs 39.0/40.2). The proportion of patients with hypertension increased each year, especially in the last 5 years (25.7% vs 34.4% vs 50.2%). Compared with 2003-2007 and 2008-2012, incidence of NS showed an upward trend in 2013-2017 (38.8% vs 24.8%/22.0%). Interestingly, according to light microscopy, the proportion of glomerular segmental sclerosis decreased each year, while the proportion of glomerular global sclerosis increased each year ($p < 0.05$) (**Figure 2B**). Using multiple linear regression of factors, including gender, age, hypertension, Scr, and NS, age was found to be an independent factor for this trend (B: 0.25, $p < 0.01$). The proportion of patients with vascular lesions gradually increased in recent years, as observed by thickening of the renal arteriole wall (31.4% vs 45.8% vs 61.6%) and hyaline degeneration of the renal arteriole (34.2% vs 46.6% vs 60.3%).

Characteristics of each variant under the Columbia classification

Of the 361 patients classified by the Columbia classification, significant differences were found between 5 variants (**Table 2**). NOS variant was the oldest of the 5 variants, while perihilar and tip variants were younger than the other three variants. In collapsing and tip variants, the proportion of male patients reached more than 70%. Perihilar variants showed a higher incidence of hypertension (60.9%) and lower hematuresis (29.4%). The tip variant showed a higher occurrence rate of NS than the other 4 variants. Additionally, the tip variant showed the highest 24-hour proteinuria and the lowest Alb of the 5 variants ($p < 0.05$). The collapsing variant showed the highest Scr and lowest eGFR, while tip and perihilar variants showed the lowest Scr and highest eGFR. Overall, 80.4% of perihilar variants and 78.8% of tip variants were in CKD1-2. All collapsing variants were in CKD4-5. Regarding lipid metabolism, TC and LDL of the tip variant were significantly higher than the other variants ($p < 0.05$). The proportion of glomerulosclerosis (segmental/global) was 15.8%/24.4% (NOS), 9.4%/12.5% (perihilar), 3.3%/3.1% (tip), 26.9%/42.2% (collapsing), and 10.2%/26.2% (cellular). The collapsing variant showed the highest proportion of segmental sclerosis and global sclerosis, while tip variants showed the lowest proportion of segmental sclerosis and global sclerosis. According to the TIL index, 97% of tip variants scored 0-1, followed by perihilar (80%) and NOS (60%). All collapsing and cellular variants scored 2-3 ($p < 0.05$). Perihilar showed the most serious vascular disease. Moreover, 62.7% of perihilar showed thickening of the renal arteriole wall and 82.4% of perihilar showed hyaline degeneration of the renal arteriole.

Table 1. Clinical and pathological data changes by year

		2003-2007	2008-2012	2013-2017	*p*-value
N		339	250	219	
Gender	Male (%)	55.2%	58%	58%	NS[a,b,c]
	Female (%)	44.8%	42%	42%	
Age		39.0±15.2	40.2±15.8	45.4±16.8	Ns[a], < 0.05[b,c]
Hypertension (%)		25.7%	34.4%	50.2%	< 0.05[a,b,c]
SBP (mmHg)		129.1±20.5	132.4±65.5	138.8±20.7	Ns[a], < 0.05[b,c]
DBP (mmHg)		82.4±13.8	80.3±12.1	82.2±11.3	NS[abc]
Hematuresis (%)		59.0%	62.8%	36.1%	Ns[a], < 0.05[b,c]
24 h proteinuria (g/24 h)		1.8 (2.9)	1.6 (2.6)	2.6 (4.2)	Ns[a], < 0.05[b,c]
NS (%)		24.8%	22%	38.8%	Ns[a], < 0.05[b,c]
Hb (g/L)		128.9±22.1	130.6±20.8	130.7±20.8	NS[a,b,c]
Alb (g/L)		28.6±11.9	29.8±20.9	30.5±9.8	NS[a,b,c]
BUN (mmol/L)		6.4 (5.8)	6.2 (4.6)	6.4 (4.5)	NS[a,b,c]
Scr (μmol/L)		101 (134)	97 (93)	105 (81)	NS[a,b,c]
UA (μmol/L)		382.8±113.4	390.1±107.6	387.8±92.3	NS[a,b,c]
eGFR ((EPI) ml/min/1.73 m^2)		69.6 (82.7)	72.2 (64.4)	63.7 (55.8)	NS[a,b,c]
CKD staging (%)	1	41.6%	38.4%	31.1%	< 0.05
	2	13.3%	22.0%	24.2%	
	3	19.5%	24.0%	29.2%	
	4	16.5%	11.2%	11.9%	
	5	9.1%	4.4%	3.7%	
TG (mmol/L)		2.7±2.2	2.6±1.9	2.7±2.1	NS[a,b,c]
TC (mmol/L)		7.2±3.2	6.8±3.3	6.4±2.9	Ns[a,b], < 0.05[c]
HDL (mmol/L)		1.6±1.2	1.4±0.5	1.3±0.5	< 0.05[a,c], NS[b]
LDL (mmol/L)		4.6±2.8	4.3±2.6	4.0±2.2	< 0.05[a,b,c]
The proportion of glomerular	Segmental sclerosis (%)	16.9±14.3	13.1±12.9	11.1±10.9	< 0.05[a,b,c]
	Global sclerosis (%)	15.9±20.6	22.2±22.8	25.5±23.0	< 0.05[a,b,c]
TIL	0~1 (%)	58.4%	63.9%	61.2%	< 0.05[a,b,c]
	2~3 (%)	41.6%	36.1%	38.8%	
Thickening of renal arteriole wall (%)		31.4%	45.8%	61.6%	< 0.05[a,b,c]
Hyaline degeneration of renal arteriole (%)		34.2%	46.6%	60.3%	< 0.05[a,b,c]

NS: not significant; a: 2003-2007 vs 2008-2012; b: 2008-2012 vs 2013-2017; c: 2003-2007 vs 2013-2017.

Best initial treatment of each variant under the Columbia classification

Of the 361 patients, 277 patients underwent regular follow-ups, including 215 NOS, 39 perihilar, and 23 tip. Median follow-up time was 24 months. Patients were divided into three groups (small amount of proteinuria: 24 UP ≤ 1 g, moderate proteinuria: 1 g < 24 UP ≤ 3.5 g, severe proteinuria: 24 UP > 3.5 g) when choosing the initial treatment. For patients with small amounts of proteinuria, ACEI/ARB were given as the initial treatment, regardless of variants. In patients with moderate proteinuria, data showed that different variants should take different initial treatments. For the NOS variant with moderate proteinuria, using ACEI/ARB brought a 73% remission rate (5% CR, 68% PR). ACEI/ARB + Steroids (1 mg/kg) brought an 87% remission rate (30% CR, 57% PR). ACEI/ARB + Steroids + CTX brought a 78% remission rate (33% CR, 45% PR) (**Figure 3A**). Present data shows that, for the NOS variant with moderate proteinuria, using ACEI/ARB + Steroids as the initial treatment may bring higher remission rates than using ACEI/ARB ($p < 0.05$), but using CTX did not bring higher remission rates than using steroids alone. Thus, this study recommends the use ACEI/ARB + Steroids as the initial treatment for these patients. In the

Table 2. Changes in clinical and pathological data based on the Columbia classification

		NOS	Perihilar	Tip	Collapsing	Cellular	*p*-value
N		266 (73.6%)	51 (14.1%)	33 (9.2%)	9 (2.5%)	2 (0.6%)	
Gender	Male (%)	53.0%	60.8%	72.7%	77.8%	0.0%	$< 0.05^{a,b,c,e,f}$
	Female (%)	47.0%	39.2%	27.3%	22.2%	100%	
Age		42.2±15.9	36.6±15.7	36.8±18.7	40.3±14.2	40.4±6.4	$< 0.05^{a,b}$
Hypertension (%)		43.2%	60.9%	39.4%	55.6%	100%	$< 0.05^{a,c,e,h,l}$
SBP (mmHg)		137.3±63.9	135.9±20.1	140.2±20.9	139.4±31.6	125.0±7.0	$Ns^{a,b,c,d,e,f,g,h,i,j}$
DBP (mmHg)		82.2±11.8	81.9±10.1	84.9±9.8	88.3±22.5	77.5±10.6	$Ns^{a,b,c,d,e,f,g,h,i,j}$
Hematuresis (%)		54.5%	29.4%	48.5%	55.6%	50%	$< 0.05^{a,e,f,g}$
24h proteinuria (g/24 h)		1.7 (3.1)	2.1 (3.9)	6.3 (6.5)	2.3 (1.9)	0.8	$< 0.05^{b,e,h,l}$
NS (%)		28.4%	27.5%	66.7%	11.1%	0%	$< 0.05^{b,e,h,l}$
Hb (g/L)		130.7±19.7	139.3±18.1	130±14.7	108.9±25.5	135	$< 0.05^{a,c,e,f,h}$
Alb (g/L)		31.9±19.8	31.0±10.2	19.4±9.3	30.8±8.3	38.5	$< 0.05^{b,e,h,l}$
BUN (mmol/L)		6.3 (3.9)	6.2 (3.4)	6.2 (7)	20.6 (10.6)	6.4	$< 0.05^{c,f,h,l}$
Scr (μmol/L)		104 (92)	84 (46)	82 (40)	504 (314)	90	$< 0.05^{c,f,h,l}$
UA (μmol/L)		375.5±96.9	362.8±107.4	400.3±90.5	466.7±79.4	304	$< 0.05^{c,f,h,l}$
eGFR ((EPI) ml/min/1.73 m^2)		73.2 (77.6)	94.8 (62.2)	97.1 (57.1)	10.2 (8.45)	101	$< 0.05^{c,f}$
CKD staging (%)	1	40.9%	54.9%	57.6%	0%	50%	< 0.05
	2	20.1%	25.5%	21.2%	0%	0%	
	3	26.9%	9.8%	18.2%	0%	50%	
	4	9.8%	7.8%	3%	22.2%	0%	
	5	2.3%	2%	0%	77.8%	0%	
TG (mmol/L)		2.9±2.7	2.4±2.8	2.5±1.6	1.4±0.9	1.35	$Ns^{a,b,c,d,e,f,g,h,i,j}$
TC (mmol/L)		6.6±3.6	6.8±3.2	7.9±3.5	4.2±0.3	5.1	$< 0.05^{b,h}$
HDL (mmol/L)		1.3±0.5	1.6±0.8	1.4±0.4	1.4±0.4	1.7	$< 0.05^{a}$
LDL (mmol/L)		4.1±2.7	4.1±2.3	5.7±3.0	2.3±0.3	3.2	$< 0.05^{b,e,h,l}$
The proportion of glomerular	Segmental sclerosis (%)	15.8±12.8	9.4±11.9	3.3±2.8	26.9±16.9	10.2	$< 0.05^{a,b,c,e,f,h,l}$
	Global sclerosis (%)	24.4±21.9	12.5±18.3	3.1±6.4	42.2±26.9	26.2	$< 0.05^{a,b,c,e,f,h,l}$
TIL	0~1 (%)	59.9%	80.4%	97%	0%	0%	$< 0.05^{b,c,d,e,f,g,h,l}$
	2~3 (%)	30.1%	19.6%	3%	100%	100%	
Thickening of renal arteriole wall (%)		57.2%	62.7%	42.4%	77.8%	100%	$< 0.05^{b,c,d,e,f,g,h}$
Hyaline degeneration of renal arteriole (%)		54.2%	82.4%	39.4%	22.2%	50.0%	$< 0.05^{a,b,c,e,f,h}$

NS: not significant; a: NOS vs Perihilar; b: NOS vs Tip; c: NOS vs Collapsing; d: NOS vs Cellular; e: Perihilar vs Tip; f: Perihilar vs Collapsing; g: Perihilar vs Cellular; h: Tip vs Collapsing; I: Tip vs Cellular; J: Collapsing vs Cellular.

perihilar variant with moderate proteinuria, using ACEI/ARB brought a 92% remission rate (46% CR, 46% PR) and using ACEI/ARB + Steroids (1 mg/kg) brought an 88% remission rate (33% CR, 50% PR). No significant differences were found between these two treatments. No patients used ACEI/ARB + Steroids + CTX. Present data showed that, for the perihilar variant with moderate proteinuria, using ACEI/ARB + Steroids as the initial treatment did not bring higher remission rates than using ACEI/ARB, but may bring more adverse effects. Thus, this study recommends the use of ACEI/ARB as the initial treatment for these patients. According to previous reports, Tip is responsive to steroid treatment. Thus, steroids were used for the Tip variant with moderate proteinuria, bringing a 100% remission rate (60% CR, 40% PR). The use ACEI/ARB + Steroids is recommended as the initial treatment for these patients.

For the NOS variant with severe proteinuria, using steroids brought a 79% remission rate (24% CR, 55% PR), using Steroids + CTX brought an 87% remission rate (35% CR, 52% PR), and using Steroids + CNIs brought a 64% remission rate (9% CR, 55% PR) (**Figure 3B**). Present data shows that, for the NOS variant with severe proteinuria, using steroids + CTX as the initial treatment may bring higher CR rates than using steroids or steroids + CNIs. ($p < 0.05$). Thus, this study recommends the use steroids + CTX as the initial treatment for these patients. For the Perihilar variant with severe proteinuria, no significant differences in remission rates were

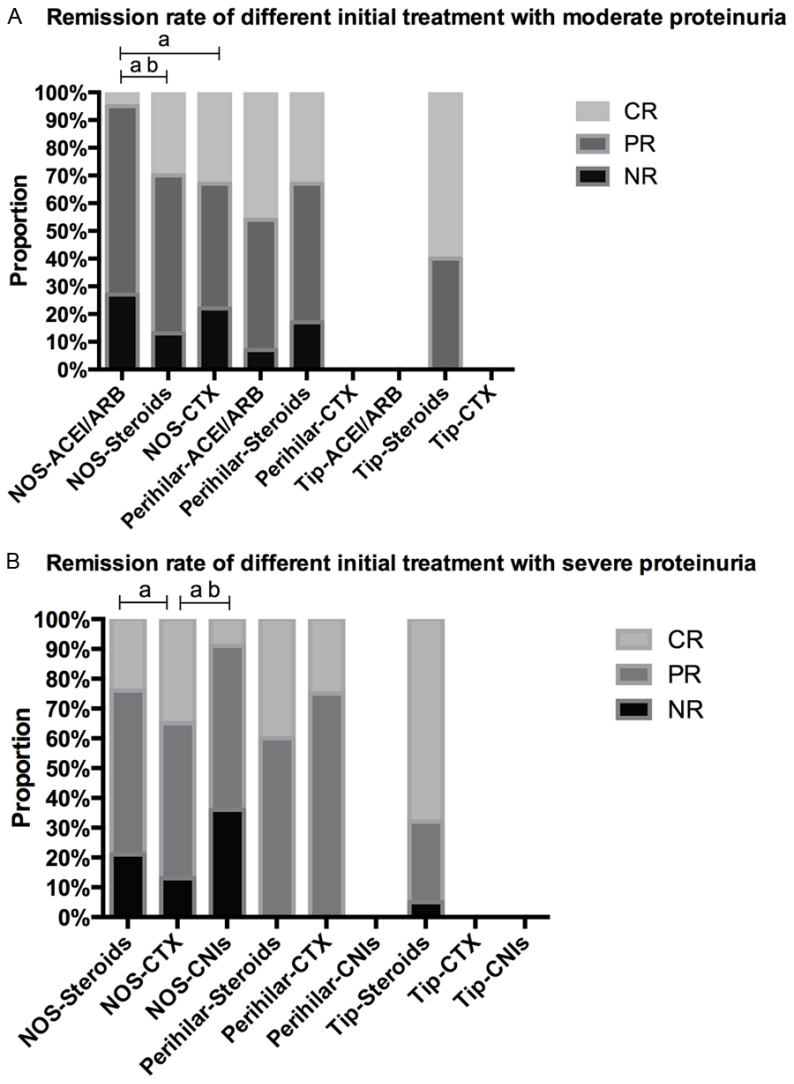

Figure 3. A. Remission rates of each variant with moderate proteinuria given different initial treatments. B. Remission rates of each variant with severe proteinuria given different initial treatments. CR: complete remission; PR: partial remission; NR: no response; a: shows significant differences in CR; b: shows significant differences in remission rates (CR + PR).

found between using only steroids and steroids + CTX. No patients used steroids + CNIs treatment. All tip variants with severe proteinuria were given simple steroid treatment, bringing a 95% remission rate (68% CR, 27% PR). This study recommends simple steroids as an effective initial treatment for these patients. According to data, the current study summed up the best initial treatment based on the proteinuria and Columbia classification (**Figure 4**).

Discussion

This retrospective study included 808 patients that were diagnosed as primary FSGS by renal biopsies in Shanghai Ruijin Hospital. All patients were of Han nationality and were from 27 provinces in China. There were more male patients than female patients (1.31:1), which is in line with a recent study of FSGS (1.32:1) [5]. In this study, onset age of patients was 14-82, of which incidence age was mainly concentrated among those aged 28-52 years. According to statistical analysis, FSGS patients showed an aging trend in recent years. This may be related to the aging of the population in China, especially in Shanghai [6]. Incidence of hypertension showed a significant upward trend in recent years (25.7% vs 34.4% vs 50.2%). This may be related to the aging trend, changes in lifestyle, and $PM_{2.5}$ pollution in China. These factors may have led to an increased incidence of hypertension in the population in general [7, 8]. A recent international epidemiological study of glomerular disease, including 29 centers in America, Europe, and Asia, showed the highest FSGS diagnosis frequencies in the Americas and the lowest in Asia (19.1% vs 6.9%). In the present center, FSGS accounted for 7.9% of glomerular diseases in the past 5 years, in accord with a previous study [9]. According to the current 15-year retrospective study, incidence of FSGS showed a gradual declining trend over the last 15 years (**Figure 2A**). A researcher from the University of North Carolina obtained similar conclusions in another 30-year review, where FSGS detection rates decreased from 27.2% to 24.7% [5, 9]. In recent years, the proportion of patients with hematuria has been declining, in accord with data from a center in Korea (36.1% vs 38.7%). The proportion of nephrotic syndrome has gradually increased

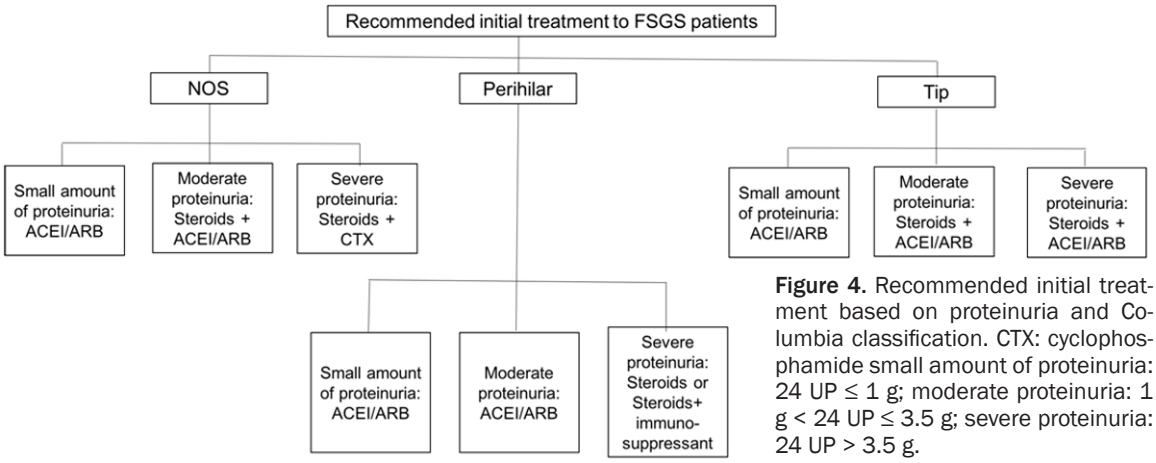

Figure 4. Recommended initial treatment based on proteinuria and Columbia classification. CTX: cyclophosphamide small amount of proteinuria: 24 UP ≤ 1 g; moderate proteinuria: 1 g < 24 UP ≤ 3.5 g; severe proteinuria: 24 UP > 3.5 g.

(2013-2017: 38.8%). Recent studies have shown that incidence of NS was 36%~70% in FSGS patients in North America, 50%~63% in Europe, and 37.8%~54.8% in Asia [10-16]. Incidence of NS in the present center was in line with incidence of NS in Asian populations. European countries and America may have a higher incidence of nephrotic syndrome because the proportions of collapsing and tip variants are higher than in Asian countries, where most of the collapsing and tip variants present as nephrotic syndrome [11].

Interestingly, the current study found that the proportion of glomerular segmental sclerosis gradually decreased each year, while the proportion of glomerular global sclerosis gradually increased ($p < 0.05$). Through multiple linear regression, it was found that age was an independent factor (B: 0.25, $p < 0.001$) for the proportion of glomerular segmental sclerosis gradually decreasing and the proportion of glomerular global sclerosis gradually increasing. Since segmental sclerosis may progress into global sclerosis after increasing, expanding, and integrating, along with age growth [17], it was assumed that aging may be an important reason for such a change. As age increases, segmental sclerosis gradually changes into global sclerosis, which can lead to the proportion of segmental sclerosis gradually decreasing and the proportion of global sclerosis increasing each year. Observing the thickening of the renal arteriole wall and hyaline degeneration of the renal arteriole, it was found that renal vascular lesions gradually increased. This may due to the aging trend and increasing proportion of patients with hypertension.

A total of 361 patients were categorized by the Columbia classification as NOS (266, 73.6%), perihilar (51, 14.1%), tip (33, 9.2%), collapsing (9, 2.5%), and cellular (2, 0.6%). According to available reports, NOS is the most highly prevalent variant, followed by perihilar, tip, collapsing, and cellular variants with the lowest prevalence. Collapsing is common in African Americans [10-13, 18, 19] (**Table 3**). NOS accounted for a large proportion of FSGS and was also the oldest among the 5 variants. Perihilar showed the most serious vascular disease under light microscopy, a lower proportion of hematuresis, and a higher proportion of hypertension than the other 4 variants. The collapsing variant showed the highest Scr and lowest eGFR. All collapsing variants were in CKD4-5. The collapsing variant also showed the highest proportion of glomerulosclerosis and the most severe interstitial injury. These factors, together, explain why the collapsing variant had the worst prognosis. In contrast, the tip variant showed the lowest Scr and highest GFR. The tip variant also showed the lowest proportion of glomerulosclerosis and the mildest interstitial injury. These factors led to the tip variant having a better prognosis. In addition, the tip variant showed the highest 24-h proteinuria and lowest Alb among the 5 variants. Moreover, 66.7% of tip variants showed NS. D'Agati reached the same conclusion in another study, showing that NS was most common in the tip variant, with up to 97% of tip variants showing NS [20]. The cellular variant was the least common, with only two in the current study. Stokes showed the importance of adequate sampling and sectioning, as approximately 30% of cellular variants were reclassified as tip variants

Table 3. Prevalence of variants in different population series

Variant by Columbia classification	Present (Chinese)	Tang (Chinese)	Shi (Chinese)	Kwon (Korean)	Nada (Indian)	Deegan (Dutch)	Thomas (African American)
Sample size (N)	361	104	102	111	210	93	197
NOS (%)	73.5	45.2	55.8	63.1	72.5	32.0	42.0
Perihilar (%)	14.2	13.5	6.9	15.3	4.0	26.0	26.0
Tip (%)	9.2	20.2	4.8	18.0	13.5	37.0	17.0
Collapsing (%)	2.5	6.7	6.9	0.9	2.0	5.0	11.0
Cellular (%)	0.6	14.4	25.5	2.7	8.0	0.0	3.0

upon deeper sectioning of the biopsy. This may explain why the detection rate of the cellular variant varies greatly among studies [21]. Some studies have suggested that cellular is the transitional stage of FSGS and may convert to other subtypes after a transient appearance as cellular. This may also explain the low detection rate of cellular FSGS [22].

The current study is the first to propose an initial treatment option based on Columbia classification. In the past, the choice of FSGS treatment was mainly based on the degree of proteinuria. However, present researchers concluded that the Columbia classification is an important factor when choosing initial treatments. Therefore, initial treatment analysis was conducted based on Columbia classification. For patients with small amounts of proteinuria, ACEI/ARB was given as the initial treatment. For patients with moderate amounts of proteinuria, the current guidelines of initial treatment are inconclusive. For these patients, should we use only ACEI/ARB or ACEI/ARB combined with steroids? Present results showed that, for Perihilar, simple ACEI/ARB as an initial treatment can bring satisfactory remission rates. For NOS and tip, ACEI/ARB combined with steroids can lead to better remission rates. Do we need to add an immunosuppressant for patients with severe proteinuria? Current results showed that, for Tip, steroids alone are able to obtain satisfactory remission rates. For NOS, the remission rate of steroids + CTX is better than that of steroids alone or steroids + CNIs. This study suggests that combining the degree of proteinuria and Columbia classification aids in selecting a better initial treatment after a renal biopsy.

The current study included 808 patients that underwent renal biopsies and were diagnosed as primary FSGS. Of these, 361 patients were classified by the Columbia classification, which is a large sample size for pFSGS. All clinical indicators were examined by the Ruijin Hospital Clinical Laboratory. They passed the ISO15189 international certification, ensuring the accuracy of clinical indicators presented in this study. All pathology reports were diagnosed by the same renal pathology team, ensuring the uniformity of diagnostic criteria. Each report was reviewed by two professional pathologists. All pathological specimens were examined by light microscopy, immunofluorescence, and electron microscopy to ensure the accuracy of pathological reports. However, this study also had several limitations. First, a portion of pathological specimens between 2003 and 2009 was not classified by the Columbia classification. Second, the sample size of the cellular variant was too small. This part of the data may be lacking in representation. Third, follow-up data of the collapsing and cellular variants was lacking. Thus, these two variants could not be included in prognostic analysis. Further studies with larger sample sizes (especially for collapsing and cellular) are needed.

Conclusion

Over the past 15 years, FSGS detection rates of renal biopsies and PGD have shown a downward trend. Over time, the proportion of glomerular segmental sclerosis has gradually decreased, while the proportion of glomerular global sclerosis has gradually increased, with aging as an independent factor in this trend. Combining proteinuria and Columbia classification may aid in selecting the best initial treatment, bringing higher remission rates.

Disclosure of conflict of interest

None.

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