

Supplementary Information

Clinical manifestations of focal segmental glomerulosclerosis in Japan from the Japan Renal Biopsy Registry: Age stratification and comparison with minimal change disease

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Supplementary Figure S1. Overview of the histologically diagnosed “focal segmental glomerulosclerosis” in the J-RBR

Supplementary Table S1. Details of the distribution of histopathologically diagnosed “focal segmental glomerulosclerosis” in the J-RBR

Supplementary Figure S2. Overview of the histologically diagnosed “minor glomerular abnormalities” in the J-RBR

Supplementary Table S2. Details of the distribution of histopathologically diagnosed “minor glomerular abnormalities” in the J-RBR

Supplementary Figure S3. Distribution and details of FSGS etiologies in the J-RBR

Supplementary Figure S4. Age-stratified distribution and proportion of the patients with FSGS and MCD in the J-RBR

Supplementary Table S3. Correlations between clinical continuous variables

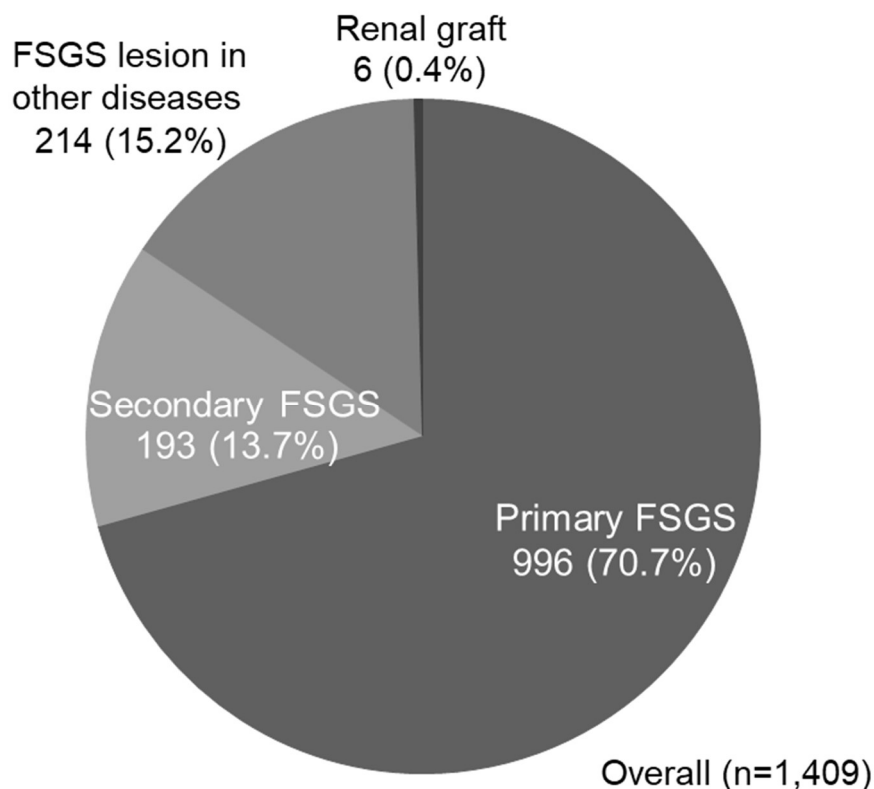
Supplementary Table S4. Clinical features of FSGS in the J-RBR

Supplementary Table S5. Comparison between FSGS and MCD cases among adult and elderly patients (age \geq 18) with nephrotic syndrome

Supplementary Table S6. Associating factors with FSGS vs. MCD among adult and elderly patients (age \geq 18) with nephrotic syndrome

Supplementary Note. The investigators and institutions participating to the Japan Renal Biopsy Registry

Supplementary Figure S1. Overview of the histologically diagnosed “focal segmental glomerulosclerosis” in the J-RBR



Registration in the J-RBR system has 3 diagnostic components: (i) clinical diagnosis, (ii) histological diagnosis by pathogenesis, and (iii) histological diagnosis by histopathology. The details of diagnostic system in the J-RBR should be referred to Sugiyama H et al., Clin Exp Nephrol 2011;15493-503.

From 30,949 patients who were registered to the J-RBR, 1,409 patients whose histological diagnosis by histopathology was “focal segmental glomerulosclerosis” were extracted for the analyses of FSGS. They included four types of patients as below.

Primary FSGS; Patients who were registered as “primary glomerular disease” in histological diagnosis (pathogenesis) without any information explaining the etiology of secondary cases.

Secondary FSGS; Patients who were registered with any information regarding the etiology of FSGS. Patients in this group could be identified only when the case has been registered with optional information about etiology.

FSGS lesion in other diseases; Patients with other type of systemic or glomerular diseases who had nonspecific segmental scarring, i.e. diabetic nephropathy, lupus nephritis and so on. Patients with any type of histological diagnosis (pathogenesis) except for “primary glomerular disease” were categorized to this group unless there were any information regarding secondary cases.

Renal graft: Patients whose clinical diagnosis was “renal transplantation” or whose histological diagnosis (pathogenesis) was “transplanted kidney”.

Supplementary Table S1. Details of the distribution of histopathologically diagnosed “focal segmental glomerulosclerosis” in the J-RBR

(A) Details of patient category

Histological diagnosis by pathogenesis	n	Primary FSGS	Secondary FSGS	FSGS lesion in other diseases	Renal graft
Primary glomerular disease*	1,024	996	28		
Hypertensive nephrosclerosis †	75		75		
Diabetic nephropathy	31			31	
Lupus nephritis	26			26	
Transplanted kidney ‡	6				6
Thin basement membrane disease	6			6	
Infection-related nephropathy	2		1	1	
Purpura nephritis	2			2	
Thrombotic microangiopathy	2			2	
Others	235		89	146	
Total	1,409	996	193	214	6

*Patients whose histological diagnosis (pathogenesis) was “primary glomerular disease” were categorized to “**Primary FSGS**” in main analyses unless they had any information about the etiology of FSGS.

Patients who were registered with any information regarding the etiology of FSGS were categorized to “**Secondary FSGS**” in main analyses.

†Patients whose histological diagnosis (pathogenesis) was “hypertensive nephrosclerosis” were categorized to “**Secondary FSGS**” as hypertension related FSGS in main analyses.

‡Patients whose histological diagnosis (pathogenesis) was “transplant kidney” were categorized to “**Renal graft**” and excluded from main analyses.

Patients who had any histological diagnosis (pathogenesis) except above were categorized to “**FSGS in other diseases**” and excluded from main analyses unless they had any information about the etiology of FSGS.

Abbreviations: J-RBR, Japan Renal Biopsy Registry; FSGS, focal segmental glomerulosclerosis

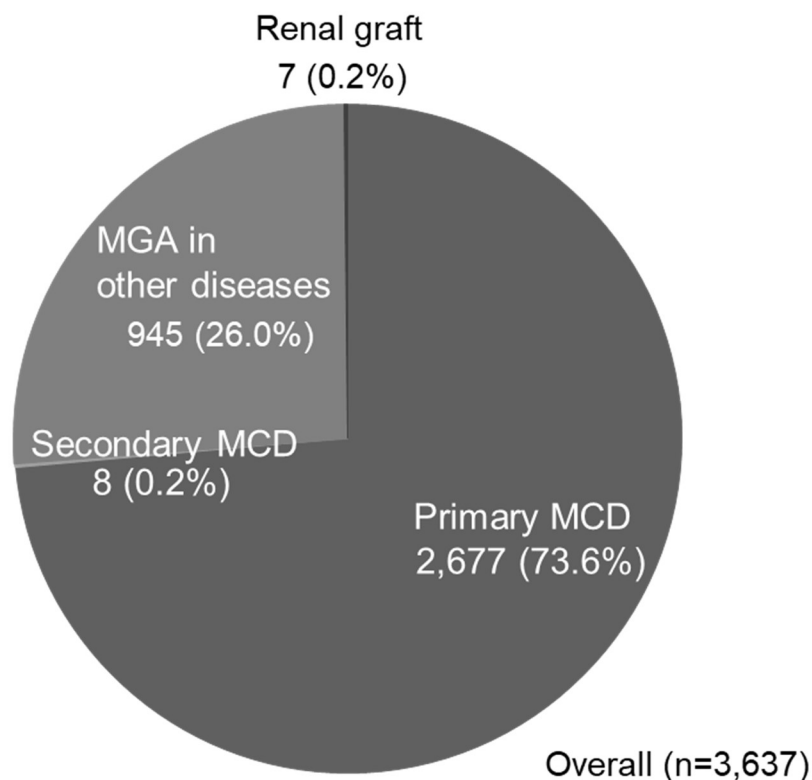
(B) Details of distribution on the secondary FSGS

Histological diagnosis by pathogenesis	Secondary FSGS	Hyper-tension	Obesity-related	Unilateral kidney or renal dysplasia	Low birth weight	Genetic	HIV infection	Cyanotic congenital heart disease	Drug-induced	Others or no detailed information
Primary glomerular disease	28		18	2	3	2				3
Hypertensive nephrosclerosis	75	75								
Infection-related nephropathy	1						1			
Others	89	2	54	8	4	4		1	1	15
Total	193	77	72	10	7	6	1	1	1	18

Patients in the “**Secondary FSGS**” could be identified when the case has been registered with optional information about etiology.

Abbreviations: FSGS, focal segmental glomerulosclerosis; HIV, human immunodeficiency virus

Supplementary Figure S2. Overview of the histologically diagnosed “minor glomerular abnormalities” in the J-RBR



Registration in the J-RBR system has 3 diagnostic components: (i) clinical diagnosis, (ii) histological diagnosis by pathogenesis, and (iii) histological diagnosis by histopathology. The details of diagnostic system in the J-RBR should be referred to Sugiyama H et al., Clin Exp Nephrol 2011;15493-503.

From 30,949 patients who were registered to the J-RBR, 3,637 patients whose histological diagnosis by histopathology was “**minor glomerular abnormalities**” were extracted for the analyses of MCD. They included four types of patients as below.

Primary MCD; Patients who were registered as “primary glomerular disease” in histological diagnosis (pathogenesis) without any information about the etiology. In this category, the patients whose clinical diagnosis was NS and who fulfilled the laboratory criteria for NS, were included to **Analysis 2**.

Secondary MCD; Patients who were registered with any information regarding the etiology of MCD. Patients in this group could be identified when the case has been registered with optional information about etiology.

MGA in other diseases; Patients with other type of systemic or glomerular diseases who had no specific glomerular findings on light microscopy i.e. thin basement membrane disease, lupus nephritis (class I) and so on. Patients with any type of histological diagnosis (pathogenesis) except for “primary glomerular disease” were categorized to this group unless there were any information regarding secondary cases.

Renal graft: Patients whose clinical diagnosis was “renal transplantation” or whose histological diagnosis (pathogenesis) was “transplanted kidney”.

Abbreviations: MCD, minimal change disease; J-RBR, Japan Renal Biopsy Registry; NS, nephrotic syndrome; MGA, minor glomerular abnormalities

Supplementary Table S2. Details of the distribution of histopathologically diagnosed “minor glomerular abnormalities” in the J-RBR

(A) Details of patient category

Histological diagnosis by pathogenesis	n	Primary MCD	Secondary MCD	MGA in other diseases	Renal graft
Primary glomerular disease*	2,679	2,677	2		
IgA nephropathy	187			187	
Thin basement membrane disease	118			118	
Hypertensive nephrosclerosis	42			42	
Alport syndrome	36			36	
Lupus nephritis	33			33	
Purpura nephritis	30			30	
Diabetic nephropathy	17			17	
MPO-ANCA positive nephritis	13			13	
Amyloid nephropathy	11			11	
Transplanted kidney †	7				7
PR3-ANCA positive nephritis	5			5	
Infection-related nephropathy	4			4	
Anti-GBM antibody nephritis	2			2	
Thrombotic microangiopathy	2			2	
Others	451		6	445	
Total	3,637	2,677	8	945	7

*Patients whose histological diagnosis (pathogenesis) was “primary glomerular disease” were categorized to “**Primary MCD**” in main analysis unless they had any information about the etiology of MCD.

Patients who were registered with any information regarding the etiology of MCD were categorized to “**Secondary MCD**” in main analysis.

Patients who had any histological diagnosis (pathogenesis) except for “primary glomerular disease” were categorized to “**MGA in other diseases**” and excluded from main analysis unless they had any information about the etiology of MCD.

†Patients whose histological diagnosis (pathogenesis) was “transplant kidney” were categorized to “**Renal graft**” and excluded from main analysis.

Abbreviations: J-RBR, Japan Renal Biopsy Registry; MCD, minimal change disease; MGA, minor glomerular abnormality

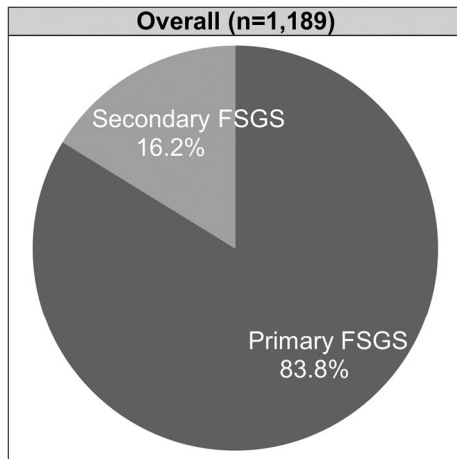
(B) Details of distribution on the secondary MCD

Histological diagnosis by pathogenesis	Secondary MCD	Malignancy	Hematological disorders	Drug-induced
Primary glomerular disease	2	3		
Others	6	1	2	3
Total	8	3	2	3

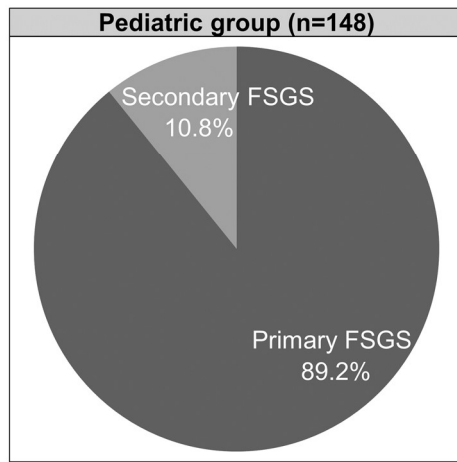
Patients in the “**Secondary MCD**” could be identified only when the case has been registered with optional information about etiology.

Abbreviations: MCD, minimal change disease

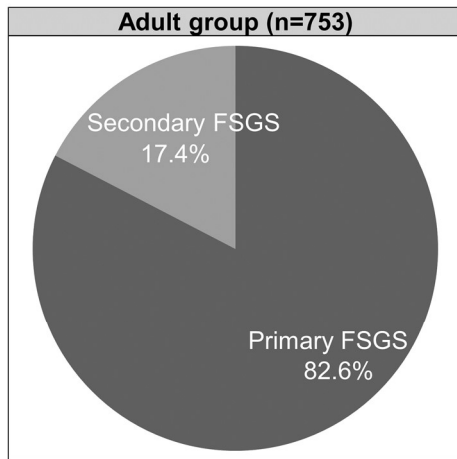
Supplementary Figure S3. Distribution and details of FSGS etiologies in the J-RBR



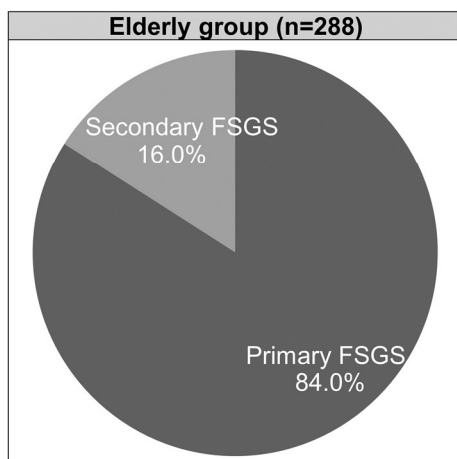
Etiologies of Secondary FSGS	n	(%)
Overall (n=193/1,189)		
Hypertension*	77	(39.9)
Obesity-related	72	(37.3)
Unilateral kidney or renal dysplasia	10	(5.2)
Low birth weight	7	(3.6)
Genetic†	6	(3.1)
HIV infection	1	(0.5)
Cyanotic congenital heart disease	1	(0.5)
Drug-induced‡	1	(0.5)
Others or no detailed information	18	(9.3)



Etiologies of Secondary FSGS	n	(%)
Pediatric group (n=16/148)		
Unilateral kidney or renal dysplasia	5	(31.3)
Low birth weight	3	(18.8)
Genetic	3	(18.8)
Obesity-related	2	(12.5)
Hypertension	2	(12.5)
Cyanotic congenital heart disease	1	(6.3)



Etiologies of Secondary FSGS	n	(%)
Adult group (n=131/753)		
Obesity-related	63	(48.1)
Hypertension	47	(35.9)
Unilateral kidney or renal dysplasia	5	(3.8)
Low birth weight	4	(3.1)
Genetic	3	(2.3)
HIV infection	1	(0.8)
Others or no detailed information	8	(6.1)



Etiologies of Secondary FSGS	n	(%)
Elderly group (n=46/288)		
Hypertension	28	(60.9)
Obesity-related	7	(15.2)
Drug-induced	1	(2.2)
Others or no detailed information	10	(21.7)

Information about etiology of FSGS was registered in 193 (16.2%) cases. The details of etiologies were shown by overall patients and three age groups: pediatric group (<18 years), adult group (18-64 years), and elderly group (≥ 65 years).

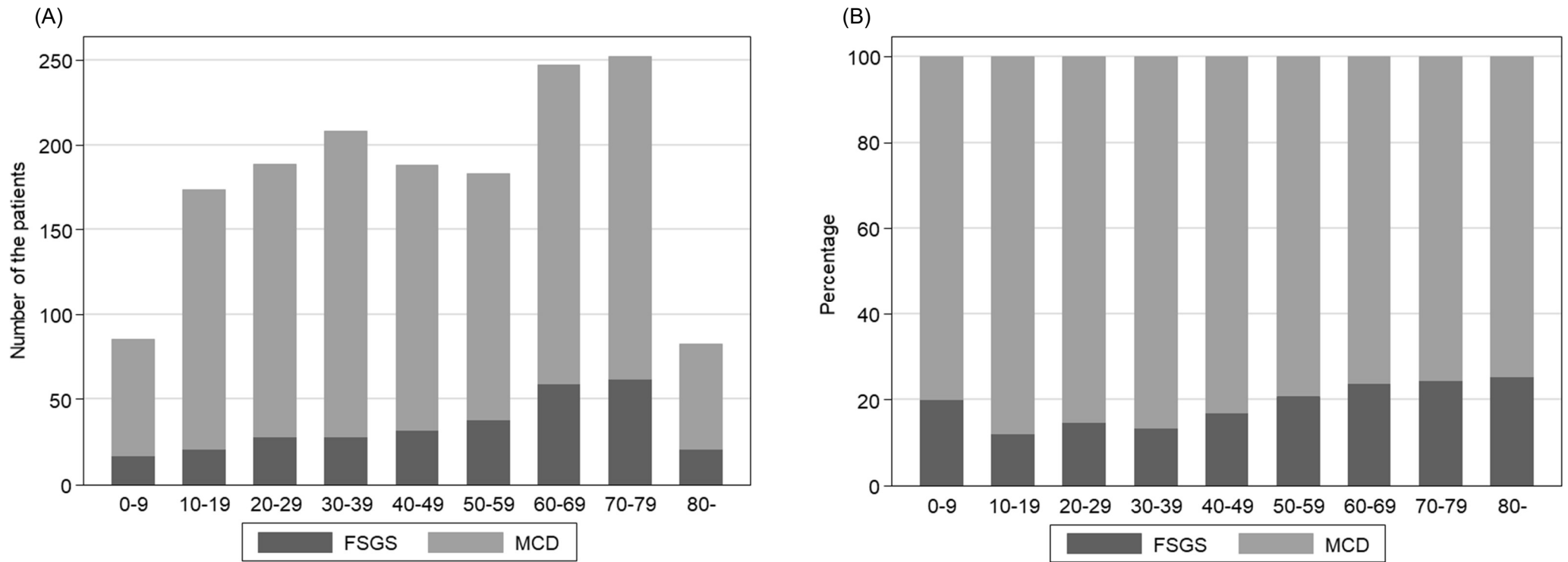
*Hypertension: cases whose histological diagnosis (pathogenesis) was “hypertensive nephrosclerosis”

†Genetic: no recorded information about mutations

‡Drug-induced: sunitinib

Abbreviations: FSGS, focal segmental glomerulosclerosis; J-RBR, Japan Renal Biopsy Registry; HIV, human immunodeficiency virus

Supplementary Figure S4. Age-stratified distribution and proportion of the patients with FSGS and MCD in the J-RBR



(A) Number of the patients with FSGS and MCD by age (B) Percentage of the patients with FSGS and MCD by age in the J-RBR.

Abbreviations: FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; J-RBR, Japan Renal Biopsy Registry

Supplementary Table S3. Correlations between clinical continuous variables

	Age	BMI	sBP	TP	Albumin	T-Cho	Log_Cre	eGFR	Log_UP (g/day)	Log_UP (g/gCr)
Age	1.00									
BMI	0.21	1.00								
sBP	0.36	0.27	1.00							
TP	0.16	-0.04	0.08	1.00						
Albumin	0.12	-0.08	0.20	0.40	1.00					
T-Cho	-0.28	0.02	-0.22	-0.26	-0.44	1.00				
Log_Cre	0.44	0.29	0.35	-0.04	-0.08	-0.17	1.00			
eGFR	-0.61	-0.26	-0.34	-0.01	0.08	0.14	-0.86	1.00		
Log_UP (g/day)	-0.15	0.15	0.01	-0.21	-0.23	0.14	0.15	-0.09	1.00	
Log_UP (g/gCr)	0.02	0.02	-0.01	-0.04	-0.21	0.08	0.06	-0.14	0.35	1.00

To avoid inclusion of variables with strong correlations in multivariate logistic regression, we evaluated correlations between continuous variables. Numbers in cells indicate Pearson's correlation coefficients. Correlation coefficients >0.40 or <-0.40 are shown in **bold font**.

Abbreviations: BMI, Body Mass Index; sBP, systolic blood pressure; TP, total protein, T-Cho, total cholesterol; Cre, creatinine; eGFR, estimated glomerular filtration rate; UP, urinary protein

Supplementary Table S4. Clinical features of FSGS in the J-RBR

	obs	Overall (n=1,189)			Age groups						P-value
					Pediatric group (n=148)		Adult group (n=753)		Elderly group (n=288)		
Patient characteristics											
Age	1,189	48	[29-64]	11	[5-15]	44	[32-55]	72	[68-77]	<0.001	
Sex (male)	1,189	724	(60.9)	93	(62.8)	446	(59.2)	185	(64.2)	0.29	
Number of biopsies											
First		637	(53.6)	59	(39.9)	404	(53.7)	174	(60.4)		
Second	1,189	73	(6.1)	25	(16.9)	39	(5.2)	9	(3.1)	<0.001	
≥3 times		28	(2.4)	11	(7.4)	15	(2.0)	2	(0.7)		
Unknown		451	(37.9)	53	(35.8)	295	(39.2)	103	(35.8)		
Clinical diagnosis											
Nephrotic syndrome		535	(45.0)	97	(65.5)	264	(35.1)	174	(60.4)		
Chronic nephritic syndrome	1,189	577	(48.5)	41	(27.7)	436	(57.9)	100	(34.7)	<0.001	
Others		77	(6.5)	10	(6.8)	53	(7.0)	14	(4.9)		
Secondary FSGS*	1,189	193	(16.2)	16	(10.8)	131	(17.4)	46	(16.0)	0.138	
Body Mass Index	1,173	23.5	[20.5-27.0]	18.5	[16.2-21.9]	24.2	[21.0-28.1]	23.7	[21.6-26.0]	<0.001	
Systolic blood pressure	1,004	130	[118-142]	116	[105-122]	129	[120-141]	138	[126-150]	<0.001	
Diastolic blood pressure	1,004	78	[69-87]	70	[61-78]	80	[70-89]	77	[70-86]	<0.001	
Antihypertensive drugs	984	526	(53.5)	35	(33.0)	316	(49.6)	175	(72.6)	<0.001	
Diabetes mellitus	885	131	(14.8)	5	(5.3)	79	(13.9)	47	(21.8)	0.005	
Laboratory data											
Total protein, g/dL	1,181	6.4	[5.2-7.1]	6.2	[5.2-7.0]	6.6	[5.3-7.1]	5.8	[4.9-6.8]	<0.001	
Albumin, g/dL	1,178	3.6	[2.4-4.1]	3.8	[2.6-4.3]	3.8	[2.7-4.2]	2.8	[2.1-3.7]	<0.001	
Total cholesterol, mg/dL	1,165	228	[190-302]	228	[172-369]	228	[193-291]	233	[191-314]	0.74	
HbA1c (NGSP), %	742	5.7	[5.4-6.0]	5.5	[5.3-5.8]	5.7	[5.4-6.0]	5.8	[5.5-6.1]	0.009	
Creatinine, mg/dL	1,187	0.98	[0.70-1.34]	0.49	[0.33-0.72]	0.95	[0.74-1.28]	1.26	[0.93-1.69]	<0.001	

eGFR, mL/min/1.73 m ²	1,180	60	[40-83]	102	[80-131]	63	[46-82]	40	[29-57]	<0.001
Urinary protein, g/gCr	837	2.48	[0.95-6.04]	1.28	[0.16-5.18]	2.07	[0.88-4.70]	5.11	[2.33-9.16]	<0.001
Urinary protein, g/day	842	1.90	[0.73-4.90]	1.16	[0.20-5.47]	1.67	[0.70-4.24]	3.14	[1.10-5.90]	<0.001
Consistent with NS †	1,189	339	(28.5)	32	(21.6)	177	(23.5)	130	(45.1)	<0.001
Urinary occult blood										
(-)		420	(35.3)	84	(56.8)	263	(34.9)	73	(25.4)	
(±)		176	(14.8)	15	(10.1)	117	(15.5)	44	(15.3)	
(1+)	1,189	197	(16.6)	11	(7.4)	119	(15.8)	67	(23.3)	<0.001
(2+)		227	(19.1)	20	(13.5)	146	(19.4)	61	(21.2)	
(3+)		169	(14.2)	18	(12.2)	108	(14.3)	43	(14.9)	
Urinary occult blood present ‡	1,189	593	(49.9)	49	(33.1)	373	(49.5)	171	(59.4)	<0.001
Urinary RBC, /HFP										
(-)		197	(16.6)	39	(26.4)	118	(15.7)	40	(13.9)	
<5		545	(45.8)	56	(37.8)	351	(46.6)	138	(47.9)	
5-10	1,189	186	(15.6)	19	(12.8)	116	(15.4)	51	(17.7)	0.017
10-30		151	(12.7)	17	(11.5)	94	(12.5)	40	(13.9)	
many		110	(9.3)	17	(11.5)	74	(9.8)	19	(6.6)	
Urinary RBC present §	1,189	447	(37.6)	53	(35.8)	284	(37.7)	110	(38.2)	0.88
Hematuria present	1,189	408	(34.3)	42	(28.4)	263	(34.9)	103	(35.8)	0.26

Data are presented as median [interquartile range] for continuous variables and count (percentage) for categorical variables.

* Details of secondary FSGS are summarized in Figure 3.

† Laboratory criteria for nephrotic syndrome, for pediatric patients (age <18): urinary protein ≥ 40 mg/hour/m² or ≥ 2.0 g/gCr and serum albumin ≤ 2.5 g/dL; for adult and elderly patients (age ≥ 18): urinary protein ≥ 3.5 g/day or ≥ 3.5 g/gCr and serum albumin ≤ 3.0 g/dL.

‡ Urinary occult blood present, (1+), (2+), (3+) on dipstick.

§ Urinary RBC present, ≥ 5 /HPF in urine sediment.

|| Hematuria present, (1+), (2+), (3+) on dipstick and ≥ 5 /HPF in sediment.

Abbreviations: J-RBR, Japan Renal Biopsy Registry; obs, number of observations; eGFR, estimated glomerular filtration rate; NGSP, National Glycohemoglobin Standardization Program; NS, nephrotic syndrome; RBC, red blood cell; HPF, high powered field

Supplementary Table S5. Comparison between FSGS and MCD cases among adult and elderly patients (age≥18) with nephrotic syndrome

	Nephrotic FSGS age≥18			MCD age≥18			P-value
	(n=277)			(n=1,135)			
	obs	Median, n	[IQR], (%)	obs	Median, n	[IQR], (%)	
Patient characteristics							
Age	277	60	[40-72]	1,135	50	[33-68]	<0.001
Sex (male)	277	168	(60.7)	1,135	648	(57.1)	0.28
Body Mass Index	277	23.3	[20.9-26.4]	1,128	23.8	[21.4-26.7]	0.25
Systolic BP	246	138	[124-150]	996	124	[113-136]	<0.001
Diastolic BP	246	80	[70-90]	996	76	[68-84]	<0.001
Antihypertensive drugs	223	129	(57.9)	964	303	(31.4)	<0.001
Diabetes mellitus	198	32	(16.2)	873	131	(15.0)	0.68
Laboratory data							
Total protein, g/dL	275	4.7	[4.2-5.3]	1,131	4.5	[4.1-5.0]	<0.001
Albumin, g/dL	277	1.9	[1.5-2.4]	1,135	1.7	[1.3-2.1]	<0.001
Total cholesterol, mg/dL	273	331	[268-418]	1,130	406	[320-494]	<0.001
HbA1c (NGSP), %	202	5.6	[5.3-6.0]	845	5.6	[5.4-6.0]	0.159
Creatinine, mg/dL	275	1.10	[0.80-1.70]	1,134	0.89	[0.69-1.16]	<0.001
eGFR, mL/min/1.73 m ²	275	51.1	[30.3-68.9]	1,134	67.8	[48.0-84.6]	<0.001
Urinary protein, g/gCr	222	8.08	[5.52-10.79]	916	8.43	[5.60-11.57]	0.25
Urinary protein, g/day	216	6.28	[4.61-8.67]	902	7.02	[4.80-10.20]	0.006
Urinary occult blood							
		24	(8.7)		194	(17.0)	
		35	(12.6)		193	(17.1)	
(1+)	277	77	(27.8)	1,135	241	(21.2)	<0.001
(2+)		95	(34.3)		376	(33.1)	
(3+)		46	(16.6)		131	(11.5)	
Urinary occult blood present*	277	218	(78.7)	1,135	748	(65.9)	<0.001
Urinary RBC, /HPF							
		20	(7.2)		153	(13.5)	
<5		112	(40.4)		609	(53.7)	
5-10	277	74	(26.7)	1,135	193	(17.0)	<0.001
10-30		46	(16.6)		131	(11.5)	
many		25	(9.0)		49	(4.3)	
Urinary RBC present*	277	145	(52.4)	1,135	373	(32.9)	<0.001
Hematuria present*	277	142	(51.3)	1,135	351	(30.9)	<0.001

*Definition: Urinary occult blood present, (1+), (2+), (3+) on dipstick; Urinary RBC present, ≥5/HPF in urine sediment; Hematuria present, (1+), (2+), (3+) on dipstick and ≥5/HPF in sediment.

Abbreviations: FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; RBC, red blood cell; HPF, high powered field

Supplementary Table S6. Associating factors with FSGS vs. MCD among adult and elderly patients (age≥18) with nephrotic syndrome

Variables	Univariate			Multivariable					
				Model 1 [†]			Model 2 [‡]		
	OR	[95%CI]	P-value	OR	[95%CI]	P-value	OR	[95%CI]	P-value
Age (every10 years)	1.16	[1.08–1.25]	<0.001				1.00	[0.91–1.10]	0.94
Sex (Male)	1.16	[0.89–1.51]	0.28						
Body Mass Index	1.00	[0.97–1.03]	0.95						
Systolic BP (every10 mmHg)	1.38	[1.28–1.49]	<0.001	1.24	[1.14–1.37]	<0.001	1.31	[1.19–1.44]	<0.001
Anti-hypertensive drugs	2.99	[2.22–4.04]	<0.001						
Diabetes mellitus	1.09	[0.72–1.67]	0.68						
HbA1c (NGSP)	0.82	[0.64–1.05]	0.111						
Total protein	1.47	[1.22–1.76]	<0.001						
Albumin	2.29	[1.81–2.91]	<0.001	2.17	[1.58–3.00]	<0.001	2.00	[1.46–2.72]	<0.001
Total cholesterol (every 10 mg/dL)	0.95	[0.94–0.96]	<0.001						
Log_creatinine	2.23	[1.77–2.81]	<0.001						
eGFR (every 10 mL/min/1.73 m ²)	0.82	[0.78–0.87]	<0.001	0.87	[0.81–0.93]	<0.001			
Log_urinary protein (g/gCr)	0.88	[0.68–1.13]	0.32						
Log_urinary protein (g/day)	0.77	[0.61–0.98]	0.029	0.78	[0.58–1.05]	0.099	0.81	[0.60–1.10]	0.180
urinary occult blood present*	1.91	[1.40–2.61]	<0.001						
urinary RBC present*	2.24	[1.72–2.93]	<0.001						
Hematuria present*	2.35	[1.80–3.07]	<0.001	1.74	[1.22–2.46]	0.002	2.02	[1.46–2.72]	<0.001

* Definition: Urinary occult blood present, (1+), (2+), (3+) on dipstick; Urinary RBC present, ≥5/HPF in urine sediment; Hematuria present, (1+), (2+), (3+) on dipstick and ≥5/HPF in sediment.

† Multivariable model 1: Adjusted for systolic blood pressure, albumin, eGFR, daily urinary protein (log-transformed), hematuria.

‡ Multivariable model 2: Adjusted for age, systolic blood pressure, albumin, daily urinary protein (log-transformed), hematuria.

Abbreviations: FSGS, focal segmental glomerulosclerosis; OR, odds ratio; CI, confidence interval; BP, blood pressure; eGFR, estimated glomerular filtration rate; RBC, red blood cell; HPF, high powered field

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