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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Focal segmental glomerulosclerosis (FSGS) is a serious condition leading to kidney failure. We aimed to investigate the clinical characteristics of FSGS and its differences compared with minimal change disease (MCD) using cross-sectional data from the Japan Renal Biopsy Registry. In Analysis 1, primary FSGS (n = 996) were stratified by age into three groups: pediatric (<18 years), adult (18–64 years), and elderly (≥65 years), and clinical characteristics were compared. Clinical diagnosis of nephrotic syndrome (NS) was given to 73.5% (97/132) of the pediatric, 41.2% (256/622) of the adult, and 65.7% (159/242) of the elderly group. In Analysis 2, primary FSGS (n = 306) and MCD (n = 1303) whose clinical diagnosis was nephrotic syndrome (NS) and laboratory data were consistent with NS, were enrolled. Logistic regression analysis was conducted to elucidate the variables which can distinguish FSGS from MCD. On multivariable analysis, higher systolic blood pressure, higher serum albumin, lower eGFR, and presence of hematuria associated with FSGS. In Japanese nationwide registry, primary FSGS patients aged 18–64 years showed lower rate of NS than those in other ages. Among primary nephrotic cases, FSGS showed distinct clinical features from MCD.

Focal segmental glomerulosclerosis (FSGS) presents with proteinuria, often accompanied by nephrotic syndrome (NS), and may lead to end-stage renal disease. FSGS originally referred to steroid-resistant nephrotic syndrome in pediatric patients with segmental obliteration of glomerular capillaries, with or without hyalinosis on light microscopy. The entity of FSGS has been expanded and FSGS is currently regarded as a group of kidney diseases sharing common glomerular lesions. There are two pathophysiological types of FSGS: primary and secondary ones. In primary FSGS, it is postulated that circulating permeability factors cause podocyte injury, inducing NS. Whereas, secondary cases have underlying etiologies such as hypertension, obesity, viruses, drugs, genetic mutations, or adaptive conditions, and they do not always manifest NS. Therefore, the clinical presentations of FSGS are diverse. Cases with NS (usually the primary form) show a different clinical course compared with minimal change disease (MCD) i.e. poor therapeutic response, worse renal prognosis, and rapid recurrence.
of proteinuria after kidney transplantation. However, it is difficult to clearly distinguish nephrotic FSGS from MCD because of their similar clinical presentations and the sampling limitations of pathological specimens. To date, few studies have described the clinical features of FSGS, as well as the distinction between nephrotic FSGS and MCD using a large sample size.

The Japan Renal Biopsy Registry (J-RBR) is a nationwide, web-based, registry of renal biopsies established by the Japanese Society of Nephrology in 2007. Cross-sectional studies using this database have described the clinical features of several kidney diseases in Japan. The J-RBR Japan Renal Biopsy Registry, FSGS focal segmental glomerulosclerosis, MCD minimal change disease, NS nephrotic syndrome.

**Results**

Among 30,949 patients who registered to J-RBR between July 2007 and June 2016, 1,410 cases were extracted for the evaluation of FSGS. Additionally, 3,656 patients were also extracted for the evaluation of MCD (Fig. 1).

**General demographics of FSGS in the J-RBR.** After removing a patient with multiple registration, 1,409 patients were registered as histologically diagnosed focal segmental glomerulosclerosis in J-RBR database. Of these, 996 were primary FSGS and 193 were secondary FSGS (Supplementary Fig. S1). The annual incidence of FSGS accounted for 3.5–4.5% of all registered cases in the J-RBR database. The percentage of primary FSGS were constant at approximately 3% of all during 2007 to 2016 (Fig. 2). The details of distribution of histopathologically diagnosed minor glomerular abnormalities including minor glomerular abnormalities in other diseases are shown in Supplementary Fig. S2 and Supplementary Table S2.

**Analysis 1: description of clinical features of primary FSGS in the three age groups.** For Analysis 1, 996 primary FSGS cases were divided into three age groups: pediatric group (n = 132), adult group (n = 622), and elderly group (n = 242). The detailed age-stratified distribution of the prevalence and proportion...
of patients with FSGS and MCD are shown in Supplementary Fig. S4. The clinical features of the patients are summarized in Table 1. Patients who underwent biopsy more than twice were the most common in the pediatric group (26.5%). In clinical diagnosis, NS was the most common (51.4%), followed by chronic nephritic syndrome (44.4%) in total. A clinical diagnosis of NS was 73.5% in the pediatric group, 41.2% in the adult group, and 65.7% in the elderly group. In the adult group, prevalence of chronic nephritic syndrome (54.3%) was higher than that of NS. Body mass index was greater and kidney function was worse in the adult and elderly groups than in the pediatric group (P < 0.001). The elderly group showed the highest systolic blood pressure and highest prevalence of concomitant hypertension on antihypertensive drugs (68.8%) and diabetes mellitus (18.8%). Baseline estimated glomerular filtration rate (eGFR) was highest in the pediatric group, followed by the adult group and elderly group (eGFR: 106, 64, and 40 mL/min/1.73 m², respectively). Fewer patients who were consistent with NS in laboratory data at biopsy were found in the pediatric group and adult group than in the elderly group (24.2%, 27.5%, and 51.2%, respectively).

Analysis 2: comparison between nephrotic FSGS and MCD. Of 1410 patients with “focal segmental glomerulosclerosis” and 3656 with “minor glomerular abnormalities” on histological diagnosis (histopathology), 306 with nephrotic FSGS and 1303 with MCD were included in Analysis 2 (Fig. 1). The characteristics of nephrotic FSGS and MCD at the biopsy are summarized in Table 2. FSGS cases were older (FSGS: 58 vs. MCD: 44 years), had a higher prevalence of hypertension on antihypertensive drugs (56.2 vs. 28.7%), and lower eGFR (53 vs. 72 mL/min/1.73 m²). FSGS patients also had higher serum albumin (1.9 vs. 1.7 g/dL), lower daily urinary protein levels (6.28 vs. 7.00 g/day) and higher prevalence of hematuria (52.9 vs. 29.8%) at biopsy.

As summarized in Table 3, univariate logistic regression analysis revealed that age, systolic blood pressure, serum albumin, serum total cholesterol, serum creatinine (log-transformation), eGFR and presence of urinary red blood cells and hematuria were significantly associated with a diagnosis of FSGS. The correlations between continuous variables are shown in Supplementary Table S3. Patient age, systolic blood pressure, serum albumin, eGFR, daily urinary protein level (log-transformation), and presence of hematuria were used in the multivariate model (Table 3). Because of the strong correlation between patient age and eGFR, we evaluated two models that took one of them: Model 1 and Model 2. In Model 1, FSGS was associated with higher systolic blood pressure (OR 1.25, 95% confidence interval [CI] 1.14–1.36, for every increase of 10 mmHg), higher serum albumin (OR 2.13, 95% CI 1.56–2.91), lower eGFR (OR 0.90, 95% CI 0.85–0.95, every increase of 10 mL/min/1.73m²), and presence of hematuria (OR 1.92, 95% CI 1.36–2.69). In Model 2, higher systolic blood pressure (OR 1.31, 95% CI 1.31–2.69), higher serum albumin (OR 2.02, 95% CI 1.49–2.73), and presence of hematuria (OR 2.18, 95% CI 1.56–3.04).

Discussion
The present study used the data from a Japanese nationwide kidney biopsy registry. This is a unique study focusing on the clinical manifestations of FSGS with a large sample size. Furthermore, this study is the first one to describe the clinical features of primary FSGS from two different viewpoints: age stratification and comparison between nephrotic FSGS and MCD.

In the J-RBR database, FSGS occupied 3.4–4.5% in total number of kidney biopsy. The Research Group on Progressive Renal Disease from the Ministry of Health, Labor and Welfare of Japan reported that the annual number of native kidney biopsy in Japan was estimated 18,000 to 21,00020. Therefore, approximately 800 patients per year were inferred to be diagnosed with FSGS by biopsy in our country. The prevalence of FSGS varied among races and countries21. An international survey revealed that FSGS accounted for 19.1% of primary glomerular disease in North America, 14.9% in Europe, 6.9% in Asia, and 15.8% in Latin America22. A part of this...
## Table 1.
Clinical features of primary FSGS in the Japan Renal Biopsy Registry. Data are presented as median [interquartile range] for continuous variables and count (percentage) for categorical variables.

| Patient characteristics | Obs | Overall (n = 996) | Age groups | P-value |
|-------------------------|-----|------------------|------------|---------|
| Age                     |     |                  |            |         |
|                         | 996 | 47 [89–64]       | 10 [4–15]  | 43 [32–55] | 72 [68–77] | <0.001 |
| Sex (male)              | 996 | 592 (59.4)       | 80 (60.6)  | 360 (57.9) | 152 (62.8) | 0.40   |
| Number of biopsies      |     |                  |            | <0.001   |
| First                   | 996 | 516 (51.8)       | 52 (39.4)  | 322 (51.8) | 142 (58.7) |         |
| Second                  | 66  | (6.6)            | 24 (18.2)  | 33 (5.3)   | 9 (3.7)    |         |
| ≥3 times                | 26  | (2.6)            | 11 (8.3)   | 14 (2.6)   | 1 (0.4)    |         |
| Unknown                 | 388 | (39.0)           | 45 (34.1)  | 253 (40.7) | 90 (37.2)  |         |
| Clinical diagnosis      |     |                  |            | <0.001   |
| Nephrotic syndrome      | 996 | 512 (51.4)       | 97 (73.5)  | 256 (41.2) | 159 (65.7) |         |
| Chronic nephritic syndrome | 442 | (44.4)           | 31 (25.5)  | 338 (54.3) | 73 (30.2)  |         |
| Others                  | 42  | (4.2)            | 4 (3.0)    | 28 (4.5)   | 10 (4.1)   |         |
| Body Mass Index         | 982 | 22.9 [20.3–26.2] | 18.5 [16.3–21.5] | 23.5 [20.8–27.1] | 23.6 [21.4–25.9] | <0.001 |
| Systolic blood pressure | 828 | 129 [118–142]   | 113 [103–121] | 129 [119–141] | 138 [125–150] | <0.001 |
| Diastolic blood pressure| 828 | 78 [68–86]      | 68 [60–78]  | 80 [70–88]  | 77 [70–86]  | <0.001 |
| Antihypertensive drugs  | 817 | 414 (50.7)      | 31 (34.1)  | 244 (46.6) | 139 (68.8) | <0.001 |
| Diabetes mellitus       | 717 | 99 (13.8)       | 4 (3.0)    | 61 (13.4)  | 34 (17.5)  |         |
| Laboratory data         |     |                  |            | 0.013    |
| Total protein, g/dL     | 988 | 6.2 [4.9–7.0]   | 6.1 [5.0–6.9] | 6.5 [5.0–7.0] | 5.5 [4.8–6.6] | <0.001 |
| Albumin, g/dL           | 986 | 3.5 [2.2–4.1]   | 3.6 [2.6–4.2] | 3.7 [2.3–4.1] | 2.6 [2.0–3.7] | <0.001 |
| Total cholesterol, mg/dL| 975 | 235 [195–323]  | 250 [177–399] | 232 [195–308] | 242 [195–325] | 0.53   |
| HbA1c (% NGSP)          | 608 | 5.7 [5.4–6.0]   | 5.5 [5.3–5.8] | 5.6 [5.4–6.0] | 5.8 [5.4–6.0] | 0.043  |
| Creatinine, mg/dL       | 994 | 0.96 [0.70–1.31]| 0.44 [0.31–0.66]| 0.95 [0.73–1.26]| 1.24 [0.93–1.69]| <0.001 |
| eGFR, mL/min/1.73 m²    | 987 | 60 [41–84]      | 106 [83–134] | 64 [47–83]  | 40 [29–57]  | <0.001 |
| Urinary protein, g/gCr  | 697 | 2.9 [1.02–6.93] | 1.86 [0.16–6.16] | 2.27 [0.98–5.46] | 5.66 [2.83–9.70] | <0.001 |
| Urinary protein, g/day  | 680 | 2.24 [0.84–5.49]| 1.65 [0.17–6.80] | 1.96 [0.84–5.01]| 3.68 [1.24–6.44]| <0.001 |
| Consistent with NSa     | 996 | 327 (32.8)      | 32 (24.2)  | 171 (27.5) | 124 (51.2) | <0.001 |
| Urinary occult blood    |     |                  |            | <0.001   |
| (−)                     | 996 | 323 (32.4)      | 70 (53.0)  | 205 (33.0) | 48 (19.8)  |         |
| (±)                     | 143 | (14.4)          | 14 (10.6)  | 94 (15.1)  | 35 (14.5)  |         |
| (1+)                    | 170 | (17.1)          | 10 (7.6)   | 100 (16.1) | 60 (24.8)  |         |
| (2+)                    | 208 | (20.9)          | 20 (15.2)  | 129 (20.7) | 59 (24.4)  |         |
| (3+)                    | 152 | (15.3)          | 18 (13.6)  | 94 (15.1)  | 40 (16.5)  |         |
| Urinary occult blood presenta | 996 | 530 (53.2) | 48 (36.4)  | 323 (51.9) | 159 (65.7) | <0.001 |
| Urinary RBC/HFP         |     |                  |            | <0.001   |
| (−)                     | 996 | 154 (15.5)      | 32 (24.2)  | 94 (15.1)  | 28 (11.6)  |         |
| (<5)                    | 448 | (45.0)          | 49 (37.1)  | 287 (46.1) | 112 (46.3) | 0.025  |
| 5–10                    | 163 | (16.4)          | 18 (13.6)  | 97 (15.6)  | 48 (19.8)  |         |
| 10–30                   | 129 | (13.0)          | 16 (12.1)  | 77 (12.4)  | 36 (14.9)  |         |
| Many                    | 102 | (10.2)          | 17 (12.9)  | 67 (10.8)  | 18 (7.4)   |         |
| Urinary RBC presentb   | 996 | 394 (39.6)      | 51 (38.6)  | 241 (38.8) | 102 (42.2) | 0.64   |
| Hematuria presentc     | 996 | 363 (36.5)      | 41 (31.1)  | 226 (36.3) | 96 (39.7)  | 0.26   |

Table 1. Clinical features of primary FSGS in the Japan Renal Biopsy Registry. Data are presented as median [interquartile range] for continuous variables and count (percentage) for categorical variables. obs number of observations, eGFR estimated glomerular filtration rate, NGSP National Glycohemoglobin Standardization Program, NS nephrotic syndrome, RBC red blood cell, HFP high powered field, *Laboratory criteria for nephrotic syndrome, for pediatric patients (age < 18): urinary protein ≥ 40 mg/h/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/HFP in urine sediment. §Hematuria present, (1+), (2+), (3+) on dipstick and ≥ 5/HFP in sediment.
epidemiological difference could be explained by the presence of genetic variants in apolipoprotein L1 (APOL1) among people with sub-Saharan ancestry. Additionally, several studies reported that the incidence of FSGS was increasing, especially in the US. The present study shows that incidence of FSGS in Japan was lower than that in reports from other regions and it had not changed for the past decade.

To evaluate the population with FSGS, it is necessary to distinguish primary FSGS from secondary FSGS. However, distinguishing secondary FSGS is challenging and the incidence of secondary FSGS remains unclear. D’Agati reported that 10–20% of FSGS patients are secondary ones. In J-RBR, secondary cases constituted 16.2% of the total FSGS patients, and our results showed that the etiologies in these patients were different among the age groups; 10.8%, 17.4% and 16.0% among the pediatric, adult and elderly group, respectively. As the etiology, hypertension and obesity were the most common in total or among the adult and elderly group. Unilateral kidney or renal dysplasia, low birth weight and genetic disorders were leading causes of FSGS among the pediatric group.

Analysis 1 described the clinical characteristics of primary FSGS in three age groups. We showed that the proportion of NS was different in each age group. Previous studies reported that nephrotic-range proteinuria is more frequently seen in children than in adults in FSGS. In our study, the pediatric group showed the highest prevalence of NS (78.1%). However, the urinary protein level was the lowest in this group. This discrepancy between clinical diagnosis and laboratory data could be explained by the effect of immunosuppressive treatment. Because of the quite high occupancy of MCD in NS of pediatric age, children with NS typically receive empiric treatment centering glucocorticoids and the indication of kidney biopsy are limited to the cases with refractory clinical course i.e., steroid-resistant or frequent relapse. Therefore, it is possible that most pediatric

### Table 2. Comparison between nephrotic FSGS and MCD cases. FSGS focal segmental glomerulosclerosis, MCD minimal change disease, eGFR estimated glomerular filtration rate, RBC red blood cell, HPF high powered field. *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.
FSGS patients had already received immunosuppressive treatment by the time of biopsy. However, we cannot distinguish whether the data was obtained before or after initiation of immunosuppressive treatment, in the J-RBR data. The adult group showed the lowest prevalence of NS (41.2%) and the highest prevalence of chronic nephrotic syndrome (54.3%). Whereas, the elderly group showed a higher prevalence of NS (65.7%) than the adult group. This suggested the differences in indications for renal biopsy among age groups. In Japan, a nationwide health examination program for all community residents, including urinalysis screening, has been conducted for over 40 years. This regular screening enables early detection of urine abnormalities and early referral to a nephrologist. The suggested indication for renal biopsy in adult patients in Japan is ≥ 0.5 g/day of proteinuria or urinary occult blood present, ≥ 5/HPF in urine sediment; Hematuria present, (1+), (2+), (3+) on dipstick and ≥ 5/HPF in sediment.

Table 3.  Associating factors with FSGS vs. MCD. 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. *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. b Multivariable model 1: Adjusted for systolic blood pressure, albumin, eGFR, daily urinary protein (log-transformed), hematuria. c Multivariable model 2: Adjusted for age, systolic blood pressure, albumin, daily urinary protein (log-transformed), hematuria.

| Variables                        | Univariate | Multivariable Model 1 | Multivariable Model 2 |
|----------------------------------|------------|-----------------------|-----------------------|
|                                  | OR [95% CI] | P-value               | OR [95% CI] | P-value               | OR [95% CI] | P-value               |
| Age (every 10 years)             | 1.13 [1.07–1.20] | < 0.001              | 0.98 [0.90–1.07] | 0.72                  |
| Sex (male)                       | 1.12 [0.87–1.44] | 0.40                  | 0.95 [0.79–1.15] | 0.48                  |
| Body Mass Index                  | 1.00 [0.98–1.03] | 0.82                  | 1.00 [0.97–1.03] | 0.95                  |
| Systolic BP (every 10 mmHg)      | 1.38 [1.28–1.48] | < 0.001              | 1.25 [1.14–1.36] | < 0.001              | 1.31 [1.19–1.44] | < 0.001              |
| Anti-hypertensive drugs          | 3.19 [2.39–4.24] | < 0.001              | 2.86 [2.27–3.64] | < 0.001              |
| Diabetes mellitus                | 1.16 [0.77–1.76] | 0.48                  | 1.00 [0.68–1.51] | 1.00                  |
| HbA1c (NGSP)                     | 0.86 [0.68–1.09] | 0.21                  | 0.86 [0.68–1.07] | 0.24                  |
| Total protein                    | 1.11 [0.99–1.22] | 0.066                 | 1.09 [0.97–1.23] | 0.24                  |
| Albumin (every 10 mg/dL)         | 2.24 [1.79–2.82] | < 0.001              | 2.13 [1.56–2.91] | < 0.001              | 2.02 [1.49–2.73] | < 0.001              |
| Total cholesterol (every 10 mg/dL)| 0.96 [0.95–0.97] | < 0.001              | 0.96 [0.95–0.97] | < 0.001              |
| Log_creatinine                   | 1.96 [1.59–2.41] | < 0.001              | 1.96 [1.59–2.41] | < 0.001              |
| eGFR (every 10 mL/min/1.73 m²)   | 0.86 [0.83–0.90] | < 0.001              | 0.90 [0.85–0.95] | < 0.001              |
| Log_uroinary protein (g/gCr)     | 0.89 [0.72–1.11] | 0.31                  | 0.89 [0.72–1.11] | 0.31                  |
| Log_uroinary protein (g/day)     | 0.81 [0.65–1.01] | 0.061                 | 0.78 [0.59–1.04] | 0.093                | 0.81 [0.61–1.08] | 0.146                |
| urinary occult blood present     | 2.07 [1.55–2.78] | < 0.001              | 2.07 [1.55–2.78] | < 0.001              |
| urinary RBC present              | 2.65 [2.06–3.41] | < 0.001              | 2.65 [2.06–3.41] | < 0.001              |
| Hematuria present                | 2.65 [2.06–3.42] | < 0.001              | 2.65 [2.06–3.42] | < 0.001              |

This study has several limitations. First, the J-RBR system did not collect detailed information regarding the etiology of FSGS. All the information was provided by the local coinvestigators. The J-RBR also lacked the information of the findings in electron microscopy and detailed genetic testing that could help discriminating primary and secondary FSGS. It is possible that primary FSGS may include some secondary cases and, therefore, the percentage of secondary FSGS may be underestimated in our study. Second, the J-RBR did not collect the information about total number of glomeruli. Therefore, it was possible that we included the patients without...
adequate number of glomeruli to distinguish FSGS from MCD in the present study. Third, this study was based on cross-sectional data. Although eGFR was lower in FSGS than in MCD, it was difficult to determine whether the impaired kidney function indicated chronic kidney disease or acute kidney injury. Fourth, as mentioned above, the J-RBR data do not include information on whether the data were obtained before or after the initiation of immunosuppressive treatment. Modification of the J-RBR system has been conducted to achieve a more accurate description of pathological diagnoses, including etiological information. Another limitation of this study is the lack of information regarding pathological subgroups of FSGS: variants of the Columbia classification. Previous studies reported that morphologic variants of FSGS demonstrate distinct features in their clinical presentation and prognosis. A longitudinal investigation is currently underway based on J-RBR database including the additional information regarding Columbia classification.

In conclusion, nation-wide registry system revealed the characteristics and clinical features of FSGS in Japan. The results show that the incidence of FSGS in Japan is lower than that in other countries. When primary FSGS patients were divided into three age groups, the incidence of NS was lowest in the adult group (18–64 years), suggesting that the indications for renal biopsy might have been stricter among pediatric and elderly patients. When the analysis was focused on primary NS at the time of renal biopsy, FSGS showed distinct clinical features, such as younger age, higher blood pressure, higher serum albumin, lower eGFR, lower daily urinary protein level and presence of hematuria compared with MCD.

Methods
Overview of the J-RBR system. This cross-sectional study used the data from the J-RBR. The details of the J-RBR system were described in a previous publication. As of June 2016, 143 nephrology centers participated in this registry, which included 30,949 patients. The J-RBR enters patient clinical information at biopsy. The J-RBR diagnosis consists of three components: (i) a clinical diagnosis, (ii) a histological diagnosis by pathogenesis, and (iii) a histological diagnosis by histopathology.

Patients. Among the patients who registered to J-RBR between July 2007 and June 2016, cases whose histological diagnosis (histopathology) was "focal segmental glomerulosclerosis" were extracted for the evaluation of FSGS. Additionally, patients whose histological diagnosis (histopathology) was "minor glomerular abnormalities" were also extracted for the evaluation of MCD (Fig. 1).

General demographics of FSGS in the J-RBR. Primary FSGS and secondary FSGS in the J-RBR database were included. From the patients with histological diagnosis (histopathology) of "focal segmental glomerulosclerosis" without multiple registration (n = 1409), the patients whose histological diagnosis (pathogenesis) was "primary glomerular disease" were defined as primary FSGS unless they had information of etiologies. The patients with identified information of their etiologies (i.e. obesity, hypertension, etc.) were defined as secondary FSGS. For example, when hypertension was considered to be a cause of FSGS, the case was classified into secondary FSGS. When hypertension was considered as just a concomitant condition, the case was classified into primary FSGS. FSGS lesions in other diseases (i.e. diabetic nephropathy, lupus nephritis, etc.) and renal graft were excluded. The details of selection for FSGS patients were described in Supplementary Fig. S1 and Supplementary Table S1.

The annual incidence of FSGS and proportion of primary and secondary FSGS and were described. Then, two main analyses were conducted as follows.

Analysis 1: description of clinical features of primary FSGS in the three age groups. The cases with primary FSGS were divided into three age groups: pediatric group (<18 years), adult group (18–64 years), and elderly group (≥65 years) (Fig. 1). Clinical parameters were compared among the age groups.

Analysis 2: comparison between nephrotic FSGS and MCD. To compare the clinical characteristics of nephrotic FSGS with those of MCD, patients who fulfilled the following criteria were included in Analysis 2 (Fig. 1).

Nephrotic FSGS. (i) primary cases, (ii) clinical diagnosis of NS, and (iii) laboratory data consistent with NS, which was defined as urinary protein ≥ 40 mg/h/m² or ≥ 2.0 g/gCr and serum albumin ≤ 2.5 g/dL for pediatric patients (age < 18) and urinary protein ≥ 3.5 g/day or ≥ 3.5 g/gCr and serum albumin ≤ 3.0 g/dL for adult and elderly patients (age ≥ 18). The body surface area (m²) of pediatric patients was calculated by the DuBois formula: height (cm)0.725 x body weight (kg)0.425 x 0.007184.

Nephrotic MCD. From the patients with histological diagnosis (histopathology) of “minor glomerular abnormalities”, following patients were included: (i) primary MCD, (ii) clinical diagnosis of NS, and (iii) laboratory data consistent with NS. Patients with multiple registrations, secondary MCD, other diseases with no obvious light microscopic glomerular findings (i.e., thin basement membrane disease, Class I lupus nephritis, etc.), and renal graft were excluded. The details of selection for MCD patients were described in Supplementary Fig. S2 and Supplementary Table S2.

Clinical parameters were compared between nephrotic FSGS and MCD patients.

Data collection. Clinical data at biopsy such as patient characteristics (age, sex, height, body weight, blood pressure), comorbidities (concomitant hypertension and diabetes), urinary findings (urinalysis, daily proteinu-
ria), and blood test findings (serum creatinine, total protein, albumin, total cholesterol) were extracted from the J-RBR database.

eGFR was calculated using equations based on serum creatinine (sCr) level for Japanese children (age < 18): eGFR [mL/min/1.73 m²] = 110.2 × reference-sCr/sCr (mg/dL) + 2.93, reference-sCr = −1.259 × Height (m)² + 7.815 × Height (m) – 18.57 × Height (m)³ − 11.71 × Height (m) + 2.628 (if male), eGFR [mL/min/1.73 m²] = 194 × sCr (mg/dL)−1.094 × Age−0.287 × 0.739 (if female). Additional diagnostic information, including details of etiology were also extracted.

Statistics
Analysis 1: description of clinical features of primary FSGS in the three age groups. Clinical characteristics were expressed as median/interquartile range and frequency number/percentage. We used the Kruskal–Wallis test to compare continuous variables and the chi-squared test to compare the proportions of categorical variables among the age groups.

Analysis 2: comparison between nephrotic FSGS and MCD. We used the Mann–Whitney U test to compare continuous variables and the chi-squared test to compare the proportions of categorical variables between nephrotic FSGS and MCD. Logistic regression analysis was used to evaluate the association between each variable and diagnosis of FSGS compared to MCD. Variables with P < 0.05 in univariate analysis and variables with clinical importance (age, eGFR, and urinal protein level) were included in the multivariable model, while we excluded variables with strong correlations (Pearson’s correlation coefficients > 0.40) or clinical relevance.

Statistical analyses were conducted using STATA IC version 14.0 (StataCorp LLC, College Station, TX, USA). The statistical significance level was set at P < 0.05.

Ethics. Written informed consent was obtained from all participants and/or their legal guardians. All procedures performed in the present study were in accordance with the standards of the ethics committee of the Japanese Society of Nephrology (approval number: 40, J-RBR201604) and the ethics committee of Nagoya University (approval number: 2016-0492-2), and with the Helsinki Declaration of 1975 and its later amendments. J-RBR is registered in the UMIN Clinical Trial Registry (UMIN00000618).

Data availability
The datasets generated and analyzed during the current study are not publicly available because the consent obtained from the participants does not cover unlimited public sharing of the data but are available from the corresponding author on reasonable request.

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Author contributions

All authors contributed to the conception and design of the work; H.Y., H.Sugiyama, H.Sato contributed to data extraction and supervision of the project; T.O. performed statistical analysis; All authors contributed to the interpretation of the results; T.O. and S.M. wrote the main manuscript and all authors reviewed and revised it; all authors approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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