

Indications for kidney biopsy in idiopathic childhood nephrotic syndrome

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Abstract

Background Most cases of childhood nephrotic syndrome (NS) are due to minimal change disease (MCD), while a minority of children have focal segmental glomerulosclerosis (FSGS) and an unfavorable clinical course, requiring a kidney biopsy to confirm diagnosis. We hypothesized that clinical characteristics at diagnosis and initial response to corticosteroid treatment accurately predict FSGS and can be used to guide consistent practice in the indications for kidney biopsy. **Methods** This was a case control study (1990–2012). Inclusion criteria included age 1–17 years, meeting the diagnostic criteria for NS, and having biopsy-proven FSGS or MCD. Clinical characteristics at diagnosis included age, kidney function [estimated glomerular filtration rate (eGFR)], hypertension, hematuria, nephritis (reduced eGFR, hematuria, hypertension), and response to steroids. **Results** From a total of 169 children who underwent kidney biopsy for NS we included 65 children with MCD and 22 with FSGS for analysis. There were no significant between-group differences in age, sex, or eGFR at the time of diagnosis. The FSGS group had a higher proportion of hypertension (40 vs. 15%; $p = 0.02$), hematuria (80 vs. 47%; $p = 0.01$), and nephritis (22 vs. 2%; $p = 0.004$) and was more likely to be steroid resistant after 6 weeks of treatment than the MCD group (67

vs. 19%; $p < 0.001$). As predictors of FSGS, hematuria had a high sensitivity of 0.80 [95% confidence interval (CI) 0.56–0.93] and low specificity of 0.53 (95% CI 0.39–0.66), nephritis had a low sensitivity of 0.22 (95% CI 0.07–0.48) and high specificity of 0.98 (95% CI 0.88–0.99), and steroid resistance had a low sensitivity of 0.67 (95% CI 0.43–0.85) and high specificity of 0.81 (95% CI 0.68–0.90). The combination of steroid resistance after 6 weeks of therapy and/or nephritis at diagnosis yielded the optimal sensitivity and specificity at 0.80 (95% CI 0.56–0.93) and 0.75 (95% CI 0.60–0.86), respectively, confirmed by the highest receiver operator characteristic area under the curve of 0.77.

Conclusion Steroid resistance after 6 weeks of therapy and/or nephritis at initial presentation is an accurate predictor of FSGS in children with NS and will be used as the indication for kidney biopsy in our newly developed clinical pathway. This approach will maximize the yield of diagnostic FSGS biopsies while minimizing the number of unnecessary MCD biopsies.

Keywords Childhood · Nephrotic syndrome · Minimal change disease · Focal segmental glomerulosclerosis · Biopsy

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Background

Childhood nephrotic syndrome (NS) is one of the most common pediatric kidney disorders, with an incidence of 1–17 per 100,000 children and a prevalence of 16 per 100,000 children aged <16 years [1–4]. This syndrome is characterized by heavy urinary protein losses leading to hypoalbuminemia and edema. Idiopathic NS (INS) can be a clinical manifestation of one of multiple underlying pathologies, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and membranoproliferative

glomerulonephritis (MPGN), each identified by specific characteristics on kidney biopsy specimens [5, 6].

Children with MCD usually respond to standard corticosteroid therapy and have an excellent long-term prognosis. Children with FSGS, the most common form of non-MCD, may require intensified treatment and often have an atypical clinical course with unfavorable outcomes, warranting early detection [7–16]. While kidney biopsy is the gold standard test to determine the pathological type of NS, it is an invasive procedure with inherent costs and medical risks. In addition, the exact indications for its use are unclear. Recent consensus recommendations for kidney biopsy in children with NS include those cases with a “high index of suspicion” for an underlying pathology different from MCD; yet the exact indications are not well defined [17, 18].

In a large multicenter cohort, the International Study of Kidney Disease in Children (ISKDC) demonstrated that 77% of children with incident idiopathic NS had MCD, suggesting that the majority of children at diagnosis should not need a biopsy [19]. Subsequent studies have shown that approximately 90% of children with MCD respond to corticosteroid therapy and, furthermore, approximately 90% of all children with NS who respond to treatment will have MCD. These observations suggest that response to therapy is a useful measure of underlying histopathology. While these studies have informed clinical practice, there continues to be a lack of consensus among nephrologists or evidence-based guidelines regarding the specific indications for performing kidney biopsies in children with NS. In fact, in a number of case series of children with NS who underwent kidney biopsy, MCD continues to be the most common pathological diagnosis [20–22]. While the ISKDC studies provided important information about the clinical characteristics of the different forms of INS, they were not able to use these characteristics to differentiate between MCD and FSGS at diagnosis [19].

In this study we sought to reconsider the ability of clinical characteristics to predict FSGS in our population of children with NS who had biopsy-proven MCD or FSGS, given that (1) the epidemiology of childhood FSGS has changed, with an increasing incidence over the past four decades [22–25]; (2) our contemporary measures of kidney health have also changed since the original ISKDC report, with estimates of kidney function based on standardized and validated glomerular filtration rate (GFR) formulae, with high blood pressure defined as greater than the 95th percentile of current population data, and with hematuria evaluated by high power microscopic counts instead of Addis counts on timed urine collections; and (3) we wanted to apply standardized recommendations to our local population.

Our specific objectives were to: (1) evaluate the ability of clinical characteristics at diagnosis and the response to induction therapy to predict FSGS, (2) evaluate the best combination of clinical characteristics which, if used as

indications to perform a kidney biopsy, would optimize the number of FSGS biopsies while minimizing the number of unnecessary biopsies, and (3) develop recommendations for kidney biopsy indications to inform our local clinical pathway for childhood NS.

Methods

We used the search term “nephrotic syndrome” to identify children from the British Columbia Children’s Hospital Division of Nephrology clinical and kidney biopsy databases. Information was extracted from the hospital and clinic charts. When additional information was required, the primary care physician was contacted after informed consent from the child’s primary caregiver.

Case definition Cases were defined as children with biopsy-proven FSGS, while controls were children with biopsy-proven MCD. Cases of FSGS were identified through the biopsy dataset and met the remaining eligibility criteria. Children with MCD were identified through the clinical and biopsy datasets and met the eligibility criteria. The children were designated “biopsy-proven MCD” or “presumed MCD” according to whether or not they underwent a kidney biopsy that confirmed MCD. While we have included the cases with presumed MCD for the purpose of comparison with the biopsy-proven MCD cases, only the biopsy-proven cases were used in the analysis.

Case ascertainment Children were included if they: (1) were 1–17 years of age, (2) met the diagnostic criteria for NS, including edema, heavy proteinuria (urinary protein to creatinine ratio >200 mg/mmol, urinalysis >3 g/L, or ≥3+ protein on urine dipstick) and hypoalbuminemia (<25 g/L) [19], and (3) had FSGS or MCD diagnosed by kidney biopsy or had presumed MCD.

Children were excluded if they had their initial episode of NS treated outside the province of British Columbia, lacked sufficient clinical information from the historical record, had a congenital renal anomaly or other significant past history of kidney disease, or a kidney biopsy/clinical history/laboratory investigations suggesting a secondary form of NS, such as that seen with systemic lupus erythematosus, Henoch–Schönlein purpura, or IgA nephropathy.

In this report, we sought to define the ability of specific clinical characteristics to predict FSGS among a group of children who a priori have been identified as having either MCD or FSGS by kidney biopsy. We therefore also excluded the other conditions causing idiopathic NS. These conditions, including MPGN and membranous, C1q, and IgM nephropathies, often share features similar to FSGS, such as steroid resistance and nephritis at presentation, but can have different

clinical courses and responses to therapy, and were therefore excluded.

Clinical variables We sought to define the clinical indications for kidney biopsy in cases and controls from our center. We first studied the reason for biopsy as indicated in the patient's clinical record by the attending nephrologist. We then objectively evaluated the presence or absence of these characteristics through review of the clinical notes and laboratory test results.

The following clinical characteristics at presentation were selected for analysis as tests for predicting FSGS: (1) age, (2) kidney function, (3) blood pressure, (4) hematuria, (5) nephritis, and (6) response to steroid induction therapy. Impaired kidney function was defined as an estimated GFR (eGFR) of <90 ml/min/1.73 m² on at least two consecutive samples, calculated using the most recent modified Schwartz formula [26]. Since a reduced eGFR at presentation might be due to intravascular volume depletion and/or acute kidney injury, we considered the eGFR to be reduced only if it was persistently low on more than two different occasions. For hospitalized children, this time frame was usually within 2 days from presentation. If a subsequent reading was still high but normalized after albumin infusion and hydration, the eGFR was not considered to be reduced. Hypertension was defined as a diastolic and/or systolic blood pressure (BP) of $\geq 95\%$ for age, gender, and height on two separate readings on different days and/or if being treated with an anti-hypertensive medication [27]. All the BP readings considered were either before or within 2 days of starting steroids in the cases admitted to hospital at presentation. Over the course of the study, single BP measurements were typically obtained at clinic visits or in the emergency room and measured either by using an automated oscillometric BP machine or manually by auscultation. Hematuria was defined as the presence of ≥ 4 red blood cells (RBCs) per high power field (hpf) on microscopy (and then further categorized as ≥ 4 , ≥ 21 , and ≥ 51 RBCs/hpf). Nephritis was defined as the combination of hematuria (≥ 21

RBCs/hpf), hypertension (systolic and/or diastolic BP $\geq 95\%$), and impaired kidney function (eGFR <90 ml/min/1.73 m²), as described above.

The response to induction steroid therapy was also assessed as a predictor of FSGS. Clinical response to induction steroid therapy was initially defined as that designated by the treating nephrologist. However, given the variability of practice at our site, we then used clinical records and established standardized definitions to objectively assess clinical response. The treatment response patterns included steroid-sensitive (SS) or steroid-resistant (SR) patterns as defined in Table 1 [28]. We were also interested in defining the true prevalence of frequently relapsing (FR) and steroid-dependent (SD) patterns in our MCD population, as defined in Table 1.

Statistical methods Normally distributed data were expressed as means and standard deviation, non-parametric data as medians and interquartile range (IQR), and categorical variables as proportions. Differences between the groups were analyzed by two-sided Student's *t* test, by the Mann–Whitney *U* test, and by the chi-square or Fisher's exact test where appropriate, with $p < 0.05$ as the threshold for statistical significance. We considered each of the clinical variables and response to treatment as predictors of FSGS histology on kidney biopsy. We calculated proportions (percentages) for the presence of the specific variable for the groups. To assess the performance of FSGS predictors, we calculated their sensitivities and specificities and tested their performance using receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). Characteristics with high sensitivities have low false negative rates; that is, most cases with FSGS will have the characteristic. Characteristics with high specificities have low false positive rates, meaning that cases that do not have FSGS usually do not have the characteristic. All statistical analyses were performed using SPSS software, version 24 (IBM Corp., Armonk, NY).

Table 1 Standardized definitions of clinical course of nephrotic syndrome and response to therapy

Treatment response pattern	Description
Remission	Three consecutive days of negative or trace protein on a first morning urine dipstick (equivalent to urinalysis <0.3 g/L or urine PCR <25 mg/mmol)
Relapse	Three or more consecutive days of $\geq 3+$ protein on a first morning urine dipstick (equivalent to urinalysis >3 g/L or urine PCR >200 mg/mmol)
Steroid-sensitive (SS)	Remission within 6 weeks of daily prednisone therapy from the time of diagnosis
Steroid-resistant (SR)	Persistence of proteinuria after 6 weeks of daily prednisone therapy from the time of diagnosis (urine dipstick $\geq 1+$, urinalysis ≥ 0.3 g/L, or urine PCR ≥ 25 mg/mmol on a first morning urine sample)
Frequently relapsing (FR)	Four or more relapses in any 12-month period or ≥ 2 relapses in the 6 months after the initial response
Steroid-dependent (SD)	Same as frequently relapsing nephrotic syndrome, but with at least 2 of the relapses while on weaning doses of prednisone therapy, or within 2 weeks of stopping prednisone

Results

Case ascertainment We identified a total of 169 children with the diagnostic code “nephrotic syndrome” from the Division of Nephrology databases who underwent a kidney biopsy. We included 87 children in the analysis, of whom 65 had MCD and 22 had FSGS (Fig. 1). From a total of 420 children with the diagnosis “nephrotic syndrome”, we identified 156 as MCD, 91 with presumed MCD, and 65 with biopsy-proven MCD (Electronic Supplementary Material Fig. 1).

Indication for kidney biopsy as documented by the pediatric nephrologist As illustrated in Table 2, the most common indication for kidney biopsy documented by the attending nephrologist was a SD or FR course (44%), steroid resistance (28%), age ≥ 12 years at the time of presentation (13%), the presence of hypertension, hematuria, or elevated serum creatinine (10%), and the presence of nephritis (8%).

Kidney biopsy histopathology Of the 121 children with INS who underwent kidney biopsy, 65 (54%) with complete clinical data had MCD while 22 (18%) had FSGS (Table 3). A total of eight children with INS had neither MCD nor FSGS, including three children with MPGN, three with MN, one child with IgM nephropathy, and one child with C1q nephropathy. When we included children with presumed MCD and children with incomplete follow-up data, 77% (188/243) of the total children with presumed INS (with and without kidney biopsy confirmation) were considered to have MCD and 10% (23/243) to have FSGS (Table 3).

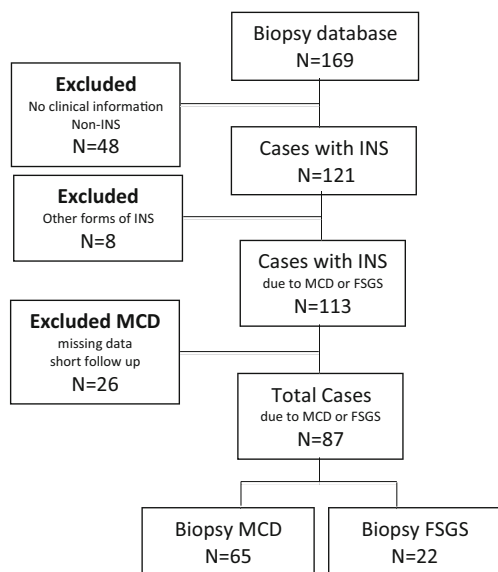


Fig. 1 Identification of biopsy-confirmed cases. A total of 169 children with the diagnostic code “nephrotic syndrome” were identified as having had a kidney biopsy. After exclusions, a total of 87 children were identified, of whom 65 had minimal change disease (MCD), while 22 had focal segmental glomerulosclerosis (FSGS). INS Idiopathic NS

Clinical biomarkers in MCD When all cases were combined, there was a total of 156 children with MCD. Their clinical characteristics at the time of diagnosis and their response to initial prednisone therapy are summarized in Table 4. Within this group, 65 children had biopsy-proven MCD, while the remaining 91 had presumed MCD. We then compared the clinical characteristics of both groups. There were no significant differences in the proportion of females (32 vs. 31%; $p = 0.84$), eGFR (119 ± 54 vs. 120 ± 48 ml/min/1.73 m²; $p = 0.91$), and proportion of children with hematuria ≥ 4 RBCs/hpf (47 vs. 47%; $p = 0.94$), decreased eGFR to < 90 ml/min/1.73 m² (24 vs. 20%; $p = 0.58$), and nephritis (2 vs. 0%; $p = 0.48$) between the biopsy-proven and presumed MCD groups, respectively. Children with biopsy-proven MCD were significantly older [median 4.8 (IQR 8.4) vs. 3.7 (IQR 3.10) years; $p < 0.001$], were less likely to have hypertension (36 vs. 57%; $p = 0.01$), and had a more complicated clinical course than those with presumed MCD. The biopsy-proven MCD group was more likely to be SR at 6 weeks (19 vs. 0%; $p < 0.001$), to have a FR or SD course in the first 2 years after induction therapy (59 vs. 24%; $p < 0.001$), to have more relapses in the first year after initial induction treatment (2.44 ± 0.18 vs. 1.57 ± 0.18 ; $p = 0.008$), to have been started on a second line agent (30 vs. 11%; $p = 0.003$), and to have started a second-line agent earlier after initial induction therapy [median 109 (IQR 273) vs. 511 (IQR 644) days; $p = 0.005$].

Clinical biomarkers in MCD and FSGS When the clinical characteristics at the time of diagnosis were compared between children with biopsy-proven FSGS and MCD, there were no significant differences in age, sex, or eGFR at presentation (Table 4). However, in the FSGS group there was a higher proportion of cases with hypertension (systolic and diastolic) (40 vs. 15%; $p = 0.02$), hematuria (80 vs. 47%; $p = 0.01$), and nephritis (22 vs. 2%; $p = 0.004$). We evaluated steroid resistance at various time points, including 4, 6, and 8 weeks after the initiation of prednisone therapy. In our cohort, all children who responded to prednisone did so by 6 weeks of induction therapy. We therefore defined steroid resistance in this study as a lack of a complete response to prednisone therapy by 6 weeks. When the response to 6 weeks of induction prednisone therapy was compared between the two groups, children with FSGS were more likely to be SR than those with MCD (67 vs. 19%; $p < 0.001$), but less likely to have a FR or SD course (14 vs. 59%; $p < 0.001$) (Table 4).

Clinical biomarkers as predictors of FSGS To determine the performance of the individual clinical biomarkers to predict FSGS, we calculated sensitivities and specificities. The data for each of the clinical characteristics are presented in Table 5. While none of the tests individually performed well with optimal sensitivity and specificity, the presence of hematuria (≥ 4 RBCs per hpf) had a high sensitivity of 0.80 [95% confidence interval (CI) 0.56–0.93], while nephritis had a high

Table 2 Indications for kidney biopsy in children with idiopathic nephrotic syndrome (focal segmental glomerulosclerosis and minimal change disease) as indicated by the attending nephrologist

Indications for kidney biopsy	Values
Steroid dependence/FR	38/87 (44%)
Steroid resistance	24/87 (28%)
Age ≥12 years	11/87 (13%)
Hypertension <u>or</u> hematuria <u>or</u> elevated serum creatinine level	9/87 (10%)
Nephritis (hypertension <u>and</u> hematuria <u>and</u> elevated serum creatinine level)	7/87 (8%)

Values in table are presented as the number of patients with the percentage in parenthesis

specificity of 0.98 (95% CI 0.88–0.99). Therefore, if children were biopsied on the basis of hematuria alone, most FSGS cases would be captured (high sensitivity, low false negative rate), but a high number of MCD cases would also be included (low specificity, high false positive rate) (0.53, 95% CI 0.39–0.66). If children were biopsied on the bases of nephritis alone, a large number of FSGS cases would be missed (low sensitivity, high false negative rate) (0.22, 95% CI 0.07–0.48), but almost no MCD cases would be included (high specificity, low false positive rate). As a predictor of FSGS, a FR or SD course had a low sensitivity of 0.14 (95% CI 0.04–0.36) and a low specificity of 0.41 (95% CI 0.29–0.54). In addition, of the three cases with FSGS who had a FR/SD course, two children developed early steroid dependence during induction prednisone therapy and the other developed a late FR course 8 years after the initial diagnosis.

In our cohort, steroid resistance after 6 weeks of therapy as a predictor of FSGS had a sensitivity of 0.67 (95% CI 0.43–0.85) with a specificity of 0.81 (95% CI 0.68–0.90), meaning a high false negative rate and a low false positive rate. To improve individual test performance, we combined steroid resistance with various clinical biomarkers at diagnosis (Table 5). The combination of steroid resistance and/or nephritis yielded the best result in terms of maximizing sensitivity

and specificity, achieving a sensitivity of 0.80 (95% CI 0.56–0.93) and a specificity of 0.75 (CI 0.60–0.86). This corresponded to the optimal ROC AUC of 0.77 (CI 0.63–0.90). When the combined indication of steroid resistance at 6 weeks and/or nephritis was applied to our cohort of children with MCD and FSGS (who were diagnosed and whose clinical course was labeled using the standardized definitions), 28 children with INS would have had a kidney biopsy, representing up to 59 fewer biopsies or a theoretical reduction of 68% (6 less in the FSGS group and, more importantly, 53 less in the MCD group).

Discussion

We have recently developed an evidence-based provincial clinical care pathway for childhood NS. Unfortunately, there are several aspects of other existing childhood NS clinical pathways for which there was insufficient evidence to help guide a number of our recommendations, including the indications for kidney biopsy. Additionally, results of our local practice audit demonstrated considerable variation in the reasons for performing kidney biopsies. Over 50% of all our biopsies of children with INS showed MCD, suggesting that many of these may have been unnecessary. We therefore sought to develop standardized indications to minimize the number of unnecessary biopsies (i.e. cases with MCD) while maximizing the yield of FSGS biopsies through a detailed analysis of whether the various clinical characteristics at initial diagnosis and response to initial therapy could predict FSGS.

Previous reports distinguishing the various forms of NS based upon clinical features at the time of diagnosis have yielded conflicting results [22]. We chose to study the predictors of FSGS as this is the most common non-MCD form of INS (10% in our INS population) and has in general a poor prognosis [29–31]. We sought to identify clinical characteristics at diagnosis that distinguished FSGS from the more common MCD (77% of our INS population) [18]. The proportion of cases with hypertension, hematuria, nephritis, and who were resistant to a 6-week course of steroids at diagnosis was higher in the FSGS group than in the MCD group. However, none of these characteristics, including steroid resistance, could individually predict FSGS and therefore be

Table 3 Biopsy classification of children with idiopathic nephrotic syndrome

Histopathology	All INS biopsies	All INS children
MCD	65/121 (54%)	188/243 (77%) ^a
FSGS	22/121 (18%)	23/243 (10%)
MPGN	3/121 (3%)	3/243 (1%)
MN	3/121 (3%)	3/243 (1%)
IgM	1/121 (1%)	1/243 (1%)
C1q	1/121 (1%)	1/243 (1%)
Missing data	26/121 (22%)	24/243 (10%)

Values in table are presented as the number of patients with the percentage in parenthesis

MCD, Minimal change disease; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; IgM, IgM nephropathy; C1q, C1q nephropathy

^a Includes children with presumed MCD and MCD with incomplete follow-up data

Table 4 Clinical characteristics of children with biopsy-proven focal segmental glomerulosclerosis versus minimal change disease

Clinical characteristics	All MCD cases	Biopsy-proven MCD cases	FSGS	<i>p</i> value
Number	156	65	22	
Median age (years) [IQR]	4.1 [5.5]	4.8 [8.4]	3.7 [6.6]	0.52
Age ≥6 years	48/156 (31%)	27/65 (42%)	11/22 (50%)	0.49
Age ≥10 years	29/156 (19%)	19/65 (29%)	5/22 (23%)	0.56
Age ≥12 years	23/156 (15%)	16/65 (25%)	5/22 (2%)	0.86
Sex: female	49/156 (31%)	21/65 (32%)	10/22 (46%)	0.27
Hypertension ^a	31/142 (22%)	9/61 (15%)	8/20 (40%)	0.02*
Hypertension ^b	68/142 (48%)	22/61 (36%)	12/20 (60%)	0.06
Hematuria ^c	62/132 (47%)	27/57 (47%)	16/20 (80%)	0.01*
Hematuria ^d	10/132 (8%)	6/57 (11%)	8/20 (40%)	0.003*
Hematuria ^e	2/132 (2%)	1/57 (2%)	2/20 (10%)	0.10
Mean eGFR (ml/min/1.73 m ²) (± SD)	119 ± 50	119 ± 54	103 ± 33	0.20
eGFR <60 ml/min/1.73 m ²	4/135 (3%)	2/59 (3%)	2/22 (9%)	0.29
eGFR <75 ml/min/1.73 m ²	10/135 (7%)	5/59 (9%)	3/22 (14%)	0.49
eGFR <90 ml/min/1.73 m ²	29/135 (22%)	14/59 (24%)	8/22 (36%)	0.26
Nephritis ^f	1/120 (1%)	1/52 (2%)	4/18 (22%)	0.004*
Steroid resistance at 4 weeks	17/149 (11%)	13/58 (22%)	14/21 (67%)	<0.001*
Steroid resistance at 6 weeks	11/149 (7%)	11/58 (19%)	14/21 (67%)	<0.001*
Steroid resistance at 8 weeks	11/149 (7%)	11/58 (19%)	14/21 (67%)	<0.001*
Steroid resistance and/or hematuria ^d	21/128 (16%)	17/53 (32%)	17/22 (77%)	<0.001*
Steroid resistance and/or hematuria ^e	13/128 (10%)	12/53 (23%)	15/22 (68%)	<0.001*
Steroid resistance and/or nephritis	12/116 (10%)	12/48 (25%)	16/20 (80%)	<0.001*
Steroid resistance and/or eGFR <90 ml/min/1.73 m ²	34/128 (27%)	19/52 (37%)	18/22 (82%)	<0.001*
FR or steroid dependency	60/155 (39%)	38/64 (59%)	3/21 (14%)	<0.001*

*Significant difference between biopsy MCD and FSGS at *p* < 0.05

IQR, Interquartile range; SD, standard deviation; eGFR, estimated glomerular filtration rate

Values in table are presented as a number with the percentage in parenthesis, unless indicated otherwise

^a Systolic and diastolic blood pressure (BP)

^b Systolic or diastolic BP

^c ≥4 red blood cells (RBCs) per high power field (hpf)

^d ≥21 RBCs per hpf

^e ≥51 RBC per hpf

^f Combination of hematuria (≥21 RBCs/hpf), hypertension (systolic and/or diastolic BP ≥95%), and eGFR <90 ml/min/1.73 m²

used as a single indication for biopsy. As a predictor of FSGS, steroid resistance had a high false negative rate and a low false positive rate. If used as the sole indication for kidney biopsy, while few cases of MCD would be biopsied, it would miss an unacceptably high number of FSGS cases. These findings are similar to the original ISKDC data, however steroid resistance was not reported in the data specifically as a test for FSGS [32].

To improve the performance of individual clinical characteristics as indications for kidney biopsy, we looked for the optimal combination of presenting clinical features. In practical terms, we sought to optimize the number of cases of FSGS (high sensitivity) while minimizing the number of MCD cases (high specificity) when planning a kidney biopsy in a child

with INS. In doing so, we would thereby reduce the number of unnecessary biopsies. Our highest sensitivity predictors included hematuria (≥4 RBCs per hpf) and steroid resistance after 6 weeks of therapy, while our highest specificity predictors included an eGFR of <60 ml/min/1.73 m², nephritis, and steroid resistance after 6 weeks. Unfortunately, there is a trade-off between individual predictors in terms of sensitivity and specificity; optimizing both is important to maximize the yield of FSGS cases while minimizing MCD cases. This was achieved by combining steroid resistance after 6 weeks of therapy with nephritis at the time of diagnosis. Of note, while a standardized definition of steroid resistance does not exist, we chose a lack of complete response to prednisone therapy after 6 weeks as our definition based upon previous consensus

Table 5 Sensitivity and specificity of clinical characteristics in predicting focal segmental glomerulosclerosis

Clinical characteristics	Sensitivity (95% CI)	Specificity (95% CI)	ROC AUC (95% CI)
Age <6 years	0.50 (0.29–0.71)	0.51 (0.37–0.64)	0.58 (0.42–0.74)
Age ≥10 years	0.23 (0.09–0.46)	0.71 (0.58–0.81)	0.46 (0.30–0.62)
Age ≥12 years	0.23 (0.09–0.46)	0.75 (0.63–0.85)	0.49 (0.33–0.65)
Sex: female	0.46 (0.25–0.67)	0.68 (0.55–0.78)	0.67 (0.51–0.83)
Hypertension ^a	0.40 (0.20–0.64)	0.85 (0.73–0.93)	0.61 (0.45–0.77)
Hypertension ^b	0.60 (0.36–0.80)	0.64 (0.51–0.76)	0.61 (0.46–0.77)
Hematuria ^c	0.80 (0.56–0.93)	0.53 (0.39–0.66)	0.61 (0.45–0.76)
Hematuria ^d	0.40 (0.20–0.64)	0.89 (0.78–0.96)	0.64 (0.49–0.81)
Hematuria ^e	0.10 (0.02–0.33)	0.98 (0.89–0.99)	0.55 (0.38–0.72)
eGFR <60 ml/min/1.73 m ²	0.09 (0.02–0.31)	0.97 (0.87–0.99)	0.54 (0.37–0.70)
eGFR <75 ml/min/1.73 m ²	0.14 (0.04–0.36)	0.92 (0.81–0.97)	0.54 (0.37–0.70)
eGFR <90 ml/min/1.73 m ²	0.36 (0.18–0.59)	0.76 (0.63–0.86)	0.58 (0.42–0.74)
Nephritis	0.22 (0.07–0.48)	0.98 (0.88–0.99)	0.61 (0.44–0.78)
Steroid resistance at 4 weeks	0.67 (0.43–0.85)	0.78 (0.64–0.87)	0.70 (0.54–0.85)
Steroid resistance at 6 weeks	0.67 (0.43–0.85)	0.81 (0.68–0.90)	0.72 (0.57–0.87)
Steroid resistance at 8 weeks	0.67 (0.43–0.85)	0.81 (0.68–0.90)	0.72 (0.57–0.87)
Steroid resistance and/or nephritis ^f	0.80 (0.56–0.93)	0.75 (0.60–0.86)	0.77 (0.63–0.90)
Steroid resistance and/or hematuria ^d	0.77 (0.54–0.91)	0.68 (0.54–0.80)	0.71 (0.57–0.86)
Steroid resistance and/or hematuria ^e	0.68 (0.45–0.85)	0.77 (0.63–0.87)	0.74 (0.60–0.88)
Steroid resistance and/or eGFR <90 ml/min/1.73 m ²	0.82 (0.59–0.94)	0.63 (0.49–0.76)	0.74 (0.61–0.88)
FR or steroid dependency	0.14 (0.04–0.36)	0.41 (0.29–0.54)	0.20 (0.09–0.32)

CI, Confidence interval; ROC, receiver operating characteristic curve; AUC, area under the curve

^a Systolic and diastolic BP

^b Systolic or diastolic BP

^c ≥4 RBCs per hpf

^d ≥21 RBCs per hpf

^e ≥51 RBCs per hpf

^f Two children had both steroid resistance and nephritis

reports [18]. In addition, all of the children in our cohort who responded to induction steroid therapy did so by 6 weeks.

While nephrologists continue to perform kidney biopsies in children with SS NS who have a frequent relapsing or SD course [33], in the absence of other abnormal clinical characteristics, this clinical pattern is rarely associated with FSGS and therefore not a standard indication for kidney biopsy [25, 32, 34]. In our study a FR or SD course was a poor predictor of FSGS, with both a low sensitivity and specificity.

Our study did have some limitations. An inherent drawback of the retrospective design of this study was the large number of excluded cases either because of missing information to allow inclusion into the study or because of a lack of sufficient follow-up clinical data. While we cannot be certain whether these cases differed significantly from those included, they were more likely to be cases of MCD given the poor prognosis of FSGS children who universally end up in the care of a tertiary care center like ours. If they had been included, they would likely have enriched our numbers of presumed

MCD, and therefore in most cases enhanced the specificity of the clinical characteristics to predict FSGS.

Additionally, we have restricted the ability of specific clinical characteristics to predict FSGS among a group of children who a priori have been identified as having either MCD or FSGS by kidney biopsy. We deliberately excluded the other conditions of INS which may also present with nephrotic syndrome. These conditions often share features similar to FSGS, such as steroid resistance and nephritis at presentation, but can have different clinical courses and responses to therapy. When the non-MCD cases were included with the FSGS cases to constitute a non-MCD group, the results of the analysis were similar, with nephritis and steroid resistance being good predictors of non-MCD. So, if we use the criteria suggested by our results to perform a biopsy, we are confident we would also identify the non-FSGS cases of non-MCD.

The overarching objective of this study was to use the clinical characteristics of our local cohort of children with NS and historical practice variation to define the indications

for kidney biopsy and therefore inform our local clinical pathway. We conclude that by applying standardized definitions of clinical responses to therapy and combining these with well-defined clinical biomarkers at presentation of disease, we will optimize the yield of diagnostic kidney biopsies while reducing the number of unnecessary procedures. Our clinical pathway now has recommended indications for kidney biopsy as: (1) steroid resistance at 6 weeks, or (2) nephritis upon presentation. Moving forward, consistent use of these pathway recommendations will lend itself to audit to determine if we have maximized FSGS diagnoses and minimized MCD diagnoses compared to historical data.

Compliance with ethical standards This was a case control study approved by the University of British Columbia and the British Columbia Children's Hospital Research Ethics committees. Informed consent was waived as the study was deemed minimal risk and data were obtained through a chart review.

Conflict of interest The authors declare no conflict of interest.

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