

# Prediction of Short- and Long-Term Outcomes in Childhood Nephrotic Syndrome



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**Introduction:** It is unknown whether steroid sensitivity and other putative risk factors collected at baseline can predict the disease course of idiopathic nephrotic syndrome in childhood. We determined whether demographic, clinical, and family reported factors at presentation can predict outcomes in idiopathic nephrotic syndrome.

**Methods:** An observational cohort of 631 children aged 1 to 18 years diagnosed with idiopathic nephrotic syndrome between 1993 and 2016 were followed up until clinic discharge, 18 years of age, end-stage kidney disease (ESKD), or the last clinic visit. Baseline characteristics were age, sex, ethnicity, and initial steroid sensitivity. Of these, 287 (38%) children also reported any family history of kidney disease, preceding infection, microscopic hematuria, and history of asthma/allergies. The outcomes were complete remission after initial steroid course, need for a second-line agent, frequently relapsing disease, and long-term remission. The discriminatory power of the models was described using the c-statistic.

**Results:** Overall, 25.7% of children had no further disease after their initial steroid course. In addition, 31.2% developed frequently relapsing disease; however, 77.7% were disease-free at 18 years of age. Furthermore, 1% of children progressed to ESKD. Logistic regression modeling using the different baseline exposures did not significantly improve the prediction of outcomes relative to the observed frequencies (maximum c-statistic, 0.63; 95% confidence interval [CI], 0.59–0.67). The addition of steroid sensitivity did not improve outcome prediction of long-term outcomes (c-statistic, 0.63; 95% CI, 0.54–0.70).

**Conclusions:** Demographic, clinical, and family reported characteristics, specifically steroid sensitivity, are not useful in predicting relapse rates or long-term remission in idiopathic nephrotic syndrome. Further studies are needed to address factors that contribute to long-term health.

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**KEYWORDS:** child; epidemiology; nephrotic syndrome; outcomes; pediatric; prognosis

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## See Commentary on Page 383

Corticosteroids are the mainstay of therapy for children with nephrotic syndrome, and clinicians

primarily use steroid sensitivity as the marker of overall prognosis. Families of children presenting with their first episode of nephrotic syndrome wish to know whether their child will achieve complete remission, and what their child’s kidney outcome will be. At presentation, most children with nephrotic syndrome are indistinguishable phenotypically and all are treated with an initial treatment course consisting of 3 to 5 months of steroids. Yet, the subsequent clinical course

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and outcomes are highly variable. We are unable to distinguish at disease onset between those children who will never relapse again and those who relapse infrequently or frequently. Furthermore, we cannot predict which patients will require 1 or more steroid-sparing medications or those who are at risk of progressing to ESKD.

Previous studies have shown differences in the frequencies of idiopathic nephrotic syndrome outcomes when stratified according to characteristics available at presentation such as sex, age, and ethnicity.<sup>1–5</sup> Male sex has been associated with a higher risk of relapsing disease after presentation.<sup>4,6</sup> Children younger than 5 years of age at presentation also have been reported to have a higher chance of subsequent relapses and frequently relapsing disease.<sup>5–7</sup> More recently, we have shown that despite a higher incidence of nephrotic syndrome among children with South Asian or East/Southeast Asian ancestry, these ethnic groups appear to be at a lower risk of frequently relapsing disease compared with children of European ancestry.<sup>2</sup> It also is unknown whether self-reported characteristics such as allergies or infections at presentation can provide better prediction of subsequent outcomes.

After diagnosis, a lack of response to the initial steroid course within 8 weeks is defined as initial steroid resistance and is associated with worse kidney outcomes.<sup>8,9</sup> It has been reported previously that approximately 20% of children with initial steroid-resistant nephrotic syndrome develop kidney failure in childhood.<sup>10–12</sup> More recent studies have shown that although a genetic diagnosis heralds a poor kidney outcome in steroid-resistant nephrotic syndrome, the absence of a genetic abnormality in these children is strongly predictive of response to calcineurin inhibitor therapy and better outcomes.<sup>13</sup> Moreover, 67% of children with genetic causes of steroid-resistant nephrotic syndrome developed ESKD compared with 27% of those with a nongenetic diagnosis.<sup>13</sup> Initial counseling of parents regarding both steroid-sensitive and steroid-resistant nephrotic syndrome remains generic and cannot be individualized. Counseling about steroid resistance is also delayed while waiting for genetic testing results.

We aimed to determine whether baseline demographic, clinical, and self-reported factors present at the onset of nephrotic syndrome could be used to predict long-term outcomes, specifically relapse rates, complete remission, and ESKD.

## METHODS

### Study Population and Data Collection

We studied 2 cohorts of children with presumed idiopathic nephrotic syndrome (i.e., nephrotic range

proteinuria, edema, hyperlipidemia, and hypoalbuminemia) at presentation aged between 1 and 18 years who presented across the Greater Toronto Area in Canada. Children with secondary or congenital causes of nephrotic syndrome (age, <1 year) were excluded from both cohorts. The first cohort consisted of 287 participants enrolled in the Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics (INSIGHT) study. INSIGHT collected self-reported data at baseline and then annually, and also longitudinal outcomes from incident and prevalent children with nephrotic syndrome from 2005 to 2016. The cohort study design has been described previously.<sup>2,14</sup> Ethics review board approval was obtained.

The second cohort consisted of 344 children presenting with presumed idiopathic nephrotic syndrome identified retrospectively using a pre-existing institutional database from 1993 to 2011. If a child was diagnosed after 2011, and was not enrolled in the INSIGHT study, they were not included in the present study ( $n = 87$ ). Basic demographic data were available but there was no self-reported information for this group. For both cohorts, data on urinalysis, relapse dates, second-line medications, discharge dates, and ESKD were abstracted from electronic medical records from the time of initial diagnosis onward.

The initial treatment protocol consisted of prednisone (or prednisolone) 60 mg/m<sup>2</sup>/day for 6 weeks followed by a standard tapering course since 2000, which was previously described.<sup>2,14</sup> Second-line agents consisted of cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, and levamisole. Third-line agents included other second-line agents not already tried and rituximab.

### Exposure

All children had their sex, age at diagnosis, and ethnicity recorded. Ethnicity was determined using the self-reported ethnicities of the child's 4 grandparents. If not available by self-report, ethnicity was determined using health records or from the naming databases Nam Pehchan and Quan's Chinese Name List as described previously.<sup>2</sup> Parents (or child-reported questionnaires) provided information on prior history of eczema, asthma, rhinitis, hay fever, kidney disease in the family (defined as a history of kidney disease or requirement for a kidney transplant), preceding infections (fever, tuberculosis, jaundice, or malaria 12 months before diagnosis, or viral illness in the past 6 months), or low birth weight/prematurity. All questionnaires used standard definitions for allergic conditions. Microscopic hematuria was defined as urinalysis positive for heme at or shortly after the diagnosis of nephrotic syndrome. Insufficient information from

families was available on time to remission of proteinuria after initiation of steroids. We therefore defined initial steroid resistance as starting a second-line agent during the initial steroid course by the attending nephrologist owing to lack of response.

## Outcomes

Outcomes assessed were complete remission after initial course, receipt of a second-line agent, frequently relapsing disease, and long-term remission in childhood. Complete remission after the initial steroid course was defined as no further relapses or prescribed medications after the initial 16-week period and subsequent discharge from the clinic. A second-line agent was defined as any immunosuppressant other than steroids. Frequently relapsing disease was defined according to the Kidney Disease: Improving Global Outcomes guidelines as follows: 2 or more relapses within 6 months, or 4 or more relapses within any subsequent 12-month period.<sup>8</sup> Long-term remission during childhood was defined as discharge from the clinic before age 18 years. We also calculated the proportion of children discharged from the clinic who were 18 years of age or older at the censor date. ESKD in childhood was recorded as the date of chronic dialysis commencement or receiving a kidney transplant.

## Statistical Analysis

Descriptive statistics of all exposure variables included means, medians, and proportions, and were compared between the 2 cohorts. Frequency estimates for all outcomes of interest were estimated from the combined cohort.

All combinations of baseline covariates were examined in individual outcome models. The ability of the different models to discriminate between outcomes was assessed by receiver operating characteristic analysis. The area under each receiver operating characteristic curve (equal to the concordance statistic [c-statistic]) was evaluated and 95% CIs were estimated using the bootstrap method with 10,000 replicates. A c-statistic of 1.0 indicated that the model discriminated the outcomes perfectly, whereas a c-statistic of 0.5 indicated that the model provided no discrimination. We tested whether results were similar when the analyses were restricted to those who were age 18 years or older at the censoring date. All analyses were performed in R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

A total of 631 children were followed up for a median of 3.9 years (interquartile range, 2.1–6.6 years). A total of 287 (46%) children had reported exposures available at disease onset, collected using the child-reported

questionnaire. All children were followed up until a disease-free discharge from the clinic ( $n = 358$ ), transitioned to adult care ( $n = 56$ ), received dialysis or kidney transplant ( $n = 7$ ), or until the last clinic follow-up ( $n = 210$ ). For our analyses, we excluded children whose care was transferred to another center shortly after diagnosis ( $n = 10$ ) or were lost to follow-up ( $n = 13$ ).

Baseline characteristics are summarized in [Table 1](#). The ratio of males to females was 1.6:1, with median age at diagnosis of 3.7 years (interquartile range, 2.6–6.3 years). Major ethnic ancestry subgroups within the cohort were South Asian (33.6%), European (26.0%), and East/Southeast Asian (9.0%). Microscopic hematuria was present among 42.5% at disease onset. The median time from diagnosis to recruitment and assessment of baseline exposures via questionnaire was 18.6 months (interquartile range, 3.6–48 months). Among those with self-reported or family reported exposures, 70.4% had a history of prior infection, 61.3% had a history of allergies or wheezing, and 26.5% had a family history of renal disease. Initial steroid resistance was diagnosed in 6.7% of children. Baseline and clinical characteristics of children who had initial steroid resistance are summarized in [Supplementary Table S1](#).

**Table 1.** Baseline demographic and clinical characteristics of children with childhood nephrotic syndrome by cohort

	N (%)			P value
	INSIGHT (n = 287)	Historical (n = 344)	Combined (n = 631)	
Male	186 (64.8)	201 (58.4)	387 (61.3)	0.8
Female	101 (35.2)	143 (41.6)	244 (38.7)	
Age at diagnosis, median (IQR)	3.6 (2.7–5.8)	3.8 (2.6–7.4)	3.7 (2.6–6.3)	0.3
South Asian	115 (40.0)	98 (28.5)	213 (33.6)	0.02
European	69 (24.0)	95 (27.6)	164 (26.0)	
East Asian	24 (8.3)	33 (9.6)	57 (9.0)	
Other background	74 (27.5)	118 (34.3)	197 (31.2)	
Initial steroid resistance	15 (5.2)	27 (7.8)	42 (6.7)	0.2
Positive family history of kidney disease	76 (26.5)	–	–	
Presence of microscopic hematuria	122 (42.5)	–	–	
Any history of allergies or wheezing	176 (61.3)	–	–	
Any history of prior infections	202 (70.4)	–	–	
Low birth weight/premature children	34 (11.8)	–	–	
Underwent kidney biopsy	14 (4.9)	82 (23.8)	96 (15.2)	<0.01
Minimal change disease	5 (1.7)	46 (13.4)	51 (8.1)	0.06
Focal segmental glomerulosclerosis	9 (3.1)	26 (7.7)	35 (5.5)	
Other <sup>a</sup>	0	10 (2.9)	10 (1.6)	
Months from diagnosis to enrollment, median (IQR)	18.6 (3.6–47.8)	–	–	

INSIGHT, Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics; IQR, interquartile range.

<sup>a</sup>Other includes membranous nephropathy, IgA nephropathy, no pathogenic diagnosis.

Overall, 25.7% had complete remission after the initial course. The frequency of long-term remission in childhood was 85.2% in the historical cohort and 56.7% in the combined cohort. Of 301 children who were age 18 years or older at the census date, 234 (77.7%) had been discharged from the clinic. The frequency of complete remission after the initial course, the use of a second-line agent, and frequently relapsing disease at 6, 12, and 18 months was similar in both cohorts (Table 2). In the historical cohort, 29.7% of children satisfied the criteria for frequently relapsing disease, 13.1% of children were transitioned to adult care, and 1.7% developed ESKD in childhood. Baseline and clinical characteristics of children who developed ESKD are summarized in Supplementary Table S2. There were no deaths observed during the study.

Figure 1 summarizes the disease course observed as categorized by initial steroid response, subsequent disease course, and by the final outcome. After disease onset, 143 children (24%) with initially steroid-sensitive nephrotic syndrome achieved complete remission. There were 193 (33%) initially steroid-sensitive children who had a frequently relapsing course. The remaining 253 children (43%) with steroid-sensitive disease had an infrequently relapsing course.

**Table 2.** Outcome frequencies in childhood nephrotic syndrome

	N (%)			P value
	INSIGHT (n = 287)	Historical (n = 344)	Combined (n = 631)	
Years followed up, median (IQR)	3.3 (1.8–5.5)	4.6 (2.5–7.4)	3.9 (2.1–6.6)	<0.001
Complete remission after initial course	74 (25.6)	88 (25.6)	162 (25.7)	0.9
Received a second-line agent <sup>a</sup>	146 (50.9)	156 (45.3)	302 (47.9)	0.2
Cyclophosphamide	3 (1.0)	21 (6.1)	23 (3.6)	<0.001
Levamisole	4 (1.4)	54 (15.7)	58 (16.9)	<0.001
Calcineurin inhibitors	139 (48.4)	128 (37.2)	267 (42.5)	0.005
Mycophenolate mofetil/ mycophenolate	19 (6.6)	19 (5.5)	38 (6.0)	0.6
Rituximab	13 (4.5)	6 (1.7)	19 (3.0)	0.06
Frequently relapsing disease (any)	95 (33.1)	102 (29.7)	197 (31.2)	0.4
Frequent relapses within 6 mo	54 (18.9)	62 (18.1)	116 (18.4)	0.8
Frequent relapses within 12 mo	42 (14.6)	47 (13.7)	89 (14.1)	0.7
Frequent relapses within 18 mo	38 (13.2)	35 (10.2)	73 (11.6)	0.3
Long-term remission in childhood	65 (22.6)	293 (85.2)	358 (56.7)	<0.001
ESKD in childhood	4 (1.4)	6 (1.7)	10 (1.6)	0.8
Transitioned to adult care	11 (3.8)	45 (13.1)	56 (8.9)	<0.001
Still actively followed up	210 (73.2)	0 (0)	210 (33.3)	–

ESKD, end-stage kidney disease; INSIGHT, Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics; IQR, interquartile range.

<sup>a</sup>Any treatment after that with the first-line agent is classified as treatment with a second-line agent. Note that a patient may receive multiple second-line treatments according to this definition.

For those children with initial steroid resistance, 19 (45%) had no further relapses and were discharged after treatment with a second-line agent. Similarly, 19 children (45%) with initial steroid resistance who responded to second-line therapy had subsequent relapses.

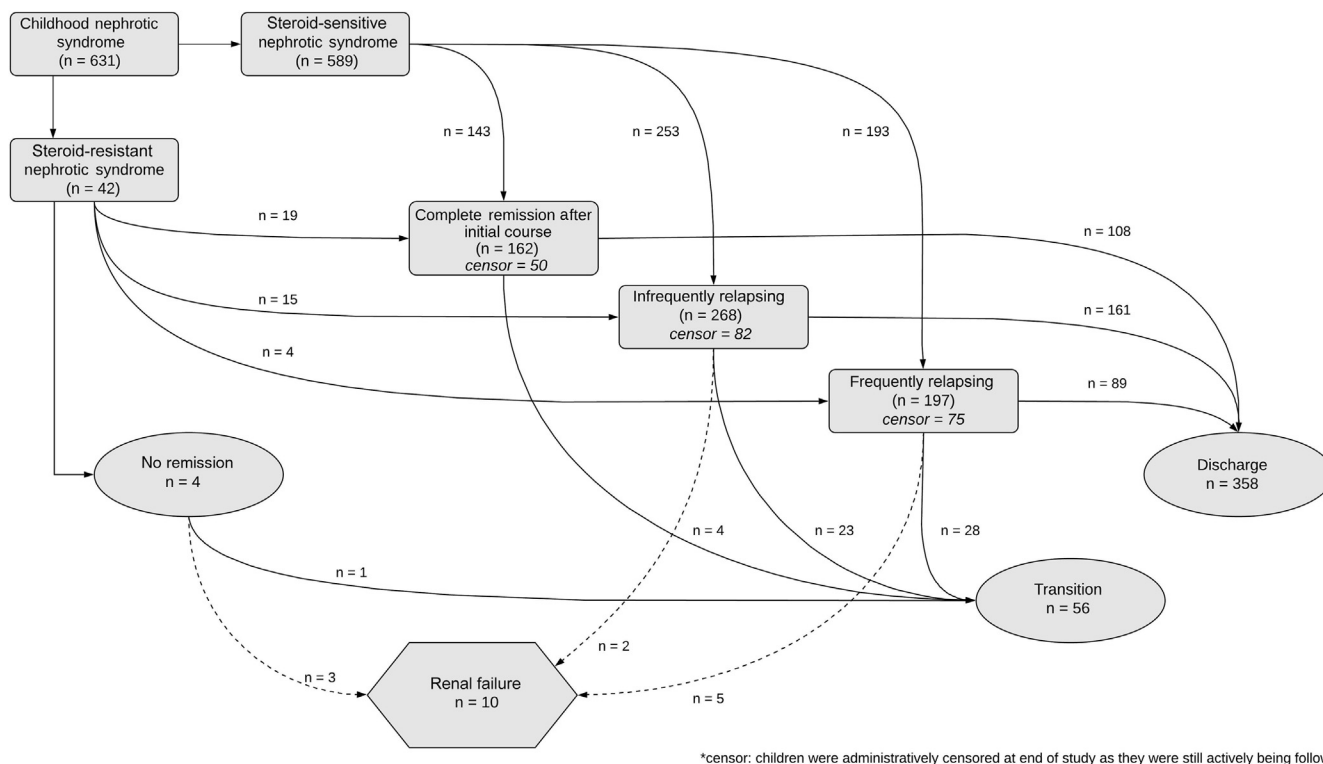
Overall, 1.7% of children ( $n = 10$  of 631) developed ESKD; approximately 1% of children who were initially steroid sensitive ( $n = 7$  of 589), and approximately 7% of children who were initially steroid resistant ( $n = 3$  of 42;  $P = 0.02$ ) (Figure 1). There was higher odds of steroid response and ESKD (odds ratio, 6.40; 95% CI, 1.34–24.00). Receiver operating characteristic analysis for ESKD showed that steroid resistance or other factors were not predictive because all 95% CIs contained 0.5 which indicates that the model provides no discrimination (Supplementary Table S3).

Table 3 compares the predictive performance of the logistic regression models for the outcomes of complete remission after presentation, receipt of a second-line agent, frequently relapsing disease, and long-term remission in childhood. Despite the slightly higher proportion of ESKD among those with initial steroid resistance, all models, which included demographic characteristics and initial steroid response, provided poor discrimination with only modest improvement from the line of identity (maximum c-statistic, 0.63; 95% CI, 0.59–0.67). Furthermore, the addition of a history of allergies, preceding infection, baseline body mass index, low birthweight/prematurity, a family history of kidney disease, presence of microscopic hematuria at presentation, and initial steroid resistance did not improve model predictive performance measures (maximum c-statistic, 0.63; 95% CI, 0.54–0.70) beyond multivariable adjustment for age, sex, and ethnicity (maximum c-statistic, 0.63; 95% CI, 0.55–0.70). The measures of association of baseline demographic and clinical characteristics with these outcomes are shown in Supplementary Table S4.

Among those age 18 years or older at the census date, age at diagnosis was a fair predictor of long-term remission in childhood (c-statistic, 0.71; 95% CI, 0.63–0.79); older age was associated with lower odds of long-term remission in childhood (per 1-year increase: odds ratio, 0.84; 95% CI, 0.80–0.89). Discrimination remained poor for the outcomes of complete remission after presentation, receipt of a second-line agent, and frequently relapsing disease (data not shown). Furthermore, these results were robust to restricting the analysis to participants with at least 4 years of follow-up.

## DISCUSSION

In a large multiethnic cohort, we showed that children with nephrotic syndrome have an excellent prognosis,



**Figure 1.** Flow diagram indicating the number of children with idiopathic childhood nephrotic syndrome categorized by disease course and by outcome in childhood.

with almost 80% achieving long-term remission before 18 years of age. Only 1.7% progressed to ESKD. Steroid-sensitive and initially steroid-resistant disease also had comparable long-term outcomes. A quarter of children achieve complete remission after the initial course of steroid, approximately 40% have infrequently relapsing disease, and 30% have frequently relapsing disease. We report that despite incorporating known and putative baseline risk factors such as age, sex, ethnicity, preceding allergies or infection, or a family history of kidney disease, we remain unable to improve prediction of the subsequent disease trajectory in childhood nephrotic syndrome. Most importantly, incorporating initial steroid resistance failed to improve prediction of any short- or long-term outcome.

Families living with nephrotic syndrome should be counseled using the overall observed frequencies of various outcomes and not adjusted for baseline characteristics, such as age at diagnosis, sex, or ethnicity. Complete remission after the initial course occurs in approximately 1 in 4 children, similar to previous reports of 20% to 30%.<sup>4,15</sup> Frequently relapsing disease occurs in approximately 1 in 3 children, and 1 in 2 children receive second-line therapy, consistent with studies previously reporting 16% to 67%.<sup>1,11,15,16</sup> Ultimately, 3 in 4 children can expect to achieve freedom from disease in childhood. This observation is consistent with the common advice that the disease will

likely become quiescent by age 18. Kidney failure is also rare in childhood and importantly there were no deaths observed. Conveying this information to families is important for counseling and understanding the longitudinal course in the majority of children with nephrotic syndrome. An educational infographic was designed to communicate this essential information and better inform families, while improving knowledge retention (available at <https://lab.research.sickkids.ca/parekh/patients>, and as a [Supplementary Infographic](#)).<sup>17,18</sup>

Prior studies have suggested an inverse linear relationship between length of remission and subsequent relapse,<sup>3</sup> with 25% to 40% of children continuing to relapse after puberty and into adulthood.<sup>16,19,20</sup> We estimated that approximately 80% of children were discharged from the clinic with complete remission in childhood and likely no subsequent disease during adulthood. However, without follow-up evaluation after 18 years of age, we cannot be completely certain that the majority of people with childhood-onset nephrotic syndrome remain disease-free in adulthood.

Most significantly, initial steroid resistance only marginally improved predictive model performance, but was not a reliable prognostic indicator of frequently relapsing course. The most accurate model using steroid resistance had a c-statistic of 0.67, compared with 0.63 without steroid resistance, which

**Table 3.** Discriminatory performances of logistic regression models in childhood nephrotic syndrome

Covariate(s)	Complete remission after initial course	Requirement for second-line agents	Frequently relapsing disease (any)	Long-term remission in childhood
	Discrimination: c-statistic (95% CI)			
Combined cohort				
Age	0.55 (0.50–0.60)	0.50 (0.46–0.55)	0.53 (0.48–0.58)	0.63 (0.59–0.67)
Sex	0.52 (0.48–0.57)	0.51 (0.47–0.55)	0.51 (0.47–0.55)	0.50 (0.46–0.54)
Ethnicity	0.53 (0.48–0.58)	0.55 (0.51–0.59)	0.56 (0.51–0.61)	0.53 (0.49–0.58)
Initial steroid resistance	0.53 (0.51–0.56)	□	0.53 (0.52–0.55)	0.51 (0.49–0.53)
Baseline BMI	0.55 (0.49–0.62)	0.46 (0.40–0.52)	0.52 (0.46–0.58)	0.55 (0.49–0.61)
Age, sex, ethnicity	0.57 (0.52–0.63)	0.55 (0.51–0.60)	0.58 (0.53–0.63)	0.55 (0.51–0.60)
Age, sex, ethnicity, initial steroid resistance	0.59 (0.54–0.64)	□	0.58 (0.53–0.62)	0.55 (0.51–0.60)
Age, sex, ethnicity, initial steroid resistance, baseline BMI	0.60 (0.54–0.67)	0.56 (0.50–0.62)	0.51 (0.45–0.58)	0.54 (0.48–0.60)
INSIGHT				
Age	0.52 (0.44–0.60)	0.53 (0.46–0.60)	0.51 (0.44–0.58)	0.64 (0.56–0.71)
Sex	0.55 (0.48–0.61)	0.55 (0.50–0.61)	0.51 (0.45–0.57)	0.51 (0.44–0.58)
Ethnicity	0.55 (0.48–0.63)	0.52 (0.45–0.58)	0.53 (0.46–0.59)	0.55 (0.47–0.62)
Hematuria	0.50 (0.43–0.57)	0.52 (0.45–0.58)	0.55 (0.49–0.61)	0.55 (0.48–0.62)
Initial steroid resistance	0.55 (0.51–0.59)	□	0.54 (0.52–0.56)	0.51 (0.49–0.54)
Allergies	0.53 (0.46–0.59)	0.51 (0.45–0.56)	0.55 (0.49–0.61)	0.54 (0.48–0.62)
Prior infection	0.51 (0.45–0.57)	0.51 (0.46–0.56)	0.51 (0.45–0.56)	0.51 (0.45–0.57)
Family history	0.53 (0.46–0.59)	0.55 (0.50–0.61)	0.51 (0.45–0.57)	0.51 (0.44–0.57)
Low birth weight/prematurity	0.52 (0.47–0.56)	0.52 (0.48–0.56)	0.50 (0.46–0.54)	0.51 (0.46–0.56)
Baseline BMI	0.55 (0.47–0.63)	0.58 (0.51–0.65)	0.55 (0.48–0.62)	0.58 (0.49–0.66)
Age, sex, ethnicity	0.57 (0.49–0.65)	0.57 (0.51–0.64)	0.54 (0.47–0.61)	0.63 (0.55–0.70)
Age, sex, ethnicity, initial steroid resistance	0.61 (0.53–0.69)	□	0.56 (0.50–0.63)	0.64 (0.57–0.71)
Age, sex, ethnicity, hematuria	0.58 (0.50–0.66)	0.60 (0.53–0.66)	0.57 (0.49–0.64)	0.63 (0.56–0.71)
Age, sex, ethnicity, hematuria, initial steroid resistance	0.63 (0.54–0.70)	□	0.53 (0.45–0.62)	0.63 (0.56–0.71)
Age, sex, ethnicity, hematuria, initial steroid resistance, allergies, family history, prior infection	0.61 (0.53–0.69)	□	0.57 (0.48–0.65)	0.63 (0.55–0.71)
Age, sex, ethnicity, hematuria, initial steroid resistance, allergies, family history, prior infection, low birth weight/prematurity, baseline BMI	0.63 (0.55–0.71)	□	0.55 (0.46–0.64)	0.67 (0.60–0.75)

BMI, body mass index; INSIGHT, Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics.

□Models including initial steroid resistance were not reported because these patients received a second-line agent by definition.

NB, null value for C statistics is 0.50.

is slightly better than 0.5, indicating no better than random chance. Furthermore, we observed similar outcome frequencies in children with either initial steroid resistance or steroid sensitivity, which has implications for family counseling. Although there was a greater proportion of children with initial steroid resistance (~7%) who developed ESKD, there was a large portion of children with steroid resistance who responded to calcineurin inhibitors (90%). Initial steroid-resistant nephrotic syndrome necessitates the use of calcineurin inhibitors. In this group, response to treatment has a more favorable long-term outcome in those in whom no genetic abnormality was found,<sup>13</sup> resulting in preservation of renal function.<sup>9</sup> We challenge the current model of counseling families early in the disease course regarding prognostic information based on initial steroid sensitivity alone given the heterogeneity of patients classified as steroid resistant.

Demographic, clinical, and self-reported factors do not usefully predict outcomes in childhood nephrotic syndrome. Some reports correlate male sex with a higher likelihood of a subsequent relapsing course.

This is not consistent in all studies, possibly owing to small sample size, variable follow-up, or variability in the outcomes reported.<sup>3,4,6,15,21</sup> The higher incidence of nephrotic syndrome in boys possibly relates to disease onset only, and does not improve the ability to predict long-term outcomes. Younger age at diagnosis also is associated with a relapsing course,<sup>3,5–7</sup> but not consistently.<sup>21–23</sup> Some studies have suggested that teenagers presenting with nephrotic syndrome have a higher likelihood of kidney failure, with rates of ESKD from 3.6% to 10.2%.<sup>24,25</sup> The higher rates observed may be owing to selection bias, with a focus on children who have progressive or relapsing disease. In contrast, we account for all children with incident nephrotic syndrome, with standardized ascertainment of outcomes over follow-up and we report low rates of progressive kidney disease.

Previously, we reported that the incidence of nephrotic syndrome differed by ethnic subgroups, and that children of South and East Asian ancestry were less likely to relapse, have frequently relapsing disease, or receive a second-line agent compared with children

of European ancestry.<sup>2,26</sup> Even though the relative risk of various outcomes differed by ethnic subgroup, the effect of ethnicity in conjunction with age and sex in prediction of outcomes was only modest. In addition, the clinical course after using steroid-sparing agents is similar regardless of ethnicity. Ethnicity, similar to age and sex, may point to specific factors that are associated with development of disease rather than the interindividual variability resulting in frequent relapses.

Viral illness or allergy often precede the initial development of nephrotic syndrome and are associated with frequent relapses. Viral illness accompanying relapses predicts steroid-dependent disease, but again does not predict long-term outcomes.<sup>23</sup> Children with atopic conditions have a higher frequency of nephrotic syndrome compared with controls.<sup>27–29</sup> Yet in our study the presence or absence of allergic conditions did not usefully predict worse disease outcomes. Previous studies were unable to show that allergic diseases are associated with a frequently relapsing disease course.<sup>23,30</sup> Likewise, microscopic hematuria occurs in 30% to 50% of patients at presentation, which is similar to other studies, yet it was not associated with worse outcomes.<sup>1,4,22</sup>

The strengths of this study were the inclusion of a large, multiethnic, multicenter cohort that had baseline characteristics recorded and long-term follow-up. This approach was less prone to selection bias than previous retrospective cohorts, which may have omitted patients with few or no relapses because these patients are less likely to be captured in tertiary nephrology clinics because general pediatricians may manage the first presentation. This also may explain the lower observed incidence of initial steroid resistance (6.7%) because we captured the full spectrum of all incident cases with idiopathic nephrotic syndrome. With some of the participants recruited well after the initial diagnosis, there may be recall bias among those completing the questionnaire on viral or allergic exposure. However, analyses limited to those enrolled within the first year did not change the results.

There were clear limitations to this study. We had self-reported or family reported exposures in 45% of the cohort. Also, we included children with ongoing follow-up, however, an additional analysis in 301 children with complete follow-up to age 18 years showed similar results. The absence of data on hematuria, allergies, infection, family history, and low birthweight from the historical cohort prevented these individuals from being included in a subset of the composite models, but given the poor performance of these models, we do not believe that their inclusion would alter our conclusions. We used previously validated questionnaires to define certain covariates,

however, some factors such as preceding infection had limited scope. Our definition of microscopic hematuria was based on dipstick results because urine microscopy was not performed routinely and systematically recorded in the child's medical chart. In addition, with any self-reported questionnaire, there is a possibility of recall bias when parents are asked about events that occurred before diagnosis. We had insufficient time-to-initial remission of proteinuria data to incorporate into our analyses. Children whose time-to-initial remission of proteinuria after starting steroids was longer than 9 days, compared with those with remission within 9 days, had a higher risk of frequently relapsing disease, steroid dependency, and chance of receiving a second-line agent.<sup>15,22,23,31–33</sup> Therefore, incorporation of time-to-event data in the models may have improved outcome prediction. It is not a clinically or practically useful variable for initial prediction of outcomes because it still requires the initial steroid therapy course similar to defining initial steroid-resistant disease, and this lacked prognostic capability. In addition, we found that there was a higher odds of initial steroid resistance with ESKD; however, steroid resistance was not predictive of the absolute risk of ESKD as a factor alone or with other clinical factors.<sup>34</sup> Furthermore, there still may be differences by steroid response status if the definition of steroid resistance was refined further to account for those who never respond to any immunosuppressives versus those who do respond (e.g., calcineurin inhibitors) and then compare with those who are steroid sensitive. Finally, we acknowledge the possibility of selection bias in long-term patient outcomes given that the historical cohort has inherently longer follow-up times.

Clinicians should counsel families using the overall frequencies of outcomes in nephrotic syndrome and not prognosticate based on demographic, clinical, or family reported characteristics or initial steroid resistance. Predictive models are useful to guide therapy or provide prognostic information to families based on risk, however, we respectfully challenge the current paradigm of counseling families early in the disease course with prognostic information based on steroid sensitivity alone. Currently, we lack an understanding of the pathophysiological mechanisms leading to childhood nephrotic syndrome. Future research targeting noninvasive biomarkers may better define prognosis. Successful predictive modeling in childhood nephrotic syndrome will require identification of novel factors implicated in the causal pathways leading to relapses.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

**Table S1.** Baseline demographic and clinical characteristics of children with steroid-resistant nephrotic syndrome.

**Table S2.** Baseline demographic and clinical characteristics of children with childhood nephrotic syndrome who developed end-stage kidney disease ( $N = 10$ ).

**Table S3.** Association of baseline demographic and clinical characteristics of end-stage kidney disease in childhood nephrotic syndrome.

**Table S4.** Association of baseline demographic and clinical characteristics with outcomes in childhood nephrotic syndrome.

**Supplementary Infographic.** Infographic developed based on study data knowledge dissemination to health care professionals and families.

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