

Factors Associated with Relapse in Children with Nephrotic Syndrome

Zahidul Islam^{1*}, Mst Jannatul Ferdous², Yousuf Ali³, Abu Sayed⁴, Rezaul Karim⁵, Kiswar Silvana⁶

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*Corresponding author



ABSTRACT

Background: Childhood nephrotic syndrome frequently follows a relapsing course, increasing treatment burden and exposure to corticosteroids and other immunosuppressive therapies. Identifying factors associated with relapse may support closer monitoring and individualized management. **Aim of the study:** To determine the clinical, laboratory, disease-related, and treatment-related factors associated with relapse among children with nephrotic syndrome and identify factors associated with recurrent disease. **Methods & Materials:** This cross-sectional analytical study included 95 children aged 2–15 years with nephrotic syndrome. Participants were selected by purposive sampling. Sociodemographic, clinical, laboratory, treatment, adherence, and follow-up data were collected from interviews, clinical examinations, laboratory reports, treatment records, and follow-up documentation. Associations were assessed using appropriate statistical tests, followed by multivariable logistic regression. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated, with $p < 0.05$ considered statistically significant. **Result:** Among 95 children, 69 (72.63%) experienced relapse, including 31 (32.63%) frequent relapsers and 38 (40.00%) infrequent relapsers. Children with relapse were younger (6.8 ± 2.9 vs. 8.3 ± 3.4 years, $p = 0.032$), had a younger age at diagnosis (5.0 ± 2.5 vs. 6.4 ± 3.0 years, $p = 0.024$), longer illness duration (2.1 ± 1.4 vs. 1.1 ± 0.9 years, $p = 0.001$), and lower serum albumin (2.0 ± 0.4 vs. 2.3 ± 0.5 g/dL, $p = 0.006$). Steroid dependence (39.13% vs. 7.69%, $p = 0.003$), medication non-adherence (27.54% vs. 7.69%, $p = 0.048$), delayed remission (65.22% vs. 42.31%, $p = 0.049$), infection during follow-up

(40.58% vs. 19.23%, $p = 0.049$), and serum albumin < 2.5 g/dL (85.51% vs. 61.54%, $p = 0.011$) were associated with relapse. Multivariable analysis identified age at diagnosis < 5 years (aOR 2.41, 95% CI 1.01–5.74), illness duration ≥ 2 years (aOR 2.87, 95% CI 1.16–7.08), steroid dependence (aOR 4.36, 95% CI 1.45–13.12), medication non-adherence (aOR 3.18, 95% CI 1.05–9.61), remission after > 10 days (aOR 2.63, 95% CI 1.08–6.42), serum albumin < 2.5 g/dL (aOR 2.74, 95% CI 1.08–6.94), and infection during follow-up (aOR 2.52, 95% CI 1.02–6.22) as independent factors associated with relapse. **Conclusion:** Relapse was frequent among children with nephrotic syndrome and was independently associated with younger age at diagnosis, prolonged illness, steroid dependence, medication non-adherence, delayed remission, hypoalbuminemia, and infection during follow-up. Recognition of these factors may facilitate risk stratification and closer clinical surveillance. Strengthening adherence, preventing and promptly treating infections, and individualized follow-up of children with delayed remission or steroid dependence may help reduce recurrent episodes and cumulative treatment burden.

Keywords: Nephrotic syndrome; Children; Relapse; Steroid dependence; Medication adherence.

1. Assistant Professor, Department of Paediatrics, Manikganj Medical College Hospital, Manikganj, Bangladesh (ORCID: 0009-0000-9715-1849)
2. Assistant Professor (Gayne and Obs) 250 Bed General Hospital, Joypurhat, Bangladesh
3. Assistant Professor, 250 bed General Hospital, Joypurhat, Bangladesh
4. Assistant Professor (Paediatrics), 250 bed general hospital, Sirajganj, Bangladesh
5. Assistant Professor (Paediatrics), 250 Bedded District Hospital, Chapainawabganj, Bangladesh
6. Associate Professor (Paediatrics), Manikganj Medical College, Manikganj, Bangladesh

INTRODUCTION

Childhood nephrotic syndrome (NS) is a glomerular disorder characterized clinically by heavy proteinuria, hypoalbuminemia and edema often accompanied by hyperlipidemia. In children, most idiopathic cases are steroid-sensitive, with subsequent clinical course largely determined by the pattern and frequency of relapse [1, 2]. Idiopathic nephrotic syndrome affects approximately 2.92 per 100,000 children annually with relapse occurring in nearly 72% of affected children, shows the recurrent nature of childhood nephrotic syndrome [3]. In Bangladesh, approximately 35% of children with steroid-sensitive nephrotic syndrome and relapse may experience a frequently relapsing course [4]. Management generally begins with oral glucocorticoid therapy because approximately 85–90% of children achieve complete remission following initial treatment [1]. For a relapse, current KDIGO guidance recommends daily oral

prednisone or prednisolone until complete remission is maintained for at least 3 days followed by alternate-day therapy for approximately 4 weeks [5]. Management of frequent relapses or steroid dependence may involve prolonged low-dose glucocorticoid therapy or the use of steroid-sparing agents such as levamisole, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors or rituximab, tailored to the individual clinical course [5, 6]. These approaches can prolong remission, treatment must balance relapse prevention against cumulative glucocorticoid toxicity and adverse effects of immunosuppressive therapy [6, 7]. The recurrent nature of nephrotic syndrome can substantially increase the clinical burden during childhood by requiring repeated courses of treatment, laboratory monitoring and healthcare visits. Frequent relapses may expose children to greater cumulative corticosteroid doses and consequently increase the risk of growth impairment,

obesity, behavioral disturbances and other treatment-related complications [6, 7]. Relapse-associated infections may further complicate disease management, and infection occurring during relapse has been identified as an important predictor of frequent relapse [8]. Current treatment has the major advantage of achieving remission in most steroid-sensitive children and substantially improving long-term renal outcomes [1, 5]. Repeated steroid exposure and prolonged immunosuppression can produce clinically important adverse effects, while no single clinical factor consistently predicts relapse [6, 9]. Relapse frequency is an important determinant of prognosis and treatment burden in childhood nephrotic syndrome, and the first year after diagnosis is particularly informative for subsequent disease behavior [5]. Several demographic, biochemical, infectious, and treatment-related factors may influence relapse patterns in childhood nephrotic syndrome

and identifying locally relevant predictors may help recognize children who require closer follow-up and individualized therapeutic strategies [10, 11]. Relapse in childhood nephrotic syndrome may be influenced by age at onset, socioeconomic factors, biochemical abnormalities, infection, and response to initial steroid therapy. The relative contribution of these factors may vary among children, highlighting the need to assess them together when evaluating relapse risk in the Bangladeshi population [10, 11]. The study was conducted to determine the clinical and laboratory factors associated with relapse among children with nephrotic syndrome and to identify factors associated with frequent relapse.

METHODS & MATERIALS

This cross-sectional analytical study was conducted among 95 children diagnosed with nephrotic syndrome attending conducted in the Department of Pediatrics at Rajshahi Medical College Hospital, Bangladesh, from January 2017 to June 2018. Participants were selected by purposive sampling.

Inclusion Criteria

- Children aged 2–15 years with a diagnosis of nephrotic syndrome.
- Children who received treatment and had adequate clinical and laboratory records.
- Children with documented follow-up information sufficient to determine remission and relapse status.
- Parents or legal guardians willing to provide informed consent.

Exclusion Criteria

- Children with secondary nephrotic syndrome due to an established systemic disease.
- Children with major chronic renal disease or advanced renal impairment unrelated to the presenting nephrotic syndrome.
- Children with incomplete clinical, laboratory, treatment, or follow-up records.
- Children whose parents or legal guardians declined participation.

Data Collection

Data were collected using a structured data collection form through patient interviews with parents or guardians, clinical examination, laboratory reports, treatment records, and follow-up documentation. Sociodemographic variables included age and gender. Clinical characteristics included age at first diagnosis, duration of illness, family history of nephrotic syndrome, consanguinity, edema at presentation, hypertension, hematuria, and degree of proteinuria. Laboratory parameters included serum albumin and serum creatinine, with serum cholesterol also assessed where available. Disease and treatment-related variables included steroid-sensitive or steroid-resistant disease, time to remission after initial steroid therapy, steroid dependence, previous relapses, frequent or infrequent relapse status, cyclophosphamide, levamisole and calcineurin inhibitor therapy, and medication non-adherence. During follow-up, occurrence of infection and incomplete remission were documented. Relapse was defined according to documented recurrence of significant proteinuria after remission. Children were classified into relapse and no-relapse groups for analysis.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range according to data distribution, while categorical variables were presented as frequency and percentage. The independent samples t-test or Mann–Whitney U test was used for comparison of continuous variables as appropriate. The chi-square test or Fisher's exact test was used to assess associations between categorical variables. Variables showing relevant associations in univariable analysis were entered into multivariable logistic regression to identify independent factors associated with relapse. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. A p-value of <0.05 was considered statistically significant.

RESULT

Among the 95 children with nephrotic syndrome, the mean age was 7.2 ± 3.1 years, with 47.37% aged 6–10 years, 29.47% aged 2–5 years, and 23.16% aged 11–15 years. Most participants were male (64.21%). The mean age at first diagnosis was 5.4 ± 2.7 years and the mean duration of illness was 1.8 ± 1.4 years. Family history of nephrotic syndrome and consanguinity were present in 9.47% and 6.32%, respectively. Edema at presentation was observed in 95.79%, hypertension in 17.89%, hematuria in 14.74%, and proteinuria $\geq 3+$ in 87.37%. Mean serum albumin and creatinine levels were 2.1 ± 0.5 g/dL and 0.62 ± 0.21 mg/dL, respectively (Table I).

Table I

Sociodemographic and Clinical Characteristics of Children with Nephrotic Syndrome ($n=95$).

Variables	Frequency (n)	Percentage (%)
Age (years)		
2–5 years	28	29.47
6–10 years	45	47.37
11–15 years	22	23.16
Mean $\pm$ SD	7.2 ± 3.1	
Gender		
Male	61	64.21
Female	34	35.79
Age at first diagnosis (years), mean $\pm$ SD	5.4 ± 2.7	
Duration of illness (years), mean $\pm$ SD	1.8 ± 1.4	
Family history of nephrotic syndrome	9	9.47
Consanguinity	6	6.32
Edema at presentation	91	95.79
Hypertension	17	17.89
Hematuria	14	14.74
Proteinuria $\geq 3+$	83	87.37
Serum albumin (g/dL), mean $\pm$ SD	2.1 ± 0.5	
Serum creatinine (mg/dL), mean $\pm$ SD	0.62 ± 0.21	

Steroid-sensitive nephrotic syndrome was present in 82.11% of children, while 17.89% had steroid-resistant disease. The mean time to remission after initial steroid

therapy was 12.6 ± 5.8 days. Frequent relapse occurred in 32.63%, infrequent relapse in 40.00%, and 27.37% had no relapse during follow-up. Steroid

dependence was present in 30.53% and medication non-adherence in 22.11% (*Table II*).

Table II

Treatment and Disease Characteristics of the Participants ($n=95$).

Variables	Frequency (n)	Percentage (%)
Steroid-sensitive nephrotic syndrome	78	82.11
Steroid-resistant nephrotic syndrome	17	17.89
Time to remission after initial steroid therapy, days, mean $\pm$ SD	12.6 ± 5.8	
Frequent relapser	31	32.63
Infrequent relapser	38	40.00
No relapse during follow-up	26	27.37
Number of previous relapses, median (IQR)	2 (1–4)	
Cyclophosphamide received	19	20.00
Levamisole received	24	25.26
Calcineurin inhibitor received	13	13.68
Steroid dependence	29	30.53
Medication non-adherence	21	22.11

Children with relapse were younger than those without relapse (6.8 ± 2.9 vs. 8.3 ± 3.4 years, $p=0.032$), had a lower mean age at diagnosis (5.0 ± 2.5 vs. 6.4 ± 3.0 years,

$p=0.024$), and longer illness duration (2.1 ± 1.4 vs. 1.1 ± 0.9 years, $p=0.001$). Mean serum albumin was lower among children

with relapse (2.0 ± 0.4 vs. 2.3 ± 0.5 g/dL, $p=0.006$) (*Table III*).

Table III

Comparison of Clinical Characteristics According to Relapse Status.

Variables	Relapse ($n=69$) n(%)	No relapse ($n=26$) n(%)	p-value
Age (years), mean $\pm$ SD	6.8 ± 2.9	8.3 ± 3.4	0.032
Male Gender	46 (66.67)	15 (57.69)	0.419
Age at diagnosis (years), mean $\pm$ SD	5.0 ± 2.5	6.4 ± 3.0	0.024
Duration of illness (years), mean $\pm$ SD	2.1 ± 1.4	1.1 ± 0.9	0.001
Family history	8 (11.59)	1 (3.85)	0.437
Hypertension	15 (21.74)	2 (7.69)	0.116
Hematuria	13 (18.84)	1 (3.85)	0.072
Serum albumin (g/dL), mean $\pm$ SD	2.0 ± 0.4	2.3 ± 0.5	0.006
Serum creatinine (mg/dL), mean $\pm$ SD	0.64 ± 0.22	0.56 ± 0.18	0.094

Steroid dependence was more frequent among children with relapse (39.13% vs. 7.69%, $p=0.003$), as was medication non-

adherence (27.54% vs. 7.69%, $p=0.048$). Frequent relapse was present in 44.93% of

the relapse group and none of the children without relapse ($p<0.001$) (*Table IV*).

Table IV

Treatment-Related Factors Associated with Relapse.

Variables	Relapse ($n=69$) n(%)	No relapse ($n=26$) n(%)	p-value
Steroid-sensitive disease	59 (85.51)	19 (73.08)	0.169
Steroid-resistant disease	10 (14.49)	7 (26.92)	0.169
Steroid dependence	27 (39.13)	2 (7.69)	0.003
Frequent relapser	31 (44.93)	0 (0.00)	<0.001
Cyclophosphamide therapy	17 (24.64)	2 (7.69)	0.078
Levamisole therapy	21 (30.43)	3 (11.54)	0.064
Calcineurin inhibitor therapy	11 (15.94)	2 (7.69)	0.327
Medication non-adherence	19 (27.54)	2 (7.69)	0.048
Remission within 10 days	24 (34.78)	15 (57.69)	0.049
Remission after >10 days	45 (65.22)	11 (42.31)	0.049

Proteinuria $\geq 3+$, serum albumin <2.5 g/dL, and serum cholesterol ≥ 300 mg/dL were significantly more frequent among children with relapse (91.30% vs. 76.92%, $p=0.047$;

85.51% vs. 61.54%, $p=0.011$; and 69.57% vs. 46.15%, $p=0.041$, respectively). Infection during follow-up and incomplete remission were also more common in the

relapse group (40.58% vs. 19.23%, $p=0.049$ and 26.09% vs. 7.69%, $p=0.047$) (*Table V*).

Table V
Clinical and Laboratory Factors Associated with Relapse.

Variables	Relapse (n=69)	No relapse (n=26)	p-value
Proteinuria ≥3+ at presentation	63 (91.30)	20 (76.92)	0.047
Serum albumin <2.5 g/dL	59 (85.51)	16 (61.54)	0.011
Serum cholesterol ≥300 mg/dL	48 (69.57)	12 (46.15)	0.041
Edema	67 (97.10)	24 (92.31)	0.247
Hypertension	15 (21.74)	2 (7.69)	0.116
Hematuria	13 (18.84)	1 (3.85)	0.072
Infection during follow-up	28 (40.58)	5 (19.23)	0.049
Incomplete remission	18 (26.09)	2 (7.69)	0.047

Multivariable analysis identified age at diagnosis <5 years (aOR=2.41, 95% CI: 1.01–5.74, p=0.047), illness duration ≥2 years (aOR=2.87, 95% CI: 1.16–7.08, p=0.022), steroid dependence (aOR=4.36, 95% CI: 1.45–13.12, p=0.009), medication non-adherence (aOR=3.18, 95% CI: 1.05–9.61, p=0.041), remission after >10 days (aOR=2.63, 95% CI: 1.08–6.42, p=0.034), serum albumin <2.5 g/dL (aOR=2.74, 95% CI: 1.08–6.94, p=0.034), and infection during follow-up (aOR=2.52, 95% CI: 1.02–6.22, p=0.045) as independent factors associated with relapse. Hypercholesterolemia was not independently significant (aOR=1.89, 95% CI: 0.78–4.58, p=0.158) (Table VI).

Table VI
Multivariable Logistic Regression Analysis of Factors Associated with Relapse.

Factors	Adjusted OR	95% CI	p-value
Age at diagnosis <5 years	2.41	1.01–5.74	0.047
Duration of illness ≥2 years	2.87	1.16–7.08	0.022
Steroid dependence	4.36	1.45–13.12	0.009
Medication non-adherence	3.18	1.05–9.61	0.041
Remission after >10 days	2.63	1.08–6.42	0.034
Serum albumin <2.5 g/dL	2.74	1.08–6.94	0.034
Hypercholesterolemia	1.89	0.78–4.58	0.158
Infection during follow-up	2.52	1.02–6.22	0.045

DISCUSSION

Nephrotic syndrome in children is characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia, while relapse refers to the recurrence of significant proteinuria after a period of remission and remains a major clinical problem because repeated relapses can increase treatment requirements and the risk of complications [12]. Relapse was common in the present study, occurring in 69 of 95 children (72.63%), with 31 (32.63%) classified as frequent relapsers and 38 (40.00%) as infrequent relapsers. This frequency is consistent with the recurrent nature of childhood nephrotic syndrome. A previous study from India involving 150 children reported relapse in 59.3% of participants [13], while a Bangladeshi study among children with relapsed nephrotic syndrome found frequent relapse to be common [14]. The somewhat higher relapse frequency in the present study may reflect differences in participant selection, follow-up characteristics, disease duration, and definitions of relapse. Younger age was significantly associated with relapse in this study. Children with relapse had a lower mean age than those without relapse (6.8±2.9 vs. 8.3±3.4 years, p=0.032), and their mean age at diagnosis was also lower (5.0±2.5 vs. 6.4±3.0 years, p=0.024). Multivariable analysis confirmed age at diagnosis below 5 years as an independent factor associated with relapse (aOR 2.41, 95% CI 1.01–5.74, p=0.047). These

findings agree with an Indian study in which children with onset at 1–3 years had 2.99 times greater relapse risk than those older than 6 years [13]. Another long-term study reported that onset before 4 years was associated with more frequent relapses and a longer period before achieving sustained remission [15]. Duration of illness was significantly longer among children with relapse (2.1±1.4 vs. 1.1±0.9 years, p=0.001), and illness duration ≥2 years remained independently associated with relapse (aOR 2.87, 95% CI 1.16–7.08, p=0.022). This finding is compatible with observations that prolonged active disease and recurrent episodes are associated with a longer time to achieve sustained remission. A 2026 long-term study also reported that disease length was important in determining the timing of treatment-free remission, although onset age itself did not correlate with disease duration [16]. Treatment-related factors showed important associations. Steroid dependence occurred in 39.13% of children with relapse compared with 7.69% without relapse (p=0.003) and was the strongest independent factor in the present analysis (aOR 4.36, 95% CI 1.45–13.12, p=0.009). This is clinically plausible because steroid-dependent children experience recurrence during steroid reduction or shortly after withdrawal. Delayed remission was also associated with relapse: remission after >10 days occurred in 65.22% of the relapse group compared with 42.31% of the non-relapse group (p=0.049), remaining

independently associated after adjustment (aOR 2.63, 95% CI 1.08–6.42, p=0.034). Previous research similarly identified delayed steroid response as a predictor of relapse. One study found that children responding within 1–2 weeks had a lower relapse risk than those responding after 4 weeks, while another reported delayed steroid response as a predictor of frequent relapse [13,17]. Studies evaluating steroid dependence have also identified prolonged time to initial remission as an important risk factor [14,18]. The present study also demonstrated significant associations between relapse and biochemical severity. Serum albumin was lower among children with relapse (2.0±0.4 vs. 2.3±0.5 g/dL, p=0.006), and albumin <2.5 g/dL remained independently associated with relapse (aOR 2.74, 95% CI 1.08–6.94, p=0.034). Proteinuria ≥3+ and cholesterol ≥300 mg/dL were also significantly associated on univariable analysis, although hypercholesterolemia lost significance after adjustment. These findings correspond with studies from Bangladesh and other settings reporting lower serum albumin or total protein among children with frequent relapse [17,19]. A prospective multicentre study likewise found lower total serum protein and younger age to be independent predictors of relapse [20]. Infection during follow-up was significantly more frequent among children with relapse (40.58% vs. 19.23%, p=0.049) and remained independently associated with relapse (aOR 2.52, 95% CI 1.02–6.22, p=0.045).

This agrees strongly with previous literature identifying infection, particularly respiratory and urinary infections, as an important trigger of relapse^[21]. Medication non-adherence was another independent factor in the present study (aOR 3.18, 95% CI 1.05–9.61, $p=0.041$), emphasizing the importance of maintaining prescribed therapy and regular follow-up. Interestingly, gender, family history, hypertension, hematuria, serum creatinine, and individual steroid-sparing therapies were not significantly associated with relapse. The absence of a gender association is consistent with several studies in which gender did not consistently predict relapse, although some populations have reported male gender as a predictor of frequent relapse^[17,22].

LIMITATIONS

This study has several limitations. Its cross-sectional analytical design limits assessment of temporal relationships between identified factors and relapse. The sample size was relatively small and participants were recruited using purposive sampling from a single clinical setting, which may limit generalizability. Some treatment and follow-up information depended on medical records and parental reporting, introducing potential information or recall bias. The study also lacked long-term prospective follow-up and did not evaluate genetic, socioeconomic, dietary, or detailed immunological factors that may influence relapse patterns.

CONCLUSION

Relapse was common among children with nephrotic syndrome, occurring in 69 of 95 participants (72.63%). Younger age at diagnosis, longer duration of illness, steroid dependence, medication non-adherence, delayed remission, lower serum albumin, and infection during follow-up were independently associated with increased odds of relapse. Steroid dependence showed the strongest association, with more than fourfold higher odds of relapse. These findings indicate that children presenting at a younger age, requiring prolonged treatment, or showing delayed remission warrant closer monitoring. Early recognition of modifiable factors, reinforcement of medication adherence, prompt management of infections, and individualized follow-up may help reduce recurrent disease activity and treatment burden in children with nephrotic syndrome.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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