MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2023.12.567.573

Study on Risk Factors for Relapse in Childhood Nephrotic Syndrome

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Abstract

Nephrotic syndrome (NS) is a significant pediatric kidney disorder characterized by massive proteinuria, hypoalbuminemia and edema, often accompanied by hyperlipidemia. Relapse in NS, defined as the recurrence of proteinuria following remission, can lead to repeated hospitalizations, increased healthcare costs, and a significant impact on the child's quality of life. Identifying the risk factors for relapse is crucial for improving management and outcomes. This prospective observational study was conducted over ten months from October 2020 to July 2021 at Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur. A total of 70 children aged 1 to 18 years with a confirmed diagnosis of nephrotic syndrome were enrolled. Data were collected on demographic, clinical, and biochemical characteristics. The study analyzed these data using descriptive statistics, comparative analysis, and logistic regression models to identify independent predictors of relapse. The study population was divided equally into relapsers (n=35) and non-relapsers (n=35). Relapsers were significantly younger (mean age 5.8 years) compared to non-relapsers (mean age 7.2 years), with a p-value of 0.023. A higher percentage of relapsers were male (80%) compared to non-relapsers (51.4%), with a p-value of 0.013. Low socioeconomic status, delayed steroid response, respiratory infections, and family history of nephrotic syndrome were significantly more common in relapsers. Biochemical analysis showed that relapsers had lower serum albumin levels (mean 1.9 g/dL vs. 2.3 g/dL, p=0.001) and higher serum cholesterol levels (mean 350 mg/dL vs. 290 mg/dL, p=0.008). Logistic regression identified younger age, male sex, low socioeconomic status, delayed steroid response, respiratory infections, family history of nephrotic syndrome, lower serum albumin and higher serum cholesterol levels as independent predictors of relapse. The study highlights significant risk factors associated with relapse in childhood nephrotic syndrome, including younger age, male sex, low socioeconomic status, delayed steroid response, respiratory infections, family history of nephrotic syndrome, lower serum albumin and higher serum cholesterol levels. Early identification and targeted management of high-risk patients are crucial for reducing the frequency of relapses and improving clinical outcomes. These findings underscore the need for a comprehensive and multidisciplinary approach to managing childhood nephrotic syndrome.

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Key Words

Nephrotic syndrome, relapse, childhood, risk factors, steroid response, socioeconomic status, serum albumin, serum cholesterol, infections, clinical outcomes

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Received: 5 October 2023
Accepted: 27 October 2023
Published: 15 November 2023

Citation: Vimal Kumar, Satish Kumar, Kishor Kumar Sinha and Ankur Priyadarshi, 2023. Study on Risk Factors for Relapse in Childhood Nephrotic Syndrome. Res. J. Med. Sci., 17: 567-573, doi: 10.36478/makrjms.2023.12.567.573

INTRODUCTION

Nephrotic syndrome (NS) is a significant pediatric kidney disorder characterized by the triad of massive proteinuria, hypoalbuminemia and edema, often accompanied by hyperlipidemia. It presents a considerable burden on pediatric patients and their families due to its chronic nature and the potential for frequent relapses. Relapse in nephrotic syndrome, defined as the recurrence of proteinuria following remission, can lead to repeated hospitalizations, increased healthcare costs, and a significant impact on the child's quality of life[1,2].

Childhood nephrotic syndrome primarily manifests as either steroid-sensitive or steroid-resistant. The majority of children respond well to corticosteroids., however, a substantial proportion of these patients experience multiple relapses, necessitating prolonged and repeated courses of steroid therapy. This can lead to steroid toxicity and other complications, highlighting the importance of identifying patients at higher risk for relapse[2-5].

Previous studies have identified several factors that may influence the likelihood of relapse, including demographic variables such as age and sex, clinical features like the initial response to steroids and biochemical markers such as serum albumin levels. However, the interplay of these factors and their relative contribution to relapse risk remains incompletely understood[6-9].

This study aims to investigate the risk factors associated with relapse in childhood nephrotic syndrome in a cohort of patients treated at Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur, from October 2020 to July 2021. By elucidating the demographic, clinical and biochemical predictors of relapse, this research seeks to contribute to a more nuanced understanding of the disease and to inform strategies for targeted interventions. Early identification of high-risk patients could enable more personalized and effective management plans, ultimately reducing the frequency of relapses and improving outcomes for children with nephrotic syndrome.

MATERIALS AND METHODS

Study Design: This study was a prospective observational study conducted over ten months from October 2020-July 2021. The primary aim was to identify risk factors associated with relapse in childhood nephrotic syndrome. The study was carried out at Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur.

Study Population: A total of 70 children diagnosed with nephrotic syndrome were enrolled in the study. The inclusion and exclusion criteria were defined as follows:

Inclusion Criteria:

- Children aged 1-18 years.
- Confirmed diagnosis of nephrotic syndrome based on clinical presentation and laboratory findings (proteinuria >3.5 g/day, hypoalbuminemia <2.5 g/dL, edema and hyperlipidemia).
- Patients and guardians who provided informed consent.

Exclusion Criteria:

- Children with secondary nephrotic syndrome (e.g., due to systemic diseases like lupus or diabetes).
- Patients who did not consent to participate in the study.

Data Collection: Data were collected using a structured proforma, which included the following sections:

- **Demographic Data:**
- Age at diagnosis
- Sex
- Socioeconomic status (assessed based on parental occupation and income)
- **Clinical Data:**
- Duration of illness
- Number of relapses during the study period
- Treatment regimens used (initial steroid therapy, immunosuppressive agents)
- Response to initial steroid therapy (time to achieve remission)
- Presence of infections (particularly respiratory infections)
- Family history of nephrotic syndrome or other renal diseases
- **Biochemical Data:**
- Serum albumin levels at diagnosis and during follow-up
- Serum cholesterol levels at diagnosis
- Proteinuria levels (quantified by urine protein-to-creatinine ratio or 24-hour urine protein excretion)
- Renal function tests (serum creatinine, blood urea nitrogen)

Definitions:

- **Relapse:** Defined as the recurrence of significant proteinuria (>3+ on urine dipstick for three consecutive days) after having achieved remission.
- **Frequent Relapse:** More than three relapses within a 12-month period.
- **Steroid-Sensitive Nephrotic Syndrome (SSNS):** Patients who achieve remission with corticosteroid therapy.

- **Steroid-Resistant Nephrotic Syndrome (SRNS):** Patients who do not achieve remission despite corticosteroid therapy.

Statistical Analysis: The collected data were entered into a spreadsheet and analyzed using statistical software. The following statistical methods were used:

- **Descriptive Statistics:** Means, medians, and standard deviations for continuous variables; frequencies and percentages for categorical variables.
- **Comparative Analysis:**
- Independent t-tests for comparing continuous variables between relapsers and non-relapsers.
- Chi-square tests for comparing categorical variables.
- **Multivariate Analysis:**
- Logistic regression models to identify independent predictors of relapse.
- Factors included in the model were age at diagnosis, sex, socioeconomic status, response to initial steroid therapy, presence of infections, family history, serum albumin and cholesterol levels.

Ethical Considerations: Ethical approval was obtained from the Institutional Ethics Committee of JLNMCH, Bhagalpur. Informed consent was obtained from the parents or guardians of all participating children. The study was conducted in accordance with the Declaration of Helsinki, ensuring the confidentiality and privacy of patient information.

RESULTS AND DISCUSSIONS

The study enrolled 70 children diagnosed with nephrotic syndrome, divided equally into relapsers (n=35) and non-relapsers (n=35). The demographic, clinical, and biochemical characteristics were analyzed to identify risk factors for relapse.

The average age of the participants was 6.5 years. Relapsers were significantly younger (mean age 5.8 years) compared to non-relapsers (mean age 7.2 years), with a p-value of 0.023, indicating younger age as a risk factor for relapse. The male to female ratio was skewed towards males, with 65.7% of the total population being male. A higher percentage of relapsers were male (80%) compared to non-relapsers (51.4%), with a statistically significant p-value of 0.013. Socioeconomic status also played a role, with a greater proportion of relapsers coming from low socioeconomic backgrounds (60% vs. 37.1%), achieving a p-value of 0.041.

The duration of illness was longer in relapsers, averaging 14.1 months compared to 10.3 months in non-relapsers, with a p-value of 0.005. Initial response to steroid therapy was a significant factor, with a higher percentage of non-relapsers achieving early remission (91.4% vs. 62.9%), while delayed response was more common among relapsers (37.1% vs. 8.6%), with a p-value of 0.004. Respiratory infections were significantly more frequent in relapsers (74.3%) compared to non-relapsers (34.3%), indicated by a p-value of 0.001. Additionally, a family history of nephrotic syndrome was more prevalent in relapsers (42.9% vs. 14.3%), with a p-value of 0.007.

Serum albumin levels at diagnosis were significantly lower in relapsers (mean 1.9 g/dL) compared to non-relapsers (mean 2.3 g/dL), with a p-value of 0.001. Serum cholesterol levels were higher in relapsers (mean 350 mg/dL) compared to non-relapsers (mean 290 mg/dL), with a p-value of 0.008. Proteinuria levels were also higher in relapsers (mean 5.5 mg/day) compared to non-relapsers (mean 4.5 mg/day), with a p-value of 0.045. Serum creatinine levels did not show a significant difference between the two groups.

The frequency of relapse was higher in younger children (65.7% for those under 5 years) and males (60.9%). Delayed steroid response was strongly associated with higher relapse rates (81.3%), as were respiratory infections (68.4%) and a family history of nephrotic syndrome (75%). Lower serum albumin (<2.0 g/dL) and higher serum cholesterol (=300 mg/dL) were also associated with higher relapse rates, with all factors achieving statistically significant p-values.

The logistic regression analysis identified several independent risk factors for relapse. Younger age at diagnosis had an odds ratio (OR) of 0.85 (p=0.032), indicating that younger children were more likely to relapse. Male sex had an OR of 2.56 (p=0.014), low socioeconomic status had an OR of 1.91 (p=0.046), delayed steroid response had an OR of 3.42 (p=0.004), respiratory infections had an OR of 2.97 (p=0.003), and a family history of nephrotic syndrome had an OR of 3.89 (p=0.009). Lower serum albumin was protective (OR 0.43, p=0.001), while higher serum cholesterol increased relapse risk (OR 1.01, p=0.015).

During follow-up, relapsers showed a modest increase in serum albumin levels from baseline (1.9±0.4-2.2±0.6 g/dL) compared to non-relapsers, who had a greater increase (2.3±0.5-3.1±0.5 g/dL), with a p-value of 0.001 for both baseline and follow-up comparisons. Serum cholesterol levels decreased in both groups, but relapsers had higher baseline levels (350±90 mg/dL) compared to non-relapsers (290±70 mg/dL), with a significant difference in follow-up levels (310±80 vs. 250±60 mg/dL, p=0.005). Proteinuria significantly decreased more in non-relapsers (-3.0±0.7 mg/day) compared to relapsers (-2.3±0.8 mg/day), with a p-value of 0.001.

Table 1: Demographic Characteristics of Study Population

Characteristic	Total (n=70)	Relapsers (n=35)	Non-relapsers (n=35)	p-value
Age (years)				
Mean±SD	6.5±2.8	5.8±2.5	7.2±3.0	0.023*
Median (Range)	6 (1-14)	5 (1-13)	7 (2-14)	
Sex				
Male	46 (65.7%)	28 (80.0%)	18 (51.4%)	0.013*
Female	24 (34.3%)	7 (20.0%)	17 (48.6%)	
Socioeconomic Status				
Low	34 (48.6%)	21 (60.0%)	13 (37.1%)	0.041*
Middle	27 (38.6%)	10 (28.6%)	17 (48.6%)	
High	9 (12.8%)	4 (11.4%)	5 (14.3%)	

*Statistically significant

Table 2: Clinical Characteristics of Study Population

Characteristic	Total (n=70)	Relapsers (n=35)	Non-relapsers (n=35)	p-value
Duration of Illness (months)				
Mean±SD	12.2±5.1	14.1±4.9	10.3± 4.8	0.005*
Median (Range)	12 (3-24)	14 (6-24)	10 (3-18)	
Initial Steroid Response				
Early Response (<4 weeks)	54 (77.1%)	22 (62.9%)	32 (91.4%)	0.004*
Delayed Response (>4 weeks)	16 (22.9%)	13 (37.1%)	3 (8.6%)	
Infections (Respiratory)				
Yes	38 (54.3%)	26 (74.3%)	12 (34.3%)	0.001*
No	32 (45.7%)	9 (25.7%)	23 (65.7%)	
Family History of NS				
Yes	20 (28.6%)	15 (42.9%)	5 (14.3%)	0.007*
No	50 (71.4%)	20 (57.1%)	30 (85.7%)	

*Statistically significant

Table 3: Biochemical Characteristics of Study Population

Characteristic	Total (n=70)	Relapsers (n=35)	Non-relapsers (n=35)	p-value
Serum Albumin (g/dL)				
Mean±SD	2.1±0.5	1.9±0.4	2.3±0.5	0.001*
Median (Range)	2.1 (1.0-3.5)	1.8 (1.0-2.7)	2.3 (1.5-3.5)	
Serum Cholesterol (mg/dL)				
Mean±SD	320±80	350±90	290±70	0.008*
Median (Range)	310 (200-500)	350 (230-500)	280 (200-450)	
Proteinuria (mg/day)				
Mean±SD	5.0±1.5	5.5±1.8	4.5±1.2	0.045*
Median (Range)	5.0 (2.0-8.0)	5.5 (2.5-8.0)	4.5 (2.0-7.0)	
Serum Creatinine (mg/dL)				
Mean±SD	0.6±0.2	0.6±0.2	0.5±0.1	0.067
Median (Range)	0.6 (0.3-1.0)	0.6 (0.3-1.0)	0.5 (0.3-0.8)	

*Statistically significant

Table 4: Frequency of Relapse Based on Clinical and Biochemical Factors

Characteristic	Frequency of Relapse (%)	p-value
Age at Diagnosis		
<5 years	65.7	0.020*
≥5 years	34.3	
Sex		
Male	60.9	0.012*
Female	29.2	
Delayed Steroid Response		
Yes	81.3	0.001*
No	37.0	
Respiratory Infections		
Yes	68.4	0.003*
No	28.1	
Family History of NS		
Yes	75.0	0.007*
No	40.0	
Serum Albumin (g/dL)		
<2.0	74.2	0.001*
≥2.0	30.6	
Serum Cholesterol (mg/dL)		
≥300	64.7	0.014*
<300	34.2	

*Statistically significant

Table 5: Logistic Regression Analysis of Risk Factors for Relapse

Risk Factor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age at Diagnosis	0.85	0.73-0.99	0.032*
Male Sex	2.56	1.21-5.42	0.014*
Low Socioeconomic Status	1.91	1.01-3.61	0.046*
Delayed Steroid Response	3.42	1.48-7.91	0.004*
Respiratory Infections	2.97	1.43-6.17	0.003*
Family History of NS	3.89	1.39-10.90	0.009*
Serum Albumin (g/dL)	0.43	0.26-0.71	0.001*
Serum Cholesterol (mg/dL)	1.01	1.00-1.02	0.015*

*Statistically significant

Table 6: Biochemical Changes During Follow-Up in Relapsers vs. Non-relapsers

Characteristic	Relapsers (n=35)	Non-relapsers (n=35)	p-value
Change in Serum Albumin			
Baseline (g/dL)	1.9±0.4	2.3±0.5	0.001*
Follow-Up (g/dL)	2.2±0.6	3.1±0.5	0.001*
Difference	0.3±0.3	0.8±0.4	0.001*
Change in Serum Cholesterol			
Baseline (mg/dL)	350±90	290±70	0.008*
Follow-Up (mg/dL)	310±80	250±60	0.005*
Difference	-40±20	-40±15	0.065
Change in Proteinuria			
Baseline (mg/day)	5.5±1.8	4.5±1.2	0.045*
Follow-Up (mg/day)	3.2±1.0	1.5±0.5	0.001*
Difference	-2.3±0.8	-3.0±0.7	0.001*

*Statistically significant

The present study investigated the risk factors associated with relapse in childhood nephrotic syndrome (NS) in a cohort of 70 patients treated at Jawaharlal Nehru Medical College and Hospital (JLNMCH), Bhagalpur. By examining demographic, clinical and biochemical characteristics, this study provides valuable insights into predictors of relapse, emphasizing the need for early identification and tailored management strategies for high-risk patients. Our findings indicate that younger age at diagnosis is a significant risk factor for relapse, with relapsers being younger on average (mean age 5.8 years) compared to non-relapsers (mean age 7.2 years), with a p-value of 0.023. This aligns with previous studies, which reported that children diagnosed at a younger age are more prone to frequent relapses due to their immature immune systems and higher susceptibility to infections[10,11]. The male predominance among relapsers (80% vs. 51.4% in non-relapsers) also concurs with findings from past studies, suggesting that boys are more likely to experience multiple relapses, possibly due to genetic or hormonal differences[12,13].

Low socioeconomic status emerged as a significant predictor of relapse, with a greater proportion of relapsers coming from low-income families (60% vs. 37.1%), achieving a p-value of 0.041. This finding underscores the impact of social determinants of health on disease outcomes. Children from low socioeconomic backgrounds may have limited access to healthcare, poor nutritional status and higher exposure to infections, all contributing to a higher risk of relapse. This is consistent with findings from earlier studies, who highlighted that socioeconomic disparities significantly affect health outcomes in pediatric nephrotic syndrome[12-14].

The duration of illness was longer in relapsers, indicating that prolonged disease activity may predispose patients to frequent relapses. Initial response to steroid therapy was a critical factor, with delayed responders having a significantly higher risk of relapse (37.1% in relapsers vs. 8.6% in non-relapsers), with a p-value of 0.004. This finding is in line with previous research, which demonstrated that delayed response to steroids is associated with a higher likelihood of relapse and poorer long-term outcomes[14-16]. Respiratory infections were significantly more frequent among relapsers (74.3%) compared to non-relapsers (34.3%), suggesting that infections act as a major trigger for relapse. Additionally, a family history of nephrotic syndrome was more prevalent in relapsers (42.9%), indicating a potential genetic predisposition to frequent relapses, consistent with findings from earlier studies[15-17].

Lower serum albumin levels at diagnosis were strongly associated with relapse, with relapsers having significantly lower levels (mean 1.9 g/dL) compared to non-relapsers (mean 2.3 g/dL), with a p-value of 0.001. Hypoalbuminemia reflects severe protein loss and poor nutritional status, which may compromise immune function and increase susceptibility to infections. These findings are supported by earlier studies, which reported similar associations between low serum albumin levels and relapse rates in children with nephrotic syndrome[16,17]. Higher serum cholesterol levels were also associated with relapse, possibly reflecting more severe disease activity and greater disruption of lipid metabolism. This is consistent with past researches, which highlighted the correlation between hyperlipidemia and disease severity in nephrotic syndrome[17,18].

Multivariate analysis confirmed the independent predictive value of younger age at diagnosis, male sex, low socioeconomic status, delayed steroid response, respiratory infections, family history of nephrotic syndrome, lower serum albumin and higher serum cholesterol levels. These findings emphasize the multifactorial nature of relapse in childhood nephrotic syndrome and the need for a comprehensive approach to risk assessment and management[19,20].

During follow-up, relapsers showed a modest improvement in serum albumin levels from baseline (1.9±0.4-2.2±0.6 g/dL) compared to non-relapsers, who had a greater increase (2.3±0.5-3.1±0.5 g/dL), with a p-value of 0.001 for both baseline and follow-up comparisons. This suggests that non-relapsers may achieve more complete and sustained remission. Similarly, serum cholesterol levels decreased more significantly in non-relapsers, indicating better overall

disease control. Proteinuria levels decreased in both groups, but the reduction was more pronounced in non-relapsers, further supporting the better clinical outcomes in this group. These trends align with earlier findings, which demonstrated that sustained remission is associated with significant improvements in biochemical parameters[17-20].

Clinical Implications: The identification of key risk factors for relapse has important clinical implications. Early and aggressive treatment strategies, particularly for high-risk patients, may help reduce the frequency of relapses and improve long-term outcomes. This includes optimizing steroid therapy, addressing nutritional deficiencies, preventing and promptly treating infections and providing adequate support to families from low socioeconomic backgrounds.

Study Limitations: This study has several limitations, including the relatively small sample size and the single-center design, which may limit the generalizability of the findings. Additionally, the observational nature of the study precludes establishing causality. Future studies with larger, multicenter cohorts and longer follow-up periods are needed to validate these findings and further elucidate the mechanisms underlying relapse in childhood nephrotic syndrome.

CONCLUSION

This study highlights the significant risk factors associated with relapse in childhood nephrotic syndrome, including younger age, male sex, low socioeconomic status, delayed steroid response, respiratory infections, family history of nephrotic syndrome, lower serum albumin and higher serum cholesterol levels. Early identification and targeted management of high-risk patients are crucial in reducing the frequency of relapses and improving clinical outcomes. Our findings underscore the need for a comprehensive and multidisciplinary approach to the management of childhood nephrotic syndrome, addressing both medical and socio-environmental factors.

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