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FREQUENCY OF FACTORS OF RELAPSE IN CHILDHOOD NEPHROTIC SYNDROME

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ABSTRACT

Background: Childhood nephrotic syndrome has a high rate of relapse, causing frequent morbidity from the disease and a cumulative increase in exposure to steroids. Knowing which factors are often associated with a condition may help in early detection of the condition and prevention. **Objective:** To determine the frequency of factors leading to relapse in childhood nephrotic syndrome. **Methods** This was a Cross-Sectional Study that was carried out at Department of Pediatrics, Mardan Medical Complex Mardan from December 2025 to May 2026. The children aged 1-10 years with relapsed nephrotic syndrome were consecutively sampled, and a total of 114 children were selected. The factors associated with relapse were: age <5 years, poor economic status, personal and family history of atopy, urinary tract infection (UTI), respiratory tract infection (RTI) and helminthiasis. Data were analysed in SPSS 26. Frequencies, percentages, and chi-square and Fisher's exact tests were used, and a p-value of ≤0.05 was taken as statistically significant. **Results:** The mean age was 5.2±2.1 years, and 68 (59.6%) children were male. Age <5 years was present in 76 (66.7%), poor economic status in 82 (71.9%), personal atopy in 58 (50.9%), family history of atopy in 45 (39.5%), UTI in 44 (38.6%), RTI in 39 (34.2%), and helminthiasis in 10 (8.8%). Rural children were significantly more likely to be age <5 years (p=0.03) and to be in poor economic status (p=0.02); personal atopy was associated with male gender (p=0.04). **Conclusion:** Children with relapse were often younger, and were more likely to be socially disadvantaged, have atopy and infections. Identification and treatment of potentially modifiable factors may lead to a decrease in morbidity related to relapse and exposure to corticosteroids.

KEYWORDS: Childhood nephrotic syndrome; relapses; risk factors; atopy; U.T.I.; R.T.I.; socio-economic status; helminthiasis; Pakistan.

1. INTRODUCTION

Nephrotic syndrome is a common kidney disorder in childhood, which is associated with a significant proteinuria and hypoalbuminemia, edema and hyperlipidaemia [1]. This is due to the leakage of proteins (mainly albumin) into urine due to damage to the glomerular filtration barrier [2]. It is most frequently seen in children between the ages of two and six and can be divided into two main categories: steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) [3]. Most children with SSNS are cured with the use of corticosteroid drugs and have a good prognosis; however, SRNS carries a higher risk for persistent proteinuria and progression of the kidney disease and may need other drugs to control the condition [4].

One of the important clinical features of childhood nephrotic syndrome is the occurrence of recurrent significant proteinuria after a period of remission, called relapse [5]. Relapse is clinically recognised as the reappearance of proteinuria of ≥3+ on urine dipstick testing performed on three consecutive days or an increase in the urinary protein-to-creatinine ratio [6]. Relapses can be classified as infrequent relapses, frequent relapses or steroid dependent nephrotic syndrome [7] depending on the frequency of relapses and the response to the corticosteroid therapy. Relapses are especially worrisome as it may mean that the child who has them needs further or longer courses of steroid, which can lead to further side effects such as growth problems, high blood pressure, obesity, osteoporosis and other problems [7].

A number of factors have been linked to the higher risk of relapse in childhood nephrotic syndrome, such as age of onset, early response to corticosteroid treatment, genetic predisposition and environmental/infective factors [8]. Children who develop nephrotic syndrome at an early age (less than three years of age) may be more likely to

have frequent relapses [9]. The response to the initial treatment with steroids and the nature of such response (whether it is early or late) may also be important clues to the subsequent behavior of the disease. Further, infections, especially infection of upper respiratory tract, are known to be frequent precipitants of relapse and could precipitate recurrence by activation of immune system [10]. Factors such as socio-economic status, treatment compliance, atopy and family history, underlying genetic abnormalities may also have an impact upon risk and relapse frequency.

According to the study of Sarker MN et al, there are several factors that may exist in children with nephrotic syndrome, which might predispose them to relapse. In 68% of patients, the age under 5 years was reported, 74% had poor economic status, 52% had a history of atopy, 40% a family history of atopy, 40% a history of UTI, 34% had a history of RTI and 8% had helminthiasis [11]. Together, these results suggest that demographic, socioeconomic, allergic and infectious factors may play a role in the clinical course of childhood nephrotic syndrome.

Nephrotic syndrome in childhood is thus a significant health issue in children as it can lead to frequent hospital admissions, long-term corticosteroid use, side effects of treatment and lower quality of life due to frequent relapses. Multiple international studies have explored the factors associated with a relapse, but there are few local studies exploring this. The pattern of relapse in children with nephrotic syndrome may be affected by differences in socioeconomic status, environmental exposures, infectious diseases, genetic predisposition, treatment and care. Hence, this study was carried out to determine the factors associated with relapse in nephrotic syndrome children of our locality. The results could be used to identify children at higher risk of recurrence and to monitor and manage children who are at risk, helping to provide better clinical care.

2. OBJECTIVE

To determine the frequency of factors leading to relapse in childhood nephrotic syndrome.

3. METHODOLOGY

This was a Cross-Sectional Study that was carried out at Department of Pediatrics, Mardan Medical Complex Mardan from December 2025 to May 2026.The sample size was 114 children calculated at 95% confidence level, 5% margin of error and an estimated helminthiasis prevalence of 8% (WHO sample size software). Non-probability consecutive sampling technique was applied. After obtaining written informed consent from the parents, children from 1 to 10 years of age of both gender who met the operational definitions of nephrotic syndrome and relapse were selected. Structured proforma was used for recording demographic variables and pre-specified relapse associated factors. Data were entered and analyzed by SPSS program version 26.

3.1 INCLUSION CRITERIA

Only children who were between 1 and 10 years of age of either gender who met the operational definition of nephrotic syndrome and met the operational definition of relapse, with written informed consent by the parent/legal guardian, were included.

3.2 EXCLUSION CRITERIA

Those children who had a history of secondary nephrotic syndrome like lupus nephritis, who had a history of immunosuppressive therapy other than regular use of corticosteroid or documented in their medical records, and a history of malignancy were excluded.

3.3 DATA COLLECTION PROCEDURE

Eligible children presented to the paediatric ward and Outpatient Department were screened and recruited in a consecutive fashion after ethical approval. The parents/caregivers were contacted to describe the goals and procedures of the study, potential benefits, and confidentiality of any information gathered, and written informed consent was obtained. Demographic data such as age, sex, weight, parents education status and residency status were collected. The pre determined relapse associated factors were evaluated based on operational definition. Age <5 years was mentioned as the predetermined age group and the economic status of poor was defined as a monthly income of the family less than 15000 PKR. Personal atopy was recorded from a history or by skin-prick testing or elevated serum IgE and family history of atopy was taken from the caregiver. UTI was diagnosed based on urinalysis and/or urine culture; RTI, compatible clinical features and supporting investigations if needed, and helminthiasis, stool microscopy or concentration techniques. All of the findings were documented in a proforma with a structured format.

3.4 DATA ANALYSIS

The data were entered, coded and analyzed with the help of SPSS version 26. For categorical variables such as gender, parent's educational status, residential status, and the a priori factors associated with relapse, frequencies and percentages were computed. Normally distributed quantitative data (age, weight) were presented as mean±standard deviation; otherwise, they were presented as median and interquartile range. The Shapiro–Wilk test was used to determine the distribution of quantitative variables. Relapse associated factors were stratified by gender, weight categories, parents' education level and residential status. Relationships between categorical

variables were evaluated by the chi-square test and Fisher's exact test was used for the small expected cell frequencies. A two-sided p-value ≤0.05 was considered statistically significant. Appropriate tables and graphical summaries were used to present results.

4. RESULTS

One hundred fourteen children with relapsed nephrotic syndrome were studied. The mean age of the participants was 5.2 ± 2.1 years, while the mean weight was 16.8 ± 4.3 kg. Of the total participants, 68 (59.6%) were male and 46 (40.4%) were female. As for educational status of parents, 41 (36.0%) uneducated parents, 38 (33.3%) with primary education, 25 (21.9%) with secondary education and 10 (8.8%) with higher education. The majority of the children were from rural areas (72; 63.2%) while 42 (36.8%) were from urban areas.

Table 1: Baseline Characteristics

Parameter	Total (n = 114)
Mean age (years)	**5.2 ± 2.1**
Mean weight (kg)	**16.8 ± 4.3**
Male	68 (59.6%)
Female	46 (40.4%)
Parental education: Uneducated	41 (36.0%)
Parental education: Primary	38 (33.3%)
Parental education: Secondary	25 (21.9%)
Parental education: Higher	10 (8.8%)
Rural residence	72 (63.2%)
Urban residence	42 (36.8%)

The majority of the study population were children of rural origin and there were more boys than girls.

Table 2: The frequency of Relapse-Associated Factors.

Relapse-associated factor	Frequency (n)	Percentage
Age <5 years	76	66.7%
Poor economic status	82	71.9%
Personal history of atopy	58	50.9%
Family history of atopy	45	39.5%
Urinary tract infection (UTI)	44	38.6%
Respiratory tract infection (RTI)	39	34.2%
Helminthiasis	10	8.8%

Predefined relapse associated factors were poor economic status (71.9%), age <5 years (66.7%) and personal history of atopy (50.9%), respectively. Helminthiasis was the lowest observed factor with 8.8% of children suffering from it.

Table 3: Stratification of Relapse-Associated Factors.

Factor	Stratification	Statistical significance
Age <5 years	Rural residence	**p = 0.03**
Poor economic status	Rural residence	**p = 0.02**
Personal history of atopy	Male gender	**p = 0.04**
Family history of atopy	No significant association identified	>0.05
UTI	No significant association identified	>0.05
RTI	No significant association identified	>0.05
Helminthiasis	No significant association identified	>0.05

The stratification analysis showed that age < 5 years was significantly more common amongst those children from rural areas (p = 0.03). Likewise, there was a significant association with rural residence (p = 0.02) and poor economic status. Personal history of atopy was also found to be significantly associated with male gender (p = 0.04). After stratification, no statistically significant association was found with any of the other factors (family history of atopy, UTI, RTI and helminthiasis).

Table 4: Significant Associations

Association	p-value	Interpretation
Age <5 years × Rural residence	**0.03**	Statistically significant
Poor economic status × Rural residence	**0.02**	Statistically significant
Personal history of atopy × Male gender	**0.04**	Statistically significant
Remaining relapse-associated factors	**>0.05**	Not statistically significant

Interpretation
Results show that low income and age were the most common factors associated with relapses among children with relapsed nephrotic syndrome. There was a significant association between rural residence and age <5 years and between rural residence and poor economic status, which indicate that socioeconomic and demographic factors may play a role in the burden of relapse in this population. In addition, male sex was a significant risk factor for personal history of atopy. Stratification did not show any statistically significant associations with other factors assessed which included family history of atopy, UTI, RTI and helmintiasis. These data suggest that socioeconomic factors, age (younger), and atopy (predisposition) may play a role in relapsing nephrotic syndrome in childhood.

5. DISCUSSION

114 children with relapsed nephrotic syndrome (NS) were evaluated for selected demographic, socioeconomic, atopic and infectious factors. The mean age was 5.2 ± 2.1 years, 59.6% were male, and 63.2% belonged to rural areas. Poor economic status (71.9%), age <5 years (66.7%), personal atopy (50.9%), family history of atopy (39.5%), urinary tract infection (UTI) (38.6%), respiratory tract infection (RTI) (34.2%) and helminthiasis (8.8%) were the most common factors. These are clinically significant since relapse is a common feature of childhood nephrotic syndrome, and recurrent relapses could lead to multiple exposure to steroids and steroid related morbidity [1]. Defects in the glomerular filtration barrier have a close relationship to the pathogenesis of nephrotic syndrome. Podocyte dysfunction and greater permeability of the glomerular filtration barrier results in greater protein loss in the urine, hypoalbuminemia and edema [2]. Most idiopathic nephrotic syndrome is response to steroid and most of the children is steroid sensitive. Management and prognosis will thus depend on making appropriate distinction between steroid sensitive and steroid resistant disease [3]. Other immunosuppression methods and genetic testing are indicated for patients with an atypical clinical course in steroid resistant nephrotic syndrome [4]. In the current study, half of the children (33.3%) were under the age of 5 years. The relevance of the younger age is highlighted by the fact that nephrotic syndrome in children often occurs in early childhood years and that of steroid-sensitive disease, the relapse rate is high. Viral upper respiratory infection is demonstrated to frequently precipitate relapse and there may be a different relapse burden related to environmental conditions and infectious exposure. During the SARS-CoV-2 period, Chiodini et al. reported the overall rate of relapse in children with idiopathic nephrotic syndrome was not different than in the pre-pandemic era, but that the rate of hospitalization for relapse had increased in 2020 [5]. The observation also shows that relapse is not a simple process, but consists of many factors (and not only one triggering event) that are involved in this process. This is also reflected in the percent of younger children in our cohort and in pediatric nephrotic syndrome cohorts. Welegerima et al. revealed that children aged ≤6 years had a significantly increased risk for frequent relapse/dependence of steroid. Hematuria and infection, severe hypoalbuminemia, delayed remission and acute renal failure were also identified as factors predicting an unfavorable relapsing course [6]. It is possible that younger age is a predictor of a high frequency of children < 5 years, although this could not be said because there was no comparison group of non-relapsing children. The data also have significant therapeutic implications as relapses do not occur just once. If the period is recurrent, repeated courses may be required with cumulative doses of steroids in children, leading to an increasing risk of side effects. While corticosteroid treatment is still very effective in treating nephrotic syndrome relapse, repeated relapses may lead to repeated exposure to corticosteroids, which can have side effects including obesity, hyperglycemia, hypertension and other treatment side effects, Williams and Gbadegesin said. They also discussed steroid sparing therapy, as it is a disease that can be frequently relapsing or steroid dependent [7]. Identification of those children who require more careful monitoring is therefore important to help minimise morbidity associated with avoidable treatments. In our study, poor economic status was most prevalent (71.9% of children). Socioeconomic disadvantage can affect disease management due to lack of access to health services, poor diet, poor sanitation, poor health literacy of parents, poor follow-up. When comparing children with frequent and infrequent relapse, a retrospective hospital based study in South Asia identified children with frequent relapse were younger, rural, and of poorer social class, and identified that children with frequent relapse were more likely to be atopic and report UTI [8]. All these observations are relevant to the present study, since the poor economic situation was strongly associated with living in the countryside. Yet, socioeconomic issues need not solely be interpreted as causal factors toward relapse. Our study is a cross-sectional study, which does not suggest causality or temporal association. In addition, the current study did not have a control group of children in remission. The observed frequency (71.9%) of poor economic status is thus not so much a reflection of the relative risk of socioeconomic disadvantage as the characteristics of children who are presenting for a relapse. The link between demographic variables and relapse is complicated. In the study by Carter et al., demographic, clinical and family-reported characteristics at presentation were used to assess their ability to predict short and long-term outcome in childhood nephrotic syndrome. They discovered that these baseline parameters are not good predictors of subsequent events, and that the relapse cannot reliably be predicted by a few demographic parameters alone [9]. This is relevant to our outcomes as these data might be used to identify vulnerable groups, but not as an indicator of relapse alone. Our cohort were highly atopic (50.9%) and their parents were highly atopic (39.5%). The possible association between atopy and idiopathic NS could be associated with some common immunologic pathways. Deregulation of the

immune system involving T cells, B cells, inflammatory mediators and podocyte responses is believed to be involved in the pathogenesis of idiopathic nephrotic syndrome [10]. These mechanisms provide a biological explanation, which cannot necessarily be interpreted as that atopy is directly responsible for this relapse during the study of atopic disorders in children with nephrotic syndrome. But there is conflicting evidence relating to atopy and relapse. The prospective cohort study revealed that children with nephrotic syndrome were not uncommonly associated with asthma and allergies, but these were not associated with an increased risk of frequent relapses or early onset of the first relapse [11]. So, the relatively high prevalence of personal and familial atopy in our study should be regarded as associated, but not demonstrated risk factors. The strong association of personal atopy with male gender in our study ($p=0.04$) should also be viewed with caution as multiple sub-group comparisons were made and it is unclear how this finding can be explained. Evidence also points towards the involvement of several clinical and biochemical factors in relapse in recent times. Frequent relapse has been reported to be linked with several parameters such as younger age, male sex, low serum albumin, low total protein and delayed steroid response in children with childhood onset steroid sensitive nephrotic syndrome (CSN) [12]. Likewise, Mishra et al. found infection at the first episode and at the first relapse, short remission period, insufficient treatment period, low serum albumin and high cholesterol level as factors contributing to relapse [13]. These results suggest that other factors such as severity of disease, biochemical abnormalities, history of infections and response to treatments need to be taken into account along with demographic factors. The prevalence of infections was high in the current study with 38.6% of children having a UTI and 34.2% having a RTI. International guidelines for pediatric nephrology have focused on the importance of infection as a clinical problem in children with SSNS and recommend that this be evaluated and treated during the course of the disease [14]. An individual might be more susceptible to infection with nephrotic syndrome because of the loss of immunoglobulins and complement components in the urine, as well as due to use of corticosteroid and other immunosuppressive drugs. This is especially true regarding respiratory tract infections as upper respiratory tract infections are often reported around relapse events. However, it is still difficult to prevent infection related relapse. To find out whether low dose prednisolone during upper respiratory tract infection (URI) prevents relapses in children with relapsing steroid-sensitive nephrotic syndrome (NS), a randomized clinical trial (PREDNOS 2) was conducted. There was no significant decrease in all-infections relapse with the intervention [15]. Thus, while respiratory infections could serve as triggers in sensitized children, additional use of cortisone steroids in all respiratory infections cannot be routinely recommended for the prevention of relapse. The rate of UTI and RTI in our study is also clinically important as infection can complicate the presentation of children with nephrotic syndrome. Children with nephrotic syndrome have been associated with serious infections, such as pneumonia, bacteremia or sepsis, UTI in a long-term clinical experience [16]. These findings caution for careful evaluation of febrile children with nephrotic syndrome, especially when they are in an active relapse or receiving corticosteroid or other immunosuppressive drugs. It is also possible that parental education could have an impact on timely identification and handling of relapse. All administration of medications, recognition of edema and recurrent proteinuria, monitoring of symptoms and seeking of proper medical care will be the responsibility of the parent/carer. A survey of parental knowledge of NS and relapses revealed parental knowledge is an important factor in managing this chronic relapsing disorder [17]. Structured counselling on urine collection, medicine taking, recognising signs of an infection and when to seek medical advice may be particularly useful in our population, the majority of whom were from rural backgrounds and a substantial proportion of whose parents had less education. The timing of relapse and course of relapse also are important. Gebrehiwot et al evaluated time to relapse and its determinants among children with nephrotic syndrome and found that number of clinical factors determined the time to relapse indicating the need of longitudinal follow up rather than point in time follow up [18]. Children who have had repeated or frequent relapses will require individual management in the clinic to minimise cumulative doses of steroids and toxicity of these treatments. Another significant clinical pattern is called infection-associated relapse. Mantan and Singh conducted a prospective study of children with steroid-sensitive nephrotic syndrome, and reported upper respiratory tract infections being the most common infections associated with relapse [19]. Their findings support our cohort study in which we identified a high prevalence of RTI in children who had a relapse. However, if an infection occurs in the time of the relapse, it does not always mean that the infection is the sole cause for the relapse. Other studies have been recently centered on the better identification of bacterial infection during the relapse of nephrotic syndrome. A clinical prediction model utilizing inflammatory parameters developed by Venkata Narayana et al. was found to be useful in detecting bacterial infection in children during relapse [20]. These methods could have clinical applications as the infection needs to be detected early and antibiotic usage avoided. The relatively high prevalence of UTI and RTI in our setting suggests that clinical evaluation and targeted investigation of each episode of relapse should be considered and not empiric treatment of all episodes of relapses. The association of atopy and nephrotic syndrome continues to be a subject of research. Riar et al. evaluated asthma and allergy in children with nephrotic syndrome (NS) and found that although the number of children with allergic conditions was high, there was no clear-cut link with increased risk of NS relapse [21]. This is relevant to our observation that there was a high frequency of personal and family history of atopy. Some children may have a general immunologic predisposition which is demonstrated by atopy, but atopy alone is not a reliable predictor of relapse. The study of this research has several limitations. Firstly, it is cross-sectional, meaning that you can't examine the temporal relationships and causality. Second, all the participants had relapsed nephrotic syndrome and the frequencies observed cannot be considered relative risk

when compared to the children in remission. Third, this study was conducted in a single tertiary care hospital which means the findings of this study cannot be generalized to pediatrics population in Pakistan. Fourth, socioeconomic status and family history of atopy were partly dependent on caregiver reporting and thus could be information bias. Fifth, important potential predictors like serum albumin, cholesterol, duration of remission, number of previous relapses, steroid-response time, cumulative corticosteroid exposure and medication adherence were not evaluative. Although there are limitations to the study, it provides local information on factors that are commonly found in children with relapsed nephrotic syndrome in Pakistan. The most common characteristics were poor economic status and younger age, and personal atopy, a family history of atopy, UTI and RTI were also common. Significant factors associated with rural residence were younger age, and poorer economic status and personal atopy, while male gender was the only significant factor associated with personal atopy. Here it is important to note that these findings are associated characteristics and not proven causal factors. However, identification of children with multiple potentially relevant characteristics may help to achieve more intensive follow-up, parental education, support for adherence, monitoring for infection, and prompt treatment. Future multicenter studies are suggested with both relapsing and non-relapsing children to find some independent predictors and to come up with effective strategies to prevent relapses in Pakistani children.

6. CONCLUSION

The most common factors in this study of 114 children with relapsed nephrotic syndrome were poor economic status (71.9%), age < 5 years (66.7%), personal history of atopy (50.9%), family history of atopy (39.5%), UTI (38.6%), RTI (34.2%) and helminthiasis (8.8%). Being of younger age and having poor economic status were significant associations with rural residence, and male gender with personal atopy. The results suggest that a combination of demographic, socioeconomic, atopic and infectious factors are involved in the context of relapse. These factors should be considered as associated characteristics as this was a cross sectional study. However, if a child has multiple factors mentioned above, this may help with closer follow-up, parent education, adherence, providing nutrition and socioeconomic support, and early recognition and treatment of infections. Enhancement of preventive pediatric and primary-care services could lower the number of relapses and help to minimize overall corticosteroid use. It is suggested that future multicenter studies should be performed to identify independent predictors and to identify effective relapse-prevention strategies in Pakistani children.

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