



ORIGINAL ARTICLE

## Factors associated with early relapses in children with steroid-sensitive nephrotic syndrome.

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**ABSTRACT... Objective:** To determine different risk factors associated with relapse in children with steroid-sensitive nephrotic syndrome. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric Nephrology, The National Institute of Child Health, Karachi. **Period:** April 2021 to October 2022. **Material & Methods:** With a sample size of 170 Children aged 1-12 years of either gender were included in the study by non-probability consecutive sampling. Patients who had congenital nephrotic syndrome previously received immunosuppressive treatment or had any other systemic disease leading to nephrotic syndrome were excluded from the study. Frequencies and percentages were calculated for the quantitative variables while chi-square test was applied for the qualitative variables-value of <0.05 was considered significant. **Results:** The mean age of the patients was  $4.87 \pm 2.54$  years. The majority of the frequent relapsers (76) were male. The mean serum cholesterol of the patients was  $318.71 \pm 61.61$ mg/dl. Of the total sample, 37 (21.76%) were infrequent relapsers and 133 (78.23 %) were frequent relapsers. A significant association was found between upper respiratory tract infection and frequent relapse with a p-value of 0.038. **Conclusion:** Our study showed a significant association between upper respiratory tract infection and relapse in children with steroid-sensitive nephrotic syndrome.

**Key words:** Frequent Relapses, Infrequent Relapses, Relapse, Remission, Steroid Sensitive Nephrotic Syndrome.

### INTRODUCTION

Nephrotic Syndrome (NS) is one of the most common chronic renal illness in children characterized by massive proteinuria, hypercholesterolemia, hypoalbuminemia as well as profound edema caused by increased permeability of the glomerular basement membrane.<sup>1</sup> The incidence of NS varies considerably across regions and ethnicities with East Asia and Southeast Asia having the highest incidence of NS. The estimated incidence of NS is 2.92 new cases per 100,000 children per year.<sup>2</sup> Nephrotic syndrome is classified into Primary (Idiopathic Nephrotic syndrome) and due to secondary causes such as infections, systemic diseases or drugs.<sup>3</sup> Idiopathic Nephrotic Syndrome is further subdivided into three recognized histologic types which are Minimal Change Nephrotic Syndrome (MCNS), Membranous Nephropathy (MN) and focal

segmental glomerulosclerosis (FSGS). The most typical form of NS in children is minimal change nephrotic syndrome while membranous nephropathy is more typical in adults. In Pakistan the leading cause of INS in children was Minimal Change Nephrotic Syndrome 43.8%).<sup>4</sup> One of the principal glomerular diseases in both infants and adults, focal segmental glomerulosclerosis (FSGS), commonly exhibits steroid resistance and can lead to end-stage renal failure.<sup>5</sup> Majority (80-95%) of MCNS respond to steroid therapy, thus labeled as steroid sensitive NS and those who don't respond to steroid therapy are classified as steroid resistant nephrotic syndrome (SRNS).<sup>6</sup>

Despite the fact that the vast majority of these children benefit from steroid medication, 80-90 % of SSNS patients have relapses that can be labeled as either frequent relapses (FR) or infrequent relapses (IFR)(7). Frequent relapsers experience

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relapses within 6 months or a year, while infrequent relapsers experience 1-3 relapses annually.<sup>3</sup> More than half of the children with nephrotic syndrome have frequent relapses.<sup>8</sup> Numerous studies have documented many risk factors and their connection to the recurrence of nephrotic syndrome in kids. Upper respiratory tract infection or lower respiratory tract infection, urinary tract infection, diarrhea, and cellulitis are the most common causes of relapse risk factors.<sup>9</sup> Age less than 5 years is also associated with frequent relapses.<sup>10</sup> Adverse effects like excessive body weight, short stature and osteoporosis (decrease in bone mineral density) are associated with frequent relapses and repeated treatment with steroids.<sup>11</sup>

Different infections can lead to relapses of nephrotic syndrome. This study on finding out the risk factors for relapse in SSNS may be helpful in early prediction and reduction of risk of relapses in children with nephrotic syndrome. This may prevent repeated high dose steroid and steroid associated side effects in these children. Studying the factors associated with early relapses in children with steroid-sensitive nephrotic syndrome is essential to improve patient outcomes, enhance the quality of life for affected individuals, optimize healthcare resource allocation, and advance our understanding of this complex condition. Such research can lead to more personalized and effective treatment approaches for this patient population.

## OBJECTIVES

To determine different risk factors associated with relapse in children with steroid sensitive nephrotic syndrome.

## MATERIAL & METHODS

This cross sectional study was conducted at Pediatric Nephrology Department of National institute of child health, Karachi, from April 2021-october 2022, after the approval from the institutional ethical review board of NICH (IERB No:042020). A sample size of 170 was calculated by using the WHO software for "Sample size calculation" by using the prevalence reported by Balaji J, et al. with the incidence of infection

in 31.9% and hypertension in 37.5% children having relapse of nephrotic syndrome<sup>12</sup>, taking confidential interval at 95% and margin of error 5%. All newly diagnosed Patients of nephrotic syndrome, aged 1-12 years of either gender were included in the study by employing the non-probability consecutive sampling. Patients who had congenital nephrotic syndrome, previous received immunosuppressive treatment or had any other systemic disease leading to nephrotic syndrome were excluded from the study. Data was analyzed using SPSS Version 21. Frequencies and percentages were calculated for the quantitative variables while chi-square test was applied for the qualitative variables-value of <0.05 was considered significant.

## Operational Definitions and Measurements

**Nephrotic syndrome** was considered as the presence of massive proteinuria (>40 mg/m<sup>2</sup>/hr), hypoalbuminemia (serum albumin < 2.5 g/dl), hyperlipidemia (serum cholesterol > 200 mg/dl) and generalized edema.

**Remission** was considered if there was presence of proteinuria of < 4 mg/m<sup>2</sup>/hr or urine albumin nil or traces for 3 consecutive days.

**Relapse** was defined as presence of urine albumin 3+ or 4+ or proteinuria > 40 mg/m<sup>2</sup>/hr for three consecutive early morning specimens.

## Infrequent relapser

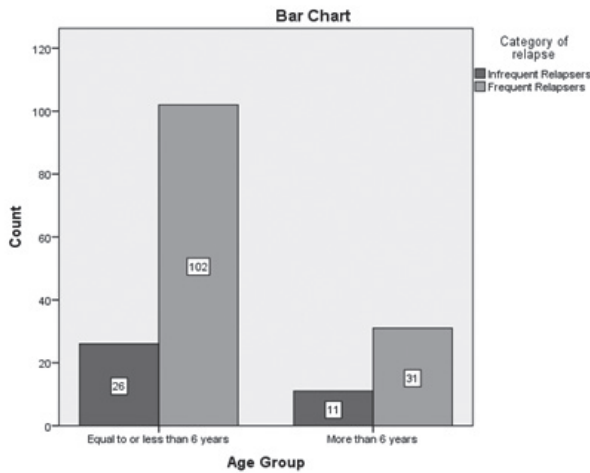
Patient was considered as an infrequent relapser if he/she had < 2 relapses within 6 months or < 4 relapses within 12 months of response to initial therapy.<sup>13</sup>

## RESULTS

A total of 170 children were included in the study of which 93 (54.7%) were male and 77 (45.3 %) were females. The mean age of the patients was 4.87±2.54 years. Majority of the frequent relapsers, 76 were male while 57 of the frequent relapsers were female. Out of total 170 Steroid Sensitive patients of nephrotic syndrome, 37 (21.76%) were infrequent relapsers and 133 (78.23 %) were frequent relapsers. The mean serum cholesterol of the patients was 318.71±61.61mg/

dl. Mean PCR of the patients was  $7.84 \pm 2.63$ .

Figure-1 shows the bar chart of the age group distribution of the frequent and infrequent relapsers. Majority of the frequent relapsers 60% were  $\leq 6$  years of age while 18.24% of the frequent relapsers were  $> 6$  years of age.



**Figure-1. Age group distribution of Frequent and Infrequent Relapsers.**

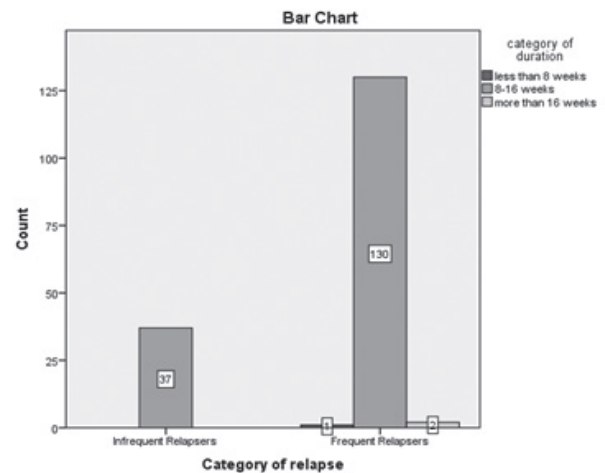
Table-I shows the Association of socio-demographic characteristics with type of relapse. In our results we did not find any significant association between age and gender with the type of relapse.

Sociodemographic Characteristics	Type of Relapse		P-Value
	Frequent Relapse	Infrequent Relapse	
<b>Age</b>			
$\leq 6$ years	102	26	0.42
$> 6$ years	31	11	
<b>Gender</b>			
Male	76	17	0.22
Female	57	20	

**Table-I. Association of age and gender with type of relapse.**

Table-II shows the comparison of the lab findings for serum cholesterol, PCR, Duration of initial steroid therapy and time between remission and relapse. Mean cholesterol level of the frequent relapsers was more than the infrequent relapsers.

We divided the duration of initial steroid therapy into categories of  $< 8$  weeks, 8-16 weeks and  $> 16$  weeks. Figure-2 shows the duration of initial steroid therapy among frequent and infrequent relapsers. Majority of the frequent relapsers (130) received the initial steroid therapy for 8-16 weeks.



**Figure-2. Duration of initial steroid therapy among frequent and infrequent relapsers**

Table-III shows the association between different disease related variables with the type of relapse. Significant association was found between upper respiratory tract infection and frequent relapse with the p-value of 0.038.

**DISCUSSION**

To determine various risk factors for relapse in children with steroid sensitive nephrotic syndrome, we studied 170 patients having SSNS.

Variables	Frequent Relapser Mean $\pm$ SD	Infrequent Relapser Mean $\pm$ SD
Serum Cholesterol	$322.41 \pm 60.22$ mg/dl	$305.41 \pm 65.47$ mg/dl
PCR	$7.85 \pm 2.52$	$7.78 \pm 3.01$
Duration of initial steroid therapy(weeks)	$12.88 \pm 2.50$	$13.14 \pm 2.28$
Duration between remission and relapse(weeks)	$22.80 \pm 25.24$	$28.62 \pm 27.77$

**Table-II. Disease related variables of frequent and infrequent relapsers.**

Variable	Category	Type of Relapse		P-Value
		Infrequent Relapse (N)	Frequent Relapse(N)	
Upper respiratory tract infection	Yes	111	65	0.038*
	No	126	68	
Acute watery diarrhea	Yes	7	19	0.48
	No	30	114	
Urinary Tract Infection	Yes	4	7	0.22
	No	33	126	
Skin infections (Dermatitis/cellulitis/Impetigo)	Yes	2	10	0.65
	No	35	123	
Asthma	Yes	0	1	0.59
	No	37	132	
Enteric infections (Typhoid)	Yes	1	2	0.62
	No	36	131	
Spontaneous	Yes	12	29	0.18
	No	25	104	

**Table-III. Association of disease related variable with type of relapse among children with steroid sensitive nephrotic syndrome.**

In our results majority of the patients were frequent relapsers 133 (78.23 %) and 37 (21.76%) were infrequent relapsers while previous studies done have shown a lower incidence of frequent relapses among children with idiopathic nephrotic syndrome. Incidence of FRNS was 120 (43.3%) and Infrequent relapse was present in 157 (56.6%) of the patients however the age less than 6 years was significantly associated with frequent relapses.<sup>14</sup> Another study done by Nakanishi et al., also reported that frequent relapses were only experienced by 19% of the patients.<sup>15</sup>

Out of the 170 children studied, majority (60%) of the frequently relapsing children belonged to the age group of <6 years which is in line with the study in which majority of the frequent relapsers were below 5.5 years and the results showed that onset of the disease at a younger age is a predictor for frequent relapses.<sup>10</sup> Mishra et al., also reported that children belonging to the age group of 1-3years were 2.99 times more likely to have relapse as compared to children who were >6 years of age.<sup>16</sup> The results were also inconsistent with the study done by Ademola in which 60 % of the patients were less than 5 years of age group.<sup>17</sup> However we did not find any significant association between age and type of relapse as also reported by a study<sup>7</sup> and Esezobor et al., also did not find any significant association of

age with relapse.<sup>8</sup> Fujinaga et al., also reported that no association was present between age and tendency to relapse.<sup>18</sup>

While determining the risk factors, our results showed that 55.29 %of the children with NS had concurrent upper respiratory tract infection, followed by acute watery diarrhea being the second most common infection (15.29%). The principal finding of our study was the significant association of upper respiratory tract infection with frequent relapses with a p-value of 0.038. One study reported that upper respiratory tract infection was the most predominant risk factor in children with nephrotic syndrome followed by urinary tract infection.<sup>19</sup> However the risk factors vary with the geographical location. One study reported peritonitis(24%) being the most common infection in children with nephrotic syndrome followed by UTI.<sup>20</sup> Peritonitis and pneumonia combined (72.9%) accounted for the major infections followed by UTI in a study done in India.<sup>21</sup> In Taiwan, pneumonia (49%) was the main cause of infection with nephrotic syndrome.<sup>22</sup>

According to very recent researches, it has been concluded that duration of initial steroid therapy does determine the outcome of patient as patients who received longer durations of steroid therapy (<12 weeks) are less likely to relapse(23) but in

our study we did not note any notable difference between the duration of initial steroid therapy as it was  $12.88 \pm 2.50$  weeks for the frequent relapsers while it was  $13.14 \pm 2.28$  weeks for the infrequent relapsers.

## CONCLUSION

Our study showed a significant association between upper respiratory tract infection and relapse in children with steroid sensitive nephrotic syndrome. We also noted that patients presenting with frequent relapses were less than 6 years of age.

## RECOMMENDATIONS

The study should be done across different provinces of Pakistan to know the incidence and risk factors for steroid sensitive nephrotic syndrome so that the burden of disease can be reduced in our population. Detailed account of viral markers and cultures should also be studied and taken into account to see which viruses are causing upper respiratory tract infections to have more reliable and scientific data which can help in reducing the burden of frequent relapses.






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