

Original Research Article

Study of risk factors for relapse in frequently versus infrequently relapsing nephrotic syndrome in 1-18 year age group: a combined prospective retrospective cohort analytical observational study

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ABSTRACT

Background: Early prediction and prevention of risk factors is the key to successful management of childhood nephrotic syndrome. This study was carried out to find the risk factors of relapse which will help in early prediction and reduce the risk of relapse in childhood nephrotic syndrome.

Methods: It was a combined prospective-retrospective cohort analytical observational study of duration 18 months with sample size of 80 patients of age group 1-18 years who fulfilled the inclusion and exclusion criteria. The variables taken into account for the present study were demographic and disease related.

Results: In the present study, 67.7% of patients with ≤ 6 year of age at first onset were frequent relapsers while 60% of patients with > 6 year of age at first onset were infrequent relapsers. A 77.1% of patients belonging to lower socioeconomic strata and 60% of patients belonging to lower-middle socioeconomic strata were frequent relapsers. 100% of patients having ≥ 4 relapses within the 1st year after diagnosis were frequent relapsers while 73.2% of patients having ≤ 3 relapses within the same period were infrequent relapsers. In present study, out of 38 patients who had received 8 weeks of steroid therapy 92.1% were frequently relapsing while out of 42 patients who received 12 weeks of steroid therapy 64.3% were found to be infrequently relapsing.

Conclusions: Younger age at first onset, higher number of relapses in first year and lower socio-economic strata is associated with frequently relapsing nephrotic syndrome. Longer duration of steroid therapy (12 weeks) lowers the chance of frequent relapses.

Keywords: Frequent, Infrequent, Nephrotic syndrome, Relapse, Risk factors

INTRODUCTION

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic range proteinuria is defined as proteinuria > 3.5 g/24 hours or a urine protein: creatinine ratio > 2 . The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤ 2.5 g/dL), edema and hyperlipidemia (cholesterol > 200 mg/dL).¹

Nephrotic syndrome in healthy children is a relatively common major disease in pediatrics. Approximately 50% affected children are between ages of 1 year 6 months to 5 years. Even the most benign form of nephrotic syndrome is by nature a recurrent disorder, so each new case is likely to manifest disease for some time.²

Most children (90%) with nephrotic syndrome have a form of idiopathic nephrotic syndrome (INS). Most frequent type (85%) of Idiopathic nephrotic syndrome is

minimal change nephrotic syndrome (MCNS) and more than 95% minimal change nephrotic syndrome well respond to steroid therapy.³ But idiopathic nephrotic syndrome is a chronic relapsing disease.

Infection is an important cause of relapse in minimal change nephrotic syndrome, prevention and treatment of which could reduce proteinuria without necessity of steroid.⁴ An upper respiratory tract infection (URTI) or a febrile episode often precipitates a relapse; occasionally there is no obvious cause.⁵ Asymptomatic urinary tract infection might be an important and under diagnosed cause of relapse.⁶

Frequency of relapses is highly variable. In a year, some patients have <3 (infrequent relapses) where as others have >4 relapses (frequent relapses). International study of kidney disease in children originally reported a relapse rate of 60% but later data suggests up to 76%-90% relapse rate with frequently relapsing rate up to 50%.⁷

Young age and low level of serum protein at the onset are independent risk for relapse.⁷ Relapse within the first year is a powerful independent predictor of subsequent relapse and relapse within first 6 months of presentation is highly predictive of subsequent course.

In our country poverty, inadequate health care facility, less organized referral system and lack of adequate knowledge about disease course among parents is a great problem in early detection and treatment of relapse. Hence prediction and prevention of risk factors is the key to successful management of childhood nephrotic syndrome.

This study was carried out to find the risk factors of relapse which will help to predict the relapse early and to reduce the risk of relapse in childhood nephrotic syndrome.

METHODS

It was a combined prospective and retrospective cohort analytical observational study. The sample size was 80 patients with 10 patients in the prospective arm from 01/07/2015 to 01/01/2016 and 70 patients in the retrospective arm starting from 1995. The duration of the study was 18 months. Study population included children of age group 1-18 years of OPD or hospitalized patients who fulfilled the inclusion and exclusion criteria.

Inclusion criteria

- Pediatric ward and nephrology OPD patients (age group 1 to 12 years) and Adult nephrology ward and OPD patients (age group of 13 to 18 years), children of age group 1 to 18 years diagnosed to have nephrotic syndrome, either gender, parent/guardian willing to give consent, child over 7 years of age willing to give assent were the inclusion criteria.

Exclusion criteria

- Children diagnosed as congenital or infantile nephrotic syndrome in the past, patient who was lost to follow up during the study period, non-availability of consent and other documented causes of edema/oliguria/hypertension/hematuria not fitting into nephrotic syndrome.

The study was carried out after obtaining approval from the institutional ethics committee and head of nephrology department (for age group 13-18). Cases were selected as per those satisfying the inclusion and exclusion criteria. Participants were enrolled in the study after obtaining written informed consent or assent from the mother/father/ guardian/child. A list was prepared of all the patients admitted in the paediatric ward, adult nephrology ward, Pediatrics OPD, Nephrology OPD of children aged 1-18 years diagnosed to have nephrotic syndrome, primary or otherwise. New patients enrolled in the first 6 months were followed up for one year and therefore fulfil the definition of frequently or infrequently relapsing nephrotic syndrome.

Patients in the retrospective arm were called 6 monthly or earlier if they had a relapse. Consent was taken from the patients in the retrospective arm. If the patient could not be contacted, then a waiver of consent permission from the ethics committee was required. Consent was taken from all the patients in the prospective arm. Data for retrospective patients was obtained from the patient's file maintained in OPD and from patient's case files.

Data for prospective arm was obtained from patients OPD and indoor papers. At every patient visit, a urine albumin sample was tested, weight, blood pressure, height measurements were obtained. If patient showed clinical signs of relapse with urine albumin 2+, 3+ then they were observed. Patients with organic causes were not included in the study. Information related to gender, socioeconomic status by modified Kuppuswamy scale, age at first onset, number of relapses within the first year of onset, infections related to relapses, duration of steroids in first episode-four weeks of intensive phase plus four weeks of alternate day steroids versus six weeks of intensive phase followed by 6 weeks of alternate day steroids was obtained. All the information included in the case record form. Qualitative and Quantitative data were recorded and analyzed. Qualitative data is represented in the form of frequency and percentage.

Qualitative data includes gender, socioeconomic status. Quantitative data is represented using Mean±SD and Median and IQR (interquartile range). Quantitative data includes age, age at first onset (months), number of relapses within first year, duration of steroids in first episode-four weeks of intensive phase daily regimen plus four weeks of alternate day versus six weeks of intensive phase followed by six weeks of alternate day steroids.

RESULTS

In present study, a total of 80 study participants with relapse of nephrotic syndrome were included, out of which 50 (62.5%) had frequent relapses and 30 (37.5%) had infrequent relapses. Maximum no of patients 47 (58.7%) were less than or equal to 6 years of age. Males (66.25%) outnumbered females (33.75%) in present study population. 48 patients (60.0%) were from the lower socioeconomic strata, 22 (27.5%) were from upper lower class and 10(12.5%) were from lower middle strata. Out of 80 patients, merely 5 patients (6.25%) presented with hypertension. In the present study 5% presented with hematuria, rest (95%) had no history of hematuria. 65 (81.25%) had age at first onset ≤6 years and 15 (18.75%) had age at first onset >6 years. The number of relapses within first year ranged from 0 to 6, out of which 30 patients (37.5%) had 4 relapses within first year, 17 patients (21.3%) had 2 and two patients (2.5%) had six relapses within first year. 38 patients (47.5%) were treated with 8 weeks of steroid therapy in first episode while the rest of 42 patients (52.5%) were treated for 12 weeks the number of associated infections per year ranged from 0 to 6 for all 80 patients of which 29 (36.5%) had four infections per year, 18 (22.5%) had two and one patient had none. Among the group >6 years, 16 (48.5%) patients had frequent relapses and 17 (51.5%) had infrequent relapses while in the group ≤6 years, 34 (72.3%) patients had frequent relapses and 13 (27.7%) had infrequent relapses. A statistically significant difference was found (p-value=0.03) (Figure 1).

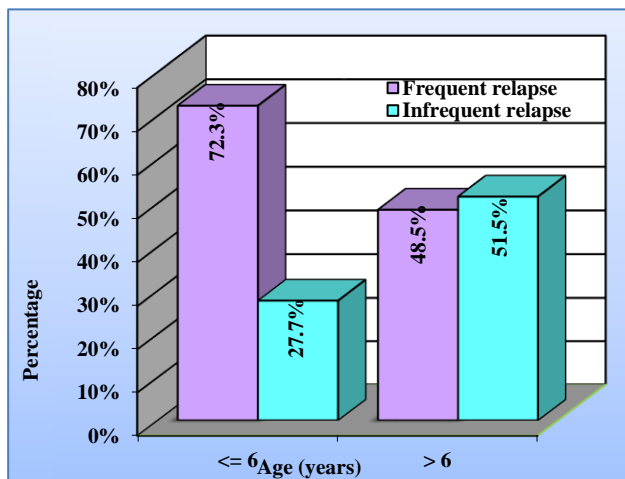


Figure 1: Association among the cases with respect to age with relapse.

Out of 80 patients, 48 patients who were from lower socioeconomic strata, 37 (77.1%) had frequent relapses and 11 (22.9%) had infrequent relapses. 22 patients belonged to upper lower strata of which 7 (31.8%) had frequent relapses and 15 (68.2%) had infrequent relapses. Out of 10 patients who belonged to lower middle

socioeconomic strata, 6 (60%) had frequent relapses and 4 (40%) had infrequent relapses.

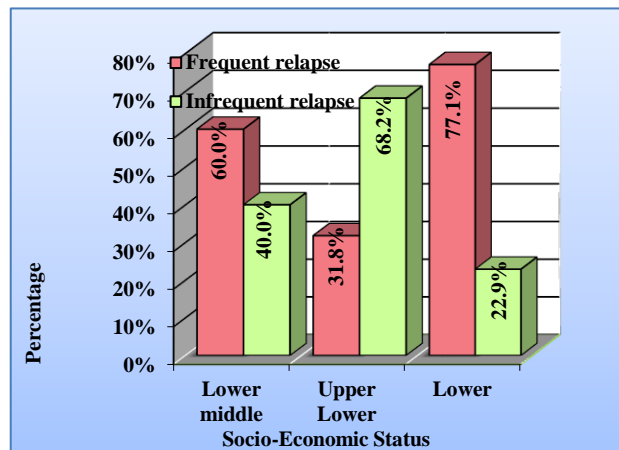


Figure 2: Association among the cases with respect to socio economic status with relapse.

A statistically significant difference was found (p-value=0.00135) (Figure 2). Children with age at disease onset ≤ 6 years were found to be more frequent relapses with 67.7% whereas infrequent relapses were higher in >6 years patients with 60%. The difference was statistically significant (p-value = 0.046) (Figure 3).

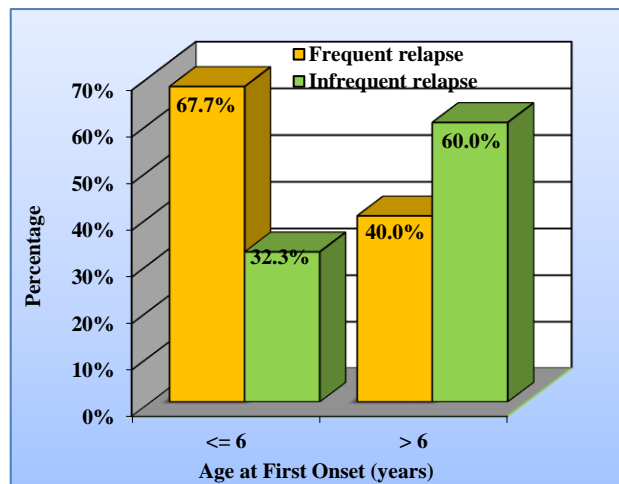


Figure 3: Association among the cases with respect to age at 1st onset with relapse status.

In the present study, the mean number of relapses within first year was 3.78 for frequent relapsing nephrotic syndrome whereas in infrequent relapsing nephrotic syndrome it was 1.4. The difference was statistically significant (p-value=0.0000000057) (Figure 4).

Number of patients treated with 8 weeks of steroid therapy in first episode having frequent relapses were 35 (92.1%) and only 3 (7.9%) had infrequent relapses.

Table 1: Comparison of various variables among all cases by relapse type.

Variables	Unit	Relapse status		Total
		Frequent	Infrequent	
Age (years)				
≤6	No.	34	13	47
	%	72.3%	27.7%	100.0%
>6	No.	16	17	33
	%	48.5%	51.5%	100.0%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%
Socio-economic status				
Lower middle	No.	6	4	10
	%	60.0%	40.0%	100.0%
Upper lower	No.	7	15	22
	%	31.8%	68.2%	100.0%
lower	No.	37	11	48
	%	77.1%	22.9%	100.0%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%
Age at first onset (years)				
≤ 6	No.	44	21	65
	%	67.7%	32.3%	100.0%
> 6	No.	6	9	15
	%	40.0%	60.0%	100.0%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%
No. of relapses within 1st year				
≤ 3	No.	11	30	41
	%	26.8%	73.2%	100%
≥ 4	No.	39	0	39
	%	100%	0%	100%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%
Duration of steroid therapy in first episode (weeks)				
8	No.	35	3	38
	%	92.1%	7.9%	100.0%
12	No.	15	27	42
	%	35.7%	64.3%	100.0%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%
No. of associated infections per year				
≤ 3	No.	15	27	42
	%	35.7%	64.3%	100%
≥ 4	No.	35	3	38
	%	92.1%	7.9%	100%
Total	No.	50	30	80
	%	62.5%	37.5%	100.0%

In case of patients treated with 12 weeks of steroid therapy, patients with infrequent relapses was 27 (64.3%) which was higher than those with frequent relapses 15 (35.7%). There was statistically significant difference (p-value=0.000000196) (Figure 5).

The mean number of associated infections per year was 3.74 for frequent relapsing nephrotic syndrome whereas in infrequent relapsing nephrotic syndrome it was 1.93. The difference was statistically significant (p-value=0.00000252) (Figure 6) (Table1).

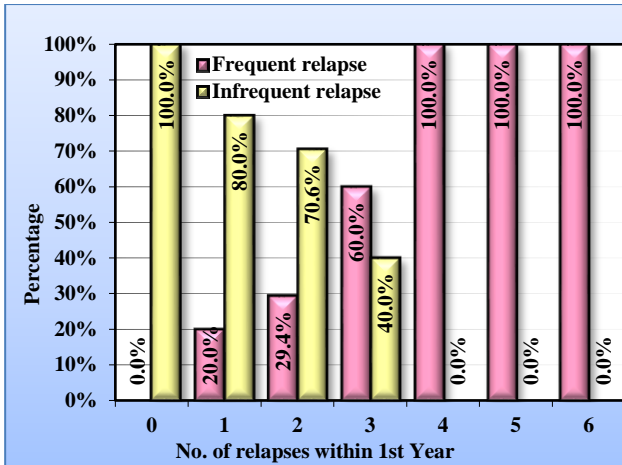


Figure 4: Association among the cases with respect to number of relapses in 1st year with relapse status.

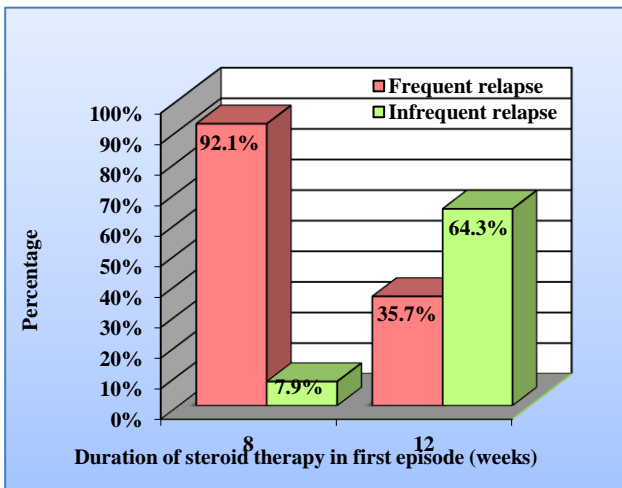


Figure 5: Association among the cases with respect to duration of steroid therapy with relapse status.

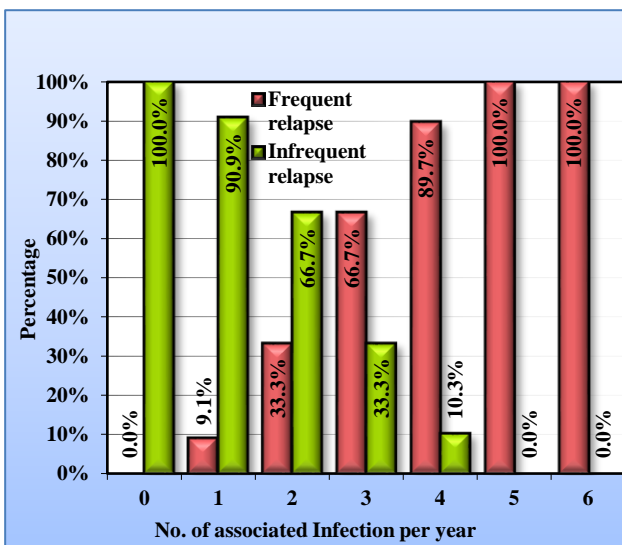


Figure 6: Association among the cases with respect to number of associated infections with relapse status.

DISCUSSION

Nephrotic syndrome is a kidney disease with higher incidence compared to other kidney diseases.^{8,9} Most children with nephrotic syndrome have a form of idiopathic nephrotic syndrome.¹⁰ It is a chronic relapsing disease.¹¹ Frequency of relapses is highly variable with some patients having ≤ 3 relapses per year (infrequent relapses) whereas others having ≥ 4 relapses per year (frequent relapses).¹⁰ There are different risk factors associated with frequency of relapses. This study was done to find out the risk factors for relapse which will help in its early prediction and reduce the risk of relapse in childhood nephrotic syndrome. Total 80 cases of relapsing nephrotic syndrome were studied. Out of them 50 were frequently relapsing and rest were infrequently relapsing nephrotic syndrome.

A total number of 80 cases were included in the present study. Maximum number of cases i.e. 47 (58.75%) were in the age group of ≤ 6 years at the time of presentation. This result was similar to the study done by Ali SH et al, which revealed that the most common age-group at presentation was 1-5 years, comprising a total of 51 patients (63.7%) out of 80 cases.¹² Similar study done by Sarker MN et al, found that, out of 100 patients, majority (67%) were between 2-6 years of age with a mean age of 5.3 ± 2.1 years.¹³ The age predominance of < 6 years was also noticed in the study done by Andersen RF et al.¹⁴

A greater male preponderance 53 (66.3%) was observed in present study as compared to females 27 (33.8%) the ratio being 1.96:1. Similar finding of male predominance was observed in the studies done by Kasim R et al, Ali SH et al and Noer MS et al, who obtained the ratios of (M:F-1.5:1), (M:F-2.2:1) and (M: F- 3.5:1) respectively.^{9,12,15} Results similar to present study were also found in the studies done by Karim MA et al, Gulati et al and Mendoza et al.^{16,17,18}

Authors used modified Kuppaswamy scale for socio-economic status stratification. Higher incidence of study population was from lower socioeconomic strata i.e. 48 (60%) followed by upper lower 22 (27.5%) and lower middle 10 (12.5%). Study done by Sarker MN et al, found similar results with 59% of cases from lower, 39% from middle and 2 % from upper socioeconomic strata.¹³ However, this finding was in contrast to the study done by Uwaezuoke SN et al, which reported lower incidence of the disease in lower socioeconomic strata (15.38%)-this variation could be due to bias in the patient selection criteria as most of the study population belonged to upper socioeconomic strata in their study.¹⁹

In present study group comprising of 80 patients, the incidence of frequent relapses for females and males were 63% and 62.3% respectively while infrequent relapses were 37% and 37.7% respectively. According to a similar study done by Sarker MN et al, gender predilection was not found to be associated with frequent relapses

($p=0.534$), and similar results were found in study done by Rahi K et al, ($p=0.467$).^{13,15} These findings were consistent with present study. Other in line studies had reported similar findings between gender and frequent relapses as observed in present study.²⁰⁻²³ In present study gender variation in frequent relapses and infrequent relapses was statistically not significant and hence is a poor predictor for relapse.

Out of eighty patients, only five patients had hypertension which contributes to 6.3% of the cases, out of which three were frequently relapsing and two were infrequently relapsing. In present study no significant association between hypertension and relapse status was found. Similar study done by Noer MS et al, found no association between hypertension and relapses (p value= 0.340).⁹ This finding of no significant association could be attributed to small number of patients who presented with hypertension in present study.

In the present study, hematuria was found only in four cases of nephrotic syndrome which contributed to 5% of cases, out of which 50% were frequently and 50% were infrequently relapsing. The study done by Rahi Karim et al, too had far less no of patients presenting with hematuria.¹⁵ A study done by Noer MS et al, found no significant correlation between the presence of hematuria at initial presentation and occurrence of frequent or infrequent relapsing nephrotic syndrome.⁹ In present study, no significant association of hematuria at initial presentation with relapse was found.

In present study we divided the population into two age groups - ≤ 6 years and > 6 years. We found that in the age group of ≤ 6 years, 34 (72.3%) had frequent relapses and 13 (27.7%) had infrequent relapses. Among the age group >6 years, 16 (48.5%) had frequent relapses and 17 (51.5%) had infrequent relapses. A statistically significant difference (p -value of 0.03) was found between younger age group (≤ 6 years) and increased frequency of relapses. In a study done by Sarker MN et al, children in the age group of <5 years were more likely to be frequently relapsing (68%) than those of age group >5 years ($p=0.019$).¹³ Findings of a similar study done by Vogt et al, were consistent with the present study.³ Similar study done by Takeda A et al, mentioned that early onset of nephrotic syndrome was associated with frequent relapses.⁷ Hence, the present study reflected that the younger age group could be a risk factor for frequent relapsing nephrotic syndrome. This may be due to lack of maturity of immune system in younger children leading to increased frequency of infection associated relapses.

Thirty-seven patients (77.1%) out of 48 from lower socioeconomic strata, 6 (60%) out of 10 from lower middle socioeconomic strata and 7 (31.8%) out of 22 from upper lower strata had frequent relapses. This finding was consistent with study done by Sarker MN et al.¹³ In this study, majority of patients (59%) were from lower socioeconomic strata and were significantly prone

to develop frequently relapsing nephrotic syndrome than the children who belonged to middle and upper strata ($p = 0.001$). This finding was comparable with the finding of Biswas et al.⁴ In the present study, a statistically significant correlation was found between lower socioeconomic strata and frequency of relapses with a p value of 0.00135. This could be attributed to a higher risk of infections due to overcrowding, poor sanitation and poor drug compliance among them.

In present study children having lower age at disease onset were found to be more frequently relapsing (67.7%) as compared to those children having disease onset after 6 years (60%). The studies done by Andersen et al, Sarker MN et al, and constantinescu AR et al, found the significant correlation of age at first onset to be lower (younger) age in frequently relapsing nephrotic syndrome.^{13,14,24} Another similar study done by Situmorang D et al, found significant association of lower (younger) age at first onset with frequent relapses ($p<0.001$).²¹ The hypothesis is that nephrotic syndrome is caused by impaired function of T cells, the presence of abnormal T cell clones that produce the chemical mediators (circulating glomerulotoxic lymphokines) that increase the permeability of the basement membrane and cause proteinuria. This abnormal T cell was suspected to be cloned in the thymus, which is most active in children.²⁵ In present study, we found significant correlation between frequent relapse and early age at onset of disease ($p = 0.046$).

In present study, out of 50 frequent relapsers 78% had ≥ 4 relapses within the 1st year after diagnosis, while all 30 infrequent relapsers had ≤ 3 relapses within the 1st year after diagnosis. In present study there was significant association between number of relapses within 1st year of diagnosis and further relapse status ($p = 0.004$). Similar study done by Sarker MN et al, found the number of relapses within first year to be significantly higher among frequently relapsing nephrotic syndrome (p value <0.001).¹³ This was also described by Takeda et al, and international study of kidney disease in children.^{26,27} This finding in present study could be attributed to lack of awareness about disease, improper initial therapy and poor compliance.

In present study, 35 (92.1%) out of 38 patients who had received 8 weeks of steroid therapy and 15 (35.7%) out of 42 patients who received 12 weeks of steroid therapy were found to be frequently relapsing. In present study, there was statistically significant association between duration of steroid therapy in initial episode and relapse status during the course of disease ($p = 0.006$). It implies that longer duration (12 weeks) of steroid therapy during the initial episode reduces the number of relapses during the course of disease. Similar studies done by Constantinescu et al, and Ali SH et al, reported less frequent relapses among their studied patients in relation to a long duration of steroid, but their results were statistically not significant.^{12,24}

In present study, 70% of frequent relapsers and only 10% of infrequent relapsers were found to have higher no. of associated infection per year (≥ 4). We found statistically significant association between number of associated infections per year and relapses. It implies that increased number of infections per year is associated with frequently relapsing nephrotic syndrome. Similar study done by Uwaezuoke SN et al found, infectious triggers of relapse predominate over the non-infectious and idiopathic triggers.¹⁹ In a retrospective study in a health facility in Pakistan, Moorani reported infections in 62.9% of relapse.²⁸

However, Sarker MN et al, studied 100 cases of which 50 were of frequent relapses and 50 cases were of infrequent relapses. 36 (72.0%) of frequent relapses and 19 (38.0%) of infrequent relapses associated with infections at initial attack ($p=0.001$).¹³ This indicates that infection is the major triggering factor for frequent relapses.

CONCLUSION

Children of younger age group and lower socioeconomic strata are more prone to develop frequent relapses. Children with age at first onset ≤ 6 years have more relapses when compared to older age group. With Increased number of relapses in first year, more are the chances of becoming frequent relapsers during the course of disease. Longer duration of steroid therapy (12 weeks) lessens the chance of frequent relapses. Increased number of infections per year is associated with frequently relapsing nephrotic syndrome.

Parent should be provided information about the course, complications and outcome of the disease and maintaining the diary containing information about proteinuria, medication and infections. As infections constitute significant proportion of morbidity, need for appropriate immunization should be stressed.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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