

Risk Factor of Frequent Relapse in Pediatric Nephrotic Syndrome

Desman Situmorang*, Nanan Sekarwana, Eddy Fadlyana

Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
*Corresponding author: dman2912@gmail.com

Abstract Background. Nephrotic syndrome (NS) is a kidney disease with high incidence. Although steroids therapy produces a good outcome with remission (80–95%), but the relapse rates are also high (60-90%). Relapsed NS patients experienced a long period treatment and become dependent on steroids, which might cause side effects such as short stature, overweight, osteoporosis, and cardiovascular disease. Some risk factors of relapse are age, late remission, first relapsed ≤ 6 months after remission, and short initial therapy. **Study design.** A cross-sectional study with retrospective data collection from medical record of patients with frequent and infrequent relapse nephrotic syndrome from January 2010 to December 2014. There were 90 patients which were divided in two groups, 45 frequent relapse and 45 infrequent relapse. Statistical analysis used bivariate and multivariate risk factor. **Result.** Boys:girls ratio was 4.6:1, with median age is 5 years and 5 month (65 months). From bivariate analysis, the first diagnosis ≤ 5 years ($p < 0.001$) and time on remission ≤ 6 month ($p < 0.001$) were the risk factor of frequent relapse. Multivariate analysis showed time on remission ≤ 6 month (OR 37.113, CI 95% (7.115–193.595)) more significant than the age at diagnosis ≤ 5 years (OR 8.0 CI 95% (2.402–26.645)) upon frequent relapse nephrotic syndrome. **Conclusion.** Time on remission ≤ 6 month and the age at diagnosis of NS ≤ 5 years were risk factor of frequent relapse in nephrotic syndrome patients.

Keywords: Nephrotic syndrome, frequent relapse, risk factor.

Cite This Article: Desman Situmorang, Nanan Sekarwana, and Eddy Fadlyana, “Risk Factor of Frequent Relapse in Pediatric Nephrotic Syndrome.” *American Journal of Medical and Biological Research*, vol. 4, no. 1 (2016): 10-12. doi: 10.12691/ajmbr-4-1-3.

1. Introduction

Nephrotic syndrome (NS) is a kidney disease with high incidence compared with other kidney disease. [1,2] Nephrotic syndrome incidence in Indonesia is 6 per 100.000 children per year on children age < 14 years old, with boys:girls ratio is 2:1. [3] Nephrotic syndrome therapy using steroid has good outcome, remission on 80–95% patients, [4,5] however with high relapse incidence (60–90%) [6,7] with frequent relapse on 50–60% patients [6,8].

Relapsed NS patient experienced a long period treatment and became dependent on steroids, which might cause side effects such as short stature, overweight, osteoporosis, and cardiovascular disease, Cushing syndrome, psychologic disorder and decreased immune system [9,10].

Previous study found that age, gender, time of remission, low serum albumin and protein, delayed time on remission, short initial therapy, poor social economy class, and atopy were risk factor for frequent relapse in nephrotic syndrome [6,11].

Our study tried to find out the risk factor of frequent relapse nephrotic syndrome which will help to predict the relapse early and to reduce relapse in childhood NS.

2. Methods

2.1. Setting

This retrospective cross-sectional study was conducted in patients with frequent and infrequent relapse nephrotic syndrome at Dr. Hasan Sadikin General Hospital, Bandung, from January 2010 to December 2014. Subjects were selected by consecutive sampling.

2.2. Inclusion and Exclusion Criteria

Children age 1–14 years old who were diagnosed with frequent and infrequent relapse nephrotic syndrome and normal renal function were included in this study. Patient were follow up for at least 1 year. Exclusion criteria were incomplete medical record and laboratory examination. (Figure 1)

2.3. Case Definition

Nephrotic syndrome is a manifestation of glomerular disease, characterized by nephrotic range proteinuria and the triad of clinical findings associated with large urinary losses of protein: hypoalbuminemia, edema, and hyperlipidemia. [4,12] Relapsed was defined by proteinuria > 40 mg/h/m² or > 50 mg/kg/day or protein

stick +++ for 3 consecutive days after having been in remission. [13] Frequent relapsed was defined if patient had 2 or more relapse within 6 months of initial response or 4 or more relapse within a period of 1 year, while infrequent relapse was defined if patient had 1 relapse in 6 months or 1–3 relapse in 12 months. [13,14] Remission defined by proteinuria <4 mg/h/m² or -/trace on protein stick for 3 consecutive days. [13] Time of remission was counted after patient had remission until patient had the first relapse. Medical record must have patient data (name, birth date, sex), history of patient (age at first diagnosis, remission and relapse time) and laboratory examination (albumin, ureum and creatinine serum). Patient was said to have normal renal function if patient had normal ureum and creatinine serum.

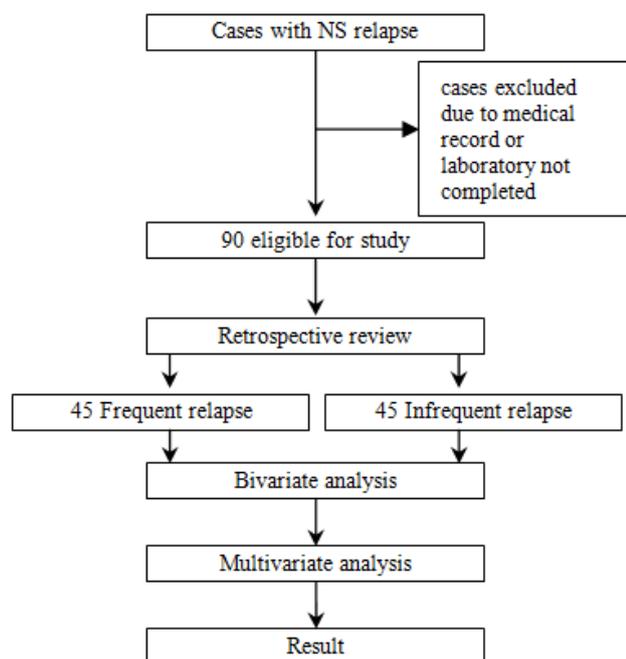


Figure 1. Study's Flow Diagram

2.4. Statistical Analysis

All risk factors were analyzed in two steps. Bivariate analysis using Chi-square test for categorical data and independent t-test or Mann-whitney test for numeric data. Categorical variable with $p < 0.25$ was included in the multivariate analysis using logistic regression analysis. The difference of variable in two groups is considered significant if p value < 0.05 . the result was also presented in odds ratio (OR) with 95% confidence interval (CI).

The study was approved by The Research Ethics Committee of Hasan Sadikin General Hospital, Bandung.

3. Result

3.1. Study Population and Bivariate Analysis

During January 2010 to December 2014, 382 cases of nephrotic syndrome were recorded in the Department of Child Health, Dr. Hasan Sadikin General Hospital. We found 123 cases with relapse nephrotic syndrome, 90 cases of which fulfilled the inclusion and exclusion criteria and were included as subject of this research. Subjects were divided in two groups, group I consisted of

45 patients with frequent relapse (FR), and group II consisted of 45 patients with infrequent relapse (IFR).

It was shown that subject consisted of 74 boys and 16 girls, with ratio was 4.6:1. Characteristics of both group were shown in Table 1.

Table 1. Characteristics of subject

Characteristic	Relapse		P value
	Frequent relapse	Infrequent relapse	
Gender			
Boys	40	34	0.098 ^a
Girls	5	11	
Age at diagnosis			
≤ 5 years	33	11	$< 0.001^a$
> 5 years	12	34	
Time of remission			
≤ 6 months	43	16	$< 0.001^a$
> 6 months	2	29	
Laboratory examination			
Albumin (mg/dL)			
Median (SD)	2,02 (0,59)	2,15 (0,64)	0.317 ^b
Range	0,80–3,30	1,10–3,60	
Total cholesterol (mg/dL)			
Median (SD)	375 (99,60)	325 (138,73)	0.067 ^c
Range	208–760	132–845	
Creatinine (mg/dL)			
Median (SD)	0,35 (0,09)	0,39 (0,11)	0.103 ^b
Range	0,17–0,55	0,15–0,67	

^a Chi-square test, ^b Independent t-test, ^c Mann-Whitney test.

All factors suspected to be associated frequent relapse were compared between both groups. No significant difference on gender between both groups ($p = 0.098$). The same with laboratory findings such as albumin ($p = 0.317$), total cholesterol ($p = 0.067$) and creatinine serum ($p = 0.103$) showed no significant difference between both groups.

From Table 1, there was significant difference in age at diagnosis between both groups. Age ≤ 5 years is more prone to develop frequent relapse than age > 5 years ($p < 0.001$). This similar to study by Sarker et al in Bangladesh. [6] Data from Table 1 showed there is significant difference in time of remission between two groups. Time of remission ≤ 6 months is more prone to develop frequent relapse than time on remission > 6 months ($p < 0.001$).

3.2. Multivariate Analysis

We did multivariate analysis on risk factor with p value < 0.25 to find association between frequent relapse and risk factor. There were 5 risk factor we include in this analysis, i.e. gender, age at diagnosis, time of remission, creatinine and total cholesterol serum. The final result was shown in Table 2.

Table 2. Logistic regression analysis in association between risk factor and frequent relapse

Risk factor	P	OR (CI 95%)
Age at diagnosis (≤ 5 years)	0,001	8.0 (2.402–26.645)
Time of remission (≤ 6 months)	$< 0,001$	37.113 (7.115–193.595)

Time of remission ≤ 6 months (OR 37.113 95% CI 7.115–193.595) and age at diagnosis ≤ 5 years (OR 8.0 95% CI 2.402–26.645) were associated with frequent relapse nephrotic syndrome.

4. Discussion

From January 2010 to December 2014, there were 123 cases of relapse nephrotic syndrome. Thirty three were excluded due to several reasons (Figure 1). From 90 subjects, 45 subjects were with frequent relapse, and 45 were with infrequent relapse. Boys:girls ratio in our study is 4.6:1, more than other study by Constantinescu et al (1.8:1) [15].

We divided age at diagnosis in two groups, ≤ 5 years old, and >5 years old. Bivariate analysis showed significant difference within two groups of age at diagnosis with frequent relapse ($p < 0.001$). This was similar with previous studies that showed age at diagnosis was younger in frequent relapse nephrotic syndrome. [6,14,16] Logistic regression analysis showed there was an association between age at diagnosis ≤ 5 years with frequent relapse (OR 8.0 95% CI 2.402–26.645). Hypothesis said that nephrotic syndrome 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, most actively in children [17].

Time of remission is shorter in frequent relapse compared with infrequent relapse. We divided time of remission in two groups, ≤ 6 months and >6 month. Bivariate analysis showed there was significant difference between both groups of time of remission with frequent relapse. Logistic regression analysis showed there was an association between time of remission ≤ 6 months with frequent relapse (OR 37.113 95% CI 7.115–193.595). A review by Uwaezuoke also said the same thing, but the mechanism was still unexplained [14].

Although our data shows all patient with relapse were dominantly in boys (4.6:1), there was no difference between boys with frequent relapse ($p = 0.098$). This was different with a study by Sureshkumar et al, who said that boys were more prone to have frequent relapse compared with girls [11].

Our laboratory data, albumin serum, creatinine serum and cholesterol serum showed there was no difference in FR group and IFR group ($p = 0.317$, $p = 0.103$, and $p = 0.067$, respectively). Study by Takeda et al and Sarker et al showed that low protein serum and albumin was indicated as risk factor for frequent relapse. [18] Our study did not show the role of low albumin serum as risk factor of frequent relapse nephrotic syndrome.

The limitation of this study was using secondary data from tertiary hospital. Some medical records and laboratory examination were incomplete, so we dropped out the subject.

5. Conclusion

Some criteria like age at diagnosis ≤ 5 years and time on remission ≤ 6 months could be used as risk factor for frequent relapse nephrotic syndrome. Clinician had to give education to patient's parent about the prognosis and the risk of therapy to become frequent relapse nephrotic syndrome, especially in patient age ≤ 5 years old or time of

remission ≤ 6 months. Further studies is needed with more subjects and variable risk factors to find out the risk factors of frequent relapse nephrotic syndrome.

Acknowledgement

The study was done with private funding. We thanked Professor Abdurachman Sukadi and Professor Herry Garna and AJL for the counseling of the study design and initial manuscript.

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