

PREDICTORS OF RELAPSE IN STEROID-SENSITIVE NEPHROTIC SYNDROME

Mohammad Sjaifullah Noer

Department of Child Health, School of Medicine, Airlangga University, Soetomo Hospital,
Surabaya, Indonesia

Abstract. The objective of this study was to identify predictors of relapse and determine the predictive score for relapse in steroid-sensitive nephrotic syndrome. Ninety-nine children with nephrotic syndrome visiting the pediatric nephrology outpatient clinic of Soetomo Hospital from 1983 to 2001 were studied. There were 63 children with relapses (50 infrequent relapses, 13 frequent relapses) and 36 children without a relapse for at least 1 year after beginning steroid treatment, which served as a control group. The selected variables were grouped into non-renal factors (age, sex, nutritional status, infection) and renal factors (histopathologic findings, hypertension, hematuria, azotemia, hypocomplementemia, rapidity of early steroid response, number of relapses within the first 6 months, time-interval between early steroid response and first relapse). Using the discriminant analysis function test, it was found that the statistically significant predictors of relapse were the time-interval between early steroid response and the first relapse, number of relapses within the first 6 months, infection during the first relapse, hematuria and sex. A prediction score can be determined using 3, 5 or 6 parameters by including the rapidity of early steroid response.

INTRODUCTION

Nephrotic syndrome is characterized by massive proteinuria (>50 mg/kg/day), hypoproteinemia, hypercholesterolemia and edema (Yao and Cheng, 2000). Hematuria and hypertension were only found in some cases. Nephrotic syndrome is one of the diseases in children that needs long-term treatment. The incidence of the disease is around 2-7 cases per 100,000 children per year (Constantinescu *et al*, 2000). In Asia the incidence is 9-16 cases per 100,000 children per year (Sharples *et al*, 1985) and in Indonesia, Wila Wirya (2002) reported 6 cases per 100,000 children per year. The male to female ratio was 2:1 with the onset of disease at 18 months - 6 years old (Constantinescu *et al*, 2000). There were 1,076 children with renal disease admitted to Soetomo Hospital during the years 1988-1992; nephrotic syndrome was the second most common renal disease (18.7%)

(Noer, 1995).

Prednisone is the drug of choice for nephrotic syndrome. The use of this drug since 1950 has lowered the mortality rate from 35% to 3% (Hodson *et al*, 2000). The international Study of Kidney Disease in Children recommends prednisone 60 mg/m²/day (maximum 80 mg/day) in divided doses for 4 weeks, followed by 40 mg/m² every other morning for the next 4 weeks. Using this protocol proteinuria disappeared in 90% of children with minimal change nephrotic syndrome.

One-third of patients will not experience a relapses after the first remission (Koskimies *et al*, 1982), however, the remaining two-thirds will. The relapse-rate in nephrotic syndrome was approximately 70% with a recurrence of proteinuria and edema (Hodson *et al*, 2000). Relapse-type can be classified into infrequent relapses (<2 relapses within 6 months) and frequent relapses (≥2 relapses within 6 months). Patients with frequent relapses are at risk of severe steroid toxicity, because of the continuous, high dose prednisone used to induce remission (Durkan *et al*, 2001). The adverse effects of glucocorticoids are legion and well known, particularly regarding of statural growth. (Report of the

Correspondence: Mohammad Sjaifullah Noer, Department of Child Health, Medical School Airlangga University, Soetomo Hospital, Jalan Prof Dr Moestopo 6-8, Surabaya 60286, Indonesia.
Tel: +62-8123517032
E-mail: msnoer@pediatrik.com

International Study of Kidney Disease in Children, 1982).

The purpose of this study was to identify the predictors of relapse and to determine the predictive score for relapse in steroid-responsive nephrotic syndrome.

MATERIALS AND METHODS

This study was conducted on all children with nephrotic syndrome visiting the pediatric nephrology outpatient clinic, Soetomo Hospital from 1983 to 2001, and for at least 12 months of follow-up. Patients who were resistant to steroid therapy were excluded from the study. Data were collected on age, sex, nutritional status, infection, histopathologic findings, hypertension, hematuria, azotemia, hypocomplementemia, rapidity of early steroid response, number of relapses within the first six months, and time-interval between the first relapse and early steroid response. Chi-square analysis and discriminant analysis function test (Wilks' and Lambda) were used in this study.

RESULTS

Ninety-nine of 144 children with nephrotic syndrome visiting the pediatric nephrology outpatient clinic Soetomo Hospital from 1983 to 2001 were eligible for the study. Sixty-three (63.6%) children had relapsing nephrotic syndrome consisting 50 (50.5%) infrequent-relapsers and 13 (13.3%) frequent-relapsers. The remaining 36 (36.4%) children who did not have any relapses for at least 1 year after remission served as the control group.

The variables for predicting relapse were grouped into non-renal factors (age, sex, nutritional status, and infection), and renal factors (histopathologic findings, hypertension, hematuria, azotemia, hypocomplementemia, rapidity of early steroid response, number of relapses within the first six months, time-interval between the first relapse, and early steroid response).

Non-renal factors

Thirteen children with frequently-relapsing nephrotic syndrome were aged between 2.5-8 years old, consisting of 11 (84.6%) children aged

Table 1
Non-renal predictors of relapse in steroid-sensitive nephrotic syndrome.

Variables	FR (%)	IFR(%)	NR (%)	n (%)	p
Age					
≤ 6 years old	11 (84.6)	30 (60)	18 (50)	59 (59.6)	>0.05
> 6 years old	2 (15.4)	20 (40)	18 (50)	40 (40.4)	
Sex					
Male	10 (7.9)	38 (76)	29 (80.6)	77 (77.8)	0.945
Female	3 (23.1)	12 (24)	7 (19.4)	22 (22.2)	
Nutritional status					
Well-nourished	8 (61.5)	30 (60.0)	26 (72.2)	64.4 (64.7)	0.945
Under-nourished	3 (23.1)	13 (26.0)	6 (16.7)		
Severe malnourished	2 (15.4)	5 (10.0)	4 (11.1)		
Overweight	-	2 (4.0)	-		
Infections at 1 st diagnosis					
Respiratory tract	2 (15.4)	8 (16.0)	5 (13.9)	15 (15.2)	0.770
Urinary tract	-	-	1 (2.8)	1 (1.0)	
No infection	11 (84.6)	42 (84.0)	30 (83.3)	83 (83.8)	
Infections at 1 st relapse					
Respiratory tract	8 (61.5)	23 (46.0)		31 (31.3)	0.001
Gastrointestinal tract	2 (15.4)	-		2 (2.0)	
No infection	3 (23.1)	27 (54.0)		66 (66.7)	

FR = frequent-relapser; IFR = infrequent-relapser; NR = non-relapser

Table 2
Renal factors for relapse in steroid-sensitive nephrotic syndrome.

Variables	FR (%)	IFR (%)	NR (%)	n (%)	p
Histo-pathologic findings					0.843
MCNS	4 (100)	7 (77.8)	8 (61.5)	19 (73.1)	
FSGS	-	1 (7.4)	2 (15.4)	3 (11.5)	
DMP	-	1 (7.4)	2 (15.4)	3 (11.5)	
MPGN	-	-	1 (7.7)	1 (3.9)	
Others	-	2 (22.2)	5 (38.5)	7 (26.9)	
Hypertension					0.340
Hypertension	3 (23.1)	9 (18.0)	10 (27.8)	22 (22.2)	
Normotension	10 (76.9)	41 (82.0)	26 (72.2)	77 (77.8)	
Hematuria at 1 st diagnosis					0.340
Hematuria	2 (15.4)	13 (26.0)	7 (19.4)	22 (22.2)	
No hematuria	11 (84.6)	37 (74.0)	29 (80.6)	77 (77.8)	
Hematuria at 1 st relapse					0.309
Hematuria	3 (23.1)	6 (12.0)	9 (14.3)	3 (23.1)	
No hematuria	10 (76.9)	44 (88.0)	54 (85.7)	10 (76.9)	
Azotemia					0.451
Azotemia	3 (23.1)	17 (34.0)	14 (38.9)	34 (34.3)	
Normal	10 (76.9)	33 (66.0)	22 (61.1)	65 (65.7)	
Hypocomplementemia					0.015
Examined	4 (100.0)	23 (100.0)	10 (100.0)	37 (100.0)	
Hypocomplementemia	1 (25.0)	-	1 (10.0)	2 (5.4)	
Normal	3 (75.0)	23 (100.0)	9 (90.0)	35 (94.6)	
Not examined	9	27	26	62	
Rapidity of early steroid response					0.266
Early responder					
Week I	3 (23.1)	20 (40.0)	12 (33.3)	35 (35.4)	
Week II	3 (23.1)	15 (30.0)	8 (22.2)	26 (26.3)	
Week III	3 (23.1)	4 (8.0)	5 (13.9)	12 (12.1)	
Week IV	-	3 (6.0)	5 (13.9)	8 (8.1)	
Late responder					
Week V	2 (15.4)	2 (4.0)	4 (11.1)	8 (8.1)	
Week VI	1 (7.7)	4 (8.0)	1 (2.8)	6 (6.1)	
Week VII	1 (7.7)	-	-	1 (1.0)	
Week \geq VIII	-	2 (4.0)	1 (2.8)	3 (3.0)	
Number of relapses within the first 6 months					0.001
< 2	-	50 (100)		50 (79.4)	
\geq 2	13 (100)	-		13 (20.6)	
Number of relapses within the second 6 months					0.002
< 2	5 (38.5)	40 (80.0)		45 (71.4)	
\geq 2	8 (61.5)	10 (20.0)		18 (28.6)	
Interval between early steroid response and first relapse (months)					0.001
< 1	1 (7.7)	-		1 (1.6)	
1-3	9 (69.2)	7 (14.0)		16 (25.4)	
> 3	3 (23.1)	43 (86.0)		46 (73.0)	

FR = frequent-relapser; IFR = infrequent-relapser; NR = non-relapser

≤ 6 years old and 2 (15.4%) children aged > 6 years old. In the infrequently-relapsing nephrotic syndrome group, there were 50 children aged between 1.5–15.5 years old consisting of 30 (60%) children aged ≤6 years old and 20 (40%) children aged >6 years old. Thirty-six non-relapsing nephrotic children aged between 2–12 years old were 18 (50%) children aged ≤6 years old and 18 (50%) children aged > 6 years old.

There were no significant differences in age, sex, nutritional status, or infections at first diagnosis among the frequently-relapsing, infrequently-relapsing, and non-relapsing steroid-sensitive nephrotic syndrome groups except for infections at first relapse, between the frequently-relapsing and infrequently-relapsing steroid-sensitive nephrotic syndrome group (Table 1).

Renal factors

Percutaneous renal biopsies performed in 26 of 99 patients showed four types of histopathologic findings: minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), diffuse membranoproliferative (DMP), and membranoproliferative glomerulonephritis

(MPGN), where the most common histopathologic finding was minimal change disease. There were no significant differences in the histopathologic findings among the frequent-relapsers, infrequent-relapsers and non-relapsers. There were also no significant differences in hypertension, hematuria at first diagnosis, azotemia, and rapidity of early steroid response among the frequently-relapsing, infrequently-relapsing and non-relapsing steroid-sensitive nephrotic syndrome groups. There were no significant differences in hematuria at first relapse between the frequent relapsers and infrequent relapsers (Table 2).

Significant differences were found in hypocomplementemia and the number of relapses within the second six months after steroid response among the frequently-relapsing, infrequently-relapsing and non-relapsing steroid-sensitive nephrotic syndrome groups. There were also significant differences in the number of relapses within the first 6 months and the second 6 months after steroid response, and interval between early steroid response and first relapse between frequently-relapsing and infrequently-

Table 3
Predictive score for relapse in steroid responsive nephrotic syndrome.

No.	Variables	Score		
		3 parameters	5 parameters	6 parameters
1	Interval between early steroid response and first relapse (months)			
	<1	3	3	3
	1-3	5	5	5
	>3	3	3	3
2	Number of relapses within the first 6 months after diagnosis			
	<2	1	1	1
	≥2	4	4	4
3	Infection at first relapse			
	Infection	3	3	3
	No infection	1	1	1
4	Hematuria			
	Positive		2	2
	Negative		1	1
5	Sex			
	Male		2	2
	Female		1	1
6	Rapidity of early steroid response (week)			
	≤4			1
	>4			2

relapsing steroid-sensitive nephrotic syndrome groups (Table 2).

Predictive score for relapse in steroid-sensitive nephrotic syndrome

The statistically significant variables for renal and non-renal factors were calculated to determine the parameters for the predictive score for relapse. The three variables that had a lot of influence on relapse were the interval between early steroid response and first relapse, number of relapses within the first six months after diagnosis, and infection at first relapse. Wilks' and Lambda analysis also revealed 2 other variables that had some influence on relapse: hematuria and sex. By including the rapidity of early steroid response as a theoretically significant variable, we could add a 6th parameter to the predictive score.

The scoring system and cut-off point for the predictive score were based on the results of the chi-square analysis, discriminant function test analysis (Wilks' and Lambda) and supporting theories (Table 3).

If we used 3 parameters consisting of time-interval between early steroid response and first relapse, number of relapses within the first six months after diagnosis, and infection at first relapse, the total predictive score ranged between 5 and 12 with cut-off point at 5 (chi-square; $\chi^2 = 39.990$, $df = 1$, $p = 0.001$). Patients with a total score >5 will have a greater possibility of being a frequent relapser and a total score ≤ 5 will more likely result in an infrequent or non-relapser.

If we used 5 parameters consisting of the three parameters above plus hematuria and sex, the total predictive score ranged between 7 and 16 with a cut-off point at 9 (chi-square; $\chi^2 = 33.760$, $df = 1$, $p = 0.001$). A patient with a total score >9 will have a greater possibility of being a frequent relapser and a total score ≤ 9 will more likely result in an infrequent or non-relapser.

Using 6 parameters consisting of the five parameters above plus rapidity of early steroid response, the total predictive score ranged between 8 and 18 with a cut-off point at 10 (chi square; $\chi^2 = 33.261$, $df = 1$, $p = 0.001$). A patient with a total score >10 will have a greater possibility of being a frequent relapser, but a to-

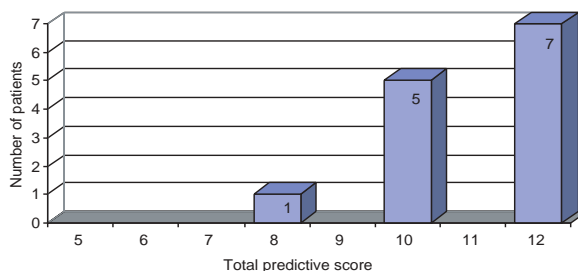


Fig 1—Distribution of the predictive score with 3 parameters (time-interval between early steroid response and first relapse, number of relapses within first six months after diagnosis, and infections at first relapse) in frequently-relapsing steroid-sensitive nephrotic syndrome (n=13).

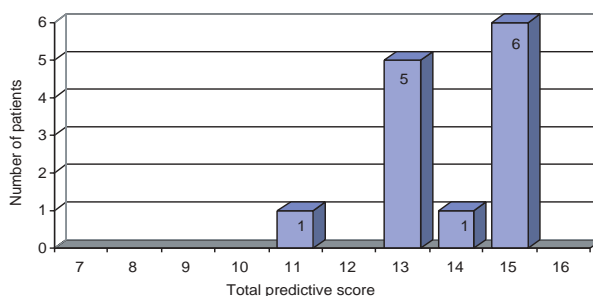


Fig 2—Distribution of the predictive score with 5 parameters (time-interval between early steroid response and first relapse, number of relapses within first six months after diagnosis, infection at first relapse, hematuria, and sex) in frequently-relapsing steroid-sensitive nephrotic syndrome (n=13).

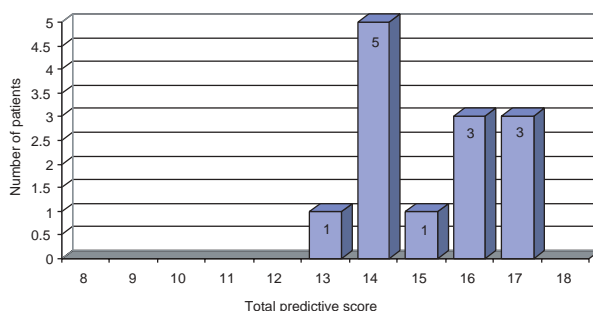


Fig 3—Distribution of the predictive score with 6 parameters (time-interval between early steroid response and first relapse, number of relapses within first six months after diagnosis, infection at first relapse, hematuria, sex, and rapidity of early steroid response) in frequent relapsers of steroid-sensitive nephrotic syndrome (n= 13).

tal score ≤ 10 will more likely result in an infrequent or non-relapser.

DISCUSSION

Lewis *et al* (1989) and Kabuki *et al* (1998) stated that there is a correlation between age at onset of nephrotic syndrome and the frequency of relapses. Onset at age less than 4 years old will lead to frequent relapses. This present study showed a similar result but there were no significant differences in age among the frequently, infrequently and non-relapsing steroid-sensitive nephrotic syndrome groups. Comparing to Wila Wirya (2002) and Damanik (1997) who reported a male to female ratio of 2:1, and 2.9:1 respectively, this study showed a greater male to female ratio, where the male to female ratios for frequent-relapsers, infrequent-relapsers, and non-relapsers were 3.3:1, 3.2:1 and 4.1:1, respectively.

The international Study of Kidney Disease in Children (1982) stated that there was no significant correlation between the sex and number of relapses within 6 months ($p > 0.1$). Based on the chi-square test, our data showed that there were also no significant differences in sex among frequent-relapsers, infrequent-relapsers and non-relapsers ($p > 0.05$), but the discriminant analysis function test showed a contradicting result. Sex was one of variables that had an influence on relapse (Wilks' and Lambda = 0.042, $\chi^2 = 301.699$, $df = 4$, $p = 0.001$).

The susceptibility to infection increases in nephrotic children due to the decrease in immunoglobulin, protein deficiency, defect in bacterial opsonization, hypofunction of spleen and immunosuppressant therapy (Bellow *et al*, 1982; Report of the International Study of Kidney Disease in Children, 1984). The occurrence of relapses increases the susceptibility to infection (Arbeitsgemeinschaft für Pädiatrische Nephrologie, 1998). This theory is supported by the results of our study. At the beginning of the disease only 16 (16.2%) patients showed signs of infection. The number of patients with infection increased at the first relapse. Ten out of 13 (76.9%) frequent relapsers and 23 out of 50 (46%) infrequent relapsers showed signs of in-

fection. There were significant differences in infection at first relapse between frequent relapsers and infrequent relapsers ($p < 0.05$).

The other non-renal factors, age at onset and nutritional status, did not show any significant differences, so they were not used as predictors of relapse.

Only 4 out of 8 renal factors were found to be predictors of relapse: hematuria, rapidity of early steroid response, number of relapses within the first 6 months, and time-interval between early steroid response and first relapse.

Siegel *et al* (1972) reported that hematuria, hypertension and transient azotemia at first diagnosis had a significant correlation with the frequency of relapses within the first 2 years. Hematuria was found at first diagnosis of nephrotic syndrome in 22 (22.2%) patients, but there were no significant differences in hematuria at first diagnosis among the frequently-relapsing, infrequently-relapsing and non-relapsing steroid-sensitive nephrotic syndrome groups. The results of our study are similar to Siegel's findings, as shown in the results of the discriminant analysis function test that hematuria was one of the significant variables leading to frequent-relapses.

Only 9 out of 63 relapsing nephrotic children showed hematuria upon first relapse. There were no significant differences in hematuria at first relapse between frequently-relapsing and infrequently-relapsing steroid-sensitive nephrotic syndrome.

The underlying histopathologic characteristics are very important in determining the response to steroid therapy and long-term prognosis of nephrotic syndrome (Gulati *et al*, 1999). Unfortunately, only 26 (26.3%) patients in our study underwent biopsies. Because of the small number of biopsies, it is difficult to draw any conclusions based on the histopathologic findings, but based on analysis of the results there were no significant differences in the histopathologic findings among the frequently-relapsing, infrequently-relapsing and non-relapsing steroid-sensitive nephrotic syndrome groups.

Constantinescu *et al* (2000) stated that the earliest predictor for relapse was the number of days the patient need to enter remission after

beginning prednisone therapy. The longer the time to remission the greater the possibility of becoming a frequent relapser or steroid dependent. Patients who had no hematuria and responded well within the first week to steroid therapy had a greater chance of becoming infrequent relapsers. In the present study, 9 of 13 (69.2%) children who were frequent-relapsers achieved remission ≤ 4 weeks after steroid therapy were named early responders. This data differs from the findings of Constantinescu (2000), in that among the infrequent relapsers there were 42 of 50 (84%) early responder and there were 30 of 36 (83.3%) patients among the non-relapsers. There were no significant differences in rapidity of early steroid response among the frequent relapsers, infrequent relapsers and non relapsers ($p > 0.05$).

The international Study of Kidney Disease in Children (1982) stated that the earliest predictor of frequent relapse is the number of relapses within first 6 months after steroid response. In the present study, all of the frequent relapsers had ≥ 2 relapses within the first 6 months after steroid response and all of the infrequent relapsers had < 2 relapses within the same period. There were significant differences in the number of relapses within the first 6 months after steroid response among the frequently-relapsing, infrequently-relapsing and non-relapsing steroid-sensitive nephrotic syndrome groups. The Wilks' and Lambda analysis test concluded the number of relapses within the first 6 months after steroid response has a close correlation with the pattern of relapse.

Eight (61.5%) patients of the frequent-relapsers had ≥ 2 relapses within the second 6 months after steroid response and 5 (38.5%) of the patients had only < 2 relapses within the second 6 months. All children who were infrequent-relapsers had < 2 relapses within the second 6 months. There were significant differences in the number of relapses within the second 6 months after steroid response between the frequent-relapsers and infrequent-relapsers, but based on the Wilks' and Lambda analysis it was concluded that there was no correlation between the number of relapses within the second 6 months after steroid response and the pattern

of relapse.

The International Study of Kidney Disease in Children (1979) already proved that patients who relapsed within the first 6 months after steroid response had longer intervals between the first relapse and early steroid response if they were receiving standard prednisone therapy. The interval between the first relapse and early steroid response was 1.48 months. In the present study the majority of relapses (69.2%) occurred within 1-3 months after the early steroid response among frequent-relapsers but in the infrequent-relapsers the majority of relapses (86%) occurred > 3 months after the early steroid response and none of them had a relapse less than 1 month after an early steroid response. There were significant differences in the time-interval between the early steroid response and the first relapse between frequently relapsing and infrequently relapsing steroid-sensitive nephrotic syndrome. This variable also appeared to be an important factor in the pattern of relapse.

If the predictive score is applied to frequently-relapsing steroid-sensitive nephrotic syndrome in this study the results will be as follows:

It is clear that the predictive score for relapse with 3 parameters gives a better distribution, since almost all of the scores were close to the highest score. This was proved by the results of statistical analysis (chi-square; $\chi^2 = 39.990$, $df = 1$, $p = 0.001$).

In conclusion, predictors of relapse in this study consisted of interval between early steroid response and first relapse, number of relapses within the first 6 months after diagnosis, infection at first relapse, hematuria and sex. The predictive score could be determined by using 3 parameters, 5 parameters or 6 parameters by including the rapidity of early steroid response variables. The best predictive score was the predictive score using 3 parameters (time-interval between early steroid response and first relapse, number of relapses within the first six months after diagnosis, and infections at first relapse) (Chi-square; $\chi^2 = 39.990$, $df = 1$, $p = 0.001$).

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