

# Procalcitonin in Children with Relapsing Steroid-Sensitivenephrotic Syndrome

1<sup>st</sup> Dian Ismawardani  
*Department of Child Health  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia.  
 dianida84@gmail.com*

2<sup>nd</sup> Oke Rina Ramayani  
*Department of Child Health  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia*

3<sup>rd</sup> Yazid Dimiyati  
*Department of Child Health  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia*

4<sup>th</sup> Zulfikar Lubis  
*Department of Clinical Pathology  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia*

5<sup>th</sup> Atan Baas Sinuhaji  
*Department of Child Health  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia*

6<sup>th</sup> Rita Evalina  
*Department of Clinical  
 Department of Child Health  
 Medical School  
 University of Sumatera Utara  
 Medan, Indonesia*

**Abstract**—Sensitive-Steroid Nephrotic Syndrome (SSNS) is the most common chronic glomerular disease in children with high incidence of relapse. Infections were statistically significant risk factors for recurrence in SSNS. Current findings suggest that procalcitonin (PCT) may not only be a valid marker for infection and inflammation but also a pro-inflammatory cytokine-like mediator. To identify the relationship between procalcitonin and relapse in childhood SSNS. A cross-sectional study was conducted from February 2017 to February 2018. Complete blood count, procalcitonin, and urinalysis were obtained. Data was analyzed by *chi-square* test with P-value <0.05 considered significant. Of all 55 samples, the percentage of relapsing SSNS in this study is 72.7%. On Receiver Operating Characteristic (ROC) curve, the total Area Under Curve (AUC) was 73.6% with P = 0.007. There was a statistically significant correlation between procalcitonin level cut off 0.065 ng / dL with relapse occurrence (P value = 0.002), with a prevalence ratio of 8.308 (CI :95% range: 1.993-34.636). Procalcitonin with cut off value > 0.065 ng / dl gave the best accuracy (70.9%), which predicted relapse with sensitivity 67.5%, specificity 80%. The occurrence of relapsing nephrotic syndrome is influenced only with procalcitonin in this study.

**Keywords**—procalcitonin, minimal change nephropathy, steroid-sensitive nephrotic syndrome, children, relapse

## I. INTRODUCTION

Nephrotic syndrome (NS) is the most common chronic glomerular disease in children. The incidence of NS is 2-7 per 100.000 children per year and the prevalence is 12-16 per 100.000 children [1]. The incidence in Indonesia is reported 6 per 100.000 children per year. The ratio of boys to girls is 2:1 [2]. Most cases of children with NS (90%) are idiopathic NS [3]. The causes include minimal change disease (85%), mesangial proliferation (5%), and focal segmental glomerulosclerosis (10%) [4].

Patients with minimal change disease mostly show a response to corticosteroid treatment. Sensitive-Steroid Nephrotic Syndrome (SSNS) is the most common form of childhood NS and responds to corticosteroid therapy. However 80-90% cases will relapse so steroid therapy will be repeated [5]. Patients with SSNS receive frequent steroids due to recurrent relapse, whereas steroid-resistant nephrotic syndrome receives fewer recurrent doses due to steroid-sparing agent use. Based on the course of their illness, 76 to 93% patients with SNSS will experience relapse, 30% of them will have frequent relapse, 10-20% will have infrequent relapse, while the remaining 40-50% will have steroid-dependent nephrotic syndrome (SDNS) [6]. There have been several studies published on long-term outcomes of children with SNSS. The study reported by long-term remission was observed in over 90% of children with minimal NS abnormalities, so the SSNS was considered a benign disorder with an excellent prognosis [7]. However, recent studies have shown that 33-42% of children experience relapse into adolescence and adulthood [8]. This may be associated with increased complications in children so as to increase mortality and morbidity.

The response of steroid therapy during initial therapy, hematuria and infection was statistically significant as a risk factor for recurrence in nephrotic syndrome [9]. Procalcitonin (PCT) serum is a very accurate and specific marker of infection in patients with normal renal function [10]. Recent studies show that PCT does not serve only as a valid infection marker but also as a mediator of proinflammatory cytokines [19]. The combination of C-reactive proteins and PCT can be used to evaluate infections in SSNS patients and predict the incidence of relapse [11]. However studies associated with procalcitonin as infection markers and relapse risk factors in SSNS is still very limited. This study aims to

determine the relationship between PCT as a risk factor for relapse in children with SSNS in RSUP Haji Adam Malik Medan.

## II. MATERIALS AND METHODS

This is a cross sectional study conducted in RSUP Haji Adam Malik Medan North Sumatera from February 2017 to February 2018. Target population is children aged 1 to 18 years. Accessible population is target population diagnosed with NS. Sample is an accessible population that meets the inclusion and exclusion criteria. Samples were taken on a consecutive basis where patients with SSNS were examined for PCT when they visit outpatient clinic.

### Inclusion criteria:

- Children aged 1 - 18 years who have been diagnosed with SSNS in RSUP Haji Adam Malik Medan and visit nephrology outpatient clinic for control on third day and are in remission or relapse phase with or without infection or infection history

### Exclusion criteria:

- Patients with steroid-resistant NS
- Patients with congenital NS
- Patients who refused informed consent

Parents/guardians and children with SN who visit nephrology outpatient clinic that meet the inclusion criteria are given explanations and informed consent which states agree to follow this research. When patients with SSNS visit the outpatient clinic, data collection of age, gender and blood sampling for complete blood examination, PCT and urinalysis examination was performed. Patients were identified as SN Relapse or Non Relapse. Data collected in the analysis by comparing age, sex, PCT, leukocyte, neutrophil/lymphocyte ratio. This study was approved by the Research Ethics Committee of Medical School of University of Sumatera Utara.

### 2.1 Variables and Operational Definition

The independent variables in this study were age, type, sex, PCT, leukocyte, neutrophil/lymphocyte ratio while the dependent variable was nephrotic syndrome. Nephrotic syndrome is a clinical condition characterized by symptoms such as severe proteinuria  $> 40 \text{ mg /hour/m}^2$ , protein /creatinin ratio  $> 0.2 \text{ gram/mmol}$ , hypoalbuminemia  $< 2.5 \text{ g/dL}$ , hyperlipidemia with total cholesterol  $170\text{-}200 \text{ mg/dL}$ . Steroid-sensitive nephrotic syndrome is a patient who achieves complete remission with steroid therapy for four weeks.

Non relapse (Remission) is a negative proteinuria or trace (proteinuria  $< 4 \text{ mg/m}^2 \text{ LPB/hour}$ ) for 3 consecutive days in 1 week. Relapse is proteinuria  $\geq 2+$  (proteinuria  $> 40 \text{ mg/m}^2 \text{ LPB/hour}$ ) for 3 consecutive days within 1 week. Procalcitonin level is the value of PCT serum taken when the patient visit outpatient clinic RSHAM. Neutrophils/Lymphocyte ratio is a marker (biomarker of infection) in which a ratio increase (cut off  $> 10$ ) indicates a diagnosis of bacteremia. Leukocytes are a haematological parameter as a marker of infection.

## 2.2 Data analysis

Collected data is processed, analyzed, and presented using software, SPSS 15.0. The data is presented as simple data of the number or percentage using chi-squared test. To test the statistically significant differences between different parameters, the number and percentage of probability values were used. P-value  $< 0.05$  is considered significant.

## III. RESULTS AND DISCUSSION

In this study, there are 55 samples that fulfill the inclusion criteria.

TABLE I. CHARACTERISTICS OF SUBJECTS

Characteristics	N=55
Mean age, year (SD)	9.8 (4.03)
Sex, n (%)	
Male	36 (65.5)
Female	19 (34.5)
Mean leukocyte / $\mu\text{L}$ (SD)	12 320.5 (5 597.46)
Mean neutrophil, % (SD)	62.8 (15.38)
Lymphocyte rate, % (SD)	28.5 (13.18)
Mean procalcitonin, ng/mL (SD)	6.4 (36.78)
Relapsing nephrotic syndrome, n (%)	
Relapse	40 (72.7)
Non relapse	15 (27.3)

Most subjects in this study were male (65.5%). The percentage of relapse NS in this study is quite high (72.7%). To determine the level of PCT as a relapse predictor in children with NS, an analysis of the ROC curve was performed. The total area under the curve was 73.6% with  $P = 0.007$ .

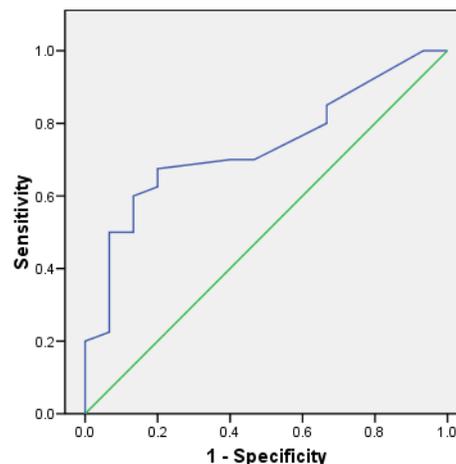


Fig. 1. Procalcitonin ROC curve levels in predicting the occurrence of relapse

Chi-squared test was used to determine the association between serum PCT level and relapse occurrence of SSNS. Procalcitonin levels used as cut off were the highest sensitivity and specificity (0.065 ng/dL), the highest sensitivity but low specificity (0.025 ng/dL), and the highest specificity but low sensitivity (0.195 ng/dL).

Procalcitonin level with cut off value >0.065 ng/dl gave the best accuracy (70.9%), which predicted relapse with sensitivity 67.5%, specificity 80%, positive predictive value 90%, negative predictive value 48%, positive likelihood ratio 3.4, negative likelihood ratio 0.5.

**TABLE II. ACCURACY OF PCT LEVELS TO PREDICT RELAPSE IN PATIENTS WITH SSNS**

Cut off PCT	Sensitivity	Specificity	PPV	NPV	PLR	NLR	Accuracy
>0,025	85%	33,3%	77,3%	45,5%	1,27	0,45	70,9%
>0,065	67,5%	80%	90%	48%	3,4	0,4	70,9%
>0,195	50%	93,3%	95,2%	41,2%	7,46	0,5	61,8%

There was a statistically significant correlation between PCT level cut off 0.065 ng / dL with relapse occurrence (P value = 0.002) using Chi-squared test. The prevalence ratio of 8.308 (95% CI = 1.993-34.636) indicates that children with SSNS who have PCT level greater than or equal to 0.065 ng / dL have a risk of relapse 8.308 times compared with children who have less PCT level from 0.065 ng / dL.

**TABLE III. RELATIONSHIP BETWEEN PCT LEVEL AND RELAPSE OCCURANCE**

Procalcitonin level (ng/dL)	SSNS		P*	PR	CI 95%
	Relapse (%)	Non Relapse (%)			
≥0.065	27 (67.5)	3 (20,0)	0.002	8.308	1.993-34.636
<0.065	13 (32.5)	12 (80.0)			

Risk factors of relapse occurrence in children with NS in this study were analyzed using logistic regression test. Based on these tests, the occurrence of relapse in NS is not influenced by demographic factors and is associated only with PCT levels.

**TABLE IV. RISK FACTORS OF RELAPSE OCCURENCE**

Risk Factors	Constant	Wald	P*
Age	0.909	1.016	0.615
Sex	0.676	0.253	0.615
N/L ratio	-	0.001	0.999
Leukocyte	3.846	2.481	0.115
Procalcitonin	8.737	7.892	0.005

\* Logistic regression test

The test showed that children with NS who had PCT levels greater than or equal to 0.065 had a risk of relapse 8.737 times compared with children with PCT less than 0.065 (P = 0.005).

Idiopathic NS in children is most often caused by minimal change nephrotic syndrome (MCNS) and has a high relapse rate with almost 50% of children being a steroid-dependent NS [13]. Function on T cells causes the release of certain

cytokines, which cause changes in glomerular permeability and led to relapse [12].

Most samples in this study were male (65.5%). The percentage of relapsing NS in this study is quite high (72.7%). Although there was no statistically significant relationship between sex and the occurrence of relapse in children with NS (P = 0.452). This study has the same results as the study conducted in united states [1].

The study found that relapses were mainly found in male sex, with a male to female ratio was 1.5:1. The total sample size was 80 people with relapse occurrence of 228 and the majority of patients with relapse frequency were 62 (77.5%). Mean age of study subjects was 1-16 years with an average age of 7.47 years [1]. Retrospective studies based on medical record found that most relapsed patients are often <5 years old [14]. While in this study had an average age of 9.8 years and incidence relapse more frequently at age above 9.8 years.

Infection is a major cause of morbidity and mortality in childhood NS and one of the risk factors for relapse [15, 16]. An estimated 52-70% of relapse in developing country children is mainly followed by upper respiratory tract infections, other common infections include skin infections such as impetigo and cellulitis, acute gastroenteritis or dysentery, urinary tract infections and primary peritonitis [9, 23]. Age, sex, history of atopy, race, history of hematuria, presence of respiratory infections as comorbidities and days required for remission is a significant risk factor for the occurrence of steroid-dependent nephrotic syndrome [15, 17]. However, in this study there is no specific discussion of the basic infection that triggers the occurrence of relapse, history of atopy, race, history of hematuria and there are no significant relationship was found between sex and age with relapse in this study.

Mean of leukocyte, neutrophil, and lymphocyte value in this study was 12.320,5/μL, 62.8% and 8.5%, respectively. There was no statistically significant association between neutrophil/lymphocyte ratio and the relapse occurrence of NS (P = 0.275). This is different in previous research results, leukocytes have a significant difference in frequent relapsing nephrotic syndrome compared with SSNS [18]. Neutrophil values were higher (p <0.05) while the lymphocyte values were lower (p <0.05) in patients with relapse nephrotic syndrome. However, no mention of the ratio between neutrophils / lymphocytes in the study [18].

Study related to PCT as an infection marker and risk factor of relapse in SSNS is still very limited. A pilot study found the role of PCT in differentiating relapse of minimal change nephrotic syndrome (MCNS) with proteinuria related infections in children, have noted sensitivity x specificity in relapse and infection-related status for PCT was 0.472 and 0.628, respectively and for CRP is 0.183 and 0.762, respectively [20]. The optimal cut-off value of PCT to predict relapse or proteinuria caused by infection by the ROC test in this study was 0.385 with a sensitivity of 96.2% specificity of 49.1% [11].

In this study found levels of cut off lower than previous studies. Procalcitonin levels used as cut off were PCT level with the highest sensitivity and specificity (cut off =0.065 ng/dL, sensitivity 67.5%, specificity 80%). Based on chi-squared test, there was a statistically significant correlation between PCT level cut off 0.065 ng/ dL with relapse occurrence (P value = 0.002). The prevalence ratio of 8.308 (95%CI = 1.993-34.636) indicates that children with SSNS who have PCT levels greater than or equal to 0.065 ng/dL have a relapse risk of 8,308 times compared with children who have less PCT level from 0.065 ng/dL.

Procalcitonin is a specific bacterial infection marker compared to C-Reactive Protein (CRP) and estimated sedimentation rate (ESR) [22]. The normal level of serum procalcitonin is <0.05 ng / mL. The value of  $\geq 0.5-2$  is noted to have a tendency for systemic bacterial infection (Chaudhury,2013). While as mentioned earlier infection is a risk factor for relapse [16]. Procalcitonin levels can be detected within 3-4 hours and within 6-24 hours reaching the highest levels means earlier than CRP and ESR [8, 22]. Cut off value in our study was lower than previous study with total AUC obtained 73.6% with P value = 0.007. This study is limited to discussing procalcitonin levels in children with relapsed nephrotic syndrome without comparing with other marker levels such as CRP and ESR.

This study has limitations where the study is a cross-sectional design and specifically does not address specific infections that trigger relapse. In addition, the study did not compare other infection markers such as CRP and ESR as did previous pilot studies. However, this study is the first study to examine the relationship between procalcitonin levels and relapses in pediatric patients with NS in Haji Adam Malik Hospital.

#### IV. CONCLUSION

The mean age of children who participated in the study was 9.8 years. The occurrence of relapse was higher in children over 9.8 years old. Most of the samples in this study were male. Relapse events in boys higher than girls, PCT level > 0.065 ng/dL could be used to predict relapse. There was no statistically significant correlation between age, sex, neutrophil/lymphocyte ratio, leukocytes with relapse SSNS incidence in this study.

Cohort study with a larger sample size is expected to provide more detailed and accurate results about the role of PCT in the occurrence of relapse/proteinuria in NS associated with the incidence of infection.

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