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Risk Factors for Progressive Chronic Kidney Disease in Children with Idiopathic Nephrotic Syndrome at Dr. Mohammad Hoesin General Hospital Palembang

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A B S T R A C T

Nephrotic syndrome (NS) is a kidney disease that is often found in children. NS can cause infectious and non-infectious complications, such as upper respiratory tract infections, urinary tract infections, edema, acute kidney injury (AKI), and hypertension. This study aimed to determine the risk factors of age, gender, nutritional status, hypertension, hematuria, AKI, hyperfiltration, and steroid sensitivity to the progression of chronic kidney disease (CKD) in children with the initial idiopathic NS in the pediatric ward of Dr. Mohammad Hoesin General Hospital Palembang. This study was an analytic observational study with a cross-sectional design. A total of 72 secondary data of research subjects were included in this study. Risk factor analysis was carried out with the help of SPSS version 24 software in univariate, bivariate, and multivariate ways. The most common risk factor for children with the initial idiopathic NS is age ≥10 years, males and females gender obtained the same number, and the nutritional status of obesity, hematuria, AKI, and hyperfiltration have quite low rates. However, hypertension and SRNS have high rates in children with initial idiopathic NS. In conclusion, hypertension and hyperfiltration are risk factors that play a role in initiating the progression of idiopathic NS to CKD in the pediatric ward of Dr. Mohammad Hoesin General Hospital, Palembang.

1. Introduction

Nephrotic syndrome (NS) is a kidney disease that is often found in children. The incidence of NS in the Western Hemisphere is reported to be 2-7/100,000 children. In South Asia, it is 12-16/100,000 children, and in Indonesia, it is 6/100,000 per year in children <14 years with a male and female gender ratio of 2: 1.[1,2,3] NS complications can be divided into two groups, namely acute complications in the form of infection and non-infection. Subandiyah (2000-2003) and Emilia (2004) reported that complications of infection in steroid-resistant nephrotic syndrome (SRNS) were more common than in steroid-sensitive nephrotic syndrome (SSNS). In Subandiyah's study, 16 (100%) SRNS children had upper respiratory tract infections, and 10 (62.5%) children had urinary tract infections. It was also found that more infectious complications occurred in boys, as many as 57 children (63%), and aged ≤6 years.[4,5]

In NS, non-infectious complications can occur in the form of edema caused by fluid leakage from the intravascular space to the interstitium.[4] In addition,

non-infectious complications can be in the form of acute kidney injury (AKI), which is a risk factor for CKD progression.[6] Non-infectious complications also have risk factors that can support the progression to CKD, such as hypertension, recurrent macroscopic hematuria, and nutritional status, such as obesity.[7,8,9] In addition, the progression of CKD in NS also occurs by reducing kidney mass, resulting in structural and functional hypertrophy of the remaining nephrons as compensation, which is mediated by vasoactive molecules such as cytokine growth factors that result in hyperfiltration.[10] However, information on hyperfiltration in NS is quite limited, so we use the example of hyperfiltration in sickle cell anemia (SCA) because we discuss albuminuria which also occurs in NS. In children with albuminuria, significantly increased GFR in childhood.[11] This study aimed to determine the risk factors that contribute to the progression of CKD in children with initial idiopathic NS at the pediatric ward of Dr. Mohammad Hoesin General Hospital Palembang.

2. Methods

This study was an analytic observational study with a cross-sectional approach and used secondary data in the form of medical record data. A total of 72 research subjects were included in this study. The inclusion criteria are in the form of all pediatric patients with the initial idiopathic NS who were hospitalized in the pediatric ward of Dr. Mohammad Hoesin General Hospital Palembang. in 2018-2021 and aged between 1-18 years. This study was approved by the medical and health research ethics committee of the Faculty of Medicine, Universitas Sriwijaya.

Data was collected and recorded according to the variables required for the study, namely age, gender, nutritional status, hypertension, hematuria, AKI, hyperfiltration, and steroid sensitivity. Then, the data is processed using SPSS statistics 24 software. Then, the data is presented in the form of tables and diagrams and explained in narrative form. Data analysis was performed bivariate and multivariate with $p<0.05$.

3. Results and Discussion

Table 1 shows the age distribution data for children with the initial idiopathic NS in the 2018-2021 period. From these data, it was found that of the 72 children with initial idiopathic NS, based on age, 34 (47.2%) of them were <10 years old, and 38 (52.8%) of them were aged $\geq$ 10 years. By gender, 36 (50%) of the children were males, and 36 (50%) were females. Nutritional status showed that 12 (16.7%) children were obese, and 60 (83.3%) children were non-obese. Of the 60 non-obese idiopathic NS children, there were 11 overweight children, 43 well-nourished children, 3 malnourished children, and 3 malnourished children. Based on the blood pressure of the initial idiopathic NS children, 42 (58.3%) of the children had hypertension, and 30 (41.7%) of the children did not have hypertension. Hematuria was found in 24 (33.3%) children and 48 (66.7%) children had no hematuria. Based on AKI, 8 (11.1%) children had AKI, and 64 (88.9%) children did not AKI. Based on the glomerular filtration rate, 31 (43.1%) children had hyperfiltration, and 41 (56.9%) children did not have hyperfiltration. Steroid sensitivity in children with initial idiopathic NS found that 47 (65.3%) children had steroid-resistant nephrotic syndrome (SRNS), and 25 (34.7%) children had steroid-sensitive nephrotic syndrome (SSNS). Of the 25 children who had SSNS, they were divided into 10 children with rare relapses, 11 children with frequent relapses, and 4 children with steroid-dependent NS. This shows that initial idiopathic NS children are more in ages $\geq$10 years, males and females gender have the same number, hypertension has a high number of patients, obesity nutritional status, hematuria, AKI, and hyperfiltration have a low number in children with initial idiopathic NS, and steroid sensitivity is the most in children SRNS.

Table 1. Baseline characteristics of children with initial idiopathic NS (n=72).

Risk factors	Total	
	N	Percentage %
Age		
≥10 years	38	52.8
<10 years	34	47.2
Gender		
Male	36	50
Female	36	50
Nutritional status		
Obesity	12	16.7
Non-obesity	60	83.3
More Nutrition	11	18.3
Good Nutrition	43	71.7
Malnutrition	3	5
Malnutrition	3	5
Hypertension		
Yes	42	58.3
No	30	41.7
Hematuria		
Yes	24	33.3
No	48	66.7
Acute kidney injury		
Yes	8	11.1
No	64	88.9
Hyperfiltration		
Yes	31	43.1
No	41	56.9
Steroid sensitivity		
SRNS	47	65.3
SSNS	25	34.7
NS relapse infrequently	10	40
NS relapse frequently	11	44
NS dependent steroid	4	16
Chronic kidney disease		
Stadium 1	39	54.2
Stadium 2	8	11.1
Stadium 3	5	6.9
Stadium 4	4	5.6
Stadium 5	16	22.2
Total	72	100

Table 2 shows the relationship between anal risk factors and idiopathic NS and the progression of CKD. Hypertension and hyperfiltration factors are two risk factors that play a role in the initiation of idiopathic NS to CKD. The results of the study of 72 children with initial idiopathic NS, it was found that the number of children who had hypertension was 42 (58.3%) children and 30 (41.7%) children did not have hypertension. From the results of bivariate statistical analysis of hypertension in initial idiopathic NS patients with CKD progression, the score p-value is 0.001, which means that there is a significant relationship between hypertension in initial idiopathic NS patients and CKD progression. However, other studies have shown lower results. Siti Salamah et al. (2001-2016) stated that 15 (13.4%) of 112 children with NS had hypertension.[16] Another research conducted by Marvin at Prof. Dr. R. D. Kandou General Hospital. Manado (2016-2019) stated that 13 (37.1%) of 35 patients with NS had hypertension (p = 0.392).[12] Manjuri Sharma et al. (2012-2015) stated that 147 (41.4%) of 355 children with NS had hypertension (p = <0.0001).[13-15] Patients with initial idiopathic NS have the inability to excrete sodium in the distal nephron, which causes volume retention and hypertension. Salt and water retention, activation of the renin-angiotensin-aldosterone system, and progression of kidney damage can increase BP.[17-21]

Several other factors associated with hypertension, including renal fibrosis, decrease GFR and lead to the development of CKD.[22]

Table 2 shows that of the 72 children with initial idiopathic NS, the number of children who had hyperfiltration was obtained as many as 31 (43.1%) children, and 41 (56.9%) children did not experience hyperfiltration. From the results of a bivariate statistical analysis of hyperfiltration in patients with initial idiopathic NS with CKD progression, a p-value of 0.000 was found, which means that there was a significant relationship between hyperfiltration in initial idiopathic NS patients and CKD progression. However, information and research on hyperfiltration in NS are quite limited, so researchers use the example of hyperfiltration in sickle cell anemia (SCA) because they discuss albuminuria as it occurs in NS. Children with albuminuria significantly increased GFR. Jeffrey (2018) reported that 12 out of 91 children with persistent albuminuria had an increase in GFR with an average GFR of 171 mL/min/1.73 m^2. Hyperfiltration occurs as a result of compensation for the high protein load. An increase in glomerular volume involves an expansion of the matrix component and an increase in the number of endothelial and mesangial cells so that mature podocyte cannot proliferate. This non-immunologic process causes injury to the podocytes and glomerular microvasculature, which contributes to proteinuria, fibrosis, and progressive decline in renal function.[23-25] Another opinion explains that monocytes are useful for predicting whether hyperfiltration develops into CKD or not. A higher monocyte count can be used as a predictor of CKD in subjects with hyperfiltration.[25]

Table 2. Relationship between children risks factors and initial idiopathic NS and CKD progressiveness.

Risk factors	**Progressivity of chronic kidney disease**				**p***	**PR***	**CI 95%**	
	Stadium 3-5		**Stadium 1-2**				**Min**	**Max**
	n	%	n	%				
Age								
≥10 years	17	23.6	21	29.2	0.737	1.251	0.339	3.834
<10 Years	8	11.1	26	36.1				
Gender								
Male	12	16.7	24	33.3	0.804	0.923	0.490	1.740
Female	13	18.1	23	31.9				
Nutritional status								
Obesity	3	4.2	9	12.5	0.524	0.682	0.242	1.919
Non-obesity	22	30.6	38	52.8				
Hypertension								
Yes	21	29.2	21	29.2	0.001	3.750	1.434	9.805
No	4	5.6	26	36.1				
Hematuria								
Yes	9	12.5	15	20.8	0.726	1.125	0.585	2.162
No	16	22.2	32	44.4				
Acute kidney injury								
Yes	5	6.9	3	4.2	0.116	2.000	1.046	3.824
No	20	27.8	44	61.1				
Hyperfiltration								
Yes	3	4.2	28	38.9	0.001	14.67	3.059	66.549
No	22	30.6	19	26.4				
Steroid sensitivity								
SRNS	19	26.4	28	38.9	0.163	1.684	0.773	3.671
SSNS	6	8.3	19	26.4				

*Adjusted value, logistic regression test, p<0,05.

4. Conclusion

Hypertension and hyperfiltration are risk factors that play a role in initiating the progression of idiopathic NS to CKD in the pediatric ward of Dr. Mohammad Hoesin General Hospital Palembang.

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