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Original Article

Risk factors for progression of chronic kidney disease in children with nephrotic syndrome

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Abstract

Background Nephrotic Syndrome (NS) is a progressive kidney disease in children that can lead to chronic kidney disease (CKD). Understanding the interactions between various risk factors is critical in developing new strategies to prevent the progression of CKD in pediatric patients with NS.

Objective To determine the risk factors for the progression of CKD in children with nephrotic syndrome at Dr. Zainoel Abidin Public Hospital, Banda Aceh, Aceh.

Methods This analytical observational study with a cross-sectional approach was conducted from September 2021 to September 2023. Data were obtained from medical records of 52 children aged 2 to 18 years in the inpatient and outpatient wards of Dr. Zainoel Abidin Public Hospital, Banda Aceh, Aceh, who met the inclusion criteria. Bivariate analysis using the Chi-square and Fisher's tests and multivariate analysis using logistic regression test were performed.

Results Of 52 subjects, most were male and over ten years of age; 53.8% of subjects had stage 1 CKD. The majority of stage 3-5 of CKD cases had immunosuppressive toxicity and anemia, while the majority of all subjects had hyperfiltration and proteinuria. Risk factors for CKD progression in children with NS are Hypertension (OR 2.54; 95%CI 0.32 to 20.1; P=0.003), immunosuppressant toxicity with (OR 33.67; 95%CI 2.59 to 437.5; P=0.007) and anemia (OR 33.92; 95%CI 2.77 to 414.5; P=0.006).

Conclusion Hypertension, immunosuppressant toxicity and anemia for CKD progression in children with NS. **[Paediatr Indones. 2025;65:291-6; DOI: https://doi.org/10.14238/pi65.4.2025.291-6]**.

Keywords: *nephrotic syndrome; chronic kidney disease; risk factors for progression; children*

Chronic kidney disease (CKD) is a worldwide health problem with increasing incidence and prevalence. A large proportion of patients receive delayed treatment due to low knowledge and awareness among patients, families, and healthcare professionals, in addition to financial constraints, all of which contribute to increased mortality. A survey by the *Persatuan Nefrologi Indonesia/PERNEFRI* (*Indonesian Nephrology Association*) in 2012 showed that more than 25 million Indonesians experienced decreased kidney function. [1,2]

Nephrotic syndrome is a clinical condition characterized by proteinuria, hypoalbuminemia, edema, and hyperlipidemia. At the time of initial symptoms, 80% of children achieve complete remission within 4 weeks of corticosteroid therapy, which is called steroid sensitive nephrotic syndrome (SSNS). However, 60-70% of children have more than one recurrence, of whom 30% will develop frequent

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recurrences of NS or steroid-dependent NS. Steroid resistance was defined as the absence of remission after therapy with prednisone at a dose of 2 mg/kg/day for 4 weeks. Patients with steroid-resistant nephrotic syndrome (SRNS) are more challenging to treat, with 36-50% progressing to end stage renal disease (ESRD).[3,4]

As one of the most common risk factors for CKD, NS is associated with increased morbidity, high recurrence rates, drugs with serious side effects, extended hospital stays, and the potential for ESRD. [5] It has an incidence rate of 16 in 100,000 in the pediatric population. Children with SRNS and Focal Segmental Glomerulosclerosis (FSGS) have a poor prognosis. The rate of occurrence of ESRD in children with SRNS for 10 years varies from 34% to 64%, and in cases of FSGS for 5 years, ESRD can develop in around 64%.[6]

A study found that NS was the cause of 36% of stage 3 and 4 CKD cases at the Nephrology Polyclinic, Department of Child Health, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital.[7] Likewise, other studies showed that the majority of causes of CKD were NS (55.5%), followed by urinary tract infections (28.3%), chronic kidney failure (7%), neurogenic bladder (2.6%), and lupus nephritis (2.3%).[8] Among 268 pediatric patients aged less than 19 years for 10 years, retrospective study found that the most common etiology of CKD was glomerular disease (35.2%), predominantly nephrotic syndrome (FSGS) (19.4%).[9]

Methods

This analytical observational study included subjects selected by a total sampling method based on secondary data from medical records from September 2021 to September 2023. The inclusion criteria were children aged 2 years to 18 years with a history of NS and were diagnosed with stages 1-5 CKD. In particular, the *Kidney Disease Improving Global Outcomes* (KDIGO) guidelines have defined CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications to health.[1] The exclusion criteria were incomplete laboratory data from medical records. The Ethics Committee of Dr. Zainoel Abidin Public Hospital, Banda Aceh approved the research. Data were analyzed using both bivariate analysis (Chi-square and Fisher's tests) and multivariate analysis (logistic regression test). The significance level used in this study was $P < 0.05$.

Results

Subjects were 52 children with NS and diagnosed with CKD stages 1-5. The majority of children who developed CKD alongside NS were aged 10-18 years. (61.5%). Nearly 70% mostly of the subjects were male. (69.2%). Generally, the onset age of NS was over 10 years (53.8%). Additionally, around half of the subjects (53.8%) were diagnosed with Stage 1 CKD, as detailed in **Table 1**.

The predominant type of NS was SRNS, found in nearly 80% of subjects. Immunosuppressant toxicity was absent in 71.2% subjects, while hypertension was absent in half of the subjects. Additionally, more than 80% of subjects were not classified as obese, as indicated in **Table 2**. Laboratory tests revealed that the majority of subjects did not exhibit anemia (67.3%), dyslipidemia (55.8%), or hyperuricemia (76.9%). Glomerular filtration rate results indicated hyperfiltration conditions in 61.5% of cases. Most urinalysis tests showed proteinuria (92.3%), as detailed in **Table 3**.

Bivariate analysis indicated that risk factors associated with progression of stages 3-5 CKD were hypertension, immunosuppressant toxicity, anemia, and no hyperfiltration, as shown in **Table 4**.

In addition, multivariate analysis using logistic regression test was conducted to identify risk factors for CKD progression in children with NS. The five variables in the multivariate logistic regression analysis were hypertension, immunosuppressant toxicity, anemia, dyslipidemia, and hyperfiltration. Multivariate analysis revealed that Hypertension, immunosuppressant toxicity and anemia were risk factors for CKD progression in children with NS (**Table 5**).

Discussion

We collected 52 medical records of children with NS diagnosed with stages 1-5 CKD at Dr. Zainoel Abidin

Table 1. Basic characteristics of study subjects

Characteristics	(N=52)
Age, n (%)	
2-5 years	5 (9.6)
5-10 years	15 (28.9)
10-18 years	32 (61.5)
Gender, n (%)	
Male	36 (69.2)
Female	16 (30.8)
Age of NS onset, n (%)	
<10 years	24 (46.2)
>10 years	28 (53.8)
CKD stage, n (%)	
1	28 (53.8)
2	5 (9.6)
3	7 (13.5)
4	4 (7.7)
5	8 (15.4)

Public Hospital, Banda Aceh, from September 2021 to September 2023. Subjects were divided into two groups by CKD stage: 33 children with stages 1-2 CKD and 19 children with stages 3-5 CKD. Most subjects were male (69.2%). A previous study in Malaysia reported that of 112 pediatric patients with NS, 63.4% were male and had CKD in 2001-2016. Their study was from the Universiti Sains Malaysia Hospital.10 Many cases of CKD in males are caused by testosterone triggering podocyte apoptosis, while estrogen receptors in female podocytes can prevent apoptosis. Estrogen is a protective agent against CKD.[11]

The CKD stage was based on GFR classification, which was predominantly stage 1 CKD (53.8%),

Table 2. Clinical characteristics of study subjects

Clinical characteristics	Total subjects (N=52)	CKD stages	
		1-2 (n=33)	3-5 (n=19)
NS type, n (%)			
SSNS	11 (21.2)	9	2
SRNS	41 (78.8)	24	17
Immunosuppressant toxicity, n (%)			
Yes	15 (28.8)	4	11
No	37 (71.2)	29	8
Hypertension, n (%)			
Yes	23 (44.2)	9	14
No	29 (55.8)	24	5
Obesity, n (%)			
Yes	9 (17.3)	6	3
No	43 (82.7)	27	16

Table 3. Laboratory characteristics of study subjects

Laboratory characteristics	Total subjects (N=52)	CKD stages	
		1-2 (n=33)	3-5 (n=19)
Anemia, n (%)			
Yes	17 (32.7)	3	14
No	35 (67.3)	30	5
Dyslipidemia, n (%)			
Yes	23 (44.2)	12	11
No	29 (55.8)	21	8
Hyperuricemia, n (%)			
Yes	9 (17.3)	4	5
No	43 (82.7)	29	14
Hyperfiltration, n (%)			
Yes	32 (61.5)	28	4
No	20 (38.5)	5	15
Proteinuria, n (%)			
Yes	48 (92.3)	31	17
No	4 (7.7)	2	2

Table 4. Bivariate analysis of risk factors for progression of CKD stage

Risk factors	CKD stages		P value	OR	95%CI
	Stage 1-2 (n=33)	Stage 3-5 (n=19)			
Age, n			0.63	1.59	0.48 to 5.23
2-10 years	14	6			
>10-18 years	19	13			
Gender, n			0.40	0.46	0.12 to 1.73
Male	21	15			
Female	12	4			
Age of NS onset, n			0.87	1.24	0.41 to 4.03
<10 years	16	8			
>10 years	17	11			
Hypertension, n			0.003	0.13	0.03 to 0.48
Yes	9	14			
No	24	5			
Obesity, n			1.00	1.18	0.26 to 5.40
Yes	6	3			
No	27	16			
NS type, n			0.29	3.18	0.61 to 16.6*
SSNS	9	2			
SRNS	24	17			
Immunosuppressant toxicity, n			0.001	0.10	0.02 to 0.40
Yes	4	11			
No	29	8			
Anemia, n			0.0001	0.03	0.00 to 0.17
Yes	3	14			
No	30	5			
Proteinuria, n			0.61	1.82	0.23 to 14.1*
Yes	31	17			
No	2	2			
Dyslipidemia, n			0.22	0.41	0.13 to 1.31
Yes	12	11			
No	21	8			
Hyperuricemia, n			0.26	0.38	0.90 to 1.66*
Yes	4	5			
No	29	14			
Hyperfiltration, n			0.0001	21.0	4.89 to 90.1
Yes	28	4			
No	5	15			

Table 5. Bivariate analysis of risk factors for CKD progression in NS

Variables	P value	OR	95%CI
Hypertension	0.003	2.54	0.32 to 20.1
Immunosuppressant toxicity	0.001	33.6	2.59 to 437.5
Anemia	0.0001	33.9	2.77 to 414.5
Dyslipidemia	0.22	2.47	0.31 to 19.6
Hyperfiltration	0.05	0.12	0.01 to 1.03

followed by stage 5 (15.4%), stage 3 (13.5%), stage 2 (9.6%) and stage 4 (7.7%). A study in the pediatric ward at Dr. Mohammad Hoesin Public Hospital, Palembang, in 2018-2021found that predominantly stage 1 CKD (54.2%) in 72 children undergoing treatment.[12] The occurrence of CKD stage 1 is due to kidney damage accompanied by GFR within normal/high limits (eGFR > 90 mL/minute/1.73 m^2).[13]

Bivariate analyses revealed a relationship between children with NS and the progression CKD. A retrospective study in the Bonsucesso Federal Hospital, Rio de Janeiro, Brazil towards 136 patients with SRNS discovered that 7% of subjects without ESRD and 26.5% with ESRD had hypertension (P=0.007).[6] Both extra-renal and renal variables might contribute to hypertension associated with NS. Renal factors include albuminuria, sodium retention, renin angiotensin aldosterone system (RAAS) activation, and fibrosis/decreased GFR. Extra-renal factors include drug side effects, genetics, diet, lifestyle, and cardiovascular risk factors.[14]

The CKD occurrence in children with NS and toxicity of immunosuppressants like cyclosporine were significantly and positively associated. Our results were consistent with a previous study which confirmed the involvement of cyclosporine in drug-induced kidney damage. Drug induction mechanisms include tubular atrophy, interstitial fibrosis, and arteriolar hyalinosis.[15] A high rate of ESRD development and cyclosporine resistance in SRNS therapy was also observed, specifically, ESRD developed in 17.3% of cyclosporine-sensitive patients, 60.7% of cyclosporine-resistant patients, and 55.4% of patients who were not given cyclosporine treatment (P <0.0001).[6]

Various immunosuppressants, such as high dosages of corticosteroids, cyclophosphamide, chlorambucil, levamisole, tacrolimus, vincristine, and cyclosporine, have been employed in the treatment of NS. However, treatment responses vary, with frequent unsatisfactory outcomes. Many patients exhibit resistance to one or more immunosuppressant drugs, which can result in side effects, including severe infections, thrombosis, and kidney failure.[16]

The most frequently reported immunosuppressant toxicity is associated with cyclosporine, leading to renal tubular atrophy, interstitial fibrosis, and arteriolar hyalinosis. This results in decrease glomerular filtration rate (GFR) and renal plasma flow, as well as the development of tubulointerstitial lesions, as observed in histological examinations. Some nephrons undergo atrophy, prompting the kidneys to adapt to the damage by increasing GFR through the remaining normal nephrons. This leads to hyperfiltration, subsequently causing progressive glomerular damage. This cycle perpetuates, resulting in further nephron damage until it culminates in terminal kidney failure.[8,17,18]

Anemia also had a significant, positive relationship with progression of CKD. Paik et al. found that in children with NS, a quarter of the subjects had mild anemia (25.8%), followed by 64.5% with moderate anemia, and 9.6% with severe anemia.[19] Anemia is usually microcytic hypochromic, caused by iron deficiency, and erythropoietin deficiency resulting from reduced serum transferrin or reduced erythropoietin in the urine.[20] Moreover, anemia is a common problem in patients with CKD (36.6%). Anemia rises as CKD stages advance, from 31% in stage 1 to 93.3% in stages 4 and 5.8 In patients with CKD, anemia is associated with high rates of morbidity and mortality. Anemia-related complications include cardiovascular disease, CKD progression, prolonged hospital stays, and decreased quality of life. Anemia and tissue hypoxia contribute to the progression of CKD to the terminal stage. Interstitial fibrosis, tubular damage, an increase in the extracellular matrix, and the production of cytokines are all driven by tubular cell hypoxia, leading to renal fibrosis.[20]

Our study had a few limitations. Due to its retrospective design and participation by only one health center, our results may not represent all children with CKD and NS. The lack of renal biopsy and genetic testing made it challenging to establish a conclusive diagnosis of glomerular abnormalities and the prognosis of NS. In conclusion, anemia, hypertension and immunosuppressant toxicity are risk factors that play a role in initiating the progression of NS to CKD in the Zainoel Abidin Public Hospital, Banda Aceh.

Conflict of interest

None declared.

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