



# Serum Podocalyxin Level as a Potential Biomarker for Diagnosis of Nephrotic Syndrome and Prediction of Steroid Response

## Nefrotik Sendromun Tanısı ve Steroid Yanıtının Tahmininde Potansiyel Biyobelirteç Olarak Serum Podokaliksin Düzeyi

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### ABSTRACT

**Objective:** Idiopathic nephrotic syndrome (NS) is a common pediatric glomerular disorder. Podocyte damage constitutes a central mechanism in its pathophysiology. Podocalyxin, a major sialoglycoprotein expressed on podocytes, has been found to be elevated in urine samples from patients with glomerular diseases. However, its potential role in serum and its association with steroid responsiveness in NS remain unexplored.

**Methods:** This observational study included 17 children diagnosed with NS and age-matched controls without kidney pathology. Serum podocalyxin levels were measured at diagnosis using enzyme-linked immunosorbent assay. Patients received standard corticosteroid therapy at a dose of 2 mg/kg/day for four weeks, followed by a gradual taper. Based on clinical response, patients were classified as steroid-sensitive or steroid-dependent NS (SDNS). Serum podocalyxin levels were compared between patients and controls, and among subgroups based on treatment response.

**Results:** Serum podocalyxin levels were significantly higher in NS than in the control group [1.87 ng/dL [interquartile range (IQR: 0.87)] vs. 1.54 ng/dL (IQR: 0.29),  $p=0.031$ ]. All patients initially achieved remission with corticosteroids; however, six patients subsequently developed SDNS. Among these, 4 responded to calcineurin inhibitors, while 2 required rituximab to achieve remission. Current results indicate that serum podocalyxin levels do not provide sufficient predictive value for estimating steroid response or disease course. No significant correlations were found between podocalyxin levels and other laboratory parameters.

**Conclusions:** Serum podocalyxin levels are elevated in pediatric NS and may reflect the degree of podocyte injury. However, current findings indicate that serum podocalyxin levels are insufficient for predicting disease severity or steroid response. Additional studies involving larger patient cohorts are needed to further substantiate findings.

**Keywords:** Children, nephrotic syndrome, podocalyxin, steroid response

### ÖZ

**Amaç:** İdiyopatik nefrotik sendrom (NS), yaygın bir pediyatrik glomerüler bozukluktur. Podosit hasarı, patofizyolojisinde önemli bir rol oynar. Podositlerde eksprese edilen başlıca sialoglikoprotein olan podokalsin, glomerüler hastalıkları olan hastaların idrar örneklerinde yüksek seviyelerde bulunmuştur. Ancak, serumdaki potansiyel rolü ve NS'de steroid yanıtıyla ilişkisi henüz araştırılmamıştır.

**Yöntemler:** Bu gözlemlsel çalışmaya, NS tanısı konmuş 17 çocuk ve böbrek patolojisi olmayan yaşıtları kontrol grubu olarak dahil edilmiştir. Serum podokalsin düzeyleri, tanı sırasında enzim bağlantılı immünosorbant analiz kullanılarak ölçülmüştür. Hastalar standart kortikosteroid tedavisi (4 hafta boyunca 2 mg/kg/gün) almış, ardından doz kademe olarak azaltılmıştır. Klinik yanıtlarına göre, hastalar steroid duyarlı veya steroid bağımlı NS (SDNS) olarak sınıflandırılmıştır. Serum podokalsin düzeyleri, hastalar ve kontrol grubu arasında ve tedavi yanıtına göre alt gruplar arasında karşılaştırıldı.

**Bulgular:** Sonuçlar, NS'de kontrol grubuna kıyasla serum podokalsin düzeylerinin anlamlı olarak daha yüksek olduğunu ortaya koydu [1,87 ng/dL çeyrekler arası aralık (IQR: 0,87) vs. 1,54 ng/dL (IQR: 0,29),  $p=0,031$ ]. Tüm hastalar başlangıçta kortikosteroidlerle remisyon elde etmişlerdir; ancak 6'sı (%35,2) SDNS gelişmiştir. Bunların 4'ü kalsinörin inhibitörlerine yanıt verirken, 2'si remisyon elde etmek için rituksimaba ihtiyaç duymuştur. Mevcut sonuçlar serum podokaliksin seviyesinin steroid yanıtını veya hastalık seyrini tahmin etmek için yeterli öngörüye sahip olmadığını göstermiştir. Ayrıca, podokalsin düzeyleri ile diğer laboratuvar parametreleri arasında anlamlı bir korelasyon bulunmamaktadır.

**Sonuçlar:** Serum podokalsin düzeyleri pediyatrik NS'de yüksektir ve podosit hasarının derecesini yansıtabilir. Ancak, mevcut bulgular serum podokaliksin düzeylerinin hastalığın ciddiyetini veya steroid yanıtını tahmin etmek için yetersiz olduğunu göstermektedir. Daha büyük kohortlarla daha fazla çalışma yapılması gerekmektedir.

**Anahtar kelimeler:** Çocuklar, nefrotik sendrom, podokalsin, steroid yanıtı

A preliminary version of this study was previously presented as a poster at the 57th Annual Meeting of the European Society for Paediatric Nephrology (ESPN) in Athens, Greece. The abstract of this presentation was published in the congress abstract book.\*

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**Cite as:** Leventoglu E, Soran M, Can U. Serum podocalyxin level as a potential biomarker for diagnosis of nephrotic syndrome and prediction of steroid response. Medeni Med J. 2025;40:262-268

**Received:** 07.08.2025

**Accepted:** 26.11.2025

**Published:** 31.12.2025



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## INTRODUCTION

Idiopathic nephrotic syndrome (NS) is a clinical entity characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Light microscopy typically demonstrates minimal structural alterations; however, electron microscopy reveals substantial glomerular podocyte injury characterized by diffuse foot-process effacement and disruption of the slit diaphragm<sup>1</sup>. The integrity of foot processes and the slit diaphragm is crucially maintained by the specialized protein complexes. Any abnormalities of these molecules result in severe proteinuria<sup>2</sup>.

Podocalyxin is a sialoglycoprotein that constitutes a major structural component of the podocyte glycocalyx<sup>3</sup>. It interacts with the actin cytoskeleton of the podocytes, facilitating the normal formation of the negatively charged surface of the foot processes<sup>4</sup>. Its expression was universally reduced in patients with podocytopathies such as minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and lupus nephritis<sup>5,6</sup>. Although podocalyxin expression is reduced, urinary podocalyxin levels are markedly elevated in patients with NS<sup>7</sup>. Elevated urinary podocalyxin levels have also been observed in patients with immunoglobulin A (IgA) nephropathy, IgA vasculitis-associated nephritis, and diabetic nephropathy<sup>8,9</sup>. In addition to podocytes, podocalyxin is expressed on the surface of vascular endothelial cells in several organs, such as the heart, lungs, and kidneys. It contributes to the maintenance of vascular integrity by modulating interactions with the extracellular matrix and basement membranes<sup>10</sup>. In preeclamptic women with endothelial damage, serum and urinary podocalyxin levels increase<sup>11</sup>.

Serum podocalyxin levels have not previously been assessed in NS. The objectives of this study were to investigate the diagnostic utility of serum podocalyxin levels in pediatric NS and to assess their ability to predict response to steroid therapy.

## MATERIALS and METHODS

### Selection of Study Subjects and Definitions

This observational study was conducted in children with NS who had regular-follow-up at the tertiary pediatric nephrology clinic of a single hospital. Fifty-one age- and sex-matched children without tubular and/or glomerular pathology were used as the control group. Patients with known cardiovascular disease were excluded. All participants enrolled in the study were between 2 and 18 years of age. Written informed consent

was obtained from all participants and their parents before enrollment.

The NS was identified by massive proteinuria (spot urine protein:creatinine ratio (UPCR)  $>2.0$  mg/mg or proteinuria  $>40$  mg/m<sup>2</sup>/hour), hypoalbuminemia ( $<2.5$  g/dL), and edema<sup>1</sup>. The standard treatment for idiopathic NS is prednisolone administered orally at 2 mg/kg per day (maximum 60 mg per day) for 4 weeks. Patients in complete remission who had trace or negative protein on urinalysis for three consecutive days were considered to have steroid-sensitive NS. In these patients, steroid therapy was continued on alternate days for another 4 weeks. Afterwards, the daily dose is usually tapered over 2-4 months and then discontinued. Relapse was defined by the presence of 2+ protein on the urinary albumin dipstick on three consecutive days after complete remission. In the event of a relapse, steroid treatment is resumed. Steroid-dependent NS (SDNS) was diagnosed when two consecutive relapses occurred during tapering of prednisone or prednisolone, or within 15 days of steroid withdrawal<sup>12,13</sup>.

### Data Collection and Assessment of Laboratory Parameters

Participants' actual age, sex, weight, height, and blood pressure were recorded. Weight gain was calculated for patients whose weight had been recorded before the onset of NS. Patients with a history of upper respiratory tract infection (URTI) were identified. Z-scores for height and weight were derived from the reference standards reported by Neyzi et al.<sup>14</sup> Blood pressure was assessed using a manual auscultatory method. Hypertension was identified in accordance with the 2017 "Clinical Practice Guideline for Screening and Management of High BP in Children and Adolescents"<sup>15</sup>.

Laboratory results for participants at their initial presentation were recorded. Biochemical tests, including serum creatinine, albumin, electrolytes, urinalysis, and UPCR, were recorded. In addition to routine tests, serum podocalyxin levels were measured using a competitive enzyme-linked immunosorbent assay. The assay plate supplied with the kit was pre-coated with an antibody directed against human podocalyxin. Samples or standards were added to the wells, where they bound to the specific antibody. Next, a biotinylated detection antibody specific for human podocalyxin and an avidin-horseradish peroxidase (HRP) conjugate were added sequentially to each well and then incubated. Unbound components were removed by washing. A substrate solution was then added to each well. Only wells containing human podocalyxin, the biotinylated

detection antibody, and the avidin-HRP conjugate would develop a blue color. The enzymatic reaction was terminated by the addition of a stop solution, resulting in a color change to yellow. Absorbance was subsequently measured at 450 nm using a spectrophotometer and found to be proportional to the human podocalyxin concentration. Sample concentrations were calculated by comparison with a standard calibration curve.

Patients were started on treatment according to the Kidney Disease: Improving Global Outcomes 2021 Glomerular Disease Management Guidelines<sup>12</sup>. At week 4 of treatment, patients were divided into subgroups based on steroid response. Whether serum podocalyxin levels at diagnosis differed between patient and control groups and by steroid response was evaluated.

The authors confirm that all procedures performed in this study were conducted in accordance with national ethical guidelines for human research and the Declaration of Helsinki. The study was approved by the KTO Karatay University Medical Ethics Committee with decision no.:2024/257, date:18.12.2024.

### Statistical Analysis

Data normality was evaluated using the Shapiro-Wilk test. Non-normally distributed continuous variables were summarized using the median and interquartile range (IQR), while categorical data were reported as numbers and percentages. Comparisons between two independent groups were performed using the Mann-Whitney U test for non-normally distributed data. The relationships between serum podocalyxin levels and other clinical or laboratory parameters were assessed using simple linear regression. Regression equations, adjusted R<sup>2</sup> values, and p-values were presented. Categorical variables were compared using Fisher's exact test and the chi-square test. A p-value <0.05> was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics, version 22.

## RESULTS

### General Study Population

A total of 17 patients diagnosed with idiopathic NS were included in the study. The median age was 5.9 years (IQR: 5.6), with a male-to-female ratio of 2.4. All patients were diagnosed on presentation with edema; 7 patients (41.1%) developed edema following a non-specific URTI. None of the patients had symptoms or findings such as fever, rash, arthralgia, or myalgia.

At admission, the median height standard deviation score (SDS) and weight SDS were -0.23 (IQR: 1.49) and 0.01 (IQR: 1.31), respectively. In patients with a known previous weight (n=13), the median weight gain at the time of admission was 2.20 kg (IQR: 2.85 kg). All patients were normotensive. Laboratory examination showed a median serum creatinine level of 0.21 mg/dL (IQR: 0.14) and a median serum albumin level of 1.95 g/dL (IQR: 0.50). The UPCR was 6.21 mg/mg (IQR: 2.78). Median erythrocyte count in urine was 4/high-power field (IQR: 17); 3 (17.6%) patients had microscopic hematuria. No bacterial growth was detected in urine cultures. Viral markers were negative. Immunologic assessment revealed negative results for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-double-stranded DNA antibodies. The median complement C3 level was 86.5 mg/dL (IQR, 19.6 mg/dL; normal range, 80-178 mg/dL).

All patients received oral prednisolone at a dose of 2 mg/kg per day (maximum 60 mg/day). After four weeks of treatment, remission was achieved in all of them. However, SDNS was observed in six (35.2%) patients during prednisone tapering. Complete remission was achieved in 4 (66.6%) of these patients after a calcineurin inhibitor (CNI) was added to the treatment. In the remaining two (33.3%) patients, relapses continued despite CNI during steroid tapering. In these patients, remission was achieved with rituximab.

The clinical and laboratory features of the participants are summarized in Table 1.

### Assessments of Podocalyxin Levels in Predicting Steroid Response

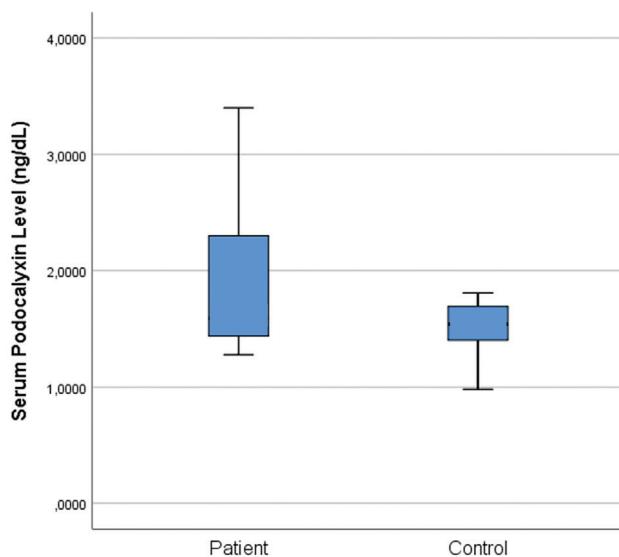
At initial presentation, the median serum podocalyxin level in patients was higher than that in the control group [1.87 ng/dL (IQR: 0.87) vs. 1.54 ng/dL (IQR: 0.29); p=0.031] (Figure 1). Also, its median level at diagnosis was numerically higher in patients who developed SDNS than in patients who never relapsed; however, this difference did not reach statistical significance [1.95 ng/dL (IQR: 1.17) vs. 1.65 ng/dL (IQR: 0.92), p=0.148]. Evaluations of podocalyxin levels in relation to clinical characteristics and steroid response are shown in Table 2.

In the linear regression analysis, no significant relationship was found between serum podocalyxin levels and other laboratory data (Table 3).

**Table 1. Clinical and laboratory characteristics of the patients.**

	General study group		
	n (%)	Median (IQR)	Min-max
<b>Initial Features</b>			
Age (years)		5.9 (5.6)	1.9-15.6
Sex			
Male	12 (70.5)		
Female	5 (29.5)		
<b>History of URTI</b>	7 (41.1)		
<b>Anthropometric measures</b>			
Height (SDS)		-0.23 (1.49)	-2.11-1.09
Weight (SDS)		0.01 (1.31)	-1.55-0.97
Weight gain (kg) (n=13)		2.20 (2.85)	1.5-5.4
<b>Blood pressure measurements</b>			
SBP (SDS)		-0.22 (1.12)	-0.66-0.99
DBP (SDS)		0.44 (0.85)	-0.08-1.48
Hypertension	0 (0)		
<b>Blood</b>			
Hemoglobin (g/dL)		13.1 (1.6)	11.5-16.3
Hematocrit (%)		41.7 (5.4)	34.7-51.5
Platelets (/µL)		379000 (164500)	199000-562000
White blood cell (/µL)		10035 (6415)	6150-18150
Creatinine (mg/dL)		0.21 (0.14)	0.17-0.75
BUN (mg/dL)		11 (10)	5-43
Uric acid (mg/dL)		4.1 (1.9)	2.4-7.2
Albumin (g/L)		1.95 (0.5)	1.4-2.4
Protein (g/L)		4.0 (0.5)	3.2-4.5
Ca (mg/dL)		7.60 (0.8)	6.8-8.6
P (mg/dL)		4.65 (0.6)	3.6-6.8
Na (mmol/L)		135.5 (4.0)	126-141
K (mmol/L)		4.45 (0.4)	4-5.9
Cl (mmol/L)		105 (8)	92-112
Urine			
Gravity		1034 (19)	1002-1045
pH		6.5 (0.5)	5.5-7.5
Erythrocyte (/HPF)		3 (9)	0-27
Microscopic hematuria	3 (17.6)		
UPCR (mg/mg)		6.21 (2.78)	1.9-15.2
<b>4<sup>th</sup> week results</b>	n (%)	Mean ± SD	Min-max
<b>Blood</b>			
Creatinine (mg/dL)		0.28 (0.2)	0.2-0.5
Albumin (g/L)		4.2 (0.6)	3.6-4.7
Urine			
UPCR (mg/mg)		0.15 (0.05)	0.11-0.22
Steroid response	n (%)		
SSNS (no relapse)	11 (64.8)		
SDNS	6 (35.2)		
CNIs	4 (66.6)		
Rituximab	2 (33.3)		

URTI: Upper respiratory tract infection, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, UPCR: Spot urine protein:creatinine ratio, SRNS: Steroid resistant nephrotic syndrome, SSNS: Steroid sensitive nephrotic syndrome, SDNS: Steroid dependent nephrotic syndrome



**Figure 1.** Comparison of serum podocalyxin levels between children with idiopathic nephrotic syndrome and healthy controls.

The median serum podocalyxin level in patients was higher compared to control group [1.87 ng/dL (IQR: 0.87) vs. 1.54 ng/dL (IQR: 0.29),  $p=0.031$ ].

IQR: Interquartile range

## DISCUSSION

This study investigated the clinical features and therapeutic responses of children with idiopathic NS, with particular emphasis on the utility of serum podocalyxin levels for predicting steroid responsiveness. All participants achieved remission following initial corticosteroid therapy; however, more than one-third (35.2%) developed SDNS during tapering. Among these patients, a subset required escalation to CNI, while two achieved remission only after rituximab therapy, indicating variability in treatment response. Notably, serum podocalyxin levels at diagnosis were markedly elevated in NS compared with controls and showed a nonsignificant trend toward higher values in those who progressed to SDNS and required more intensive treatment. These results indicate that podocalyxin may serve as a biomarker for the diagnosis of NS.

Podocytes, situated in the outer layer of the glomerular filtration barrier, play an essential role in the pathogenesis of glomerular diseases. Their detachment from the glomerular basement membrane reflects severe kidney injury. Healthy individuals have significantly lower urinary podocyte counts than patients with glomerular diseases. Therefore, quantifying podocytes in urine can be used to assess and monitor glomerular diseases. However, the determination of the podocyte-associated

**Table 2. Evaluations of podocalyxin levels in clinical characteristics and steroid response.**

	Serum podocalyxin level		
Initial features	Median (IQR)	Min-max	p-value
Control group (n=51)	1.54 (0.29)	0.61-3.18	
Patients (n=17)	1.87 (0.87)	1.27-3.59	0.031
Steroid response			
SSNS (no relapse)	1.65 (0.92)	1.27-3.40	
SDNS	1.95 (1.17)	1.42-3.59	0.148

IQR: Interquartile range, SSNS: Steroid sensitive nephrotic syndrome, FRNS: Frequently relapsing nephrotic syndrome, SDNS: Steroid dependent nephrotic syndrome

**Table 3. Evaluation of the relationship between podocalyxin level and other parameters.**

Dependent variables	Independent variables	Equation	Adjusted R <sup>2</sup>	p-value
Podocalyxin level at initial diagnosis (ng/dL)	Age (years)	2.134 - 0.023 x age	0.111	0.690
	Weight gain (kg)	1.945 + 0.041 x weight gain	0.060	0.838
	Serum albumin (g/dL)	1.202 - 0.036 x serum albumin level	0.028	0.522
	UPCR (mg/mg)	2.423 - 0.076 x UPCR	0.164	0.107

UPCR: Spot urine protein:creatinine ratio

protein podocalyxin, rather than podocyte quantification, is increasingly used in clinical practice as a simpler method to assess kidney disease and to predict its prognosis<sup>7</sup>. A recent review evaluated new biomarkers that could be used in the early assessment and longitudinal monitoring of kidney diseases, emphasizing that podocalyxin could serve as a diagnostic marker for early podocyte damage. The integration of this new biomarker into routine clinical practice is expected to contribute to the early diagnosis and personalized treatment of kidney diseases<sup>16</sup>. In a study by Giannou et al.<sup>17</sup>, urinary podocalyxin levels were evaluated in patients with various types of glomerulonephritis, and significant associations were found with serum creatinine and histological features of chronicity. The findings support the view that urinary podocalyxin levels may indicate podocyte injury and kidney dysfunction<sup>17</sup>. In another study, a sensitive liquid chromatography-tandem mass spectrometry assay was established to measure urinary podocalyxin for the early detection of chronic kidney disease; baseline levels were determined in 60 healthy controls and 20 patients. These results suggest that urinary podocalyxin levels could serve as a non-invasive biomarker of glomerular damage<sup>18</sup>. Podocalyxin levels in urine have also been shown to be a potential non-invasive biomarker for detecting the early stages of diabetic nephropathy, and these urinary levels increase even in the normoalbuminuric stage<sup>19</sup>. Additionally, podocalyxin levels in urine are significantly elevated in patients with lupus nephritis, and these levels have been found to correlate strongly with proteinuria, disease activity scores, and kidney biopsy findings. These results suggest that urinary podocalyxin may serve as non-invasive marker of renal involvement in systemic lupus erythematosus<sup>20</sup>. As seen in previous studies, podocalyxin levels were mostly assessed by measuring urinary excretion<sup>7-9,16-20</sup>. However, because of podocyte injury in NS, we can assume that podocalyxin enters the circulation and is excreted in the urine. Therefore, we measured serum podocalyxin levels in the present study. The reasons for choosing this approach include the possibility that urinary podocalyxin levels may be affected by factors such as proteinuria intensity, urine concentration, and sample processing, which may limit its reliability. A study by Khalid and Ali<sup>21</sup> found a negative correlation between serum podocalyxin levels and glomerular filtration rate, suggesting that podocyte injury may increase as kidney damage progresses, leading to increased serum podocalyxin levels. In our study, serum podocalyxin levels at initial presentation of NS were significantly higher than those in healthy controls. This confirms that there may be some degree of podocyte injury in patients with NS.

The NS is one of the most extensively researched glomerular conditions in children, and its prognosis has significantly improved over time. The goal in treating idiopathic NS is to achieve remission as quickly as possible and to prevent relapses. Corticosteroids have been used in the treatment since the 1960s<sup>13</sup>. Because steroids are the first-line drugs of choice cumulative steroid dose can reach 187.3 mg/kg even in patients with a single episode of NS; it increases to 375.7 mg/kg in patients who develop steroid resistance or experience relapses<sup>22</sup>. Glucocorticoids exert biological effects on multiple cells and systems, affecting carbohydrate metabolism, blood pressure, vascular integrity, mood and behavior, musculoskeletal and skin health, body weight, immune function, and bone growth and mineralization<sup>13,23</sup>. Therefore, predicting the response of NS to steroids and using steroid-sparing agents or other immunosuppressive agents at an early stage in patients predicted to develop relapses will be valuable for protecting against steroid side effects. Although serum podocalyxin levels were elevated in children with NS in our study, current findings indicate that their levels are insufficient to predict disease severity or steroid response. Considering that initial serum podocalyxin levels are numerically higher in patients who were subsequently diagnosed with SDNS, we believe that this limitation can be addressed by multicenter studies with longer follow-up and larger sample sizes.

### Study Limitations

The primary limitation of this study is the relatively small sample size. Although NS is a common glomerular pathology in children, we could not enroll more newly diagnosed NS cases at a single center during the relatively short study period. We believe that more statistically robust results could be obtained in a longer, multicenter study. In a study with longer follow-up, it may be possible to examine whether serum podocalyxin levels and other characteristics affect long-term prognosis. Another limitation is that the histopathological characteristics of the patients are unknown. Although kidney biopsy is not routinely indicated in children with NS, the absence of histopathological confirmation prevents us from definitively establishing the relationship between serum podocalyxin levels and podocyte injury. Also, podocalyxin is found in endothelial cells, suggesting that the results may be affected by endothelial damage. Clarifying this finding using additional markers of endothelial damage in the initial evaluation would increase the study's value.

### CONCLUSION

This study suggests that serum podocalyxin levels at diagnosis may have utility as a biomarker in children

with idiopathic NS. Although remission was achieved in all patients with initial steroid therapy, a significant proportion required additional immunosuppressive agents, highlighting the importance of early risk stratification. However, current findings indicate that serum podocalyxin levels are insufficient for predicting disease severity or steroid response. Additional studies involving larger patient cohorts are needed to further substantiate findings.

## Ethics

**Ethics Committee Approval:** The study was approved by the KTO Karatay University Medical Ethics Committee with decision no.:2024/257, date:18.12.2024.

**Informed Consent:** Written informed consent was obtained from all participants and their parents before enrollment.

## Footnotes

### Author Contributions

Surgical and Medical Practices: E.L., M.S., Concept: E.L., U.C., Design: E.L., U.C., Data Collection or Processing: E.L., M.S., U.C., Analysis or Interpretation: E.L., M.S., U.C., Literature Search: E.L., M.S., U.C., Writing: E.L., M.S., U.C.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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