Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Research article

doi: 10.31450/ukrjnd.1(89).2026.08

Heorhii Liezhentsev[1], Ievgeniia Burlaka[1], Ingretta Bagdasarova[2,3], Olena Zakrarycheva [2]

Advances in biomarker-based assessment of kidney injury in pediatric nephrotic syndrome: A narrative review

[1]Bogomolets National Medical University, Kyiv, Ukraine
[2] State Institution "O.O. Shalimov National Scientific Centre for Surgery and Transplantology of the National Academy of Medical Sciences of Ukraine," Kyiv, Ukraine
[3] International Centre for Astronomical, Medical and Ecological Research, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Citation: Liezhentsev H, Burlaka Ie, Bagdasarova I, Zakrarycheva O. Advances in biomarker-based assessment of kidney injury in pediatric nephrotic syndrome: A narrative review. Ukr J Nephrol Dialys. 2026;1(89):66-74. doi: 10.31450/ukrjnd.1(89).2026.08.

Abstract. *Pediatric nephrotic syndrome (NS) presents significant diagnostic and prognostic challenges in contemporary clinical practice. Despite advances in understanding disease mechanisms, substantial gaps persist in risk stratification frameworks, standardized diagnostic criteria for complex cases, and clinical implementation of novel biomarkers.*

The present review aimed to critically evaluate current and emerging diagnostic approaches for detecting early kidney injuries in pediatric nephrotic syndrome, examining developmental renal physiology, disease mechanisms, conventional marker limitations, novel biomarkers and multi-marker strategies to provide evidence-based recommendations for improving early detection and long-term outcomes in affected children.

The review summarizes current evidence on the clinical relevance of novel biomarkers of kidney injury, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), liver-type fatty acid–binding protein (L-FABP), N-acetyl-β-D-glucosaminidase, cystatin C, interleukin-18, and osteopontin. These biomarkers reflect different pathophysiological mechanisms such as tubular injury, inflammation, ischemia, oxidative stress, fibrosis and are able to detect subclinical renal damage before a measurable decline in glomerular filtration rate occurs. Particular attention is given to KIM-1, NGAL, and L-FABP as early indicators of tubular injury, as well as to osteopontin as a marker associated with chronic inflammation and renal fibrotic remodeling. Available data indicate that the combined use of several biomarkers improves early detection, risk stratification and monitoring of disease course in children with nephrotic syndrome.

Keywords: *pediatric nephrotic syndrome, biomarkers, risk stratification, diagnostic challenges, children.*

Article history:
Received December 30, 2025
Received in revised form February 17, 2026
Accepted February 18, 2026

Conflict of interest. The author declares no conflict of interest.

Correspondence should be addressed to Ievgeniia Burlaka: evgbur1982@gmail.com

УДК: 616.61-036.1:616.61-008.6]-053.2-071

Георгій Лєженцев[1], Євгенія Бурлака[1], Інгретта Багдасарова[2,3], Захаричева Олена[2]

Сучасні досягнення у біомаркер-орієнтованій оцінці ураження нирок у дітей з нефротичним синдромом: огляд літератури

[1]Національний медичний університет імені О.О. Богомольця, Київ, Україна
[2]Державна установа «Національний науковий центр хірургії та трансплантології імені О.О. Шалімова НАМН України», Київ, Україна
[3]Міжнародний центр астрономічних та медико-екологічних досліджень НАН України

Резюме. *Нефротичний синдром у дітей становить значні діагностичні та прогностичні труднощі у сучасній клінічній практиці. Незважаючи на прогрес у розумінні механізмів захворювання, зберігаються суттєві прогалини у підходах до стратифікації ризику, стандартизації діагностичних критеріїв у складних клінічних випадках та впровадженні нових біомаркерів у клінічну практику.*

Метою цього огляду було критично оцінити сучасні та перспективні діагностичні підходи до виявлення раннього ушкодження нирок у дітей з нефротичним синдромом з урахуванням особливостей вікової фізіології нирок, патогенетичних механізмів захворювання, обмежень традиційних лабораторних маркерів, а також ролі нових біомаркерів і мультимаркерних стратегій з метою формування доказових рекомендацій щодо покращення ранньої діагностики та довгострокових результатів у дітей.

В огляді узагальнено сучасні дані щодо клінічного значення нових біомаркерів ушкодження нирок, зокрема нейтрофільного желатиназо-асоційованого ліпокаліну (NGAL), молекули ушкодження нирки-1 (KIM-1), печінкового типу білка, що зв'язує жирні кислоти (L-FABP), N-ацетил- -D-глюкозамінідази, цистатину С, інтерлейкіну-18 та остеопонтину. Ці біомаркери відображають різні патофізіологічні механізми, включаючи тубулярне ушкодження, запалення, ішемію, оксидативний стрес і фіброз, та здатні виявляти субклінічне ураження нирок до розвитку клінічно значущого зниження швидкості клубочкової фільтрації. Особливу увагу приділено NGAL, KIM-1 та L-FABP, як раннім маркерам тубулярного ушкодження, а також остеопонтину як маркеру, пов'язаному з хронічним запаленням і фібротичним ремоделюванням ниркової тканини. Наявні дані свідчать, що комбіноване використання декількох біомаркерів підвищує ефективність раннього виявлення, стратифікації ризику та моніторингу перебігу нефротичного синдрому у дітей.

Ключові слова: *нефротичний синдром, біомаркери, стратифікація ризику, діагностичні виклики, діти*

Introduction. Nephrotic syndrome (NS) is the most common primary glomerular disorder in childhood and remains a major contributor to kidney-related morbidity worldwide. The global incidence of pediatric nephrotic syndrome is estimated at approximately 2.9 cases per 100,000 children per year, with pronounced geographic and ethnic variability. Higher incidence rates have been reported among Asian populations, reaching up to 6.1 per 100,000 children annually compared with lower rates observed in North American and European populations ranging from 2.1 to 2.4 per 100,000. These differences are thought to reflect a combination of genetic predisposition, environmental factors and population-specific disease susceptibility [1].

Clinically NS is characterized by massive proteinuria, hypoalbuminemia, generalized edema and hyperlipidemia resulting from disruption of the glomerular filtration barrier. Beyond these defining features, affected children are at increased risk of infectious complications, thromboembolic events, dyslipidemia, impaired growth and development. The clinical course of pediatric nephrotic syndrome is highly variable [1, 2]. While the majority of children initially respond to corticosteroid therapy and are defined as steroid-sensitive nephrotic syndrome up to half experience frequent relapses or develop steroid dependence, requiring prolonged or repeated exposure to immunosuppressive medications. Approximately 10–15% of pediatric patients exhibit steroid-resistant nephrotic syndrome, a form associated with a markedly increased risk of progression to chronic kidney disease (CKD) and eventual end-stage kidney disease (ESRD) [3].

Traditionally, nephrotic syndrome has been classified and managed based on clinical presentation, response to therapy, and histopathological findings. However, growing evidence indicates that nephrotic syndrome represents a group of biologically heterogeneous disorders rather than a single disease entity. The identification of circulating anti-nephrin autoantibodies in a substantial proportion of children during active disease has provided important insight into immune-mediated mechanisms of podocyte injury [4]. Additional immunological studies have demonstrated activation of inflammatory signaling pathways during disease relapse, further reinforcing the concept of ne-

Ievgeniia Burlaka
evgbur1982@gmail.com

phrotic syndrome as an immune-driven podocytopathy with distinct biological subtypes [4, 5].

Despite advances in understanding disease mechanisms, assessment of kidney function and injury in pediatric NS continues to rely primarily on conventional laboratory markers, including serum creatinine (S-Cr), blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR) [6]. These markers have significant limitations, particularly in children. Serum creatinine is a late and insensitive indicator of kidney injury, typically increasing only after substantial loss of functional nephron mass. Its interpretation is further complicated by factors intrinsic to nephrotic syndrome, including age-related variability in muscle mass, altered nutritional status, corticosteroid exposure, massive proteinuria, hypoalbuminemia and fluctuations in intravascular volume. Consequently, early or subclinical kidney injury may remain undetected using standard laboratory assessments [5, 6].

Importantly, kidney involvement in nephrotic syndrome extends beyond glomerular injury alone. Persistent proteinuria, recurrent disease activity, hemodynamic instability, infections, and exposure to potentially nephrotoxic therapies contribute to tubular damage, interstitial inflammation, and progressive fibrotic remodeling [6]. Episodes of acute kidney injury may occur during relapses or complications, while chronic tubulointerstitial injury plays a critical role in long-term renal outcome, particularly in frequently relapsing and steroid-resistant forms of the disease. Conventional functional markers are poorly suited to detect these processes at an early and potentially reversible stage [6, 7].

These limitations have driven increasing interest in novel biomarkers capable of reflecting distinct mechanisms of kidney injury, including tubular damage, inflammation, cellular stress, and fibrogenesis. Such biomarkers offer the potential to detect renal injury before overt decline in glomerular filtration becomes apparent, to differentiate disease activity from treatment-related nephrotoxicity, and to improve risk stratification in vulnerable patient subgroups [8]. In pediatric nephrotic syndrome, where long-term outcomes are shaped by cumulative injury over years of disease activity and treatment exposure, early identification of kidney damage is of particular clinical importance [9].

In this context, the present review examines current and emerging biomarkers of kidney injury in pediatric NS, focusing on their biological relevance, diagnostic potential and limitations. By integrating knowledge of developmental renal physiology, disease mechanisms and biomarker performance, this review aims to clarify how novel approaches to kidney damage assessment may improve early detection, guide clinical decision-making and ultimately enhance long-term outcomes for children with nephrotic syndrome.

Material and methods. This work represents a review of current evidence regarding novel biomarkers of kidney injury in pediatric nephrotic syndrome. A literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science and Google Scholar covering publications from January 2020 to June 2025. The search included the terms "pediatric nephrotic syndrome," "childhood nephrotic syndrome," "biomarkers," "kidney injury," "NGAL," "KIM-1," "L-FABP," "NAG," "cystatin C," "interleukin-18," "osteopontin," and "calcineurin inhibitor nephrotoxicity." Reference lists of selected articles were additionally reviewed to identify relevant publications.

The search identified 129 records. After removal of duplicates, 64 articles were screened by title and abstract; 26 studies were included in the final analysis. Eligible publications included original research articles, systematic reviews and clinical guidelines addressing biomarkers of kidney injury in children with nephrotic syndrome. Case reports, conference abstracts without full text, and non-English papers were excluded. Given the heterogeneity of study designs and outcome measures, the findings are presented in a descriptive manner without quantitative synthesis.

Aim. This narrative review aims to critically evaluate current and emerging diagnostic approaches for detecting kidney injuries in pediatric nephrotic syndrome, examining developmental renal physiology, disease mechanisms, conventional marker limitations, novel biomarkers and multi-marker strategies to provide evidence-based recommendations for improving early detection and long-term outcomes in affected children.

Nephrotic syndrome: *A basic overview*. Nephrotic syndrome is a kidney disorder characterized by four cardinal features: massive proteinuria (protein loss in urine), hypoalbuminemia (low blood albumin levels), edema (tissue swelling), and hyperlipidemia (elevated blood fats) [1-3]. The underlying problem involves damage to the glomerular filtration barrier, specifically the podocytes and their slit diaphragms, which normally prevent large proteins like albumin from leaking into urine. When this barrier becomes compromised, excessive protein loss occurs, typically exceeding 40 mg/m / hour or presenting as a urine protein-to-creatinine ratio above 200 mg/mmol in children [1].

The clinical manifestations follow a predictable pathophysiological cascade. Heavy proteinuria depletes serum albumin levels below 30 g/L, reducing plasma oncotic pressure and allowing fluid to shift from blood vessels into tissue spaces, causing edema [2]. The liver responds to low albumin by increasing synthesis of lipoproteins, resulting in hyperlipidemia. Additionally, urinary loss of immunoglobulins and complement factors increases infection susceptibility, while loss of antithrombin III and other coagulation factors elevates thrombosis risk [1, 2, 4].

In children NS encompasses several histological subtypes identifiable only through kidney biopsy. Minimal change disease (MCD) accounts for 65-75% of cases in younger children and shows no visible glomerular abnormalities under light microscopy [1]. Focal segmental glomerulosclerosis (FSGS) represents ap-

proximately 25% of cases and displays scarring in some glomeruli [2]. The distinction between steroid-sensitive nephrotic syndrome (SSNS) which responds to corticosteroid therapy and steroid-resistant nephrotic syndrome (SRNS) has critical prognostic implications. SRNS carrying substantially higher risk of progression to chronic kidney disease and eventual kidney failure [1, 2, 5].

Basic representation of the main pathophysiological processes underlying NS in children includes structural and biophysical alterations of the glomerular capillary wall, which constitute the primary pathogenic mechanism of nephrotic syndrome. Injury to the glomerular filtration barrier increases permeability to plasma proteins, leading to significant proteinuria. Ongoing urinary protein loss reduces serum albumin levels and results in hypoalbuminemia. The consequent decrease in plasma oncotic pressure facilitates fluid movement from the intravascular compartment into the interstitial space, leading to edema. At the same time, reduced albumin levels stimulate hepatic lipoprotein synthesis, contributing to disordered lipid metabolism and hyperlipidemia. These mechanisms account for the main clinical and laboratory features of nephrotic syndrome (Fig. 1).

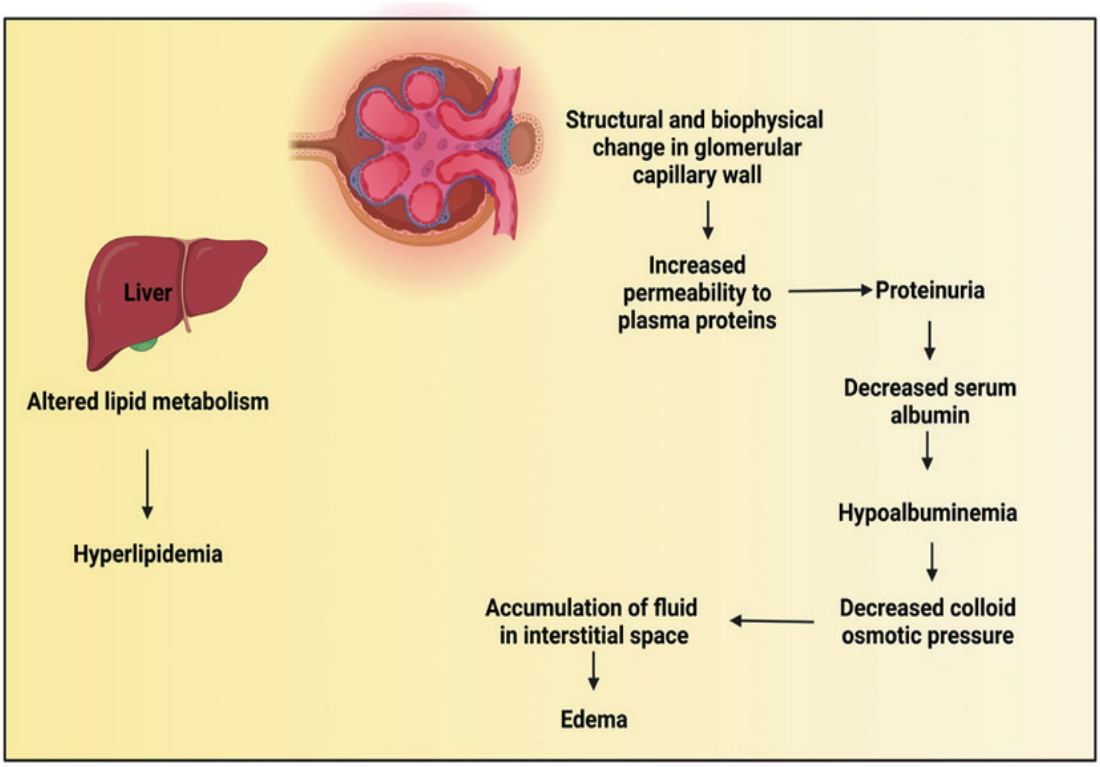

Fig. 1. Pathophysiological mechanisms underlying the development and systemic manifestations of nephrotic syndrome. The figure illustrates the cascade of events initiated by structural and biophysical alterations of the glomerular capillary wall. Increased permeability of the glomerular filtration barrier to plasma proteins leads to significant proteinuria. Sustained urinary protein loss results in decreased serum albumin levels and hypoalbuminemia.

Novel approaches in kidney damage evaluation in nephrotic syndrome: *A new look*. In children with established NS, worsening kidney function may represent acute kidney injury from hemodynamic factors (hypovolemia, hypervolemia with heart failure) or complications (infection, thrombosis); medication-induced nephrotoxicity; progression of underlying glomerular disease to CKD; or development of a superimposed kidney disease [1, 2, 5].

Traditional markers like serum creatinine and eGFR provide limited ability to distinguish among these scenarios. Novel biomarkers offer potential advantages. For instance, tubular injury markers (NGAL, KIM-1, NAG) that rise acutely suggest acute tubular damage from ischemia or toxins, whereas chronically elevated concentrations may indicate ongoing tubular injury from proteinuria or medications. Glomerular markers (proteinuria patterns, podocyturia) reflect disease activity at the glomerular level. Biomarkers of fibrosis (urinary DKK3, certain microRNAs) may indicate progressive fibrotic processes [6-9].

Children with frequently relapsing or steroid-dependent NS often receive calcineurin inhibitors (cyclosporine or tacrolimus) as steroid-sparing agents. While effective in preventing relapses, these medications have inherent nephrotoxic potential through both acute hemodynamic effects (vasoconstriction, reduced GFR) and chronic structural toxicity (tubulointerstitial fibrosis, arteriolopathy [10].

The challenge lies in distinguishing calcineurin inhibitor nephrotoxicity from underlying nephrotic syndrome progression, as both may present with ris-

ing serum creatinine and declining eGFR. Kidney biopsy remains the gold standard for diagnosis, showing characteristic features of calcineurin inhibitor toxicity, including arteriolopathy (hyaline arteriolosclerosis), striped interstitial fibrosis, and tubular atrophy [9, 10]. However, a biopsy is invasive and not suitable for frequent monitoring.

Novel biomarkers may help identify early nephrotoxicity and other clinical features of the NS course. Validation of these biomarkers specifically in pediatric NS presents a promising direction for non-invasive toxicity monitoring. Below, we discuss the main benefits of the novel markers' usage in NS.

Novel biomarkers of the kidney injury in nephrotic syndrome. Recognition of the limitations of conventional markers (serum creatinine, urea, and albuminuria) has stimulated intensive research into novel biomarkers that capture distinct dimensions of kidney injury and dysfunction, including glomerular filtration, tubular damage, inflammation and cellular stress [4-6].

Cystatin C. Cystatin C is a lowmolecularweight protein produced by all nucleated cells and freely filtered by the glomerulus. Then it is almost completely reabsorbed and catabolized by proximal tubular cells. Its serum concentration predominantly reflects GFR and is less influenced by age, sex and muscle mass than creatinine, meaning its high advantage [11]. Interestingly, creatinine did not differ between preterm and term children, whereas cystatin C was significantly higher in preterm infants, indicating superior sensitivity to subtle kidney dysfunction [12].

NGAL. NGAL is markedly upregulated in injured tubular epithelial cells with urinary levels rising within 2-6 hours after renal insult, which is substantially earlier than serum creatinine [4, 13]. A 2025 meta-analysis in pediatric cardiac surgery patients showed excellent diagnostic performance with urinary NGAL sensitivity of 91.3% and specificity of 89.7% for postoperative AKI. A urinary NGAL cutoff ≥125 ng/mL within 24 hours of admission predicted AKI with 89% sensitivity and 78% specificity. In pediatric NS, NGAL may help detect acute injuries during NS exacerbations, identify calcineurin inhibitor nephrotoxicity, monitor proteinuria-induced tubular injury and stratify progression risk. However, its interpretation is limited by poor specificity in inflammatory states, influence of heavy proteinuria, age-related variability and the lack of standardized cut-off values. The literature shows heterogeneous and sometimes contradictory findings across NS subtypes and treatment settings, with relatively few head-to-head comparisons against other tubular biomarkers and no clear consensus regarding its superiority [13].

KIM1. KIM-1 has gained increasing attention as a marker of tubular involvement in NS, reflecting the growing understanding that tubulointerstitial injury plays a key role in disease progression. Sustained proteinuria leads to excessive protein reabsorption by proximal tubular epithelial cells, resulting in oxidative stress, inflammatory activation and cellular injury, which in turn induces KIM-1 expression [14]. Elevated urinary KIM-1 levels have been reported in patients with NS, particularly in steroid-resistant forms and in conditions such as focal segmental glomerulosclerosis, where tubulointerstitial damage is more pronounced. Several studies have demonstrated associations between increased KIM-1 excretion and the severity of proteinuria, extent of interstitial fibrosis and decline in renal function. In pediatric nephrotic syndrome, elevated urinary KIM-1 levels have been particularly observed in steroid-resistant cases and in focal segmental glomerulosclerosis, reflecting more pronounced tubulointerstitial injury and correlating with proteinuria severity, interstitial fibrosis and decline in renal function. These changes often precede detectable changes in conventional markers such as serum creatinine or estimated glomerular filtration rate. However, its clinical utility is limited by variability across studies, potential influence of active proteinuria on tubular expression, lack of standardized values and limited comparisons with other tubular biomarkers, resulting in heterogeneous findings across NS populations [14-16].

LFABP. L-FABP is expressed in proximal tubular epithelial cells and released into the urine in response to hypoxia, oxidative stress and intracellular lipid accumulation. Its expression reflects tubular metabolic stress and impaired fatty acid handling. In NS, persistent proteinuria promotes tubular lipid overload and oxidative injury, creating conditions that favor increased urinary excretion of L-FABP [17]. Experimental and clinical observations suggest that L-FABP levels rise in response to proteinuria-associated lipotoxicity, calcineurin inhibitor-related tubular toxicity and ischemic injury during episodes of hemodynamic instability. Elevated L-FABP in nephrotic syndrome may serve as an early marker of tubular involvement and ongoing renal injury, preceding measurable declines in glomerular filtration. However, there is a lack of data in pediatric patients with NS, raising a high demand for studies [18].

NAG. NAG is a lysosomal enzyme abundant in proximal tubules and is released into urine upon tubular cell injury. Urinary NAG can be elevated even when GFR and serum creatinine remain within normal limits. In nephrotic syndrome, chronic heavy proteinuria drives tubular uptake of filtered proteins, promoting tubular damage and interstitial fibrosis. Elevated urinary NAG may therefore identify children at risk of progressive tubulointerstitial injury despite adequate control of proteinuria [19]. In pediatric nephrotic syndrome, urinary NAG may increase even when GFR and serum creatinine remain normal, reflecting proteinuria-driven tubular stress and early tubulointerstitial damage. However, its specificity is limited by elevations in various renal and systemic conditions, lack of standardized pediatric reference ranges and inconsistent associations with long-term outcomes, with relatively few comparisons against other tubular biomarkers and heterogeneous findings across NS cohorts [2, 8, 19].

Interleukin 18 (IL 18). IL-18 is a pro-inflammatory cytokine produced primarily by distal tubular epithelial cells and is upregulated in response to ischemic and inflammatory injury of the renal tubules. Increased urinary IL-18 levels have been described in acute tubular necrosis and reflect ongoing inflammatory damage within the kidney [20]. These findings support the potential value of IL-18 as an early marker of inflammatory tubular injury in pediatric nephrotic syndrome, particularly in settings of active disease and heightened intrarenal inflammation. However, its clinical applicability is limited by low specificity due to elevations in systemic inflammatory states, variability across studies and NS subtypes, and lack of standardized pediatric thresholds [20, 21].

Osteopontin. Osteopontin is a multifunctional glycoprotein involved in inflammatory signaling, immune cell recruitmentб tissue remodeling. This marker is expressed in several renal cell types, including tubular epithelial cells and infiltrating macrophages [22]. In NS, its expression increases in response to persistent proteinuria, tubular stress, and interstitial inflammation. Elevated osteopontin levels have been observed in association with tubulointerstitial injury, macrophage infiltration and progression of renal fibrosis. Clinical studies have shown correlations between urinary or tissue osteopontin levels and disease severity, degree of proteinuria and decline in renal function. Elevated osteopontin levels in pediatric nephrotic syndrome have been associated with tubulointerstitial injury, macrophage infiltration and progressive renal fibrosis, correlating with proteinuria severity and decline in renal function. However, its clinical utility is limited by variable findings across studies and the influence of concurrent inflammatory conditions [22].

In Table 1, we present a summary of the diagnostic values of traditional and novel markers of kidney damage in nephrotic syndrome.

Table 1

Comparison of traditional vs. novel kidney injury biomarkers in pediatric nephrotic syndrome: Strengths and limitations

Characteristic	Traditional Markers	Novel Biomarkers
Examples	• Serum creatinine (SCr) • Blood urea nitrogen (BUN) • Estimated GFR (eGFR)	– Tubular injury markers: NGAL, KIM-1, NAG – Glomerular markers: Podocyturia, proteinuria patterns
Detection Timing	• Delayed indicator SCr rises 48-72 hours after GFR declines by ~50%	– Early detection – Can identify injury before GFR decline
Sensitivity	• Low sensitivity for early kidney dysfunction	– High sensitivity for subclinical tubular and glomerular damage
Specificity	• Cannot distinguish between different causes of kidney dysfunction	– Can differentiate: – Acute tubular injury vs chronic damage – Glomerular disease activity – Fibrotic progression – Medication toxicity
Confounding Factors	• Muscle mass variation • Age and growth patterns • Nutritional status • Corticosteroid effects • Fluid retention/depletion • Hypoalbuminemia	– Less affected by muscle mass and fluid status – Provide compartment-specific information
Sample Type	Blood (serum)	Primarily urine (non-invasive, serial monitoring possible)
Clinical Utility	• Established reference ranges • Widely available • Standardized measurement • Good for monitoring advanced kidney disease	– Identifies subclinical injury – Distinguishes disease mechanisms – Monitors medication toxicity – Predicts disease progression – Guides treatment decisions
Limitations	• Cannot localize injury site (glomerular vs tubular) • Poor for distinguishing acute from chronic injury • Cannot identify specific nephrotoxicity	– Limited standardization – Variable reference ranges in children – Need validation in pediatric NS populations – Not widely available clinically – Cost considerations

Continuation of Table 1

Characteristic	Traditional Markers	Novel Biomarkers
Role in NS Management	• Standard monitoring of established kidney dysfunction	– Potential for: – Early intervention before irreversible damage – Personalized treatment strategies – Non-invasive monitoring of calcineurin inhibitor toxicity – Risk stratification
Current Status	• Clinical standard of care	– Research and emerging clinical applications; requires further validation

Discussion. Pediatric NS represents a clinically and biologically heterogeneous condition in which conventional markers of kidney function inadequately reflect the complexity and dynamics of renal injury [1]. Serum creatinine, blood urea nitrogen and estimated glomerular filtration rate remain a routine clinical assessment. Their diagnostic and prognostic values in children with NS are fundamentally limited. These parameters rise only after substantial nephron loss and are influenced by age, muscle mass, hydration status, nutritional state and corticosteroid exposure. Consequently, clinically significant kidney injury may remain undetected for prolonged periods [1, 2].

Accumulating findings indicate that renal involvement in NS is more complex than isolated glomerular barrier dysfunction and includes early and progressive tubular injury, inflammatory activation and fibrotic remodeling [3]. Recent advances in disease biology, including the identification of anti-nephrin autoantibodies during active disease and transcriptomic signatures of inflammatory pathway activation, have changed the current understanding of nephrotic syndrome as an immune-mediated disorder with distinct molecular subtypes rather than an isolated clinical condition. These insights support the concept that children with NS follow divergent biological trajectories, underscoring the need for diagnostic tools capable of capturing mechanism-specific kidney injury [3, 4].

Within this framework, novel biomarkers provide a major advantage by enabling compartment-specific assessment of renal damage. Tubular injury markers such as NGAL, KIM-1, NAG, liver-type fatty acid-binding protein and IL-18 rise early in response to ischemic, toxic, or inflammatory tubular stress, often preceding detectable changes in glomerular filtration [5-8]. This early responsiveness makes them particularly valuable for identifying subclinical kidney injury during disease relapse, hypovolemia, infection, or exposure to nephrotoxic agents. In contrast, glomerular markers, including proteinuria patterns and podocyturia, reflect disease activity at the filtration barrier level. At the same time, fibrosis-associated biomarkers such as osteopontin provide insight into chronic structural remodeling and long-term prognosis [7, 22].

One of the most clinically relevant applications of these biomarkers is the monitoring of calcineurin inhibitor therapy. Calcineurin inhibitors remain a cornerstone in the management of steroid-dependent and steroid-resistant nephrotic syndrome. However, their nephrotoxic potential presents a major therapeutic challenge [23]. Conventional laboratory tests cannot reliably distinguish calcineurin inhibitor-induced nephrotoxicity from disease progression, frequently resulting in delayed dose modification or reliance on invasive kidney biopsy. Emerging evidence suggests that increases in urinary NGAL, KIM-1 and osteopontin may precede functional decline, indicating early tubular injury and offering a non-invasive strategy for safer long-term immunosuppressive management [13-15].

Besides injury detection, novel biomarkers may play a pivotal role in risk stratification. Children with early-onset disease, frequent relapses, steroid resistance or prolonged exposure to nephrotoxic therapies represent a subgroup at particularly high risk for CKD [24]. In such patients, isolated measurements of serum creatinine provide limited prognostic information. Longitudinal assessment of biomarker profiles may allow identification of progressive injury patterns before irreversible fibrosis develops. This, in turn, enables earlier intervention and individualized monitoring strategies [25].

Despite these promising developments, significant gaps in clinical implementation persist. Most novel biomarkers lack standardized pediatric reference ranges, and inter-assay variability limits comparability across studies. Many assays remain confined to research settings, and cost considerations may restrict access, particularly in resource-limited healthcare systems. Moreover, much of the current evidence is derived from small or heterogeneous cohorts, highlighting the need for large, prospective, pediatric-specific validation studies.

In Figure 2, we demonstrate the potential role of novel biomarkers in complementing conventional measures of kidney function. Traditional markers (serum creatinine, blood urea nitrogen, estimated glomerular filtration rate) primarily reflect established functional decline. In contrast, tubular injury markers (NGAL, KIM-1, NAG, L-FABP), inflammatory mediators (IL-18) and fibrosis-associated markers (osteopontin) provide compartment-specific information and may detect subclinical renal injury at earlier stages. Integration of these biomarkers into longitudi-

nal patient monitoring may support early identification of kidney injury, differentiation between disease activity and drug-induced nephrotoxicity, assessment of progression risk and individualized therapeutic decision-making. These data emphasize the importance of a multimarker approach aimed at improving the precision and timing of clinical interventions in children with nephrotic syndrome.

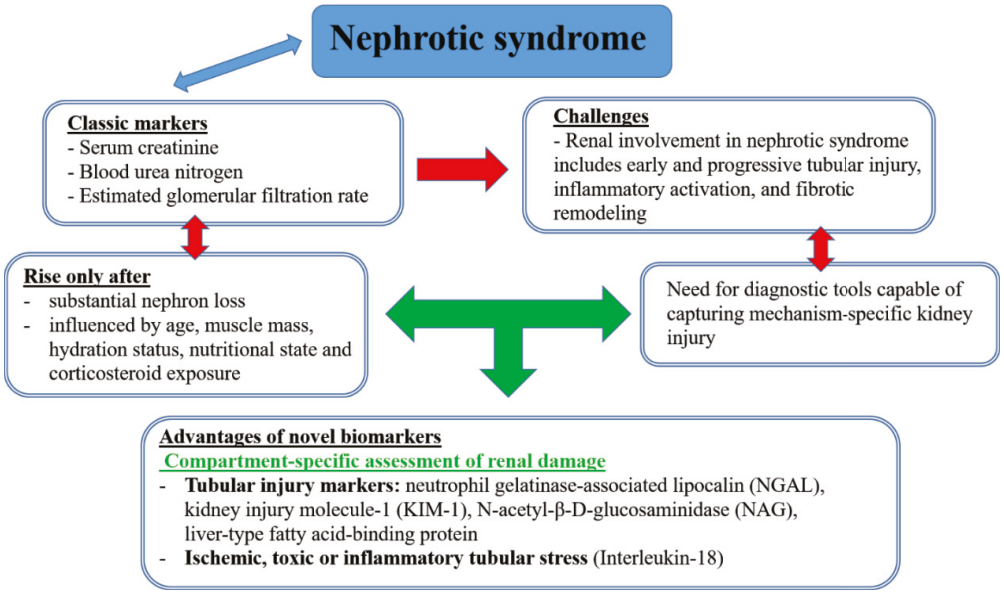

Fig. 2. Paradigm of the novel biomarkers input in NS diagnostics. The model presents a multimarker approach of the functional, tubular, inflammatory and fibrosis-associated parameters evaluation in NS.

Future research should prioritize the establishment of age-adjusted reference values, validation of multimarker panels in well-defined NS phenotypes and evaluation of biomarker-guided clinical strategies in prospective studies. Integration of biomarker findings with clinical characteristics and genetic background may support more accurate risk assessment and improved long-term outcomes for children with NS.

Conclusions:

1) Pediatric nephrotic syndrome is a clinically heterogeneous condition in which traditional indicators of kidney function, such as serum creatinine and estimated glomerular filtration rate, may not detect early renal injury.
2) Biomarkers including NGAL, KIM-1, L-FABP, NAG, IL-18 and osteopontin reflect tubular injury, inflammatory activity and early fibrotic changes before measurable reduction in glomerular filtration occurs and may have high clinical significance in NS.
3) In clinical practice, these biomarkers may support early detection of kidney injury during relapses or infectious complications, facilitate monitoring of calcineurin inhibitor-related nephrotoxicity and improve risk stratification in children with frequently relapsing or steroid-resistant disease.
4) Prospective studies are required to establish validated diagnostic thresholds and define their role in clinical management.

Acknowledgement. The corresponding author acknowledges colleagues from Karolinska Institutet.

Conflict of interest statement. None declared.

Funding source. This work was done without funding support.

Authors' contributions. All authors equally contributed to the work.

References

5. *Chan EY, Boyer O.* Childhood idiopathic nephrotic syndrome: Recent advancements shaping future guidelines. Pediatr Nephrol. 2025;40(8):2431-2442. doi: 10.1007/s00467-024-06634-9.
6. *Vivarelli M, Gibson K, Sinha A, Boyer O.* Childhood nephrotic syndrome. Lancet. 2023;402(10404):809-824. doi: 10.1016/S0140-6736(23)01051-6.
7. *Lee JM, Ahn YH, Lim SH, Kang H G.* Biomarkers Predicting Treatment-Response in Nephrotic Syndrome of Children: A Systematic Review. Childhood Kidney Diseases. 2021;25(2):92-111. doi: 10.3339/jkspn.2021.25.2.92.
8. *Wendt R, Sobhani A, Diefenhardt P, Trappe M, Völker LA.* An updated comprehensive review on diseases associated with nephrotic syndromes. Biomedicines. 2024;12(10):2259. doi: 10.3390/biomedicines12102259.
9. *Frățilă VG, Lupușoru G, Sorohan BM, Obrișcă B, Mocanu V, Lupușoru M, Ismail G.* Nephrotic syndrome: From pathophysiology to novel therapeutic

approaches. Biomedicines. 2024;12(3):569. doi: 10.3390/biomedicines12030569.

10. *Bogdanović L, Babić I, Prvanović M, Mijač D, Mladenović-Marković A, Popović D, Bogdanović J.* Uncommon factors leading to nephrotic syndrome. Biomedicines. 2025;13(8):1907. doi: 10.3390/biomedicines13081907.
11. *Ponticelli C, Moroni G.* Nephrotic syndrome: pathophysiology and consequences. J Nephrol. 2023;36(8):2179-2190. doi: 10.1007/s40620-023-01697-7. Erratum in: J Nephrol. 2025;38(7):2025. doi: 10.1007/s40620-025-02400-8.
12. *Lousa I, Reis F, Beirão I, Alves R, Belo L, Santos-Silva A.* New potential biomarkers for chronic kidney disease management: A review of the literature. Int J Mol Sci. 2021;22(1):43. doi: 10.3390/ijms22010043.
13. *Jacob M, Nimer RM, Alabdaljabar MS, Sabi EM, Al-Ansari MM, Housien M, et al.* Metabolomics profiling of nephrotic syndrome towards biomarker discovery. Int J Mol Sci. 2022;23(20):12614. doi: 10.3390/ijms232012614.
14. *Zhu Y, Chen J, Zhang Y, Wang X, Wang J.* Immunosuppressive agents for frequently relapsing/steroid-dependent nephrotic syndrome in children: A systematic review and network meta-analysis. Front Immunol. 2024;15:1310032. doi: 10.3389/fimmu.2024.1310032.
15. *Tkaczyk M, Nowicki M, Lukamowicz J.* Increased cystatin C concentration in urine of nephrotic children. Pediatr Nephrol. 2004;19(11):1278-80. doi: 10.1007/s00467-004-1566-1.
16. *Skidmore M, Spencer S, Desborough R, Kent D, Bhandari S.* Cystatin C as a Marker of Kidney Function in Children. Biomolecules. 2024;14(8):938. doi: 10.3390/biom14080938.
17. *Abdalla A, Ali A, Abufatima IO, Majzoub S, Elbasheer TAE, Ahmed SMAO, et al.* Use of urinary NGAL in steroid-resistant vs. steroid-sensitive nephrotic syndrome: a systematic review and meta-analysis. BMC Nephrol.2025;26(1):486. doi: 10.1186/s12882-025-04420-9.
18. *Zhang Y, Xiang C, Gong L, Zhang Y, Zhen J, Hu Z, Xiao X.* Kidney injury molecule-1 levels are associated with therapeutic outcomes and renal tubulointerstitial injury severity in idiopathic membranous nephropathy. Exp Ther Med. 2021;22(6):1434. doi: 10.3892/etm.2021.10869.
19. *Welliam Y, Witarto BS, Visuddho V, Wungu CDK, Budiarto RM, Susilo H.* Osteopontin, kidney injury molecule-1, and fetuin-A as prognostic markers of end-stage renal disease: A systematic review and meta-analysis. PLoS One. 2025;20(4):e0320804. doi: 10.1371/journal.pone.0320804.
20. *Tavares MB, Melo CVB, Fernandes PN, Almeida MDCC, Carneiro MFDSM, Santos RFS, et al.* Biomarkers of acute kidney injury in patients with nephrotic syndrome. J Bras Nefrol. 2021;43(1):20-27. doi: 10.1590/2175-8239-JBN-2020-0021.
21. *Nishida M, Kawakatsu H, Hamaoka K.* Urinary liver-type fatty acid-binding protein in pediatric nephrotic syndrome and tubular dysfunction. Pediatr Int. 2018;60(5):442-445. doi: 10.1111/ped.13533.
22. *Mitsides N, Mitra V, Saha A, Harris S, Kalra PA, Mitra S.* Urinary liver-type fatty acid binding protein, a biomarker for disease progression, dialysis and overall mortality in chronic kidney disease. J. Pers. Med.2023;13(10):1481. doi: 10.3390/jpm13101481.
23. *Liu X, Gong S, Ning Y, Li Y, Zhou H, He L, et al.* Urinary N-Acetyl-Beta-D-Glucosaminidase levels predict immunoglobulin a nephropathy remission status. BMC Nephrol. 2023;24(1):208. doi: 10.1186/s12882-023-03262-7.
24. *Hirooka Y, Nozaki Y.* Interleukin-18 in inflammatory kidney disease. Front Med (Lausanne). 2021;8:639103. doi: 10.3389/fmed.2021.639103.
25. *Piekoszewska-Ziętek P, Korytowska-Przybylska N, Pańczyk-Tomaszewska M, Olczak-Kowalczyk D.* Salivary interleukin-6 and interleukin-18 levels and their association with dental health in children with idiopathic nephrotic syndrome. Int. J. Mol. Sci.2025;26(7):3175. doi: 10.3390/ijms26073175.
26. *Sinha SK, Mellody M, Carpio MB, Damoiseaux R, Nicholas SB.* Osteopontin as a Biomarker in Chronic Kidney Disease. Biomedicines. 2023;11(5):1356. doi: 10.3390/biomedicines11051356.
27. *Trautmann A, Hofstetter J, Lipska-Ziętkiewicz B, Tsygin A, Ogarek I, Saeed B, et al.* Efficacy of Calcineurin Inhibition in Children With Steroid-Resistant Nephrotic Syndrome. Kidney Int Rep. 2025;10(10):3535-3548. doi: 10.1016/j.ekir.2025.07.037.
28. *Burlaka IA, Bagdasarova IV.* Molecular factors predicting steroid resistance in pediatric nephrotic syndrome. Ukr J Nephr Dial. 2021;2(70):32–37. doi: 10.31450/ukrjnd.2(70).2021.04.
29. *Barinotti A, Radin M, Cecchi I, Foddai SG, Rubini E, Roccatello D, et al.* Serum biomarkers of renal fibrosis: A systematic review. Int. J. Mol. Sci.2022;23(22):14139. doi: 10.3390/ijms232214139.