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REVIEW

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Novel acute kidney injury biomarkers and their utility in children and adolescents-overview

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Abstract

Acute kidney injury (AKI) affects a significant percentage of the pediatric population. Currently, the diagnosis of AKI in children still uses traditional laboratory methods (ex. creatinine or urea serum concentration and measurement of urine output). It has significant limitations. Early stages of AKI in children may be almost asymptomatic. In-depth assessment with the pRIFLE scale is helpful, but requires bladder catheterization and precise monitoring of hourly diuresis, as well as multiple blood draws to determine changes in creatinine concentration and estimate glomerular filtration rate (eGFR). The diagnostic methods lack a marker that would the early and potentially reversible phase of kidney damage. This paper reviews recent data on selected AKI markers in children, including their diagnostic and prognostic potential.

Keywords Acute kidney injury, Children, Protein biomarkers, Pediatric population

Introduction

Acute Kidney Injury (AKI) is a significant clinical issue, especially in the pediatric population with the incidence estimated to be 3.9 per 1,000 hospitalizations, and prevalence among children admitted to intensive care units 26.9% [1]. The problem is still increasing [2].

Since 2004, the definition of AKI has rapidly evolved with introducing the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) classification systems. In 2012, the KDIGO classification was introduced to merge the three existing systems, aiming to standardize and streamline its use across both adult and pediatric patients. This current definition, widely recognized in the literature, relies on two easily measurable factors: serum creatinine (or estimated creatinine clearance for those under 18) and urine output [3]. The RIFLE criteria were also adapted for pediatric applications, known as pRIFLE. This classification involves measuring a decline in eGFR, an increase in creatinine levels, or a reduction in urine output [4]. It is worth adding that in an observational study conducted by Sutherland et al. The incidence of AKI in hospitalized children was compared using the pRIFLE, AKIN, and KDIGO criteria, finding that the agreement between these definitions was as low as 77% [5].

AKI has often been viewed as a self-limiting condition, with a favorable prognosis when recovery occurs during hospitalization [6]. However, many studies have showed that episodes of AKI are linked to an increased risk of developing chronic kidney disease (CKD), and facing overall higher mortality rates [7, 8], though the mechanisms behind these associations are not yet fully understood [9]. AKI is a condition marked by a swift decrease

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in glomerular filtration rate, leading to the buildup of metabolic waste products [10]. It is characterized by an increase in serum creatinine level or a decrease in urine output over a period of hours to days. In children, because of specific anatomical and physiological conditions, the occurrence of AKI may have a unique background compared to adults. A detailed history and physical examination can help identify whether the cause is prerenal, intrinsic renal, or postrenal [11]. Pre-renal AKI results from impaired renal perfusion, which can be caused by dehydration, hemorrhage, heart failure or sepsis. Renal AKI results from direct damage to the renal parenchyma, related to nephrotoxic drugs, infections, autoimmune diseases or glomerulopathies. Postrenal AKI occurs because of a mechanical obstruction in the urinary tract, which leads to increased pressure and damage to the kidneys. The leading causes of AKI in pediatric patients include kidney ischemia/reperfusion injury (IRI), exposure to nephrotoxic medications, and sepsis, though it often results from multiple factors [12]. So far, traditional laboratory methods have been used in the diagnostics of AKI in children. Clinical trials have notably failed to develop effective methods for preventing, treating, or alleviating AKI in children. Two primary challenges have impeded progress in this field. First, the diagnosis of AKI using the KDIGO criteria relies on changes in serum creatinine (SCr) levels and urine output [13]. Serum creatinine level is a late and imprecise biomarker that varies significantly in chronically ill children and those with critical illness. It is challenging to interpret it in patients with low muscle mass and needs to be adjusted for fluid volume status [14]. It is a 'late marker' as it can take up to 48 h for serum creatinine concentration to rise after the glomerular filtration rate (GFR) has decreased by 50%. Urine output analysis is also complicated, especially in incontinent children and those without indwelling urinary catheters [12]. In hospitalized children, AKI is linked to higher mortality, extended hospital stays, permanent kidney function loss, and an elevated risk of developing CKD in the future [15]. Patients who recover from AKI still face an elevated long-term risk of proteinuria, hypertension and lower scores in health-related quality of life [13, 14, 16]. Prompt identification of the cause, effective management, and long-term monitoring of AKI are crucial [11].

It is important to present the characteristics of the biomarker that make it an appropriate tool for predicting the onset of AKI and tracking its impact on subsequent renal function. An ideal biomarker for AKI or CKD should rapidly and reliably reflect changes in kidney function, offering high sensitivity and specificity in diagnosis. It should correlate closely with the severity of kidney damage and provide valuable prognostic information, including the likelihood of disease progression and response to treatment. The biomarker must be stable, unaffected by external factors like medications, and applicable across different demographics. It should be easily measurable, allowing for noninvasive, repeated monitoring of kidney health. The delay in identifying AKI often results in missed chances for timely therapeutic interventions during the critical period when AKI might be reversed [17]. Current diagnostic methods do not have a marker capable of detecting early kidney damage, which is crucial for children at risk of AKI and CKD in the future. This review summarizes key studies focusing on novel biomarkers for AKI in pediatric patients, including neonates, critically ill children, and those undergoing surgery or cancer treatments.

Materials and methods

Search protocol

This review was created under PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [18]. We searched PubMed and Scopus databases. The search included articles published from January 2017 to August 2024. The search strategy included the Medical subject headings (MeSHs): "acute kidney injury," "AKI," "pediatrics," "biomarkers, "children" in several variations e.g. "AKI IN children", "biomarkers OF AKI", "biomarkers AND AKI". Inclusion criteria were: (1) human studies, (2) studies on biomarkers of AKI in children (0–18 years), (3) articles published in English, (4) studies from 2017 to 2024, (5) studies containing clinical diagnosis of AKI. The exclusion included: (1) studies on adults or animals (2) lack of full text. Articles were selected in two stages: first, a review of titles and abstracts, followed by a full-text evaluation of eligible papers by two independent reviewers. In the initial phase, 345 articles were identified. After removal of duplicates and preliminary evaluation of abstracts and full texts, 30 studies were included finally. [Figure 1]

Results and discussion

AKI is a significant contributor to morbidity and mortality in pediatric patients, particularly in those requiring intensive care, undergoing cardiac surgery, or receiving nephrotoxic medications such as chemotherapeutic agents. Early detection of AKI is crucial for initiating timely interventions that can prevent irreversible kidney damage and improve outcomes. Traditional biomarkers like serum creatinine (SCr) and urine output are insufficient for early detection, as they often change only after substantial kidney damage has occurred. Thus, the need for more sensitive and specific biomarkers has driven extensive research in recent years. Several biomarkers have been identified as potential early indicators of AKI, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cystatin C,

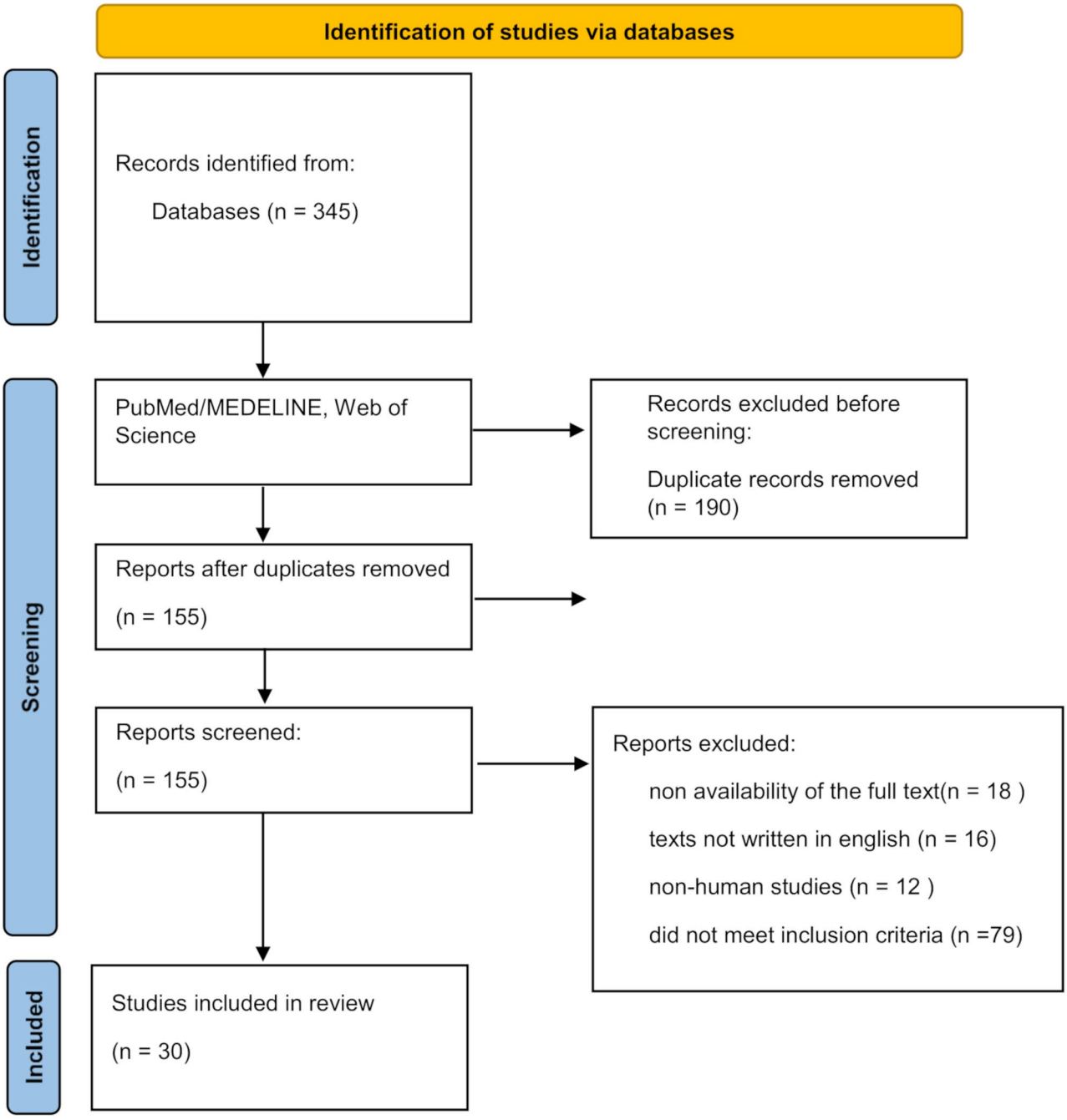

Fig. 1 Studies of the last 7 years (2017–2024) included in this review—PRISMA 2020 flow diagram. * Web of Science, PubMed/Medline

and others such as tissue inhibitor of metalloproteinases-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), urinary uromodulin (uUMOD) and liver fatty acid-binding protein (L-FABP). These biomarkers reflect different pathophysiological processes in AKI, such as tubular damage, cell cycle arrest, and glomerular injury. In this review, we discuss the findings of studies that have evaluated these biomarkers in various pediatric settings, highlighting their potential utility, limitations, and future directions. The detailed findings from studies conducted between 2017 and 2024 on protein markers associated with acute kidney injury in pediatrics are systematically summarized in Table 1.

Tubular injury biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL has been widely researched and identified as a leading biomarker because of its resistance to proteases,

Table 1 Results of the studies from the last seven years on protein markers associated with acute kidney injury in pediatric population

Year of publication	Author (s)	Title	Study Design	Results
2017	Sterling M, Al-Ismaili Z, McMahon KR, et al. [24]	"Urine biomarkers of acute kidney injury in noncritically ill, hospitalized children treated with chemotherapy."	Prospective cohort study involving hospitalized children receiving chemotherapy.	Urinary NGAL and KIM-1 levels were associated with AKI development, suggesting their potential as early biomarkers in this population.
2017	Dong L, Ma Q, Bennett M, et al. [47]	"Urinary biomarkers of cell cycle arrest are delayed predictors of acute kidney injury after pediatric cardiopulmonary bypass."	Observational study on children undergoing cardiopulmonary bypass.	Cell cycle arrest biomarkers may predict AKI after pediatric cardiopulmonary bypass.
2017	Cantinotti M, Giordano R, Scalese M, et al. [36]	"Diagnostic accuracy and prognostic value of plasmatic Cystatin-C in children undergoing pediatric cardiac surgery."	Prospective study on children undergoing cardiac surgery.	Plasma cystatin C was validated as an early and accurate predictor of AKI in pediatric cardiac surgery patients.
2017	Lau L, Al-Ismaili Z, Harel-Sterling M, et al. [37]	"Serum cystatin C for acute kidney injury evaluation in children treated with aminoglycosides."	Prospective observational study on children treated with aminoglycosides.	Serum cystatin C was found to be a reliable biomarker for the early detection of AKI in children undergoing aminoglycoside treatment.
2017	Spasojević-Dimitrijeva B, Kotur-Stevuljević J, Đukić M, et al. [30]	"Serum Neutrophil Gelatinase-Associated Lipocalin and Urinary Kidney Injury Molecule-1 as Potential Biomarkers of Subclinical Nephrotoxicity After Gadolinium-Based and Iodinated-Based Contrast Media Exposure in Pediatric Patients with Normal Kidney Function."	Prospective study with pediatric patients exposed to contrast media.	Both biomarkers were identified as potential indicators of subclinical nephrotoxicity following contrast exposure.
2017	Nakhjavan-Shahraki B, Yousefifard M, Ataei N, et al. [35]	"Accuracy of cystatin C in prediction of acute kidney injury in children; serum or urine levels: which one works better? A systematic review and meta-analysis."	Systematic review and meta-analysis.	Serum cystatin C was shown to be a reliable predictor of AKI in children, with urine levels also showing strong predictive value.
2018	Bennett MR, Pyles O, Ma Q, Devarajan P. [52]	"Preoperative levels of urinary uromodulin predict acute kidney injury after pediatric cardiopulmonary bypass surgery."	Prospective study involving children undergoing cardiopulmonary bypass surgery.	Preoperative uromodulin levels were predictive of AKI post-surgery, offering a potential early biomarker for intervention.
2018	Kari JA, Shalaby MA, Sofyani K, et al. [50]	"Urinary neutrophil gelatinase-associated lipocalin (NGAL) and serum cystatin C measurements for early diagnosis of acute kidney injury in children admitted to PICU."	Prospective observational study on children admitted to the Pediatric Intensive Care Unit (PICU).	Urinary NGAL and serum cystatin C were found to be effective early biomarkers for the diagnosis of AKI in critically ill children.
2019	Ziegelasch N, Vogel M, Müller E, et al. [54]	"Cystatin C serum levels in healthy children are related to age, gender, and pubertal stage."	Observational study on healthy children.	Cystatin C levels were found to correlate with age, gender, and pubertal stage, highlighting the need for age- and gender-specific reference ranges.
2019	Assadi F, Sharbaf FG. [43]	"Urine KIM-1 as a Potential Biomarker of Acute Renal Injury After Circulatory Collapse in Children."	Observational study on children with circulatory collapse.	Urine KIM-1 was found to be a potential early biomarker for AKI following circulatory collapse in pediatric patients.
2020	Naunova-Timovska, S., Cekovska, S., Sahpazova, E., Tasić, V. [25]	"Neutrophil Gelatinase-Associated Lipocalin as an Early Biomarker of Acute Kidney Injury in Newborns."	Observational study with newborns in a neonatal ICU.	NGAL levels were significantly higher in newborns with AKI, and they correlated with mortality.
2020	Yoneyama F, Okamura T, Takigiku K, et al. [44]	"Novel Urinary Biomarkers for Acute Kidney Injury and Prediction of Clinical Outcomes After Pediatric Cardiac Surgery."	Prospective study on children undergoing cardiac surgery.	New urinary biomarkers, including KIM-1, were effective in predicting AKI and associated clinical outcomes in pediatric cardiac surgery.
2020	Chui H., Caldwell J., Yordanova M. et al. [48]	"Tubular injury and cell-cycle arrest biomarkers to predict acute kidney injury in noncritically ill children receiving aminoglycosides."	Prospective cohort study.	Novel biomarkers such as KIM-1 and NGAL showed significant potential for predicting AKI development before clinical manifestations, allowing earlier intervention.

Table 1 (continued)

Year of publication	Author (s)	Title	Study Design	Results
2020	Fazel M, Sarveazad A, Mohamed Ali K, et al. [32]	"Accuracy of Urine Kidney Injury Molecule-1 in Predicting Acute Kidney Injury in Children; a Systematic Review and Meta-Analysis."	Systematic review and meta-analysis.	Urinary KIM-1 was identified as a moderately accurate predictor of AKI in children.
2020	Afolayan FM, Adedoyin OT, Abdulkadir MB, et al. [39]	"Acute Kidney Injuries in Children with Severe Malaria: A comparative study of diagnostic criteria based on serum cystatin C and creatinine levels."	Comparative study on children with severe malaria.	Cystatin C was more sensitive and accurate than creatinine in identifying AKI in pediatric malaria cases.
2021	Vijay P, Lal BB, Sood V, et al. [37]	"Cystatin C: best biomarker for acute kidney injury and estimation of glomerular filtration rate in childhood cirrhosis."	Comparative study on children with cirrhosis.	Cystatin C was identified as a more accurate biomarker than creatinine for estimating GFR and detecting AKI in children with cirrhosis.
2021	Hidayati E.L., Utami M.D., Rohsiswatmo R. et al. [38]	"Cystatin C compared to serum creatinine as a marker of AKI in critically ill neonates."	Observational study of critically ill neonates.	Cystatin C was shown to be a superior early biomarker compared to serum creatinine, particularly within the first 24 hours after admission.
2021	Slagle CL, Goldstein SL, Gavigan HW, et al. [26]	"Association between Elevated Urine Neutrophil Gelatinase-Associated Lipocalin and Postoperative Acute Kidney Injury in Neonates."	Observational study of neonates undergoing surgery.	Elevated urine NGAL levels were associated with an increased risk of postoperative AKI in neonates.
2021	Agarwal, Y., Rameshkumar, R., Krishnamurthy, S., et al. [29]	"Incidence, Risk Factors, the Role of Plasma NGAL and Outcome of Contrast-Induced Acute Kidney Injury in Critically Ill Children."	Prospective cohort study of critically ill children undergoing contrast procedures.	Plasma NGAL was associated with contrast-induced AKI and was predictive of poor outcomes in critically ill children.
2021	McMahon KR, Chui H, Rassekh SR, et al. [31]	"Urine Neutrophil Gelatinase-Associated Lipocalin and Kidney Injury Molecule-1 to Detect Pediatric Cisplatin-Associated Acute Kidney Injury."	Prospective cohort study involving children receiving cisplatin.	Urinary NGAL and KIM-1 levels were higher in patients who developed AKI after cisplatin treatment.
2022	Sun Q, Kang Z, Li Z, et al. [42]	"Urinary NGAL, IGFBP-7, and TIMP-2: novel biomarkers to predict contrast medium-induced acute kidney injury in children."	Prospective study on children undergoing contrast procedures.	Urinary NGAL, IGFBP-7, and TIMP-2 were found to be effective for early contrast-induced AKI prediction, with good sensitivity and specificity.
2022	Huang H, Lin Q, Dai X, et al. [40]	"Derivation and validation of urinary TIMP-1 for the prediction of acute kidney injury and mortality in critically ill children."	Prospective cohort study in critically ill children.	TIMP-1 was validated as a strong predictor of both AKI and mortality in critically ill children.
2022	Ganda IJ, Kasri Y, Susanti M, et al. [41]	"Kidney injury molecule type-1, interleukin-18, and insulin-like growth factor binding protein 7 levels in urine to predict acute kidney injury in pediatric sepsis."	Prospective cohort study involving children with sepsis.	The study aimed to evaluate KIM-1, IL-18, and IGFBP-7 as biomarkers for AKI in pediatric sepsis.
2022	Sarangam ML, Namazzi R, Datta D, et al. [50]	"Intestinal Injury Biomarkers Predict Mortality in Pediatric Severe Malaria."	Observational study of children with severe malaria.	Intestinal injury biomarkers, including TFF3 and I-FABP, were found to predict mortality and AKI in pediatric severe malaria patients.
2022	Van den Eynde J, Schuermans A, Verbakel JY, et al. [26]	"Biomarkers of acute kidney injury after pediatric cardiac surgery: a meta-analysis of diagnostic test accuracy."	Meta-analysis of studies on pediatric patients undergoing cardiac surgery.	The meta-analysis identified several biomarkers, including NGAL and KIM-1, as effective in predicting AKI post-cardiac surgery in pediatric patients.
2022	Harris RE, Yates AR, Nandi D, et al. [45]	"Urinary biomarkers associated with acute kidney injury in pediatric mechanical circulatory support patients."	Observational study on children receiving mechanical circulatory support.	Urinary biomarkers like NGAL were significant in predicting AKI in children under mechanical circulatory support.
2022	Galić S, Milošević D, Filipović-Grčić B, et al. [46]	"Early biochemical markers in the assessment of acute kidney injury in children after cardiac surgery."	Observational study of pediatric cardiac surgery patients.	Early biomarkers, including NGAL, showed promise in predicting AKI post-cardiac surgery in children.
2023	Adan D Jr, Batte A, Namazzi R, et al. [51]	"Renin as a Biomarker of Acute Kidney Injury and Mortality in Children With Severe Malaria or Sickle Cell Disease."	Prospective cohort study in children with severe malaria and sickle cell disease.	Renin was identified as a potential biomarker for predicting AKI and mortality in children with severe malaria or sickle cell disease.

Table 1 (continued)

Year of publication	Author (s)	Title	Study Design	Results
2024	Spyhalsky AM, Kim SJ, Meaney CJ, Smith NM, Shah DK, Hassinger AB, Fusco NM [48]	"Urinary biomarkers as indicators of acute kidney injury in critically ill children exposed to vancomycin."	Prospective observational study on critically ill children exposed to vancomycin.	Urinary biomarkers like NGAL and KIM-1 were found to be significant indicators of AKI in critically ill children receiving vancomycin.
2024	El-Halaby H, El-Bayoumi MA, El-Assmy M, et al. [27]	"Plasma Neutrophil Gelatinase-Associated Lipocalin (2 – 0) Index: A Precise and Sensitive Predictor of Acute Kidney Injury in Children Undergoing Cardiopulmonary Bypass."	Prospective study on children undergoing cardiopulmonary bypass.	The NGAL (2 – 0) index was highly effective in predicting AKI in pediatric patients undergoing CPB.

quick analysis capability and high sensitivity (83%) and specificity (89%) in detecting tubular injury [19]. NGAL is one of the most widely studied biomarkers for early detection of AKI. It is a small protein released from damaged renal tubular cells and is detectable in both urine and plasma. NGAL levels typically rise within a few hours of kidney injury, making it an early indicator of AKI before serum creatinine levels rise. Several studies have validated the efficacy of NGAL as an early biomarker for AKI in children. **Sterling M. et al. (2017)** [20] demonstrated that urinary NGAL could detect subclinical AKI in children undergoing chemotherapy, highlighting its potential role in monitoring renal function in noncritically ill children. Similarly, **Naunova-Timovska S. et al. (2020)** [21] focused on NGAL as an early biomarker of AKI in newborns and found that elevated NGAL levels were strongly associated with AKI and correlated with mortality. This study underscored the importance of NGAL in neonatal care, where traditional markers like creatinine may be unreliable because of the immature renal function of neonates. **Slagle C.L. et al. (2021)** [22] further supported the use of NGAL in predicting AKI, specifically in neonates undergoing surgery. Their study found a significant association between elevated urine NGAL levels and the risk of postoperative AKI, which was particularly important in neonates who underwent complex surgical procedures. These findings were consistent with other studies, such as **El-Halaby H. et al. (2024)** [23], who showed the utility of the plasma NGAL (2 – 0) index as a sensitive predictor of AKI in children undergoing cardiopulmonary bypass (CPB). A study by **Ishak et al.** [24] was conducted on urinary NGAL and microalbuminuria in a sample of 91 subjects, including 30 PICU patients, 31 diabetic patients, and 30 healthy controls. The findings showed that urinary NGAL levels were significantly higher in the PICU group, followed by the diabetic group, and the lowest in the control group ($p = 0.022$). A positive correlation was observed between urinary NGAL and microalbuminuria within the PICU group ($R = 0.585$, $p = 0.001$). These results suggest that urinary NGAL could be a valuable biomarker for detecting subclinical AKI before the onset of functional renal damage. In addition to its use in surgical patients, NGAL has shown promise in detecting AKI in other clinical contexts. **Agarwal Y. et al. (2021)** [25] investigated the role of plasma NGAL in predicting contrast-induced AKI in critically ill children and found that elevated NGAL levels were associated with both AKI development and poor clinical outcomes. These studies collectively highlight NGAL's versatility as a biomarker across different pediatric populations, including neonates, cardiac surgery patients, and children receiving nephrotoxic agents. Meta-analysis conducted by **Jef Van den Eynd et al. (2022)** [26] reviewed 56 studies on biomarkers for

predicting acute kidney injury (AKI) in children after cardiac surgery, identifying urinary neutrophil gelatinase-associated lipocalin (uNGAL) as the most accurate biomarker, with a sensitivity of 91.3% and a specificity of 89.7%. The uNGAL-to-creatinine ratio showed the highest diagnostic odds ratio and was the only biomarker with a pooled AUC ≥ 0.800. Other promising biomarkers, such as L-FABP, serum cystatin C, and IL-18, also showed potential but require further validation.

Kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembrane protein that is expressed at low levels in healthy kidneys but is upregulated in response to tubular injury. It has been identified as a promising biomarker for detecting early AKI, particularly in cases of drug-induced nephrotoxicity. **Spasojević-Dimitrijeva B. et al. (2017)** [27] explored the potential of serum NGAL and urinary KIM-1 in detecting subclinical nephrotoxicity after contrast media exposure in children. Their study showed that both biomarkers were effective in identifying early renal injury, even in the absence of clinical symptoms. **McMahon K.R. et al. (2021)** [28] extended these findings by investigating the role of NGAL and KIM-1 in detecting cisplatin-associated AKI in pediatric patients. Their study showed that both biomarkers had moderate predictive value, with urine NGAL and KIM-1 concentrations rising significantly during later treatment cycles. These findings suggest that KIM-1 may be useful in monitoring cumulative nephrotoxicity in pediatric cancer patients undergoing chemotherapy. Fazel **M. et al. (2020)** [29] conducted a meta-analysis on the accuracy of urine KIM-1 in predicting AKI in children. The meta-analysis concluded that urine KIM-1 has a moderate accuracy in predicting AKI, but its utility may be enhanced when used in combination with other biomarkers as NGAL. This combination approach could improve the early detection of AKI and provide clinicians with a more comprehensive understanding of renal injury in pediatric patients.

Glomerular-Derived biomarkers

Cystatin C

Cystatin C is a low molecular weight protein that is freely filtered by the glomerulus and reabsorbed by the renal tubules. It is also an endogenous protease inhibitor that is consistently produced by nucleated cells. Its levels remain unaffected by factors such as age, gender, or muscle mass in children [30, 31]. This makes this marker potentially better for estimating glomerular filtration rate (GFR) and detecting early AKI. Several studies have explored the role of cystatin C in pediatric AKI. Meta-analysis by **Nakhjavan-Shahraki B. et al. (2017)** [32] involving 1,948 children showed that both serum and urine cystatin C levels were significantly higher in children with acute kidney injury (AKI), with AUC values of 0.83 and 0.85, respectively, for predicting AKI. Serum cystatin C showed the best sensitivity (0.85) and acceptable specificity (0.61) for AKI detection at cut-off points between 0.4 and 1.0 mg/L. The findings suggest that cystatin C is a reliable prognostic biomarker for early AKI prediction in children, potentially serving as an alternative to traditional diagnostic methods. **Massimiliano Cantinotti et al. (2017)** [33] evaluated the diagnostic accuracy of cystatin C in children undergoing cardiac surgery and found that plasma cystatin C levels correlated significantly with the development of AKI. Their study suggested that cystatin C could serve as a valuable early predictor of AKI in pediatric cardiac patients, particularly in the immediate post-surgical period. **Vijay P. Lal et al. (2021)** [34] further showed that cystatin C was a superior biomarker for estimating GFR and detecting AKI in children with cirrhosis. Their study found that cystatin C was more accurate than serum creatinine in reflecting changes in kidney function, particularly in children with liver disease, where creatinine levels can be misleading because of reduced muscle mass. Similarly, **Hidayati E.L. et al. (2021)** [35] showed that cystatin C provided earlier detection of AKI compared to traditional serum creatinine in critically ill neonates, particularly within the first 24 h of admission. In cases of severe malaria, **Afolayan F.M. et al. (2020)** [36] found that cystatin C was more sensitive than creatinine in detecting AKI. This study emphasized the importance of cystatin C in infectious disease contexts, where rapid changes in renal function require timely and accurate biomarkers for early intervention. **Lau L. et al. (2017)** [37] in a prospective cohort study involving 81 noncritically ill children during 110 aminoglycoside treatments found that serum cystatin-C (CysC) was an effective early biomarker for acute kidney injury (AKI). CysC-AKI developed in 48% of treatments, and CysC levels predicted stage 1 SCr-AKI with an AUC of 0.75 and stage 2 SCr-AKI with an AUC of 0.85, two days before SCr-AKI was detected. A 44% rise in CysC provided the best sensitivity (65%) and specificity (83%) for predicting stage 1 SCr-AKI, and CysC was also predictive of persistent AKI with AUCs of 0.73 to 0.76.

uUMOD

Uromodulin is produced by cells in the thick ascending limb (TAL) and distal convoluted tubule (DCT) of the nephron [38]. **You et al. (2021)** [39] found in their systematic review and meta-analysis that reduced urinary uromodulin is highly associated with acute kidney injury (AKI) among various patient populations. The meta-analysis of 11 studies encompassing 3148 patients indicated that AKI patients had highly decreased urinary uromodulin levels compared to non-AKI individuals. The authors further pointed out that the association was

highly significant in pediatric patients and even in those who were coming for surgery.

Practical applications of biomarkers combination

Combining multiple biomarkers has been proposed as a strategy to enhance the sensitivity and specificity of AKI detection in pediatric patients. **Huang H. et al. (2022)** [40] explored the predictive value of urinary TIMP-1 in combination with NGAL and other biomarkers for diagnosing AKI and predicting mortality in critically ill children. Their study found that TIMP-1 had strong predictive value for both AKI and mortality, and when used with NGAL, it provided more robust early detection of renal injury. **Ganda IJ. et al. (2022)** [41] found that urinary levels of KIM-1, IL-18 and IGFBP-7 were effective in predicting acute kidney injury (AKI) in septic pediatric patients, with IL-18 showing the highest sensitivity (92.5%) and specificity (91.78%). Urinary IL-18 proved to be the most reliable biomarker for predicting AKI in children with sepsis, outperforming KIM-1 and IGFBP-7. Similarly, **Sun Q. et al. (2022)** [42] investigated the combination of urinary NGAL, IGFBP-7, and TIMP-2 for predicting contrast-induced AKI in children. Their findings showed that this biomarker combination provided good sensitivity and specificity for early AKI prediction, allowing for timely intervention in pediatric patients undergoing contrast-enhanced imaging. Also, **Asadi F. et al. (2019)** [43] in their study evaluated the effectiveness of urinary biomarkers IL-18, KIM-1, and NGAL in predicting acute kidney injury (AKI) in critically ill children with circulatory collapse. KIM-1 was found to be the most accurate early predictor of AKI, with the highest area under the curve (AUC) of 0.81, outperforming NGAL and IL-18. Unlike stable serum creatinine levels, urinary concentrations of these biomarkers increased significantly over the first 6 days of hospitalization, making them effective for early AKI detection. Study by **Yoneyama et al. (2020)** [44] found that elevated urinary L-FABP and NGAL levels post cardiac surgery were strong early predictors of AKI and were associated with longer intubation, ICU stays, and hospitalization, highlighting their usefulness for detecting AKI and predicting adverse outcomes. Furthermore, **Harris et al. (2024)** [45] measured fourteen urinary biomarkers on the first day after mechanical circulatory support (MCS) initiation and found that higher urine albumin and osteoactivin levels were significantly associated with AKI development within seven days. After adjusting for urine creatinine, a higher osteoactivin/UCr ratio was linked to increased odds of AKI (OR: 2.05; $p = 0.028$). These findings suggest an early rise in urine osteoactivin is associated with AKI in pediatric MCS patients. **Galić et al.** [46] evaluated early biochemical markers in plasma (NGAL, CysC) and urine (NGAL, KIM-1) to detect AKI in 100 children after congenital heart disease surgery. The study found that elevated CysC and plasma NGAL levels within the first 12 h were powerful predictors of AKI, with the combination of plasma CysC and urinary NGAL being the most effective at 6, 12, and 24 h post-surgery. Also, **Dong L. et al. (2017)** [47] evaluated the ability of several biomarkers to predict acute kidney injury (AKI) after pediatric cardiopulmonary bypass (CPB). While urine NGAL was the most accurate standalone predictor at 2 and 6 h post-CPB, a combination of NGAL, IL-18, and TIMP-2 improved predictive accuracy at 12 h. Also **Spyhalsky AM. et al. (2024)** [48] in their study evaluated the effectiveness of urinary biomarkers uNGAL and uKIM-1 in detecting acute kidney injury (AKI) in critically ill children exposed to vancomycin. In a cohort of 48 children, 16.7% developed AKI, and those who did showed significantly higher increases in uNGAL and uKIM-1 levels compared to those without AKI. The findings suggest these biomarkers could be valuable for early detection of AKI, potentially offering an advantage over traditional serum creatinine measurements. In contrast, a study by **Chui H. et al. (2020)** [49] evaluated NGAL, IL-18, KIM-1, TIMP2 and IGFBP7 for the detection of aminoglycoside-induced acute kidney injury (AG-AKI) in non-critically ill children. NGAL, IL-18 and TIMP2*IGFBP7 showed moderate predictive ability for AG-AKI, with an AUC ≥ 0.73 up to three days before the onset of AKI. **Kari JA et al. (2018)** [50] compared the effectiveness of serum cystatin-C (s-Cys-C) and urinary neutrophil gelatinase-associated lipocalin (uNGAL) as early biomarkers for acute kidney injury (AKI) in critically ill children. Among the 40 children studied, 22 developed AKI, with uNGAL and s-Cys-C showing strong predictive value for AKI, with AUCs of 0.76 and 0.86, respectively. The findings suggest both biomarkers can detect AKI earlier than traditional methods, with uNGAL and s-Cys-C providing good sensitivity and specificity.

Specific pediatric populations

AKI is a multifactorial condition that occurs in various pediatric populations, each with its own unique risk factors and challenges. For example, in pediatric cardiac surgery patients, biomarkers like NGAL and cystatin C have been particularly useful for predicting AKI because of ischemic injury and cardiopulmonary bypass. **Yoneyama F. et al. (2020)** [44] demonstrated that novel urinary biomarkers could predict both AKI and clinical outcomes in children undergoing cardiac surgery, further supporting the utility of these markers in high-risk surgical populations. In pediatric sepsis, **Ganda Idham Jaya et al. (2022)** [41] evaluated the utility of KIM-1, IL-18, and IGFBP-7 as biomarkers for AKI prediction. Their study found that these urinary biomarkers were significantly associated with AKI development in pediatric sepsis

cases, emphasizing the importance of early detection in critically ill septic patients. In pediatric patients with severe malaria, **Sarangam M.L. et al. (2022)** [51]and **Adan D. Jr. et al. (2023)** [52] explored the use of intestinal injury biomarkers and renin as predictors of AKI and mortality. Their studies found these biomarkers were significantly associated with both AKI and mortality, highlighting the importance of early diagnosis in infectious disease contexts. Of note is a paper in which **Bennett MR. et al. (2018)** [53] showed that low preoperative urinary uromodulin (uUMOD) strongly predicted increased risk of acute kidney injury (AKI) after cardiopulmonary bypass (CPB) in children, with an AUC of 0.90. Patients in the lowest quartile of preoperative uUMOD had a significantly higher risk of AKI, suggesting that uUMOD can stratify patients' risk before surgery to help prevent AKI.

Limitations and future directions

While biomarkers like NGAL, KIM-1, and cystatin C have shown promise in early AKI detection, several limitations remain. One of the major challenges is the variability in diagnostic accuracy depending on the clinical context, timing of measurement, and patient population. For instance, **McMahon K.R. et al. (2021)** [28] reported that the predictive value of NGAL and KIM-1 varied across different stages of cisplatin treatment, suggesting that these biomarkers may need to be tailored to specific treatment protocols. **Ziegelasch N. et al. (2019)** [54] demonstrate that factors affect CysC levels such as age, gender and growth, especially during infancy and adolescence. Therefore, it is important to use age- and gender-specific reference values for serum CysC when assessing renal function in a clinical setting. While combining biomarkers has the potential to improve diagnostic accuracy, more research is needed to determine the most effective combinations and optimal timing of measurements. Large-scale, multicenter studies are necessary to validate the clinical utility of these biomarkers across diverse pediatric populations.

Despite the promising nature of these biomarkers, there are a few hurdles in their clinical use. The greatest limitations is the heterogeneity of diagnostic results by, clinical context, patient population and evaluation time. While NGAL, KIM-1, and cystatin C have demonstrated great promise, their predictive value is heterogeneous in diverse pediatric subsets.

The cost and accessibility of biomarker testing present further obstacles to its routine use in clinical practice. Unlike creatinine, which is widely available and low-cost, most of the newer biomarkers require specialized laboratory methods that may not be accessible in every healthcare setting.

The second limitation is that there are no universal cutoffs for the interpretation of biomarkers, and hence they cannot be easily adopted in everyday clinical practice. The levels of biomarkers can vary with age, underlying illness, and concomitant inflammatory illnesses, and thus age-specific and context-specific ranges must be derived.

The future of AKI diagnosis and management in children will likely involve a multimarker approach, whereby panels of biomarkers are used to enhance diagnostic accuracy. Already, several studies have demonstrated that the use of multiple biomarkers, e.g., NGAL and cystatin C, or KIM-1 combined with IL-18 and IGFBP-7, enhances sensitivity and specificity. In addition, we recognize the urgent need for a novel biomarker that would surpass current ones in sensitivity, specificity, and clinical utility. The search for a marker able to detect AKI at its earliest, potentially reversible stage remains a high research priority. We would particularly like to add to this field by exploring novel biomarker candidates and their validation in the detection of pediatric AKI.

Conclusions

Biomarkers such as NGAL, KIM-1, and cystatin C represent significant advancements in the early detection of AKI in children. Their utility across various clinical contexts, including cardiac surgery, chemotherapy, sepsis, and infectious diseases, highlights their potential to improve patient outcomes through earlier diagnosis and intervention. However, variability in predictive accuracy and the need for further validation in heterogeneous pediatric populations remain challenges that must be addressed in future research. Integrating multiple biomarkers, along with traditional measures like serum creatinine and urine output, may ultimately provide a more comprehensive approach to AKI detection and management in pediatric patients.

Abbreviations

AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
RIFLE/pRIFLE	Risk, Injury, Failure, Loss, And End-Stage Renal Disease/ Pediatric RIFLE
KDIGO	Kidney Disease Improving Global Outcomes
AKIN	Acute Kidney Injury Network
eGFR	Estimated Glomerular Filtration Rate
IRI	Kidney Ischemia/Reperfusion Injury
NGAL/uNGAL	Neutrophil Gelatinase-Associated Lipocalin/Urine NGAL
TIMP-2	Tissue Inhibitor Of Metalloproteinases-2
KIM-1	Kidney Injury Molecule-1
IGFBP7	Insulin-Like Growth Factor-Binding Protein 7
uUMOD	Urinary Uromodulin
LFABP	Liver Fatty Acid-Binding Protein
SCr	Serum Creatinin
PICU	Pediatric Intensive Care Unit
CPB	Cardiopulmonary Bypass
CysC	Cystatin-C
IL-18	Interleukin 18
AUC	Area Under The Curve
MCS	Mechanical Circulatory Support

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The manuscript was conceptualized, researched and written by AB. AW and ARS reviewed the manuscript for intellectual content and provided critical feedback. All authors read and approved the final manuscript.

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Data availability
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Declarations

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