Biomarkers of acute kidney injury after pediatric cardiac surgery: a meta-analysis of diagnostic test accuracy

Jef Van den Eynde, Art Schuermans, Jan Y. Verbakel, Marc Gewillig, Shelby Kutty, Karel Allegaert, Djalila Mekahli

Abstract

Acute kidney injury (AKI) occurs frequently after cardiac surgery in children. Although current diagnostic criteria rely on serum creatinine and urine output, changes occur only after considerable loss of kidney function. This meta-analysis aimed to synthesize the knowledge on novel biomarkers and compare their ability to predict AKI. PubMed/MEDLINE, Embase, Scopus, and reference lists were searched for relevant studies published by March 2021. Diagnostic accuracy parameters were extracted and analyzed using hierarchical summary receiver operating characteristic (HSROC) method. Pooled estimates of the area under the curve (AUC) were calculated using conventional random-effects meta-analysis. Fifty-six articles investigating 49 biomarkers in 8617 participants fulfilled our eligibility criteria. Data from 37 studies were available for meta-analysis. Of the 10 biomarkers suitable for HSROC analysis, urinary neutrophil gelatinase-associated lipocalin (uNGAL) to creatinine (Cr) ratio yielded the highest diagnostic odds ratio (91.0, 95% CI 90.1–91.9), with a sensitivity of 91.3% (95% CI 91.2–91.3%) and a specificity of 89.7% (95% CI 89.6–89.7%). These results were confirmed in pooled AUC analysis, as uNGAL-to-Cr ratio and uNGAL were the only elaborately studied biomarkers (> 5 observations) with pooled AUCs ≥ 0.800. Liver fatty

acid-binding protein (L-FABP), serum cystatin C (sCysC), serum NGAL (sNGAL), and interleukin-18 (IL-18) all had AUCs ≥ 0.700.

Conclusion: A variety of biomarkers have been proposed as predictors of cardiac surgery-associated AKI in children, of which uNGAL was the most prominent with excellent diagnostic qualities. However, more consolidatory evidence will be required before these novel biomarkers may eventually help realize precision medicine in AKI management.

What is Known:

• Acute kidney injury (AKI) occurs in about 30–60% of children undergoing cardiac surgery and is associated with increased in-hospital mortality and adverse short-term outcomes. However, in current clinical practice, AKI definitions and detection often rely on changes in serum creatinine and urine output, which are late and insensitive markers of kidney injury.

• Although various novel biomarkers have been studied for the diagnosis of AKI in children after cardiac surgery, it remains unclear how these compare to one another in terms of diagnostic accuracy.

What is New:

• Pooled analyses suggest that for the diagnosis of AKI in children who underwent cardiac surgery, NGAL is the most accurate among the most frequently studied biomarkers.

• A number of other promising biomarkers have been reported, although they will require further research into their diagnostic accuracy and clinical applicability.

Introduction

Acute kidney injury (AKI) is a frequent and life-threatening complication of cardiac surgery in children. AKI develops in about 30–60% of children undergoing cardiac surgery [1, 2], and is not only associated with higher in-hospital mortality but also with increased duration of mechanical ventilation, need for inotropic therapy, and hospital length of stay [3,4,5]. AKI has various etiologies and may develop in different clinical settings, such as sepsis, nephrotoxicity, or cardiac surgery [6, 7]. From more than 35 different quantitative definitions of AKI in the past [8], medical professionals certainly have come a long way with the current standardized AKI definitions [9,10,11,12]. However, current standard definitions rely heavily on changes in the levels of serum creatinine (SCr) and urine output criteria. Because both are essentially markers of kidney function rather than structural kidney injury, SCr and urine output changes only become apparent after a substantial loss of functional nephrons [13, 14]. This is a significant shortcoming for the clinical detection of AKI.

In response to the need for earlier and more sensitive detection of AKI, numerous novel biomarkers have been studied in different populations over the past decades, particularly in children after cardiac surgery. Because the discovery, validation, and implementation of these novel biomarkers could lead to earlier detection and more effective preventive interventions, we aimed to summarize contemporary knowledge on the diagnostic accuracy of various biomarkers to predict AKI after pediatric cardiac surgery.

Materials and methods

Eligibility criteria, databases, and search strategy

The internationally recognized PRISMA [15] guidelines were followed. The systematic review and meta-analysis described in this article have not been registered. Studies were included if (i) the population consisted of pediatric patients (< 18 years), (ii) the patients underwent cardiac surgery, (iii) the accuracy of biomarkers for the development of postoperative AKI were investigated, and (iv) studies were prospective or retrospective observational studies or randomized controlled trials. Exclusion criteria consisted the following: (i) adult (> 18 years old) population, (ii) non-cardiac surgery, or (iii) biomarkers were not assessed in the setting of AKI.

PubMed/MEDLINE, Embase, Scopus, and reference lists of relevant articles were searched for articles in the English language meeting our inclusion criteria and published until March 15, 2021. The detailed search terms that were used are given in Supplemental Materials. The search was designed to comprehensively include all studies published on AKI after pediatric cardiac surgery and did not contain any names of biomarkers with the goal of avoiding any bias. The search string for each database was tested for rigor by a manual check for the key eligible publications and their listed citations. The following steps were taken: (1) identification of titles of records through databases searching, (2) removal of duplicates, (3) screening and selection of abstracts, 4) assessment for eligibility through full-text articles, and (5) final inclusion in the study. In steps 3–5, studies were selected by two independent reviewers (JVDE and AS) and disagreements were resolved by consensus.

Data extraction

From each study, we extracted the following information: (i) study characteristics, including year of publication, country of origin, study design, years of enrollment, sample size, population characteristics, and biomarkers being studied; (ii) AKI definition; (iii) number of documented AKI cases; (iv) timing of biomarker measurement, type of sampling (including

serum, plasma, or urine), and cutoff value; (v) numbers of true positive cases (TP), false negative cases (FN), false positive cases (FP), and true negative cases (TN), and estimates (including 95% confidence interval, CI) of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the curve (AUC). Within each study, missing data were calculated based on available data where possible, using basic algorithmic formulae as described in Supplemental Material, "Methods". The methodology for calculating the confidence intervals of AUC values is also described in Supplemental Material, "Methods". Two independent reviewers (JVDE and AS) extracted the data and disagreements were resolved by consensus.

Statistical analysis

A hierarchical summary receiver operating characteristic (HSROC) model was used to analyze and pool the diagnostic accuracy parameters across studies. This method incorporates both within- and between-study variability and the correlation between the summary statistics, thus allowing summarization of results from different cutoff values [16]. The summary estimates were plotted in "HSROC curves", including 95% confidence regions and 95% prediction regions. Subsequently, likelihood ratios after a positive (LR +) and a negative test result (LR −) as well as diagnostic odds ratios (DOR) were calculated from the bivariate model summary estimates using the Markov Chain Monte Carlo method [17]. Deeks funnel plots were performed to evaluate potential publication bias (P value < 0.1 indicating the presence of publication bias).

In addition, for all biomarkers that had at least two reported AUC values, a random-effects estimate of the composite AUC with 95% CI was calculated using an inverse variance method [18]. Chi-square test and I^2 test were performed for the assessment of statistical heterogeneity [19]. All analyses were completed using the "mada" (for HSROC analyses) and

"meta" (for pooled AUC values) packages of R Statistical Software (version 4.0.5, Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

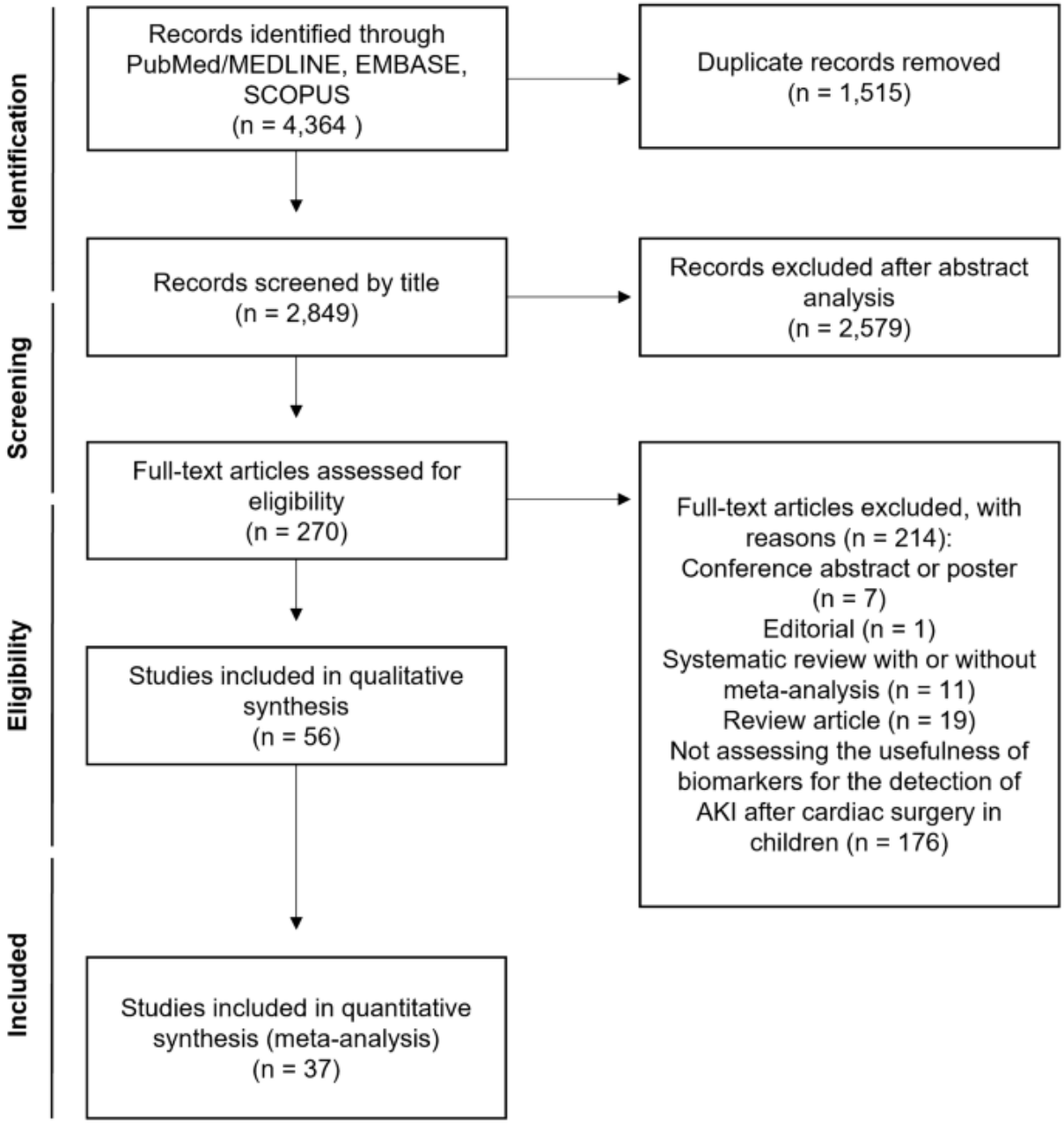
N/A.

Results

Study selection and characteristics

A total of 2849 citations were identified, of which 270 studies were potentially relevant and retrieved as full text. Fifty-six publications fulfilled our eligibility criteria, and 37 were included in the quantitative synthesis (Fig. 1). Characteristics of each study and their participants are shown in Supplemental Materials, Table S1. In all, 8617 participants (AKI: 3206 participants; no AKI: 5411 participants) were included from studies published from 2005 to 2021. All but three studies were prospectively designed and 14 were multicenter investigations. One study specifically investigated neonates [20] and five focused on infants [21,22,23,24,25]. The remainder included children of a broader age range. The vast majority of procedures involved cardiopulmonary bypass (CPB), reflecting the usual composition of pediatric cardiac surgery practices. The studies excluded patients with pre-existing kidney dysfunction.

Fig. 1



Flow diagram of studies included in data search

The studies reported 58,839 different measurements of 49 biomarkers at timepoints ranging from preoperatively to 3 days postoperatively. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) was the most extensively described marker (22 studies), followed by urinary interleukin-18 (uIL-18) (9 studies), serum cystatin C (sCysC), serum neutrophil

gelatin-associated lipocalin (sNGAL), and liver fatty acid-binding protein (L-FABP) (8 studies each). Thirty biomarkers were reported only once. Twenty-nine biomarkers originated from urine (indicated by the prefix "u-"), including 14 biomarker-to-creatinine ratios (indicated by the suffix "-/Cr"). Another 20 biomarkers were derived from either serum, plasma, or whole blood (indicated by the prefix "s-" or "serum").

Various criteria were used to define AKI. Nine studies used pRIFLE criteria [10], 1 used RIFLE [9], 9 used AKIN [11], and 16 used KDIGO [12]. The 21 remaining studies specified AKI as an increase of at least 50% in SCr concentration from baseline. Urine output criteria were included as part of the definition in only 5 studies; while all other studies defined AKI solely based on changes in SCr.

Quantitative synthesis of results

HSROC curves

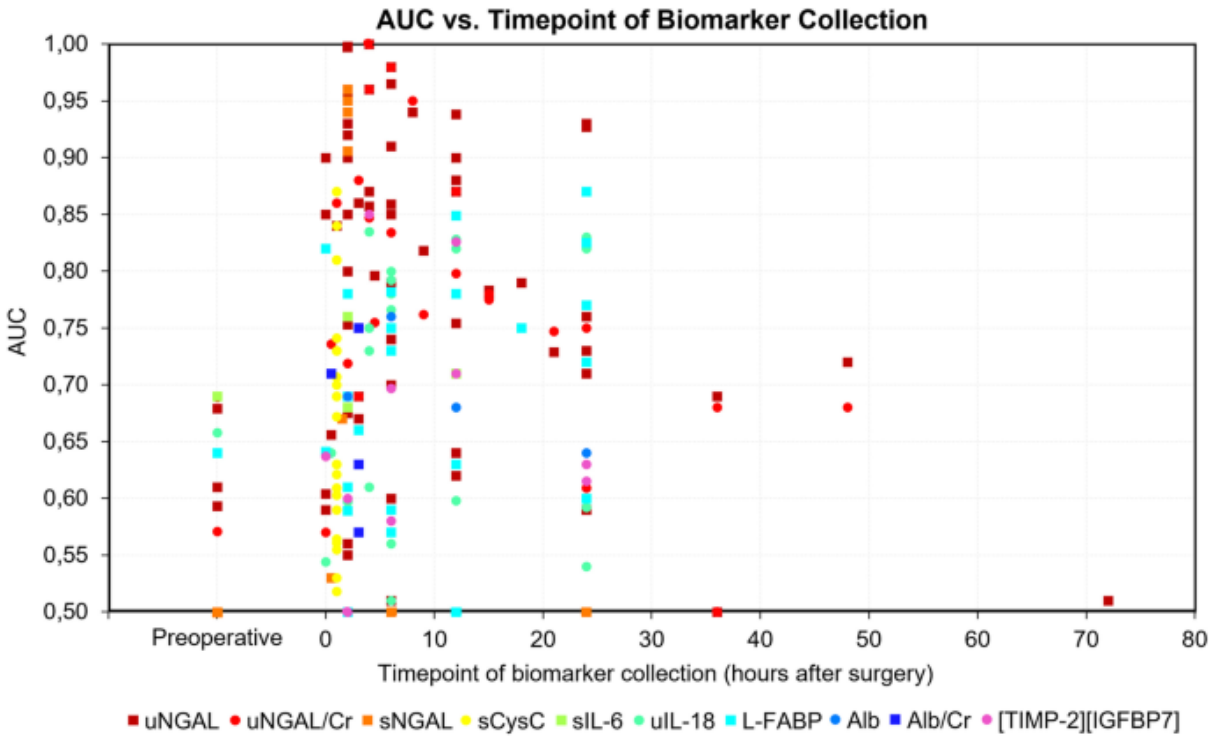
Ten biomarkers were suitable for HSROC analysis (Supplemental Material, Table S2). An overview of the pooled diagnostic accuracy values is given in Table 1 and HSROC curves are presented in Supplemental Materials, Figs. S1 and S2. Deeks funnel plot analysis (Supplemental Materials, Figs. S3 and S4) disclosed asymmetry around the axis for the effect of the following biomarkers: uNGAL ($p = 0.001$), uNGAL/Cr ($p < 0.001$), sNGAL ($p = 0.026$), and uIL-18 ($p = 0.001$). Consequently, publication bias related to these biomarkers is not unlikely. No evidence for publication bias was found for the other biomarkers.

Timing of biomarker collection

Figure 2 represents the varying diagnostic accuracies of the 10 biomarkers that were investigated in our HSROC analysis, depending on the timepoint at which they were

measured. NGAL, in both its urinary and serum forms, had the best predictive value for most postoperative timepoints. From a clinical perspective, it appears that sample measurements of NGAL can be taken within 6 h of surgery to accurately predict AKI development. Nonetheless, preoperative NGAL had considerably lower AUCs.

Fig. 2



catter plot showing AUC versus timepoint of biomarker collection for the 10 biomarkers assessed in HSROC analysis. NGAL showed the highest diagnostic accuracy at most timepoints and measurements within 6 h after surgery appeared to result in optimal prediction of AKI. AKI, acute kidney injury; AUC, area under the curve; Cr, creatinine; HSROC, hierarchical summery receiver operating characteristic; IGFBP7, insulin-like growth factor-binding protein 7; L-FABP, liver fatty acid-binding protein; sCysC, serum cystatin C; sIL-6, serum interleukin-6; sNGAL, serum neutrophil gelatinase-associated lipocalin; TIMP-2, tissue inhibitor of metalloproteinase 2; uIL-18, urine interleukin-18; uNGAL, urine neutrophil gelatinase-associated lipocalin

Pooled estimates for AUC

Fifty-four studies reported the area under the curve (AUC) of 49 biomarkers. Composite AUCs with data from more than 1 study could be calculated for 18 biomarkers, and from more than 5 studies for 7 biomarkers. As listed in Table 2, composite AUC estimations ranged from 0.510 to 0.980. Among the most elaborately studied biomarkers (> 5 observations), uNGAL and uNGAL/Cr were the only ones with pooled AUCs ≥ 0.800 (estimated values of 0.847 [95% CI 0.797–0.897] and 0.844 [95% CI 0.723–0.965], respectively). L-FABP, sCysC, sNGAL, and IL-18 had AUCs ≥ 0.700 (estimated values of 0.756 [95% CI 0.672–0.841], 0.749 [95% CI 0.669–0.829], 0.746 [95% CI 0.511–0.982], and 0.725 [95% CI 0.639–0.812], correspondingly). Kidney injury molecule-1 (KIM-1) was the marker with the lowest AUC of the most reported biomarkers, with an estimated value of 0.697 (95% CI 0.595–0.799).

For 31 biomarkers, the AUC was reported in a single study. Of these, aprotinin had the highest estimated AUC (0.980) [26]. Other biomarkers with high AUCs (≥ 0.900) were urinary homovanillic acid sulfate (HVA-SO_4) [27], uIL-6/Cr [28], and urinary uromodulin (UMOD) [29].

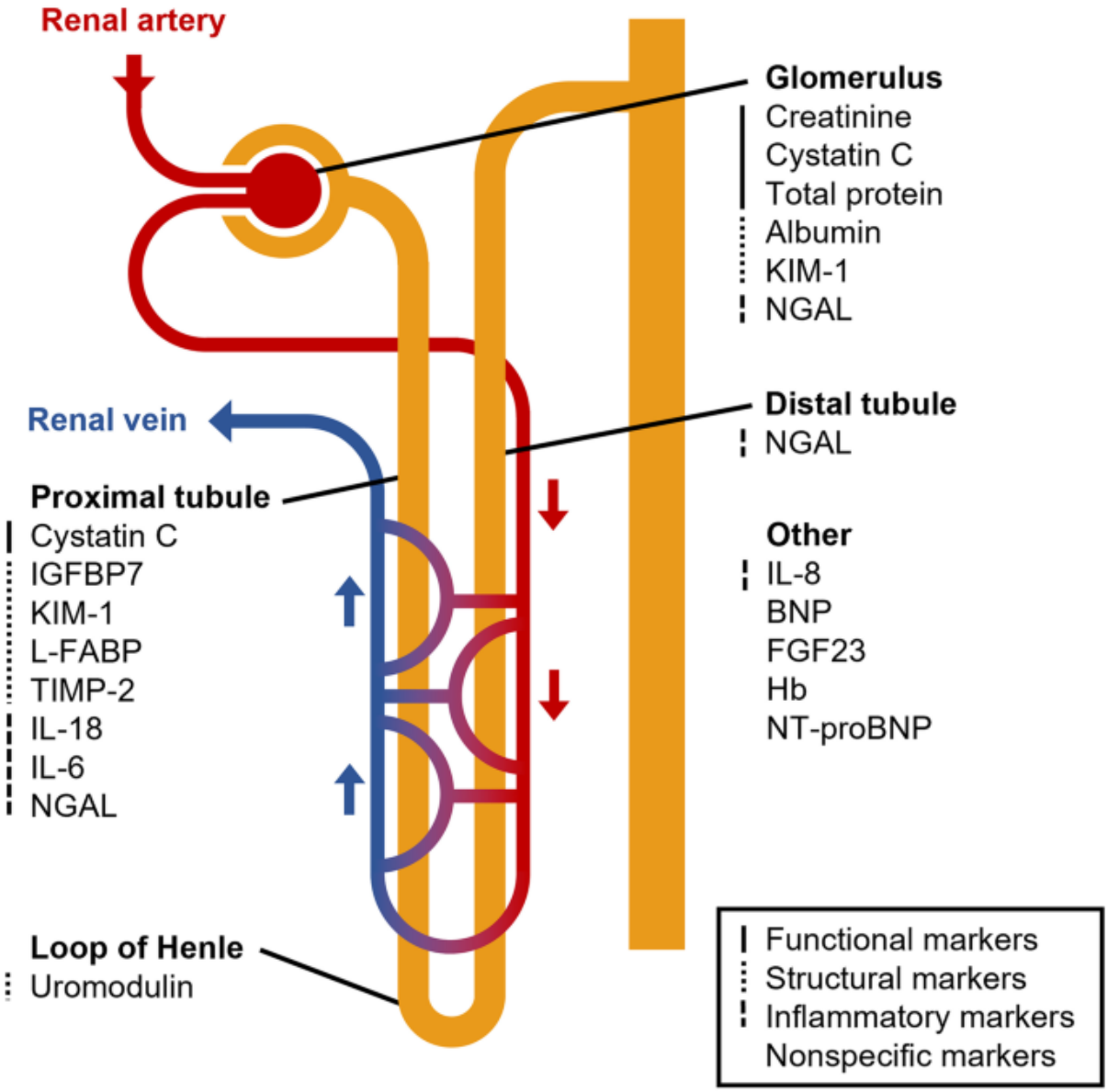
Discussion

Summary of evidence

Changes in SCr levels and urine output remain the reference standard for the diagnosis of AKI, but because of the insensitiveness and low specificity of both these for structural kidney injury, there is a need for more accurate and early biomarkers. We examined the diagnostic accuracy of novel biomarkers for the prediction of AKI after cardiac surgery in children.

Important biomarkers are shown in Fig. 3. NGAL was the most elaborately studied biomarker. HSROC analysis suggested uNGAL-to-Cr ratio as the most accurate marker for AKI after pediatric cardiac surgery, with an estimated sensitivity of 91.3% and specificity of 89.7%. NGAL had similar specificities when uncorrected for urinary creatinine or when measured in serum, although with slightly lower sensitivities. In comparison, albumin, albumin-to-Cr ratio, L-FABP, TIMP-2*IGFBP7, uIL-18, sIL-6, and sCysC had lower diagnostic accuracy on HSROC analysis. These results were largely reflected in the pooled AUC analysis, as uNGAL-to-Cr ratio and uNGAL were the only biomarkers studied by at least 5 studies with pooled AUCs ≥ 0.800. L-FABP, sCysC, sNGAL, and IL-18 had AUCs ≥ 0.700. Thirty out of 49 reported biomarkers were reported in only a single study. Altogether, these findings warrant further research into the clinical applicability of NGAL as a pediatric AKI biomarker and highlight some of the scarcely studied but potentially promising biomarkers.

Fig. 3



Overview of important biomarkers, based on location and etiology. AUC, area under the curve; BNP, brain natriuretic peptide; FGF23, fibroblast growth factor 23; Hb, hemoglobin; HSROC, hierarchical summery receiver operating characteristic; IGFBP7, insulin-like growth factor-binding protein 7; IL-6, interleukin-6; IL-8, interleukin-8; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal-pro-brain natriuretic peptide; TIMP-2, tissue inhibitor of metalloproteinase 2.

Biomarkers of kidney function, injury, and inflammation

Although SCr and urine output are indicators of kidney function instead of parenchymal kidney injury, they remain the main components of current diagnostic criteria for AKI. SCr has two main limitations: (a) its concentration changes only once about 50% of kidney function has been lost, and (b) its concentration depends on muscle mass, age, sex, medications, and hydration status [13, 14]. Next to SCr, the most studied functional AKI biomarker is CysC. In a recent meta-analysis, sCysC and uCysC had AUCs of 0.830 and 0.850 in the general pediatric population [30]. In contrast, our findings (AUCs of 0.750 and 0.780) suggest that the diagnostic accuracy might be more modest in the setting of cardiac surgery. The timing of sample collection likely explains this, as the time course of AKI differs in the setting of sepsis and nephrotoxicity, compared to cardiac surgery-associated AKI [31]. Furthermore, while less affected by factors known to confound SCr levels, such as muscle mass and protein intake, CysC concentration may be influenced by thyroid function and corticosteroids [32].

Recent research has focused on early tissue damage and the subsequent inflammatory cascade as a potential source of early biomarkers for AKI. Examples of well-studied markers of kidney injury are albumin, KIM-1, and L-FABP. Ho et al. [33] performed a meta-analysis to assess the performance of KIM-1 and L-FABP to predict AKI in adults after cardiac surgery. They estimated the AUCs of both biomarkers at 0.720, which is similar to our results (KIM-1: 0.697, L-FABP: 0.756). This suggests that both KIM-1 and L-FABP can predict AKI to a certain degree, but their diagnostic potential remains limited compared to other biomarkers. Others [34] have shown L-FABP as a sensitive predictor of in-hospital mortality, with a sensitivity of 93.2% and a specificity of 78.8%. These results indicate that biomarkers of

kidney injury can be strong predictors of adverse outcomes, while yielding modest accuracy for predicting AKI based on current criteria.

Biomarkers of inflammation are functionally related to those of kidney injury, as tissue damage induces an inflammatory cascade further aggravating tubular injury [35]. NGAL, IL-6, and IL-18 are exemplary biomarkers of inflammation. However, the use of these biomarkers in a setting of cardiac surgery can be tricky, as CPB itself provokes a systemic inflammatory response with upregulation of pro-inflammatory molecules [36]. NGAL, for example, is several-fold elevated after CPB in non-AKI patients [37]. Even so, NGAL yielded excellent results as a predictor of AKI in the present study. This is remarkable when considering the fact that NGAL yielded modest diagnostic abilities in adults after cardiac surgery [33]. The limited diagnostic accuracy of NGAL in adults may be related to the co-morbidities of diabetes and pre-existing kidney dysfunction [13, 38, 39]. These observations, along with the variation in diagnostic ability of CysC between settings, stress the importance of assessing AKI biomarkers in specific contexts, both age-wise and with regard to clinical setting.

Timing of biomarker collection

As observed in Fig. 2, most biomarkers predicted AKI with highest accuracy when measured within 6 h after surgery, but performed poorly in the preoperative setting. Illustrating this, Zheng et al. [40] found that both uNGAL and uNGAL/Cr had considerably lower AUCs when measured preoperatively (0.593 and 0.571), in comparison to their postoperative counterparts measured at 4 (0.857 and 0.847), 6 (0.859 and 0.834), and 12 h (0.754 and 0.798) after CPB. Similarly, 3 independent studies reported lower preoperative AUCs for sCysC compared to AUCs from 1 to 6 h postoperatively [41,42,43]. Therefore, some of the most extensively studied biomarkers seem to perform well in the early postoperative setting,

but might not be ideal to predict AKI before the operation. However, as will be discussed below, the combination of these biomarkers with clinical variables might nonetheless result in satisfactory performance to allow for preoperative risk stratification.

Some biomarkers were capable of predicting AKI preoperatively in children undergoing cardiac surgery. For example, de Fontnouvelle et al. [44] found that preoperative plasma interleukin-8 (IL-8) had an AUC of 0.810. Likewise, Bucholz et al. [45] reported heart-type fatty acid-binding protein (H-FABP) to exhibit a higher preoperative AUC (0.700 for preoperative compared to 0.560 for postoperative) in a cohort of 106 pediatric cardiac surgery patients. The highest preoperative AUC (0.900) was reported for UMOD, otherwise known as Tamm-Horsfall protein [29]. Lower baseline UMOD levels predicted higher incidence of AKI and longer hospital length of stay after pediatric cardiac surgery. These findings are consistent with investigations in adults undergoing CPB [46]. Accurate preoperative biomarkers can be of great value to fulfill the promises of precision medicine, because risk stratification for adverse post-surgical outcomes allows for targeted preventive interventions, as outlined in the next section. The present analyses warrant further research into the predictive properties of IL-8, H-FABP, UMOD, and other preoperative biomarkers.

Perspectives for future research and clinical practice

Our results indicate the potential of NGAL and a few other—less investigated—biomarkers for pediatric cardiac surgery-related AKI. The use of uNGAL in clinical practice could lead to health and cost benefits [47, 48]. A cost-effectiveness analysis estimated that uNGAL was cost-effective compared to current diagnostic methods [49]. Important mediators of this effect are improved risk stratification, allocation of resources, and the ability to direct early intervention. Some have even referred to the quest for AKI biomarkers as the "search for the kidney troponin I," drawing the analogy with the prompt provision of percutaneous coronary

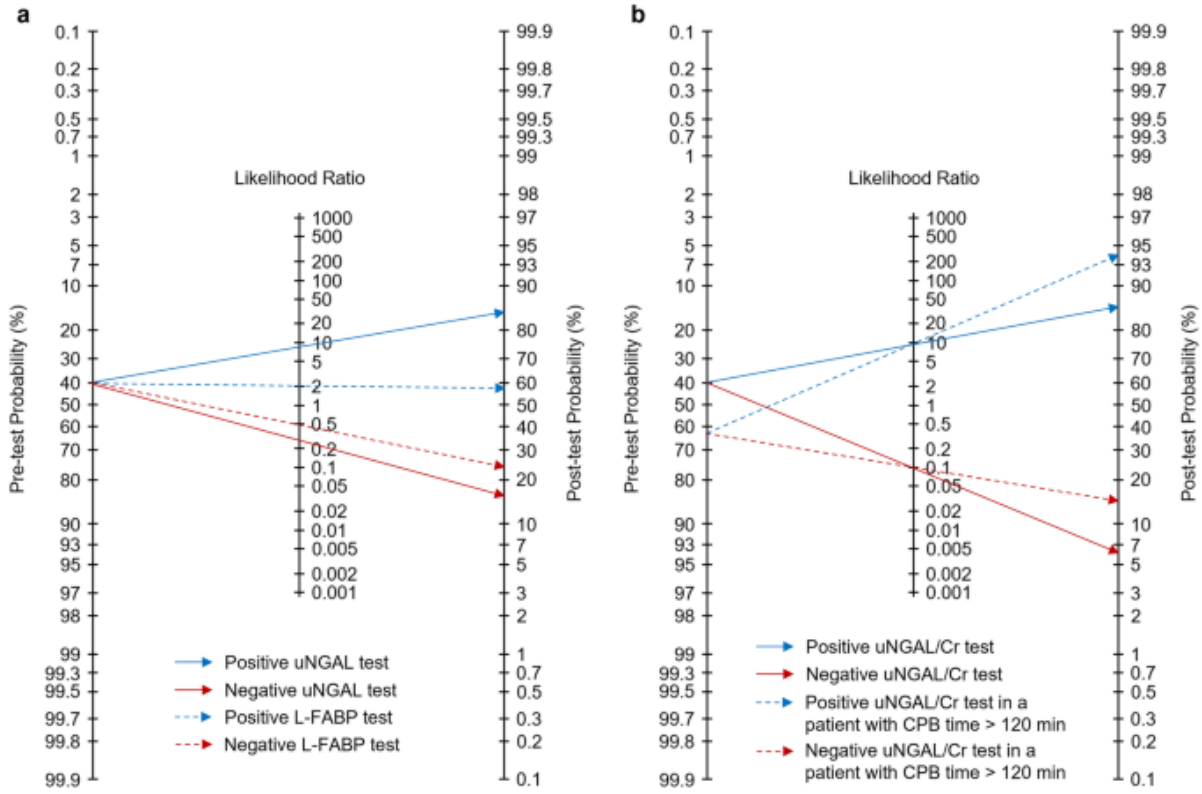
intervention in patients with acute coronary syndrome [50]. This would signify an important breakthrough compared with prior randomized controlled trials of individual pharmacological and device-oriented interventions, which have largely failed to prevent AKI after pediatric cardiac surgery [51]. Importantly, those trials were conducted in populations with heterogeneous risk profile, etiology, and pathophysiology. However, it is plausible that with proper risk stratification based on AKI biomarkers, subsets of patients may be identified who would benefit from certain strategies. Providing evidence to support this notion, the PrevAKI randomized controlled trial demonstrated that a "KDIGO bundle" consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and preventing hyperglycemia could effectively reduce the risk of AKI in high-risk adults defined as TIMP-2*IGFBP7 > 0.3 undergoing cardiac surgery (55.1 vs. 71.7%, $p = 0.004$) [52]. These observations encourage further efforts to develop, validate, and implement biomarkers of AKI in children.

It should be further explored how biomarkers can be integrated within clinical risk prediction models. Most such models have AUCs ranging from 0.720 to 0.830 [53, 54], which is likely to increase with the addition of accurate biomarkers. A promising tool is the renal angina index (RAI). This metric has been developed in critically ill children admitted to the pediatric intensive care unit (PICU), with an RAI of ≥ 8 in the first 12 h of admission exhibiting high sensitivity and negative predictive value for AKI development or persistence at 72 h (AUC = 0.77) [55]. Recent studies have revealed that the addition of uNGAL and/or other biomarkers to RAI could increase the AUC up to even 0.97 [56]. In particular, the high negative predictive value helps clinicians to focus on patients who are truly at risk, to allocate appropriate resources, and to escalate toward kidney replacement therapy when needed. Eventually, future studies using machine learning models that integrate AKI biomarkers with

data from electronic health records (including patient demographics and perioperative characteristics) are anticipated [57].

In the meantime, the findings from this meta-analysis can be clinically applied to estimate AKI risk in individual patients based on pre-test probability. Figure 4 illustrates how this can be achieved, using NGAL and L-FABP as an example. Pre-test probability is equated to the mean incidence of AKI in children undergoing cardiac surgery (40%) [1]. The resulting post-test probabilities with a positive or negative test result are presented for uNGAL and L-FABP in Fig. 4a. For example, if a patient has a positive test result for uNGAL (which has a LR + of 7.68), the post-test probability will be 84%. On the other hand, a negative L-FABP test (which has a LR- of 0.49) will result in a post-test probability of 25%. Figure 4b shows that incorporating clinical risk factors can improve the overall usefulness of biomarkers. Here, an odds ratio of 2.45 was used to calculate the elevated pre-test probability (62%) in patients with prolonged CPB (> 120 min) [58].

Fig. 4



Fagan nomogram to estimate the post-test probability of developing AKI after cardiac surgery in children, using (a) uNGAL and L-FABP and (b) uNGAL/Cr with or without integration of CPB time. **a** Pre-test probability (left axis) is equated to the mean incidence of AKI in children undergoing cardiac surgery (40%) as reported by Hoste et al. [1] The resulting post-test probabilities (right axis) with a positive or negative test result are presented for uNGAL and L-FABP. For example, if a patient has a positive test result for uNGAL (which has a LR + of 7.68), the post-test probability will be 84%. On the other hand, a negative L-FABP test (which has a LR − of 0.49) will result in a post-test probability of 25%. **b** Clinical risk prediction can further be enhanced by integrating clinical risk factors. Here, an odds ratio of 2.45 was used to calculate the elevated pre-test probability (62%) in patients with prolonged CPB (> 120 min) [58]. AKI, acute kidney injury; CPB, cardiopulmonary bypass; Cr, creatinine; L-FABP, liver fatty acid-binding protein; LR + ,

likelihood ratio of a positive test result; LR, likelihood ratio of a negative test result; uNGAL, urine neutrophil gelatinase-associated lipocalin.

A more structure-driven characterization and improved definition of AKI based on histopathological features and structural biomarkers could be valuable. The concept of precision medicine in AKI is evolving [59, 60]. Phenotyping at the cellular and molecular level may be a promising component for future trials and could possibly lead to a paradigm shift in the perception and management of AKI. These ideas have also been articulated in a recent consensus statement from the 23rd Acute Disease Quality Initiative (ADQI) meeting [61]. This document formulated 11 recommendations that suggest that a combination of biomarkers, along with clinical information, should be used to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity.

Limitation and sources of heterogeneity

This analysis has some limitations. First, it might have overestimated the actual predictive accuracies of the biomarkers studied. One source of overestimation is publication bias, for which evidence was found in some biomarkers based on Deeks funnel plots. In addition, the optimal AUC reported in each study was used for the pooled AUC estimations for each biomarker. Second, significant heterogeneity was noted for the AUC estimations of some biomarkers. Types of heart defects treated, measurement timepoints, types of sampling, assays, AKI definitions, and study population varied among studies. The timing and severity of AKI may also have differed within and between studies; severe AKI episodes occurring shortly after biomarker measurement tend to be rather easy to predict, whereas the predictive accuracy of any given biomarker for mild and late-onset episodes is usually lower [61, 62]. Nonetheless, the time-varying performance of biomarkers to detect different severity levels of

AKI could not be determined based on the available data and may require dedicated investigations. To account for the fact that diverse cut-offs were used, HSROC analysis was employed. Third, most of the various biomarkers were reported only in a single study. These biomarkers were predominant among the best scoring AUCs. When more studies examining these markers are carried out, the predictive accuracy will probably become more modest, due to the “regression to the mean” phenomenon. Fourth, HSROC analyses could only be conducted for a small fraction of all reported biomarkers, while others could not be investigated in-depth. Lastly, most studies used AKI definitions based on SCr criteria without urine output criteria. Although logistic and practical considerations were the main drivers for doing so, this practice probably accounts for a certain degree of misclassification bias. Indeed, a recent analysis of the Neonatal and Pediatric Heart and Renal Outcomes Network (NEPHRON) study demonstrated that urine output criteria lead to an important reclassification of stage 3 AKI after neonatal cardiac surgery [63].

Conclusions

This meta-analysis summarizes contemporary evidence on the diagnostic accuracy of various biomarkers to predict cardiac surgery-associated AKI in children. Several reported biomarkers are promising, but all require further assessment and validation. Future applications of these novel biomarkers in clinical care might reinforce the merit of precision medicine in AKI management.

References

1. Hoste EAJ, Kellum JA, Selby NM et al (2018) Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol 14:607–625

2. Van den Eynde J, Delpire B, Jacquemyn X et al (2021) Risk factors for acute kidney injury after pediatric cardiac surgery: a meta-analysis. Pediatr Nephrol 1:1–11. https://doi.org/10.1007/S00467-021-05297-0/FIGURES/2

3. Li S, Krawczeski CD, Zappitelli M et al (2011) Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Crit Care Med 39:1493–1499. https://doi.org/10.1097/CCM.0b013e31821201d3

4. Blinder JJ, Goldstein SL, Lee V-V et al (2012) Congenital heart surgery in infants: Effects of acute kidney injury on outcomes. J Thorac Cardiovasc Surg 143:368–374. https://doi.org/10.1016/j.jtcvs.2011.06.021

5. Van den Eynde J, Rotbi H, Gewillig M et al (2021) In-hospital outcomes of acute kidney injury after pediatric cardiac surgery: a meta-analysis. Front Pediatr 9:941. https://doi.org/10.3389/FPED.2021.733744/BIBTEX

6. Uchino S, Kellum JA, Bellomo R et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. J Am Med Assoc 294:813–818. https://doi.org/10.1001/jama.294.7.813

7. Singbartl K, Kellum JA (2012) AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int 81:819–825. https://doi.org/10.1038/ki.2011.339

8. Kellum JA, Levin N, Bouman C, Lameire N (2002) Developing a consensus classification system for acute renal failure. In: Current Opinion in Critical Care. Curr Opin Crit Care, pp 509–514

9. Bellomo R, Ronco C, Kellum JA et al (2004) Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. In: Critical care (London, England). BioMed Central, p R204

10. Akcan-Arikan A, Zappitelli M, Loftis LL et al (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 71:1028–1035. https://doi.org/10.1038/sj.ki.5002231

11. Mehta RL, Kellum JA, Shah SV et al (2007) Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31. https://doi.org/10.1186/cc5713

12. Khwaja A (2012) KDIGO clinical practice guidelines for acute kidney injury. Nephron 120:c179–c184. https://doi.org/10.1159/000339789

13. Mårtensson J, Martling CR, Bell M (2012) Novel biomarkers of acute kidney injury and failure: Clinical applicability. Br J Anaesth 109:843–850

14. Coca SG, Yalavarthy R, Concato J, Parikh CR (2008) Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 73:1008–1016

15. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372

16. Arends LR, Hamza TH, Van Houwelingen JC et al (2008) Bivariate random effects meta-analysis of ROC curves. Med Decis Mak 28:621–638. https://doi.org/10.1177/0272989X08319957

17. Rutter CM, Gatsonis CA (2001) A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 20:2865–2884. https://doi.org/10.1002/sim.942

18. DerSimonian R, Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 28:105–114. https://doi.org/10.1016/j.cct.2006.04.004

19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Br Med J 327:557–560

20. Brennan KG, Parravicini E, Lorenz JM, Bateman DA (2020) Patterns of urinary neutrophil gelatinase-associated lipocalin and acute kidney injury in neonates receiving cardiopulmonary bypass. Children 7:132. https://doi.org/10.3390/children7090132

21. Ricci Z, Netto R, Garisto C et al (2012) Whole blood assessment of neutrophil gelatinase-associated lipocalin versus pediatricRIFLE for acute kidney injury diagnosis and prognosis after pediatric cardiac surgery: cross-sectional study. Pediatr Crit Care Med 13:667–670. https://doi.org/10.1097/PCC.0b013e3182601167

22. Hazle MA, Gajarski RJ, Aiyagari R et al (2013) Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. J Thorac Cardiovasc Surg 146:861-867.e1. https://doi.org/10.1016/j.jtcvs.2012.12.012

23. Gist KM, Cooper DS, Wrona J et al (2018) Acute kidney injury biomarkers predict an increase in serum milrinone concentration earlier than serum creatinine-defined acute kidney injury in infants after cardiac surgery. Ther Drug Monit 40:186–194. https://doi.org/10.1097/FTD.0000000000000496

24.Bojan M, Vicca S, Lopez-Lopez V et al (2014) Predictive performance of urine neutrophil gelatinase-associated lipocalin for dialysis requirement and death following cardiac surgery in neonates and infants. Clin J Am Soc Nephrol 9:285–294. https://doi.org/10.2215/CJN.04730513

25. Herbert C, Patel M, Nugent A et al (2015) Serum cystatin C as an early marker of neutrophil gelatinase-associated lipocalin-positive acute kidney injury resulting from cardiopulmonary bypass in infants with congenital heart disease. Congenit Heart Dis 10:E180–E188. https://doi.org/10.1111/chd.12253

26. Nguyen MT, Dent CL, Ross GF et al (2008) Urinary aprotinin as a predictor of acute kidney injury after cardiac surgery in children receiving aprotinin therapy. Pediatr Nephrol 23:1317–1326. https://doi.org/10.1007/s00467-008-0827-9

27. Beger RD, Holland RD, Sun J et al (2008) Metabonomics of acute kidney injury in children after cardiac surgery. Pediatr Nephrol 23:977–984. https://doi.org/10.1007/s00467-008-0756-7

28. Dennen P, Altmann C, Kaufman J et al (2010) Urine interleukin-6 is an early biomarker of acute kidney injury in children undergoing cardiac surgery. Crit Care 14:R181. https://doi.org/10.1186/cc9289

29. Bennett MR, Pyles O, Ma Q, Devarajan P (2018) Preoperative levels of urinary uromodulin predict acute kidney injury after pediatric cardiopulmonary bypass surgery. Pediatr Nephrol 33:521–526. https://doi.org/10.1007/s00467-017-3823-0

30. Nakhjavan-Shahraki B, Yousefifard M, Ataei N et al (2017) 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. BMC Nephrol 18:1–13. https://doi.org/10.1186/s12882-017-0539-0

31. Koyner JL, Garg AX, Shlipak MG et al (2013) Urinary cystatin C and acute kidney injury after cardiac surgery. Am J Kidney Dis 61:730–738. https://doi.org/10.1053/j.ajkd.2012.12.006

32. Allegaert K, Mekahli D, Van den Anker J (2015) Cystatin C in newborns: a promising renal biomarker in search for standardization and validation. J Matern Neonatal Med 28:1833–1838

33. Ho J, Tangri N, Komenda P et al (2015) Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. Am J Kidney Dis 66:993–1005. https://doi.org/10.1053/j.ajkd.2015.06.018

34. Susantitaphong P, Siribamrungwong M, Doi K et al (2013) Performance of urinary liver-type fatty acid-binding protein in acute kidney injury: a meta-analysis. Am J Kidney Dis 61:430–439. https://doi.org/10.1053/j.ajkd.2012.10.016

35. Edelstein CL, Akcay A, Nguyen Q (2009) Mediators of inflammation in acute kidney injury. Mediators Inflamm 2009:12

36. Paparella D, Yau TM, Young E (2002) Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update Eur J Cardio-thoracic Surg 21:232–244

37. Cai L, Borowiec J, Xu S et al (2009) Assays of urine levels of HNL/NGAL in patients undergoing cardiac surgery and the impact of antibody configuration on their clinical performances. Clin Chim Acta 403:121–125. https://doi.org/10.1016/j.cca.2009.01.030

38. Nauta FL, Boertien WE, Bakker SJL et al (2011) Glomerular and tubular damage markers are elevated in patients with diabetes. Diabetes Care 34:975–981. https://doi.org/10.2337/dc10-1545

39. McIlroy DR, Wagener G, Lee HT (2010) Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: The effect of baseline renal function on diagnostic performance. Clin J Am Soc Nephrol 5:211–219. https://doi.org/10.2215/CJN.04240609

40. Zheng J, Xiao Y, Yao Y et al (2012) Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. Pediatr Cardiol 344(34):880–886. https://doi.org/10.1007/S00246-012-0563-6

41. Peco-Antić A, Ivanišević I, Vulićević I et al (2013) Biomarkers of acute kidney injury in pediatric cardiac surgery. Clin Biochem 46:1244–1251. https://doi.org/10.1016/J.CLINBIOCHEM.2013.07.008

42. Zheng J-Y, Xiao Y-Y, Yao Y, Han L (2013) Is serum cystatin C an early predictor for acute kidney injury following cardiopulmonary bypass surgery in infants and young children? Kaohsiung J Med Sci 29:494–499. https://doi.org/10.1016/J.KJMS.2013.01.004

43. Zappitelli M, Krawczeski CD, Devarajan P et al (2011) Early postoperative serum cystatin C predicts severe acute kidney injury following pediatric cardiac surgery. Kidney Int 80:655–662. https://doi.org/10.1038/KI.2011.123

44. de Fontnouvelle CA, Greenberg JH, Thiessen-Philbrook HR et al (2017) Interleukin-8 and tumor necrosis factor predict acute kidney injury after pediatric cardiac surgery. Ann Thorac Surg 104:2072–2079. https://doi.org/10.1016/J.ATHORACSUR.2017.04.038

45. Bucholz EM, Whitlock RP, Zappitelli M et al (2015) Cardiac biomarkers and acute kidney injury after cardiac surgery. Pediatrics 135:e945–e956. https://doi.org/10.1542/PEDS.2014-2949

46. Garimella PS, Jaber BL, Tighiouart H et al (2017) Association of preoperative urinary uromodulin with AKI after cardiac surgery. Clin J Am Soc Nephrol 12:10–18. https://doi.org/10.2215/CJN.02520316

47. Parikh A, Rizzo JA, Canetta P et al (2017) Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. PLoS ONE 12:e0178091. https://doi.org/10.1371/journal.pone.0178091

48. Shaw AD, Chalfin DB, Kleintjens J (2011) The economic impact and cost-effectiveness of urinary neutrophil gelatinase-associated lipocalin after cardiac surgery. Clin Ther 33:1713–1725. https://doi.org/10.1016/j.clinthera.2011.09.014

49. Petrovic S, Bogavac-Stanojevic N, Lakic D et al (2015) Cost-effectiveness analysis of acute kidney injury biomarkers in pediatric cardiac surgery. Biochem Medica 25:262–271. https://doi.org/10.11613/BM.2015.027

50. Goldstein SL (2011) Acute kidney injury biomarkers: renal angina and the need for a renal troponin I. BMC Med 9:1–5. https://doi.org/10.1186/1741-7015-9-135/PEER-REVIEW

51. Van den Eynde J, Cloet N, Van Lerberghe R et al (2021) Strategies to prevent acute kidney injury after pediatric cardiac surgery a network meta-analysis. Clin J Am Soc Nephrol 16:1480–1490. https://doi.org/10.2215/CJN.05800421/-/DCSUPPLEMENTAL

52. Meersch M, Schmidt C, Hoffmeier A et al (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 43:1551–1561. https://doi.org/10.1007/S00134-016-4670-3/FIGURES/2

53. Pozzoli S, Simonini M, Manunta P (2018) Predicting acute kidney injury: current status and future challenges. J Nephrol 31:209–223. https://doi.org/10.1007/s40620-017-0416-8

54. Huen SC, Parikh CR (2012) Predicting acute kidney injury after cardiac surgery: a systematic review. Ann Thorac Surg 93:337–347

55. Basu RK, Zappitelli M, Brunner L et al (2014) Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. Kidney Int 85:659. https://doi.org/10.1038/KI.2013.349

56. Menon S, Goldstein SL, Mottes T et al (2016) Urinary biomarker incorporation into the renal angina index early in intensive care unit admission optimizes acute kidney injury prediction in critically ill children: a prospective cohort study. Nephrol Dial Transplant 31:586–594. https://doi.org/10.1093/NDT/GFV457

57. Thongprayoon C, Hansrivijit P, Bathini T et al (2020) Predicting acute kidney injury after cardiac surgery by machine learning approaches. J Clin Med 9:1767. https://doi.org/10.3390/jcm9061767

58. Park SK, Hur M, Kim E et al (2016) Risk factors for acute kidney injury after congenital cardiac surgery in infants and children: a retrospective observational study. PLoS ONE 11:1–15. https://doi.org/10.1371/journal.pone.0166328

59. Kiryluk K, Bomback AS, Cheng YL et al (2018) Precision medicine for acute kidney injury (AKI): redefining AKI by agnostic kidney tissue interrogation and genetics. Semin Nephrol 38:40–51

60. Schaub JA, Heung M (2019) Precision medicine in acute kidney injury: a promising future? Am J Respir Crit Care Med 199:814–816

61. Ostermann M, Zarbock A, Goldstein S et al (2020) Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open 3:e2019209–e2019209. https://doi.org/10.1001/JAMANETWORKOPEN.2020.19209

62. Murray PT, Mehta RL, Shaw A et al (2014) Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney Int 85:513–521. https://doi.org/10.1038/KI.2013.374/ATTACHMENT/AD74C145-383D-4990-9ECF-D8F342E4CB07/MMC1.DOC

63. Alten JA, Cooper DS, Blinder JJ et al (2021) Epidemiology of acute kidney injury after neonatal cardiac surgery: a report from the Multicenter Neonatal and Pediatric Heart and Renal Outcomes Network. Crit Care Med E941–E951. https://doi.org/10.1097/CCM.0000000000005165

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Contributions

Mr. Van den Eynde and Mr. Schuermans conceptualized and designed the study, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Profs. Verbakel, Gewillig, Kutty, Allegaert, and Mekahli conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics declarations

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no competing interests.