



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

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Received: 19 October 2021 / Revised: 5 January 2022 / Accepted: 9 January 2022
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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.

Keywords Acute kidney injury · Biomarkers · Cardiac surgical procedures · Heart defects · Congenital · Meta-analysis · Pediatrics

Communicated by Gregorio Paolo Milani

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Abbreviations

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AUC	Area under the curve
CI	Confidence interval
CPB	Cardiopulmonary bypass
CysC	Cystatin C

DOR	Diagnostic odds ratio
FP	False positives
FN	False negatives
H-FABP	Heart-type fatty acid-binding protein
HSROC	Hierarchical summary receiver operating characteristic curve
HVA-SO4	Homovanillic acid sulfate
IGFBP7	Insulin-like growth factor-binding protein 7
IL-6	Interleukin 6
IL-8	Interleukin 18
KDIGO	Kidney Disease Improving Global Outcomes
KIM-1	Kidney injury molecule-1
KIU	Kallikrein inhibiting units
L-FABP	Liver fatty acid-binding protein
LR	Likelihood ratio
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NGAL	Neutrophil gelatinase-associated lipocalin
NPV	Negative predictive value
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RIFLE	Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease
SCr	Serum creatinine
TIMP-2	Tissue inhibitor of metalloproteinase 2
TP	True positives
TN	True negatives
UMOD	Uromodulin

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 [3–5]. 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 [9–12]. 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, “Methods”. 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 [21–25]. 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.

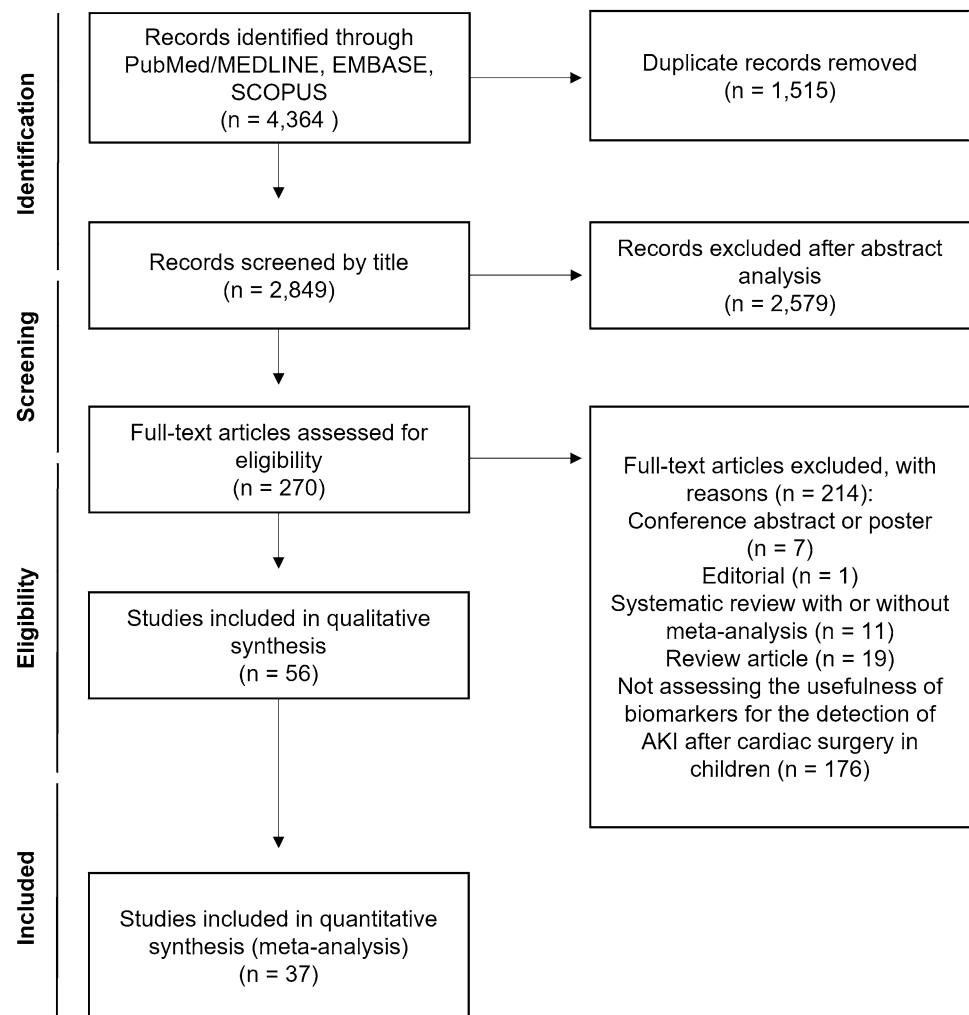
The studies reported 58,839 different measurements of 49 biomarkers at timepoints ranging from preoperatively to 3 days postoperatively. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) was the most extensively described marker (22 studies), followed by urinary interleukin-18 (uIL-18) (9 studies),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

Fig. 1 Flow diagram of studies included in data search

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, pre-operative NGAL had considerably lower AUCs.

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-SO₄) [27], uIL-6/Cr [28], and urinary uromodulin (UMOD) [29].

Table 1 HSROC models: summary of results

Biomarker	Number of observations (number of studies)	Prevalence (%)		Sensitivity		Specificity		LR+		LR-		DOR	
		%	95% CI	%	95% CI	%	95% CI	Ratio	95% CI	Ratio	95% CI	Ratio	95% CI
Albumin	4 (2)	44.0	37.5–92.2	72.7	30.6–89.2	65.6	30.6–89.2	2.11	1.20–3.73	0.42	0.23–0.76	5.08	3.83–6.73
Albumin-to-Cr ratio	8 (3)	42.3	58.4–79.8	70.2	47.7–71.1	60.0	47.7–71.1	1.76	1.47–2.09	0.50	0.40–0.61	3.53	2.79–4.47
L-FABP	8 (2)	39.6	60.9–72.2	66.8	54.7–78.2	67.5	54.7–78.2	2.06	1.45–2.91	0.49	0.40–0.60	4.18	2.49–7.01
sCysC	7 (3)	38.5	63.2–87.7	77.8	49.0–88.2	72.8	49.0–88.2	2.86	1.56–5.23	0.31	0.22–0.42	9.34	5.79–15.1
sIL-6	8 (3)	54.0	34.4–69.4	52.2	65.9–96.7	88.3	65.9–96.7	4.48	1.74–11.5	0.54	0.41–0.71	8.26	3.44–19.8
sNGAL	11 (5)	38.3	48.4–93.8	79.1	89.5–97.4	94.7	89.5–97.4	15.0	8.14–27.6	0.22	0.08–0.65	67.8	20.3–226
TIMP-2*IGFBP7	14 (2)	27.5	55.6–70.0	63.1	64.8–75.6	70.5	64.8–75.6	2.14	1.80–2.55	0.52	0.44–0.63	4.09	2.97–5.66
uIL-18	15 (4)	35.8	35.4–65.7	50.6	72.7–93.6	86.2	72.7–93.6	3.67	2.15–6.25	0.57	0.45–0.73	6.40	3.74–11.0
uNGAL	67 (10)	45.4	73.0–80.4	76.9	86.9–92.4	90.0	86.9–92.4	7.68	5.75–10.3	0.26	0.22–0.30	29.9	19.9–45.0
uNGAL-to-Cr ratio	10 (4)	40.9	91.2–91.3	91.3	89.6–89.7	89.7	89.6–89.7	8.84	8.78–8.89	0.10	0.10–0.10	91.0	90.1–91.9

CI confidence interval, Cr creatinine, DOR diagnostic odds ratio, HSROC hierarchical summary receiver-operating curve, IGFBP7 insulin-like growth factor-binding protein 7, L-FABP liver fatty acid-binding protein, LR+ likelihood ratio with a positive test result, 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

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.

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].

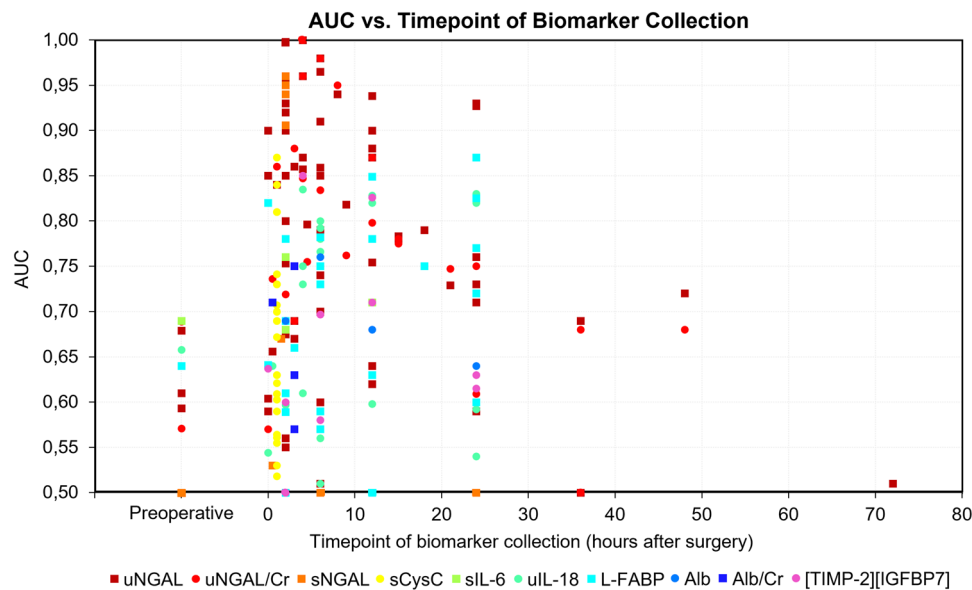


Fig. 2 Scatter plot showing AUC versus timepoint of biomarker collection for the 10 biomarkers assessed in HSROC analysis. NGAL showed the highest diagnostic accuracy at most timepoints and measurements within 6 h after surgery appeared to result in optimal prediction of AKI. AKI, acute kidney injury; AUC, area under the curve; Cr, creatinine; HSROC, hierarchical summary 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

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 [41–43]. 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.

Table 2 Pooled estimates for AUC: summary of results

Rank	Biomarker	Number of observations <i>N</i>	AUC		Heterogeneity	
			Estimate	95% CI	<i>I</i> ²	Chi-squared <i>p</i> value
1	Aprotinin	1	0.980			
2	HVA-SO ₄	1	0.950			
3	uIL-6/Cr	1	0.909			
4	UMOD	1	0.900			
5	Netrin-1/Cr	1	0.888			
6	AAG	1	0.870			
7	Phosphorus	1	0.860			
8	AIM	1	0.850			
9	uNGAL	21	0.847	0.797–0.897	0.977	<0.001
10	uNGAL/Cr	7	0.844	0.723–0.965	0.973	<0.001
11	AIM/Cr	1	0.839			
12	MA/Cr	1	0.820			
13	TIMP-2*IGFBP7	3	0.819	0.786–0.852	0.476	0.148
14	IGFBP7	1	0.802			
15	Syndecan-1/Cr	1	0.790			
16	uCysC	2	0.777	0.748–0.807	0.124	0.285
17	NT-proBNP	2	0.777	0.748–0.807	0.591	0.118
18	ST2	1	0.770			
19	Syndecan-1	1	0.770			
20	Alb	1	0.760			
21	L-FABP	8	0.756	0.672–0.841	0.831	<0.001
22	TIMP-2	1	0.754			
23	MMP-7/Cr	1	0.750			
24	sCysC	8	0.749	0.669–0.829	0.736	<0.001
25	FGF23	3	0.747	0.712–0.782	0.351	0.214
26	NAG/Cr	1	0.747			
27	sNGAL	6	0.746	0.511–0.982	0.986	<0.001
28	Hb	2	0.735	0.666–0.804	0.000	0.460
29	uIL-18/Cr	3	0.730	0.500–0.974	0.806	0.006
30	IL-8	2	0.725	0.695–0.754	0.484	0.164
31	uIL-18	9	0.725	0.639–0.812	0.907	<0.001
32	TNF α	1	0.720			
33	L-FABP/Cr	2	0.720	0.500–1.000	0.788	0.030
34	[TIMP-2*IGFBP7]/Cr	1	0.710			
35	sIL-6	3	0.706	0.627–0.786	0.000	0.727
36	ApoM	1	0.705			
37	CK-MB	1	0.700			
38	H-FABP	1	0.700			
39	KIM-1	8	0.697	0.595–0.799	0.912	<0.001
40	Alb/Cr	3	0.696	0.544–0.848	0.812	0.005
41	AGT/Cr	1	0.690			
42	Galectin-3	1	0.660			
43	hs-cTnT	1	0.620			
44	BNP	2	0.619	0.500–1.000	0.881	0.004
45	cTnI	1	0.610			
46	Lactate	1	0.590			
47	KIM-1/Cr	1	0.590			
48	ICAM-1	1	0.570			
49	E-selectin	1	0.510			

Table 2 (continued)

AIM α 1-microglobulin, *AAG* α 1-acid glycoprotein, *AGT* angiotensinogen, *Alb* albumin, *ApoM* apolipoprotein M, *AUC* area under the curve, *BNP* brain natriuretic peptide, *CI* confidence interval, *CK-MB* creatine kinase myocardial band, *Cr* creatinine, *cTnl* cardiac troponin I, *FGF23* fibroblast growth factor 23, *Hb* hemoglobin, *H-FABP* heart-type fatty acid-binding protein, *hs-cTnT* high-sensitivity cardiac troponin T, *HVA-SO₄* homovanillic acid sulfate, *ICAM-1* intercellular adhesion molecule 1, *IGFBP7* insulin-like growth factor-binding protein 7, *uIL-18* urine interleukin-18, *IL-8* interleukin-8, *KIM-1* kidney injury molecule-1, *L-FABP* liver fatty acid-binding protein, *MA* microalbumin, *MMP-7* matrix metalloproteinase 7, *NAG* N-acetyl- β -D-glucosaminidase, *NT-proBNP* N-terminal-pro-brain natriuretic peptide, *sCysC* serum cystatin C, *sIL-6* serum interleukin-6, *sNGAL* serum neutrophil gelatinase-associated lipocalin, *TIMP-2* tissue inhibitor of metalloproteinase 2, *TNF α* tumor necrosis factor α , *uCysC*; *uIL-6* urine interleukin-6, *UMOD* uromodilin, *uNGAL* urine neutrophil gelatinase-associated lipocalin

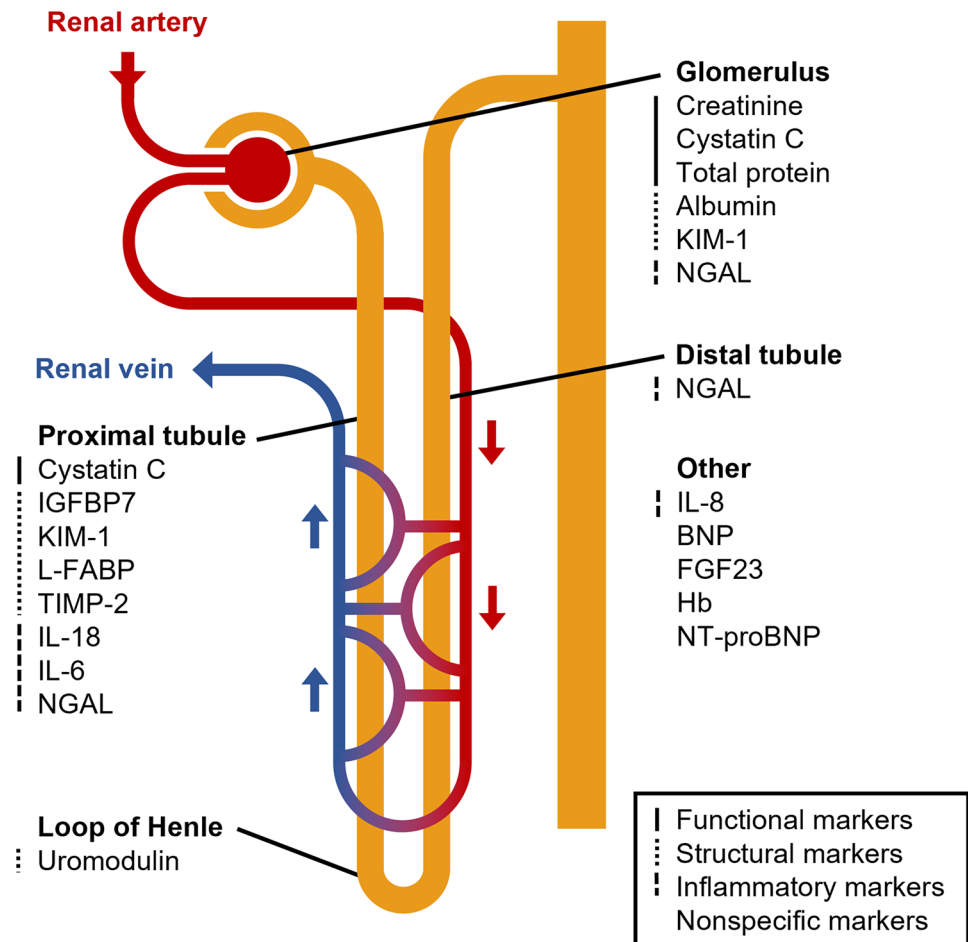
Some biomarkers were capable of predicting AKI preoperatively in children undergoing cardiac surgery. For example, de Fontnouvelle et al. [44] found that preoperative plasma interleukin-8 (IL-8) had an AUC of 0.810. Likewise, Bucholz et al. [45] reported heart-type fatty acid-binding protein (H-FABP) 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

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 summary 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



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 $\text{TIMP-2*IGFBP7} > 0.3$ 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].

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

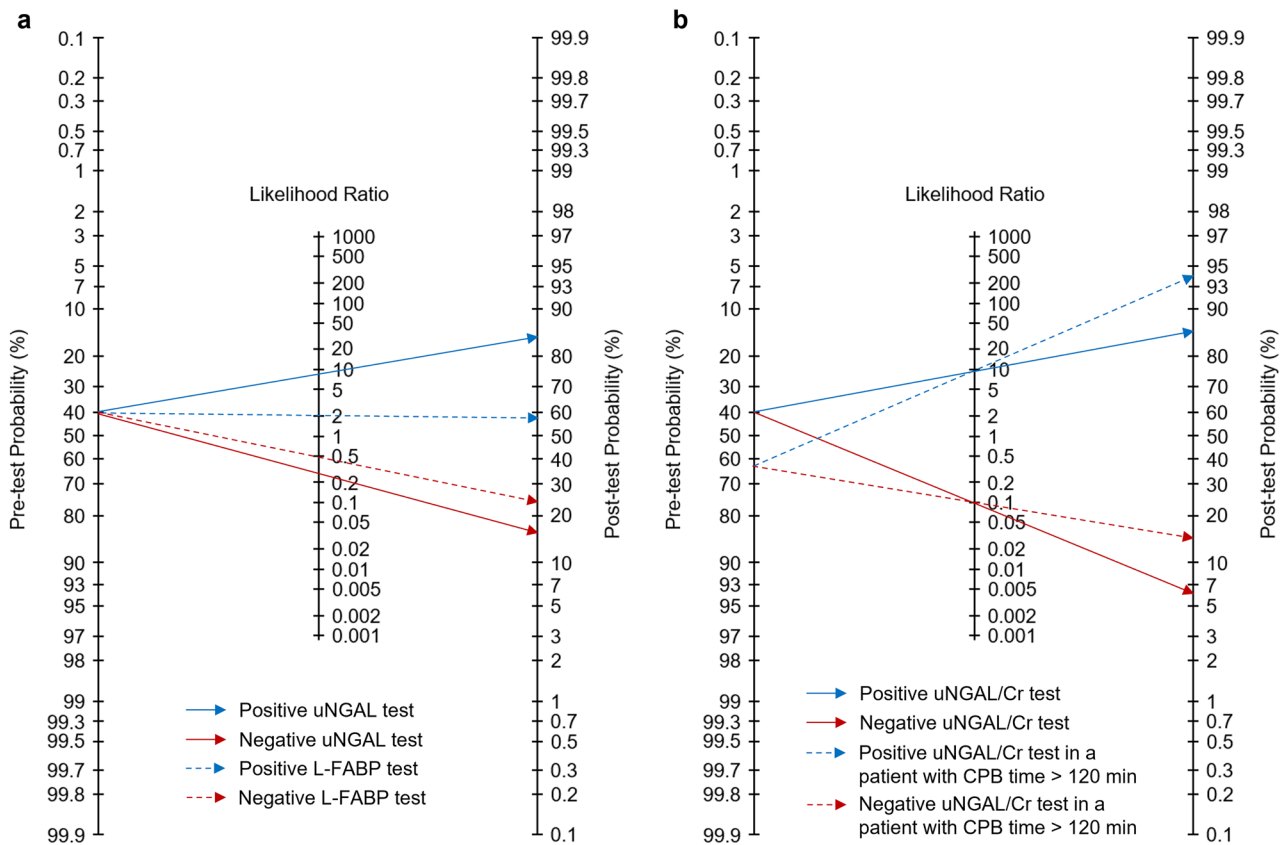


Fig. 4 Fagan nomogram to estimate the post-test probability of developing AKI after cardiac surgery in children, using (a) uNGAL and L-FABP and (b) uNGAL/Cr with or without integration of CPB time. **a** Pre-test probability (left axis) is equated to the mean incidence of AKI in children undergoing cardiac 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

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.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s00431-022-04380-4>.

Acknowledgements J. Van den Eynde was supported by the Belgian American Educational Foundation.

Authors' 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.

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.


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