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Original Investigation

Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis

Julie Ho, MD,[1,2] Navdeep Tangri, MD, PhD,[1,3,4] Paul Komenda, MD,[1,3] Amit Kaushal, MD,[1,3] Manish Sood, MD,[5] Ranveer Brar, BSc,[3] Kamal Gill, BSc,[3] Simon Walker, BSc,[3] Kerry MacDonald, MLIS,[6] Brett M. Hiebert, MSc,[7] Rakesh C. Arora, MD,[7,8] and Claudio Rigatto, MD, MSc[1,3]

Background: Early accurate detection of acute kidney injury (AKI) occurring after cardiac surgery may improve morbidity and mortality. Although several novel biomarkers have been developed for the early detection of AKI, their clinical utility in the critical intraoperative and immediate postoperative period remains unclear.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adult patients having cardiac surgery.

Selection Criteria for Studies: EMBASE, CINAHL, Cochrane Library, Scopus, and PubMed from January 1990 until January 2015 were systematically searched for cohort studies reporting the utility of novel biomarkers for the early diagnosis of AKI after adult cardiac surgery. Reviewers extracted data for study design, population, timing of biomarker measurement and AKI occurrence, biomarker performance (area under the receiver operating characteristic curve [AUROC]), and risk of bias.

Index Tests: Novel urine, plasma, and serum AKI biomarkers, measured intraoperatively and in the early postoperative period (<24 hours).

Reference Tests: AKI was defined according to the RIFLE, AKIN, or 2012 KDIGO criteria.

Results: We found 28 studies reporting intraoperative and/or early postoperative measurement of urine (n = 23 studies) or plasma or serum (n = 12 studies) biomarkers. Only 4 of these studies measured biomarkers intraoperatively. Overall, intraoperative discrimination by the urine biomarkers neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury marker 1 (KIM-1) demonstrated AUROCs < 0.70, whereas *N*-acetyl-β-D-glucosaminidase (NAG) and cystatin C had AUROCs < 0.75. In the immediate 24-hour postoperative period, the urine biomarkers NGAL (16 studies), KIM-1 (6 studies), and liver-type fatty acid binding protein (6 studies) exhibited composite AUROCs of 0.69 to 0.72. The composite AUROCs for postoperative urine cystatin C, NAG, and interleukin 18 were ≤0.70. Similarly, the composite AUROCs for postoperative plasma NGAL (6 studies) and cystatin-C (5 studies) were <0.70.

Limitations: Heterogeneous AKI definitions.

Conclusions: In adults, known urinary, plasma, and serum biomarkers of AKI possess modest discrimination at best when measured within 24 hours of cardiac surgery.

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INDEX WORDS: Cardiopulmonary bypass; alpha-1-microglobulin (A1M); hepcidin-25; liver-type fatty acid binding protein (L-FABP); monocyte chemoattractant protein 1 (CCL2); uric acid; tumor necrosis factor alpha (TNF-α); acute kidney injury; biomarker; intraoperative; early postoperative; diagnostic performance.

Acute kidney injury (AKI) is a serious and potentially lethal complication of cardiac surgery. Severe kidney failure requiring dialysis occurs in ~1% to 2% of cardiac surgery patients and is associated with a mortality rate in excess of 60%.[1,2] Importantly, less severe AKI not requiring dialysis, which can occur in up to 17% of patients,[3,4] remains independently associated with a 19-fold increase in

From the [1]Section of Nephrology, Department of Internal Medicine, and [2]Department of Immunology, University of Manitoba; [3]Seven Oaks Hospital Research Centre; [4]Department of Community Health Sciences, University of Manitoba; [5]Division of Nephrology, Department of Internal Medicine, University of Ottawa; [6]Seven Oaks Hospital Library, University of Manitoba; [7]Institute of Cardiac Sciences, St. Boniface General Hospital; and [8]Department of Surgery, University of Manitoba, Winnipeg, Manitoba, Canada.

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Address correspondence to Claudio Rigatto, MD, MSc, Section of Nephrology, University of Manitoba, 2PD03 - 2300 McPhillips Street, Winnipeg, Manitoba, Canada R2V 3M3. E-mail: crigatto@sbgh.mb.ca

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short-term mortality.[3] Even mild AKI, defined as a 25% increase in serum creatinine level over baseline, is associated with a doubling in long-term mortality up to 10 years after surgery.[4] The negative effect of AKI is independent of other prognostic factors and persists even if kidney function recovers to baseline.[4] Furthermore, AKI increases the risk for subsequent chronic kidney disease and kidney failure, with its associated morbidity and mortality.[5]

Cardiac surgery–associated AKI results from the interplay between patient susceptibility to kidney injury and intraoperative kidney insults. The dominant mechanism of injury is thought to be intraoperative ischemia-reperfusion injury. Data from animal studies show that AKI due to ischemia-reperfusion injury is potentially reversible,[6-10] provided that the therapeutic intervention is administered at or shortly after the time of injury, during a window of time corresponding to the initiation or early extension phases of ischemia-reperfusion injury.[11,12] Currently, the diagnosis of AKI relies on serum creatinine level, which takes 2 to 3 days to increase above a defined threshold due to the rate-limiting step of creatinine production and release by skeletal muscle. Interventions administered at the time of AKI diagnosis using elevated serum creatinine level may not be effective, as has been demonstrated in multiple clinical trials of promising therapies for AKI in humans.[13-15]

Accordingly, a biomarker that can detect AKI early may facilitate intervention within this narrow window of reversibility. Ideally, such a biomarker would identify injury as it occurs intraoperatively or at least within a few hours after surgery. Recent research efforts have identified multiple proteins that may provide the basis for early diagnosis of AKI.[16-19] We hypothesized that some of these novel biomarkers could predict postoperative AKI accurately. We therefore conducted a systematic review and meta-analysis of the diagnostic performance of early urinary, plasma, and serum biomarkers of cardiac surgery–associated AKI.

METHODS

Design, Search Strategy, and Study Selection

We performed a systematic review of the literature to assess the association of novel urine, serum, and plasma biomarkers with the early identification of AKI following adult cardiac surgery. The search strategy was designed and implemented under the guidance of a medical librarian (K.M.). The following electronic databases were searched from January 1, 1990, to January 1, 2015: EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Scopus, and PubMed. The search strategy was tailored to each database and included a combination of key words and subject headings. Key words used included AKI, acute kidney injury, kidney failure, kidney disease, cardiac surgery, prognosis, diagnosis, biomarkers, NGAL, neutrophil gelatinase associated lipocalin, IL-18, interleukin 18, KIM1, kidney injury molecule 1, L-FABP, liver fatty acid binding protein, hepcidin-25, cystatin, cystatins, and HAVCR1. Subject headings varied by database and included renal insufficiency, predictive value of tests, diagnosis, sensitivity and specificity, early diagnosis, and biological markers. Full search strategies are available in Item S1 (available as online supplementary material). The search string for each database was tested for rigor by a manual check for key eligible publications and their listed citations. There were no language restrictions. Retrieved citations were downloaded into RefWorks, version 2.0.

Article Eligibility Criteria

Eligibility for full-text review was determined by 2 reviewers (S.W. and K.G.) based on evaluation of the title and abstract of each citation. Any article deemed potentially relevant by either reviewer was retrieved for full-text review. Reference lists of any relevant review articles were also screened to identify studies that may have been missed in the database search. Disagreements were resolved by consensus. Included studies had to be prospective, have a clearly defined AKI outcome (RIFLE [risk, injury, failure, loss, and end-stage renal disease]: "risk [R]" or greater; AKIN [AKI Network]: stage 1 or greater; or KDIGO [Kidney Disease: Improving Global Outcomes]: creatinine criteria), have an observed outcome minimum of 10 AKI events, and report the timing of the biomarker assessment (intraoperative or <24 hours postoperatively).

Data Extraction

A Microsoft Excel data extraction form was created to capture relevant information from included studies (tables *a-b* of Item S2). K.G. conducted the extraction with verification by S.W. The following information was extracted for each study: (1) study characteristics, such as year of publication, study design, study population, type of biomarker, and sample size; (2) timing of biomarker measurement; (3) number of documented cases of AKI; (4) details of AKI definition; and (5) estimate of the area under the receiver operating characteristic curve (AUROC) for that biomarker. In cases for which biomarker AUROC was assessed at several time points, the measurement showing the best discrimination within the first 24 hours was abstracted.

Reporting Quality and Risk of Bias

We used the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool to assess risk of bias.[20] We developed operational definitions for high, low, and unclear risk of bias for each of the 14 QUADAS-2 domains (Table S1). Each study was then reviewed by C.R. and R.B. and rated as high, low, or unclear risk of bias for each of the 14 QUADAS-2 domains. Disagreements between reviewers on any item were settled by consensus between the reviewers. We summarized both individual (Fig S1) and aggregate (Fig S2) risk of bias data for the included studies.

Statistical Analysis

AUROCs with 95% confidence intervals (CIs) for each biomarker were extracted and tabulated for each time period reported (intraoperative and postoperative). These data were used to generate forest plots for each biomarker within each time period of interest. A random-effects estimate of the composite AUROC with 95% CI was calculated using the Hartung-Knapp-Sidik-Jonkman method for each biomarker having a minimum of 3 data points.[21] Individual study AUROCs were weighted inversely to the size of their standard errors. Study heterogeneity was assessed using I^2 and the Cochrane Q test; because both were concordant, we report the I^2. In separate sensitivity analyses and when numbers permitted, we recalculated the biomarker composites after: (1) excluding studies with fewer than 30 AKI events, (2) stratifying for the AKI definition used (AKIN/KDIGO vs RIFLE), (3) stratifying for use of combined urine output and creatinine criteria versus use of creatinine criteria alone, and (4) stratifying for early (≤6 hours) versus later

(>6 hours) biomarker sampling in the postoperative period. All analyses were conducted by a statistician (B.M.H.).

RESULTS

Search Results and Study Selection

The search retrieved 5,035 unique citations for screening; 265 articles were identified as potentially relevant based on title and abstract and were selected for full-text review. Of these, 28 articles met criteria for inclusion in the study[22-49] (Fig 1; Table S2).

Study Characteristics

Characteristics of the included studies are summarized in Table 1. All 28 studies were published in English, with 11 originating in North America and the rest representing an international experience from Asia and Europe. Sample sizes were greater than 100 for 13 studies. All were prospective observational studies, with the exception of one that used a randomized controlled trial cohort.[49] The included studies examined a total of 13 urinary (neutrophil gelatinase-associated lipocalin [NGAL], cystatin C, *N*-acetyl-β-D-glucosaminidase [NAG], kidney injury molecule 1 [KIM-1], interleukin 18 [IL-18], α_1-microglobulin, hepcidin 25, liver-type fatty acid binding protein [L-FABP], π- and α-glutathione *S*-transferase (GST), insulin-like growth factor-binding protein 7 [IGFBP7], tissue inhibitor of metalloproteinase 2 [TIMP-2], and hepatocyte growth factor) and 6 plasma or serum (NGAL, cystatin C, uric acid, monocyte chemoattractant protein 1 [MCP-1], plasma free hemoglobin, and tumor necrosis factor α [TNF-α]) biomarkers. In this article, we use u-, p-, and s- to indicate urinary, plasma, and serum biomarkers, respectively. The

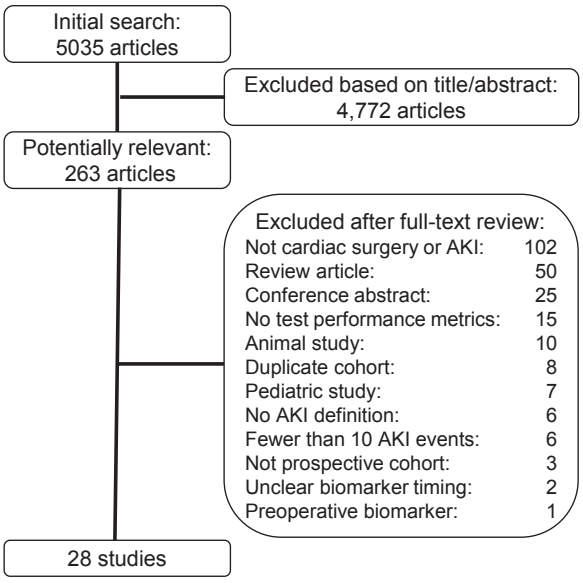

Figure 1. Selection of articles for review. Abbreviation: AKI, acute kidney injury.

studies encompassed a total of 5,122 participants, of whom 956 developed AKI. The number of studies with reportable results for each biomarker is listed in Table 1. Of these studies, 26 reported diagnostic performance in the early postoperative period, whereas 4 studies reported intraoperative data, defined as the period after induction of anesthesia to closure of the thoracic cavity.

Definition of AKI

Eight studies used the RIFLE; 16, the AKIN; and 3, the KDIGO criteria for AKI.[50] One of the studies used a combined AKIN/RIFLE scheme (Parikh et al[43]). Most studies used a minimal threshold for AKI (RIFLE R or AKIN 1), whereas 2 studies set higher thresholds (Liang et al[30]: RIFLE I; Parikh et al[43]: AKI = AKIN ≥ 2 or RIFLE ≥ I]). Only 7 studies applied both creatinine and urinary output criteria as specified in RIFLE, AKIN, and KDIGO.

Risk of Bias

Using the QUADAS-2 tool, we identified several study characteristics that might increase risk of bias (Figs S1 and S2). Domain 1 of the QUADAS addresses patient selection and diagnostic spectrum bias. Although most studies included a general cardiac surgery population with minimal exclusions, several studies did not clearly delineate the selection criteria for the test cohort. Moreover, some studies selected narrower spectrum populations based on risk of AKI (Parikh et al[43] and Meersch et al[47]) or type of surgery (aortic aneurysm [Vermeulen Windsant et al[22]]; aortic valve replacement for aortic stenosis [Kidher et al[46]]). Test performance derived from those studies may not be the same as in less selected populations.

Domain 3 addresses aspects of the reference standard. Incomplete or inconsistent operationalization of the chosen reference standard for AKI (RIFLE, AKIN, or KDIGO) was evident in many of the studies. For example, most studies did not apply the urine output subcriteria, although this is a specified component in all AKI classification schemes. Many smaller deviations were also common: for example, many studies using AKIN extended the time frame for creatinine level increase from 48 to 72 hours or applied only the absolute or relative creatinine level increase criteria, but not both.

Finally, in domain 4 (study flow), less than a third of studies provided an accurate accounting of dropouts, and less still provided a STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) or similar diagram for the study.

Intraoperative Biomarker Measurement

A total of 4 studies reported biomarkers in the intraoperative period (Table 2). Of these, urinary NGAL and urinary NAG had only 2 AUROC values reported each,

Table 1. Characteristics of the 28 Included Studies

Study	Country	Period of Biomarker Measurement	Biomarkers Assessed	N	No. of AKI Events	AKI Definition	Urine Criteria?
Haase[23] (2008)	AU	Postoperative	u-IL-18	100	20	RIFLE ≥ R	No
Koyner[24] (2008)	US	Intraoperative[a]	u-cystatin C, p-cystatin C, u-NGAL	72	34	AKIN ≥ 1	No
Wagener[25] (2008)	US	Postoperative	u-NGAL	426	85	AKIN ≥ 1	No
Haase-Fielitz[26] (2009)	AU	Postoperative	p-NGAL, p-cystatin C	100	23	RIFLE ≥ R	No
Han[27] (2009)	US	Both	u-NGAL, u-NAG, u-KIM-1	90	36	AKIN[a] ≥ 1	No
Liangos[28] (2009)	US	Postoperative	u-KIM-1, u-NGAL, u-NAG, u-IL-18, u-A1M, u-cystatin C	103	13	AKIN[a] ≥ 1	No
Koyner[29] (2010)	US	Postoperative	u-NGAL, u-cystatin C, u-KIM-1, u-HGF, u-π-GST, u-α-GST	123	46	AKIN ≥ 1	No
Liang[30] (2010)	CN	Postoperative	u-KIM-1, u-IL-18	122	30	RIFLE ≥ I	No
Perry[31] (2010)	US	Both	p-NGAL	879	75	RIFLE ≥ R	No
Ristikankare[32] (2010)	FI	Postoperative	p-cystatin C	110	62	RIFLE ≥ R	Yes
Vermeulen Windsant[22] (2010)	NL	Intraoperative	u-NAG, p-fHb	35	19	AKIN ≥ 1	Yes
Wald[33] (2010)	CA/US	Postoperative	p-cystatin C	150	47	AKIN[a] ≥ 1	No
Heise[34] (2011)	DE	Postoperative	u-NGAL, u-cystatin C, u-A1M	50	38	AKIN ≥ 1	Yes
Ho[35] (2011)	CA	Postoperative	u-hepcidin-25	338	29	RIFLE ≥ R	No
Ejaz[36] (2012)	US	Postoperative	u-NGAL, u-IL-18, s-uric acid, s-MCP-1, s-TNF-α	100	27	AKIN ≥ 1	No
Katagiri[37] (2012)	JP	Postoperative	u-NAG, u-L-FABP	77	28	AKIN ≥ 1	No
Matsui[38] (2012)	JP	Postoperative	u-L-FABP, u-NGAL, u-NAG	85	48	AKIN ≥ 1	No
Sargentini[39] (2012)	IT	Postoperative	u-NGAL	52	15	AKIN ≥ 1	
Liebetrau[40] (2013)	DE	Postoperative	u-NGAL, p-cystatin C	141	19	KDIGO	Yes
Liu[41] (2013)	CN	Postoperative	u-L-FABP, u-NGAL	109	26	AKIN ≥ 1	No
Munir[42] (2013)	PK	Postoperative	u-NGAL	88	11	AKIN ≥ 1	Yes
Parikh[43] (2013)	US/CA	Postoperative	p-NGAL, u-NGAL, u-IL-18, u-KIM-1, u-L-FABP	1,200	71	RIFLE ≥ I or AKIN ≥ 2	No
Paarmann[44] (2013)	DE	Postoperative	p-NGAL, u-NGAL, u-KIM-1, u-L-FABP	136	29	AKIN ≥ 1	No
Susantitaphong[45] (2013)	US	Postoperative	u-α-GST, u-π-GST	252	72	AKIN ≥ 1	No
Kidher[46] (2014)	UK	Postoperative	p-NGAL	53	16	RIFLE R	Yes
Meersch[47] (2014)	DE	Postoperative	u-NGAL, u-TIMP2, u-IGFBP7	50	26	KDIGO	Yes
Gaipov[48] (2015)	TR	Postoperative	p-NGAL, u-NGAL, s-uric acid	60	20	KDIGO	No
Prowle[49] (2015)	AU	Postoperative	u-α-GST, u-π-GST, u-NGAL, u-hepcidin, s-cystatin C	93	25	RIFLE ≥ R	No

Note: Design of all 28 studies was prospective cohort.

Abbreviations: A1M, α_1-microglobulin; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AU, Australia; CA, Canada; CN, China; DE, Germany; fHb, free hemoglobin; FI, Finland; GST, glutathione *S*-transferase; HGF, hepatocyte growth factor; IGFBP, insulin-like growth factor-binding protein; IL, interleukin; IT, Italy; JP, Japan; KDIGO, Kidney Disease: Improving Global Outcomes; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; MCP, monocyte chemoattractant protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NL, Netherlands; p-, plasma; PK, Pakistan; R, risk; RIFLE, risk, injury, failure, loss, end-stage renal disease; s-, serum; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; u-, urine; TR, Turkey; UK, United Kingdom; US, United States.

[a]A ≥ 50% or ≥0.3 mg/dL in serum creatinine level from the preoperative value during the first 3 days.

which was insufficient to allow calculation of a meaningful composite measure. One of the NAG studies did not report the 95% CI for the AUROC. Overall, u-NGAL and u-KIM-1 had AUROCs < 0.7, whereas u-NAG and u-cystatin C had AUROCs < 0.75.

Postoperative Biomarker Measurement

Twenty-six studies reported the early postoperative diagnostic performance of urinary and/or plasma/serum biomarkers (Table 3). Of these, calculation of a meaningful composite AUROC was possible for 8 urinary and 2 plasma biomarkers (Fig 2). u-NGAL (16 studies), u-KIM-1 (6 studies), and u-L-FABP (6 studies) exhibited composite AUROCs of 0.72. The composite AUROCs for u-cystatin C, u-NAG, u-IL-18, u-α-GST, and u-π-GST were all <0.7 (range, 0.57-0.69). A composite AUROC was not calculated for u-hepcidin (2 studies; AUROCs, 0.73 and 0.77), u-α_1-microglobulin (2 studies; AUROCs, 0.61 and 0.62), the product of u-TIMP-2 and u-IGFBP7

Table 2. Intraoperative AKI Biomarker Performance

Biomarker	Study	Sample Collection Time	N	No. of AKI Events	AUROC (95% CI)
Urine					
NGAL	Han[27] (2009)	Immediately after CPB	90	36	0.59 (0.48-0.69)
	Koyner[24] (2008)	Immediately after CPB	72	34	0.61 (0.46-0.75)
Cystatin C	Koyner[24] (2008)	Immediately after CPB	72	34	0.71 (0.57-0.84)
NAG	Vermeulen Windsant[22] (2010)	After 15-min reperfusion	35	19	0.76 (NR)
	Han[27] (2009)	Immediately after CPB	90	36	0.61 (0.50-0.71)
KIM-1	Han[27] (2009)	Immediately after CPB	90	36	0.68 (0.58-0.78)
Plasma					
NGAL	Perry[31] (2010)	Immediately after CPB	879	75	0.64 (0.58-0.71)
Cystatin C	Koyner[24] (2008)	Immediately after CPB	72	34	0.63 (0.48-0.78)
fHb	Vermeulen Windsant[22] (2010)	Peak intraoperative	35	19	0.73 (NR)

Abbreviations: AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CPB, cardiopulmonary bypass; fHb, free hemoglobin; KIM, kidney injury molecule; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; NR, not reported.

concentrations (1 study; AUROC, 0.81), and u-hepatocyte growth factor (1 study; AUROC, 0.67).

Two plasma biomarkers were meta-analyzed, and both p-NGAL (6 studies) and p-cystatin C (5 studies) had composite AUROCs < 0.75 (Fig 3). A single small study reported individual AUROCs for s-uric acid (0.77), s-TNF-α (0.76), and s-MCP-1 (0.66), respectively (Table 3).

Heterogeneity Testing and Sensitivity Analyses

Between-study heterogeneity was visually apparent on forest plots and tables for most biomarkers and was statistically significant for u-NGAL ($I^2 = 81.1\%$; $P < 0.001$), u-KIM-1 ($I^2 = 84.0\%$; $P < 0.001$), u-IL-18 ($I^2 = 59.1\%$; $P = 0.04$), and u-L-FABP ($I^2 = 83.8\%$; $P < 0.001$).

We performed several sensitivity analyses to see whether we could identify sources of this heterogeneity (Tables 4-6). First, we examined whether event rate might influence AUROC estimates by excluding all studies with fewer than 30 AKI events. In general, the composite AUROCs were similar after exclusion of low-event-rate studies. Second, we examined whether inclusion of urine output criteria in the classification of AKI had any bearing on test performance. This was possible only for u-NGAL, for which sufficient numbers of studies with and without urine output criteria were available. A clear difference was noted in measured test performance: the AUROC with urine criteria applied was 0.85 (95% CI, 0.62-1.00) versus 0.69 (95% CI, 0.64-0.75) without, suggesting that this may be an important source of variability in apparent test performance. The choice of definition of AKI may also contribute to variability in the estimates. Again, due to the paucity of data points, it was possible to directly compare definitions only for u-NGAL. Performance of u-NGAL was higher in studies using KDIGO versus AKIN. Moreover, when studies using AKIN were excluded, the performance of p-NGAL and p-cystatin C appeared modestly higher (Table 5). Finally, we examined whether timing of the urine or plasma biomarker sample affected test performance estimates. Both u- and p-NGAL appeared to perform better earlier than later (Table 6). u-KIM-1 performed slightly worse when a study with late sampling (>6 hours) was excluded. u-IL-18 performance did not change when a study with early sampling (≤6 hours) was excluded. Plasma cystatin performance was slightly less when a late sampling study was excluded. u-L-FABP and u-π- and u-α-GST performance did not appear affected by exclusion of studies sampling after 6 hours.

DISCUSSION

Our meta-analysis of biomarkers in the early detection of AKI following cardiac surgery has 2 important findings. First, we found that current biomarkers have generally poor and at best moderate discrimination for AKI when measured within the first 24 hours after cardiac surgery in adults. Second, at present, there are comparatively few data for the discrimination of these biomarkers in the intraoperative period, a time of potential active management to mitigate kidney injury. Only u-NGAL has been studied more than once, but its intraoperative diagnostic performance was limited. Our findings highlight the need for further investigation into the early detection of cardiac surgery–associated AKI, particularly given the need for early prevention and treatment of this prescheduled ischemia-reperfusion injury event.

Several other published systematic reviews have examined the performance of selected biomarkers for early diagnosis of AKI in a variety of clinical settings (eg, cardiac surgery, intensive care unit, and after coronary angiography) and age groups (ie, children vs adults).[19,50-55] These reviews have addressed multiple biomarkers,[50] NGAL,[19,51] cystatin C,[52] IL-18,[53]

Table 3. Postoperative AKI Biomarker Performance

Biomarker	Study	Sample Collection Time (h postop)	N	No. of AKI Events	AUROC (95% CI)	AKI Definition	Urine Criteria?
			Urine				
u-NGAL	Wagener[25] (2008)	18	426	85	0.61 (0.54-0.68)	AKIN ≥ 1	No
	Liangos[28] (2009)	0	103	13	0.50 (0.33-0.68)	AKIN ≥ 1	No
	Han[27] (2009)	18	90	36	0.70 (0.59-0.80)	AKIN ≥ 1	No
	Koyner[29] (2010)	6	123	46	0.72 (0.61-0.83)	AKIN ≥ 1	No
	Heise[34] (2011)	6	50	38	0.73 (0.63-0.88)	AKIN ≥ 1	?
	Ejaz[36] (2012)	24	100	27	0.62 (0.49-0.75)	AKIN ≥ 1	No
	Matsui[38] (2012)	24	85	48	0.77 (0.63-0.85)	AKIN ≥ 1	No
	Sargentini[39] (2012)	4	52	15	0.70 (0.56-0.85)	AKIN ≥ 1	No
	Liebetrau[40] (2013)	4	141	19	0.90 (0.81-0.99)	KDIGO	Yes
	Liu[41] (2013)	2	109	26	0.87 (0.78-0.97)	AKIN ≥ 1	No
	Munir[42] (2013)	4	88	11	0.91 (0.83-0.96)	AKIN ≥ 1	Yes
	Paarmann[44] (2013)	6	136	29	0.60 (0.48-0.72)	AKIN ≥ 1	No
	Parikh[43] (2013)	6	1,200	71	0.67 (0.59-0.76)	RIFLE ≥ I or AKIN ≥ 2	No
	Meersch[47] (2014)	4	50	26	0.68 (0.53-0.84)	KDIGO	Yes
	Gaipov[48] (2015)	24	60	40	0.77 (0.64-0.87)	KDIGO	No
	Prowle[49] (2015)	0	93	25	0.73 (0.60-0.86)	RIFLE ≥ R	No
	Composite		*2,906*	*555*	*0.72 (0.66-0.79)*	$I^2 = 81.1\%$; $P < 0.001$	
u-cystatin C	Liangos[28] (2009)	0	103	13	0.50 (0.27-0.72)	AKIN ≥ 1	No
	Koyner[29] (2010)	12	123	46	0.72 (0.61-0.83)	AKIN ≥ 1	No
	Heise[34] (2011)	0	50	38	0.59 (0.43-0.73)	AKIN ≥ 1	?
	Composite		*276*	*97*	*0.63 (0.37-0.89)*	$I^2 = 48.4\%$; $P = 0.1$	
u-NAG	Liangos[28] (2009)	0	103	13	0.62 (0.41-0.83)	AKIN ≥ 1	No
	Han[27] (2009)	18	90	36	0.64 (0.52-0.74)	AKIN ≥ 1	No
	Katagiri[37] (2012)	4	77	28	0.75 (0.60-0.86)	AKIN ≥ 1	No
	Matsui[38] (2012)	24	85	48	0.73 (0.62-0.84)	AKIN ≥ 1	No
	Composite		*355*	*125*	*0.69 (0.60-0.79)*	$I^2 = 0.0\%$; $P = 0.5$	
u-KIM-1	Liangos[28] (2009)	0	103	13	0.78 (0.64-0.91)	AKIN ≥ 1	No
	Han[27] (2009)	3	90	36	0.65 (0.54-0.75)	AKIN ≥ 1	No
	Koyner[29] (2010)	0-6	123	46	0.69 (0.58-0.80)	AKIN ≥ 1	No
	Liang[30] (2010)	12	122	30	0.88 (0.81-0.93)	RIFLE ≥ I	No
	Paarmann[44] (2013)	6	136	29	0.60 (0.48-0.72)	AKIN ≥ 1	No
	Parikh[43] (2013)	6	1,200	71	0.71 (0.63-0.78)	RIFLE ≥ I or AKIN ≥ 2	No
	Composite		*1,774*	*225*	*0.72 (0.59-0.84)*	$I^2 = 84.0\%$; $P < 0.001$	
u-IL-18	Haase[23] (2008)	24	100	20	0.55 (0.40-0.71)	RIFLE ≥ R	No
	Liangos[28] (2009)	0	103	13	0.66 (0.49-0.83)	AKIN ≥ 1	No
	Liang[30] (2010)	12	122	30	0.62 (0.52-0.70)	RIFLE ≥ I	No
	Ejaz[36] (2012)	24	100	27	0.65 (0.52-0.78)	AKIN ≥ 1	No
	Parikh[43] (2013)	6-12	1,200	71	0.75 (0.69-0.81)	RIFLE ≥ I or AKIN ≥ 2	No
	Composite		*1,625*	*161*	*0.66 (0.56-0.76)*	$I^2 = 59.1\%$; $P = 0.04$	
u-A1M	Liangos[28] (2009)	0	103	13	0.62 (0.47-0.76)	AKIN ≥ 1	No
	Heise[34] (2011)	0	50	38	0.61 (0.46-0.75)	AKIN ≥ 1	?
u-Hepcidin	Ho[35] (2011)	24	338	29	0.73 (0.64-0.84)	RIFLE ≥ R	No
	Prowle[49] (2015)	24	93	25	0.77 (0.67-0.86)	RIFLE ≥ R	No
u-L-FABP	Katagiri[37] (2012)	12	77	28	0.76 (0.62-0.86)	AKIN ≥ 1	No
	Liu[41] (2013)	2	109	26	0.83 (0.74-0.92)	AKIN ≥ 1	No
	Matsui[38] (2012)	3	85	48	0.85 (0.77-0.91)	AKIN ≥ 1	No
	Paarmann[44] (2013)	0	136	29	0.52 (0.40-0.64)	AKIN ≥ 1	No
	Parikh[43] (2013)	6-12	1,200	71	0.66 (0.58-0.74)	RIFLE ≥ I or AKIN ≥ 2	No
	Prowle[49] (2015)	0	93	25	0.69 (0.57-0.81)	RIFLE ≥ R	No
	Composite		*1,700*	*227*	*0.72 (0.60-0.85)*	$I^2 = 83.8\%$; $P < 0.001$	
u-α-GST	Koyner[29] (2010)	0-6	123	46	0.64 (0.52-0.76)	AKIN ≥ 1	No
	Susantitaphong[45] (2013)	2	242	72	0.56 (0.48-0.64)	AKIN ≥ 1	No
	Prowle[49] (2015)	0	93	25	0.60 (0.46-0.74)	RIFLE ≥ R	No
	Composite		*458*	*143*	*0.57 (0.46-0.68)*	$I^2 = 0.0\%$; $P = 0.5$	

(Continued)

Table 3 (Cont'd). Postoperative AKI Biomarker Performance

Biomarker	Study	Sample Collection Time (h postop)	N	No. of AKI Events	AUROC (95% CI)	AKI Definition	Urine Criteria?
u-π-GST	Koyner[29] (2010)	0-6	123	46	0.60 (0.48-0.72)	AKIN ≥ 1	No
	Susantitaphong[45] (2013)	2	242	72	0.62 (0.54-0.70)	AKIN ≥ 1	No
	Prowle[49] (2015)	0	93	25	0.75 (0.63-0.88)	RIFLE ≥ R	No
	Composite		*458*	*143*	*0.65 (0.48-0.82)*	*I^2 = 44.8%; P = 0.2*	
[u-TIMP-2] × [u-IGFBP7]	Meersch[47] (2014)	4	50	26	0.81 (0.68-0.93)	KDIGO	Yes
u-HGF	Koyner[29] (2010)	0-6	123	46	0.67 (0.45-0.88)	AKIN ≥ 1	No
		Plasma or Serum					
p-NGAL	Haase-Fielitz[26] (2009)	0	100	23	0.73 (0.56-0.88)	RIFLE ≥ R	No
	Perry[31] (2010)	24	879	75	0.67 (0.60-0.74)	RIFLE ≥ R	No
	Paarmann[44] (2013)	6	136	29	0.62 (0.50-0.74)	AKIN ≥ 1	No
	Parikh[43] (2013)	24	1,200	71	0.70 (0.62-0.78)	RIFLE ≥ I or AKIN ≥ 2	No
	Kidher[46] (2014)	3	53	16	0.83 (0.70-0.95)	RIFLE R	Yes
	Gaipov[48] (2015)	24	60	40	0.75 (0.62-0.85)	KDIGO	No
	Composite		*2,428*	*254*	*0.71 (0.64-0.77)*	*I^2 = 32.6%; P = 0.2*	
p-cystatin C	Haase-Fielitz[26] (2009)	0	100	23	0.75 (0.59-0.90)	RIFLE ≥ R	No
	Wald[33] (2010)	0	150	47	0.68 (0.58-0.78)	AKIN ≥ 1	No
	Ristikankare[32] (2010)	15-18	110	62	0.71 (0.61-0.81)	RIFLE ≥ R	Yes
	Liebetrau[40] (2013)	4	141	19	0.76 (0.65-0.94)	KDIGO	Yes
	Prowle[49] (2015)	0	93	25	0.72 (0.59-0.85)	RIFLE ≥ R	No
	Composite		*594*	*176*	*0.69 (0.63-0.74)*	*I^2 = 0.0%; P = 0.9*	
s-uric acid	Ejaz[36] (2012)	24	100	27	0.77 (0.66-0.88)	AKIN ≥ 1	No
	Gaipov[48] (2015)	24	60	40	0.86 (0.74-0.94)	KDIGO	No
s-MCP-1	Ejaz[36] (2012)	24	100	27	0.66 (0.53-0.78)	AKIN ≥ 1	No
s-TNF-α	Ejaz[36] (2012)	24	100	27	0.76 (0.65-0.87)	AKIN ≥ 1	No

Abbreviations and definitions: ?, unclear; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; A1M, α_1-microglobulin; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; fHb, free hemoglobin; GST, glutathione *S*-transferase; HGF, hepatocyte growth factor; IL, interleukin; KDIGO, Kidney Disease: Improving Global Outcomes; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; MCP, monocyte chemoattractant protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; p-, plasma; R, risk; RIFLE, risk, injury, failure, loss, end-stage renal disease; s-, serum; TNF, tumor necrosis factor; u-, urine; u-[TIMP-2] × u-[IGFBP7], product of the urinary concentrations of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor-binding protein 7.

L-FABP,[54] and KIM-1.[56] Our analysis distinguishes itself from prior studies by its focus on a single clinical setting (cardiac surgery), age group (adults only), and outcome (AKI in the postoperative period). In addition, we were able to incorporate new studies of known biomarkers, as well as summarize performance of several newer biomarkers (ie, MCP-1, TNF-α, uric acid, π- and α-GST, TIMP-2, and u-IGFBP7).

Our composite AUROC estimates for NGAL, KIM-1, cystatin C, and IL-18 are lower than the pooled estimates reported in other systematic reviews. These differences most likely relate to important differences in the study populations included. First, in most cases, previous meta-analyses included pediatric studies and pooled biomarker test performance across studies in children and adults, whereas we excluded studies in children. Because several biomarkers appear to perform better in children, inclusion of studies of children would have improved the pooled performance estimates in those studies. For example, both NGAL in the review by Haase et al[51] and IL-18 in the review by Liu et al[54] were shown in sensitivity analyses to perform better in studies of children than in studies of adults. It must be noted that this may not be true of all biomarkers because better performance in child populations was not seen for KIM-1.[55] Second, prior reviews also included and pooled studies in a variety of clinical settings, not just cardiac surgery as in our review, which may have further contributed to the differences in pooled estimates. Finally, our analysis included newer studies, some of which observed lower discrimination for a given biomarker. As a result of these differences, our pooled estimates may more closely reflect biomarker performance in adults undergoing cardiac surgery.

As with the other systematic reviews, AKI definition was an important source of heterogeneity in our study. We sought to minimize this heterogeneity by requiring included studies to adhere to a validated AKI

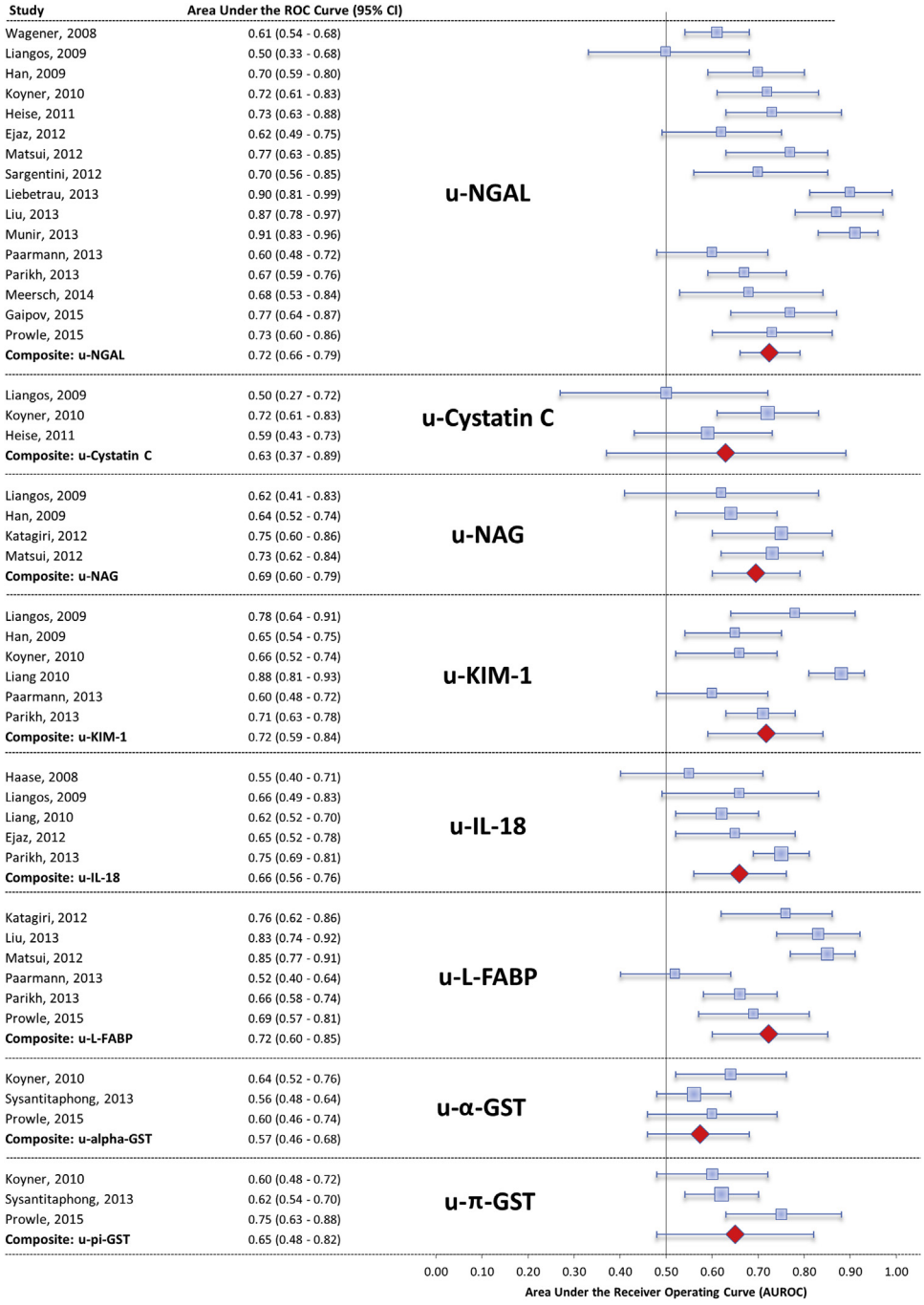

Figure 2. Forest plot of individual and composite areas under the receiver operating characteristic (ROC) curve (AUROCs) for all postoperative urinary biomarkers with more than 3 included studies. Abbreviations: CI, confidence interval; GST, glutathione *S*-transferase; IL, interleukin; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; u-, urinary.

classification scheme. Even so, most studies deviated from these criteria. The most frequent deviation was ignoring the urinary criteria altogether. Although a debate on the validity of urinary criteria for AKI is beyond the scope of this study, variable adherence to AKI criteria can lead to significant differences in estimates of test discrimination, as was observed for u-NGAL in our analysis.

It is relevant to contrast the performance of biomarkers with that of clinical AKI risk prediction models. To date, 3 independently validated models have been developed to predict renal replacement therapy after cardiac surgery.[2,57,58] Of these, the Thakar score has gained the widest acceptance, having demonstrated good to excellent discrimination in both the original derivation and validation cohorts

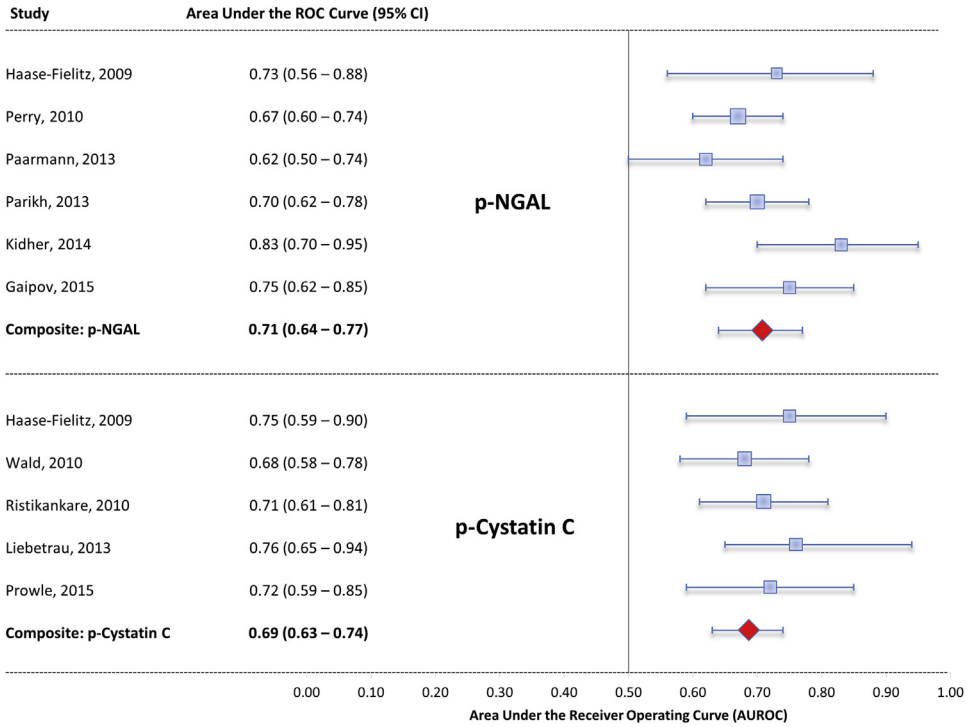

Figure 3. Forest plot of individual and composite areas under the receiver operating characteristic (ROC) curve (AUROCs) for all postoperative plasma or serum biomarkers with more than 3 included studies. Abbreviations: CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; p-, plasma.

(AUROCs of 0.81 vs 0.82, respectively) and in later independent validation studies (AUROCs of 0.86 and 0.82, respectively, for AKI requiring dialysis).[59,60] These AUROCS are significantly higher than those estimated for urine and blood biomarkers in our meta-analysis. However, it is important to clarify that clinical AKI models were derived to predict severe AKI requiring dialysis and so are not directly comparable to the studies included in our systematic review, which examined less severe forms of AKI. Only 2 studies examined the discrimination of biomarkers for moderate to severe AKI,[30,43] so it was not

Table 4. Sensitivity Analyses Showing Recalculated Composite AUROC When Studies With Low Event Count or Applying Combined Urine Output And Serum Creatinine Criteria Included

	All Studies		Excluding Studies With <30 AKI Events		Excluding all Studies With Urine Criteria Applied[a]	
Biomarker	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies
Urine						
NGAL	0.72 (0.66-0.79)	16	0.70 (0.64-0.76)	7	0.69 (0.64-0.75)	12
Cystatin C	0.63 (0.37-0.89)	3	—	—	—	—
NAG	0.69 (0.60-0.79)	4	—	—	0.69 (0.60-0.79)	4
KIM-1	0.72 (0.59-0.84)	6	0.73 (0.53-0.93)	4	0.72 (0.59-0.84)	6
IL-18	0.66 (0.56-0.76)	5	—	—	0.66 (0.56-0.76)	5
L-FABP	0.72 (0.60-0.85)	6	—	—	0.72 (0.60-0.85)	6
α-GST	0.57 (0.46-0.68)	3	—	—	0.57 (0.46-0.68)	3
π-GST	0.65 (0.48-0.82)	3	—	—	0.65 (0.48-0.82)	3
Plasma						
NGAL	0.71 (0.64-0.77)	6	0.69 (0.60-0.78)	3	0.68 (0.63-0.74)	5
Cystatin C	0.69 (0.63-0.74)	5	—	—	0.66 (0.50-0.82)	3

Note: Low event count defined as fewer than 30 AKI events.

Abbreviations: AKI, acute kidney injury; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GST, glutathione *S*-transferase; IL, interleukin; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

[a]Or unknown urine criteria.

Table 5. Sensitivity Analyses Showing Recalculated Composite AUROC When Only Studies Using AKIN, RIFLE, or KDIGO Definitions Included

	AKIN-Only Definition		RIFLE-Only Definition		KDIGO-Only Definition	
Biomarker	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies
Urine						
NGAL	0.71 (0.62-0.80)	11	—	—	0.79 (0.52-1.00)	3
Cystatin C	0.63 (0.37-0.89)	3	—	—	—	—
NAG	0.69 (0.60-0.79)	4	—	—	—	—
KIM-1	0.67 (0.56-0.78)	4	—	—	—	—
IL-18	—	—	—	—	—	—
L-FABP	0.75 (0.53-0.97)	4	—	—	—	—
α-GST	—	—	—	—	—	—
π-GST	—	—	—	—	—	—
Plasma						
NGAL	—	—	0.73 (0.53-0.94)	3	—	—
Cystatin C	—	—	0.73 (0.67-0.80)	3	—	—

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GST, glutathione *S*-transferase; IL, interleukin; KDIGO, Kidney Disease: Improving Global Outcomes; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; RIFLE, risk, injury, failure, loss, end-stage renal disease.

possible to determine whether newer biomarkers might better predict severe AKI. Moreover, even in the large Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study,[43] only 15 patients needed dialysis. Thus, the lack of studies large enough to address this question (ie, can biomarkers accurately diagnose severe AKI) reflects an important knowledge gap.

There are a number of clinical and research implications to our findings. Despite the growing availability of rapid point-of-care tests for many biomarkers, the current evidence does not support their routine clinical use for early prediction of AKI after cardiac surgery in adults. No biomarker studied to date appears to have adequate levels of discrimination for this purpose. From a research perspective, the paucity of biomarker data in the intraoperative and very early postoperative period needs to be addressed because kidney injury is most likely to be reversible shortly after the renal insult. Efforts to identify newer biomarkers or novel ways to use known biomarkers are urgently needed. Moreover, large studies are needed to examine the ability of biomarkers to diagnose severe AKI. Finally, robust clinical prediction models integrating newer biomarkers and clinical variables need to be developed and validated prior to widespread clinical use. In this context,

Table 6. Sensitivity Analyses Showing Recalculated Composite AUROC When Studies Restricted to Those Measuring Biomarkers Earlier Versus Later

	All Studies		Earlier: ≤6 Hours		Later: >6 Hours	
Biomarker	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies	Composite AUROC (95% CI)	No. of Studies
Urine						
NGAL	0.72 (0.66-0.79)	16	0.74 (0.65-0.83)	11	0.69 (0.59-0.79)	5
Cystatin C	0.63 (0.37-0.89)	3	—	—	—	—
NAG	0.69 (0.60-0.79)	4	—	—	—	—
KIM-1	0.72 (0.59-0.84)	6	0.68 (0.61-0.75)	5	—	—
IL-18	0.66 (0.56-0.76)	5	—	—	0.66 (0.51-0.80)	4
L-FABP	0.72 (0.60-0.85)	6	0.73 (0.50-0.96)	4	—	—
α-GST	0.57 (0.46-0.68)	3	0.57 (0.46-0.68)	3	—	—
π-GST	0.65 (0.48-0.82)	3	0.65 (0.48-0.82)	3	—	—
Plasma						
NGAL	0.71 (0.64-0.77)	6	0.73 (0.44-1.00)	3	0.69 (0.60-0.78)	3
Cystatin C	0.69 (0.63-0.74)	5	0.65 (0.51-0.79)	4	—	—

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; GST, glutathione *S*-transferase; IL, interleukin; KIM, kidney injury molecule; L-FABP, liver-type fatty acid binding protein; NAG, *N*-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin.

because variation in choice and application of reference AKI criteria can lead to differences in estimates of test performance, it is important that future studies use consistent and carefully applied AKI criteria, preferably focusing on the more severe and clinically significant manifestations of AKI.

Our review has several strengths. First, our search strategy included several electronic databases to maximize the chance of capturing all relevant published literature. In addition, we manually searched the bibliographies of included articles to ensure the sensitivity of our search strategy. Our inclusion criteria were focused: only prospective studies with a validated outcome (AKI) definition and clear timing of biomarker assessment in relation to AKI were included. Given the clinical goal of reliable AKI recognition in the early postoperative period to facilitate potential treatment, we focused on test performance of biomarker measurement within 24 hours postoperatively.

Our study also has limitations. Our review addressed only the question of early diagnosis of AKI in the setting of adult cardiac surgery. We cannot comment on biomarker performance for preoperative risk stratification, in prediction of long-term outcomes, or in other clinical AKI settings such as pediatric heart surgery. We included only published literature in this analysis. Although the direction and magnitude of this publication bias is unknown, it is probable that the majority of unpublished studies were negative (ie, showed weaker discrimination for AKI). Our composite AUROCs based on only published studies may therefore represent an optimistic estimate. In studies with serial biomarker measurements, we selected the most favorable time point (ie, the best AUROC), and this may also overestimate test performance. Similar to other systematic reviews, we reported and meta-analyzed only the raw univariate AUROC. This was necessary because studies either did not adjust for clinical AKI risk factors or varied widely in the choice of variables used for adjustment, precluding meaningful combination of adjusted measures of test discrimination. It follows that we cannot conclude from this analysis whether a combination of clinical variables and selected biomarkers together could create a highly discriminatory predictive model or "test" for AKI. Finally, the majority of studies measured AKI with serum creatinine level, which is known to be a flawed gold standard. Misclassification of AKI status based on this flawed gold standard could have diminished the apparent discrimination of the biomarkers studied.

In conclusion, current biomarkers exhibit at best modest discrimination for cardiac surgery–associated AKI in the early postoperative period in adults. Intraoperatively, only NGAL has been studied to any extent, and its performance is poor. Ongoing efforts to develop new tests for early diagnosis of cardiac surgery associated AKI in adults are still needed.

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Contributions: Research idea and study design: JH, NT, PK, MS, RCA, CR; content expertise: JH, CR, RCA; search strategy and systematic review: KM; data extraction and literature review: KG, SW; evaluation of study quality and bias: AK, RB; statistical analysis: BMH, CR. Each author contributed important intellectual content during the manuscript drafting and revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy and integrity of any portion of the work are appropriately investigated and resolved. JH and CR take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: QUADAS-2 criteria and operational criteria for study.
Table S2: Primary reasons for exclusion of excluded studies.
Figure S1: Individual risk of bias data for included studies.
Figure S2: Aggregate risk of bias data for included studies.
Item S1: Full search strategy.
Item S2: Sample data extraction tables for study.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.06.018) is available at www.ajkd.org

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