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Review Article

Accuracy of urinary kidney injury molecule-1 in predicting acute kidney injuries associated with cardiac surgery: a systematic review and meta-analysis

Hao Wang[1*], Wen-Juan Wang[2*], Cheng-Cheng Zhou[1], Dong Cen[1]

[1]Department of Laboratory Test, Yinzhou Second Hospital, Ningbo, Zhejiang Province, China; [2]Ningbo College of Health Sciences, Ningbo, Zhejiang Province, China. [*]Equal contributors.

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Abstract: *Objectives:* Urinary kidney injury molecule-1 (uKIM-1) is a very promising diagnostic biomarker for acute kidney injuries (AKI), but its accuracy has varied widely in different studies. The current study reviewed clinical observation studies, investigating the accuracy of uKIM-1 in predicting AKI associated with cardiac surgery. *Methods:* Central, PubMed, Embase, and Congress abstracts databases were searched for studies reporting uKIM-1 levels predicting AKI after cardiac surgery. Standardized data sheets were used to perform a meta-analysis of diagnostic studies. Bivariate and hierarchical summary models were used to calculate diagnostic odds ratios (DOR) and areas under the curve for the receiver-operating characteristic (AUROC). *Results:* Analysis included 15 observational studies in 7 countries, with a total of 4,120 patients. Of these, 983 (23.9%) developed AKI. The DOR of uKIM-1 was 2.4, with a sensitivity of 0.76, specificity of 0.84, and an AUROC of 0.71. Levels of uKIM-1 in adults (DOR: 3.7, AUROC: 0.79) and children (DOR: 2.6, AUROC: 0.76) were predicted to be more accurate than those in infants (DOR: 1.5, AUROC: 0.60). Moreover, the accuracy of using standardized detection of uKIM-1 (DOR: 2.5, AUROC: 0.78) was significantly higher than that of the research-based assay (DOR: 1.8, AUROC: 0.71). *Conclusion:* Levels of uKIM-1 can be used to diagnose AKI associated with cardiac surgery, with high sensitivity and specificity.

Keywords: Urinary kidney injury molecule-1 (uKIM-1), acute kidney injury (AKI), cardiac surgery, meta-analysis

Introduction

Acute kidney injury (AKI) is a common complication of critically ill patients, with a persistent increase in morbidity rates. The etiology and pathogenesis are complex, leading to a significant increase in mortality rates for hospitalized patients [1]. In recent years, although researchers have conducted in-depth studies on the pathogenesis of AKI and have gained new insight, there are still no effective interventions. Many studies have reported a significant increase in incidence of AKI in patients undergoing cardiac surgery, especially in critical ill patients after percutaneous coronary intervention (PCI) [2]. The use of contrast agents is an important factor leading to AKI. However, it lacks predictive biomarkers with high sensitivity and specificity, making early diagnosis and effective intervention difficult [3, 4]. At present, serum creatinine (Scr) and blood urea nitrogen (BUN) are commonly used indicators of renal dysfunction in clinical practice. However, sensitivity and specificity for diagnosis of AKI are too low [5]. The International Society of Nephrology proposed the AKI Network (AKIN) and Acute Dialysis Quality Initiative (ADQI) system for provision of early and effective assessment of severity of kidney damage and for development and validation of new predictive biomarkers of AKI [6, 7]. If AKI is diagnosed early, it could assist in timely and effectively protecting kidney function, avoiding renal replacement therapy (RRT), and improving patient survival rates.

In recent years, proteomics and genomics techniques have established that kidney injury molecule-1 (KIM-1) is an early biomarker of AKI [8]. In animal experiments, expression of KIM-1 in renal tissues and related mechanisms has been elucidated. In clinical studies, it has also been confirmed that KIM-1 can be used for

early diagnosis of AKI, having very broad application prospects [9, 10]. As an early biomarker of AKI, predictive accuracy of KIM-1 has been examined in many prospective studies for different clinical diseases, such as critically ill patients, sepsis, postoperative cardiac surgery, and patients receiving intravenous contrast agents [11-13]. Study populations included adults [14], children [15], and infants [16], with urine samples as the most commonly used measurement.

However, concerning the accuracy of urinary KIM-1 (uKIM-1) diagnosis of AKI patients after cardiac surgery, results of clinical studies have varied widely. Therefore, the accuracy of uKIM-1 as an important biomarker for future diagnosis of AKI is controversial. To clarify the accuracy of uKIM-1 in predicting AKI associated with cardiac surgery, the current study systematically evaluated published clinical observational studies. The aim was to assess the sensitivity and specificity of uKIM-1 in the diagnosis of AKI after cardiac surgery, clarifying the value of uKIM-1 for diagnosis of AKI.

Methods

Data sources and search strategy

This study conducted a search strategy for all relevant observational cohort studies. Two researchers (Hao Wang and Wen-juan Wang), independently, conducted searches in four major databases (Central, PubMed, Embase, and Congress abstracts databases), with a deadline of December 31, 2018. Keywords included "urinary kidney injury molecule-1", "kidney injury molecule-1", "KIM-1", "uKIM-1", "acute kidney injury", "AKI", and "cardiac surgery", with no restrictions on language. Irrelevant articles were excluded by reviewing the abstracts. Full texts of the remaining articles were reviewed, selecting relevant studies.

Study selection

Two researchers (Hao Wang and Wen-juan Wang) independently reviewed, screened, and finalized the studies. If the two disagreed, a third researcher (Cheng-cheng Zhou) intervened to discuss and resolve the problem. Included studies were required to be human observational studies, with the content concerning the accuracy of uKIM-1 levels in predicting AKI after cardiac surgery. The use of uKIM-1 as part of an intervention study was excluded.

Data extraction and end points

Due to different research methods and content, many included studies had different AKI definitions. Measurement times of uKIM-1 were also different, making required data extraction difficult. Standardized data collection tables and measurement unit conversions were made to facilitate uniform definition and data. Required data and content was emailed to the corresponding authors, requesting help in recalculating relevant variables, including patient age, gender, sample size, the type and time of cardiac surgery, baseline Scr levels, population, inclusion and exclusion criteria, number of patients with AKI, uKIM-1 test methods, time points of detection, and prognosis of patients.

For all included studies, uKIM-1 reagent information and measurement methods were indicated in the data sheet, especially whether to use a research-based assay or a standardized assay. Antibody information was also used in the assay. Corresponding authors needed to provide cut-off values of uKIM-1, along with corresponding sensitivity and specificity, 95% confidence intervals (CI), and area under the receiver operating characteristic curve (AUROC) values. There may have been some errors in the times of AKI and measurement times of uKIM-1. Therefore, if the time of kidney injury was known, uKIM-1 would be measured within 12 hours. If the time of kidney injury was unknown, uKIM-1 was measured within 48 hours prior to AKI diagnosis. The corresponding AUROC was also calculated. In addition, data concerning uKIM-1 sample collection, processing, and storage standards were required.

Statistical analysis

Sample-size funnel plots were used to assess publication bias. SAS software (SAS, 2012V1.3, US) "METADAS" macro was used to automatically match the bivariate model and hierarchical summary ROC (HSROC) model based on the Proc NLMIXED process [17]. Furthermore, HSROC and bivariate models in RevMan5 were used to summarize ROC curves and to average operating points [including 95% confidence intervals (CIs)] and 95% prediction regions. Mo-

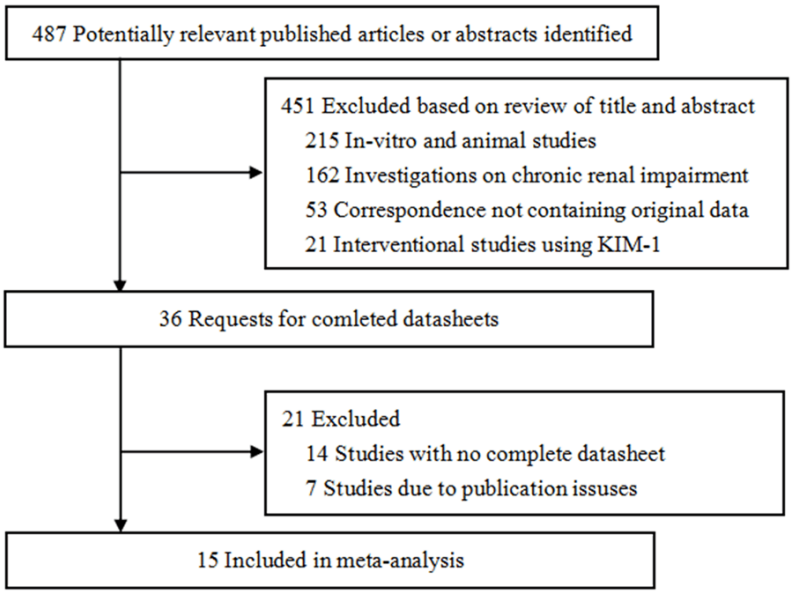

Figure 1. Flow of study selection.

reover, I^2 statistic was calculated to estimate the variation ratio of AUROC between studies. This study defines 25%-49% as the low threshold, 50%-74% as the medium threshold, and more than 75% as the high threshold [18]. AUROC >0.70 is defined as a significant risk predictor [19].

Results

Study characteristics

Based on previously identified keywords, 487 studies and abstracts on AKI after cardiac surgery were searched. After a thorough evaluation of these documents, a total of 15 studies were selected for analysis, including a Chinese-published study [20]. **Figure 1** shows the detailed process of study selection. Basic characteristics of studies included are listed in **Table 1**. All studies provided AUROC values. However, 3 studies did not provide uKIM-1 cut-off values (including sensitivity and specificity values). Moreover, these results could not be obtained by calculations [14, 21, 22].

Of the studies included, 5 were multicenter clinical trials [13, 16, 21-23], 2 were for children [21, 24], and 1 was for infants [25]. All studies excluded patients with chronic kidney diseases and long-term hemodialysis. The current study included 4,120 patients [1,617 females (39.2%)], including adults, children, and infants. The most common of these studies was AKI after CPB. Five studies did not specify the type of cardiac surgery and 1 study was open cardiac surgery [26]. Most studies tested uKIM-1 using the ELISA method. However, 1 used the MAP method [14] and 2 studies did not specify the method used [23, 26].

Quality assessment

Of included studies, 12 were prospective cohort studies [16, 12-14, 20-23, 25-28], 2 were case-control studies [15, 24], and 1 was a retrospective cohort study [29]. As shown in **Table 2**, all studies examined the accuracy of uKIM-1 levels in the diagnosis of AKI after cardiac surgery. These studies clearly defined patient inclusion criteria and exclusion criteria. A secondary analysis of the diagnostic accuracy of uKIM-1 was performed. Three studies evaluated the sample [15, 16, 24] and 12 studies used the convenience sample size [12-14, 20-23, 25-29]. All studies used a modified Jaffé method based on Scr levels to assess AKI. Patient range represented a patient that might be tested in practice. Moreover, no patients used renal biopsies or renal angiographies to diagnose AKI.

There were no studies receiving support by industry or reagent company sponsors. Thus, none of the results of these studies were commercially affected. Neither the clinician nor the laboratory doctor knew the source of urine samples. Therefore, results were not subjected to human influence. All samples were collected and processed in accordance with standardized procedures. Ten studies indicated that the sample storage temperature was -80°C [12-16, 24, 25, 27-29], while 5 studies did not specify sample storage conditions [20-21, 23, 26]. There was no evidence of significant publication bias in the results of the accuracy of uKIM-1 predictions for AKI associated with cardiac surgery (asymmetric-regression test, P<0.1).

Table 1. Characteristics of studies

Study	Country	Sample Size	Population Type	Age (y)	Females (%)	Sample Collection Time	Mean Baseline Scr (mg/dl)	AKI Definition
Han et al., 2009 [12]	United States	90	Adults	63.6	32.2%	Before and after CPB	1.1	AKIN[a]
Liangos et al., 2009 [13]	United States	103	Adults	68.0	27.2%	Before and after CPB	1.1	AKIN[b]
Koyner et al., 2010 [14]	United States	123	Adults	69.5	35.0%	Before and after CPB	1.0	AKIN
Liang et al., 2010 [15]	China	122	≥14 years old	30.0	43.3%	After CPB	1.6	RIFLE
Parikh et al., 2013 [21]	United States/Canada	1530	Adults/Children	73.0/2.5	32.2%/45.0%	Before and after CABG	1.1	RIFLE/AKIN
Arthur et al., 2014 [22]	United States	95	Adults	66.2	30.5%	After cardiac surgery	1.1	AKIN
Wang et al., 2014 [20]	China	42	Adults	60.5	45.3%	Before and after CAG/PCI	1.4	AKIN[c]
Torregrosa et al., 2015 [27]	Spain	193	Adults	63.4	23.6%	After cardiac surgery	1.0	RIFLE
Metzger et al., 2016 [29]	Germany	120	Adults	57.5	24.2%	Before and after cardiac surgery	1.1	AKIN
Elmedany et al., 2017 [26]	Egypt	45	Adults	56.8	17.8%	After cardiac surgery	1.1	AKIN
Wybraniec et al., 2017 [25]	Poland	95	Adults	65.0	30.5%	Before and after CAG/PCI	1.4	AKIN[a]
Nadkarni et al., 2017 [23]	United States	1219	Adults	71.5	33.0%	After cardiac surgery	NA	AKIN
Dong et al., 2017 [24]	United States/China	150	Children	3.83	48.7%	After CPB	1.1	AKIN[d]
Gist et al., 2018 [16]	United States	98	Infants	0.43	33.0%	After CPB	1.1	KDIGO
Wybraniec et al., 2018 [28]	Poland	95	Adults	65.0	30.5%	Before and after CPB	1.0	AKIN[b]

Abbreviations and definitions: CPB, cardiopulmonary bypass; Scr, serum creatinine; NA, not applicable; CABG, coronary artery bypass grafting; CAG, coronary angiography; PCI, percutaneous coronary intervention; AKIN, acute kidney injury network; RIFLE, "Risk"/"Injury"/"Failure"/"Loss"/"End"; KDIGO, the kidney disease improving global outcomes. [a]≥50% relative or ≥0.3 mg/dl absolute increase of serum creatinine concentration at 48 hours after the procedure. [b]≥50% absolute increase of serum creatinine concentration at 72 hours after the procedure. [c]≥25% relative or ≥2.6 mg/dl absolute increase of serum creatinine concentration at 72 hours after the procedure. [d]≥50% in serum creatinine level from baseline.

Table 2. Design characteristics of individual studies

Study	Design	Eligibility Criteria Clearly Defined	Sample Size Estimation	Representativeness of Patients (within setting)	Blinding	Funding	Storage	uKIM-1 Assay
Han et al., 2009 [12]	PC	Yes	No	Yes	Yes	No	-80 °C	ELISA[a]
Liangos et al., 2009 [13]	PC	Yes	No	Yes	Yes	No	-80 °C	ELISA[a]
Koyner et al., 2010 [14]	PC	Yes	No	Yes	Yes	No	-80 °C	MAP[b]
Liang et al., 2010 [15]	CC	Yes	Yes	Yes	Yes	No	-80 °C	ELISA[a,c]
Parikh et al., 2013 [21]	PC	Yes	No	Yes	Yes	No	NA	ELISA[d]
Arthur et al., 2014 [22]	PC	Yes	No	Yes	Yes	No	NA	ELISA
Wang et al., 2014 [20]	PC	Yes	No	Yes	Yes	No	NA	ELISA[c]
Torregrosa et al., 2015 [27]	PC	Yes	No	Yes	Yes	No	-80 °C	ELISA[c]
Metzger et al., 2016 [29]	RC	Yes	No	Yes	Yes	No	-80 °C	ELISA[e]
Elmedany et al., 2017 [26]	PC	Yes	No	Yes	Yes	No	NA	NA
Wybraniec et al., 2017 [25]	PC	Yes	No	Yes	Yes	No	-80 °C	ELISA[e]
Nadkarni et al., 2017 [23]	PC	Yes	No	Yes	Yes	No	NA	NA
Dong et al., 2017 [24]	CC	Yes	Yes	Yes	Yes	No	-80 °C	ELISA[c]
Gist et al., 2018 [16]	PC	Yes	Yes	Yes	Yes	No	-80 °C	ELISA[c]
Wybraniec et al., 2018 [28]	PC	Yes	No	Yes	Yes	No	-80 °C	ELISA[e]

Abbreviations and definitions: PC, prospective cohort study; CC, case-control study; RC, retrospective cohort study; NA, not applicable; ELISA, enzyme-linked immunosorbent assay; MAP, multi-analyte profiling. [a]Research-based assay. [b]Microsphere-based Luminex xMAP technology. [c]R&D, Minneapolis, MN, USA. [d]Sekisui Diagnostics LLC developed assays. [e]Enzo Life Sciences, Exeter, UK.

Table 3. Paired sensitivity and specificity of individual studies for KIM-1 in predicting AKI

Study	No. of Patients				KIM-1 Cutoff (ng/mg)	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)
	TP	FP	FN	TN				
Han et al., 2009 [12]	5	31	4	50	>1.20	0.56 (0.21-0.86)	0.62 (0.50-0.72)	0.65 (0.54-0.75)
Liangos et al., 2009 [13]	11	2	1	86	>0.40	0.92 (0.62-1.00)	0.98 (0.92-1.00)	0.78 (0.64-0.91)
Koyner et al., 2010 [14]	4	42	2	75	NA	0.67 (0.22-0.96)	0.64 (0.55-0.73)	0.69 (0.58-0.80)
Liang et al., 2010 [15]	13	17	1	91	>1.50	0.93 (0.66-1.00)	0.84 (0.76-0.91)	0.88 (0.81-0.93)
Parikh et al., 2013 [21]	10	103	9	1408	NA	0.53 (0.29-0.76)	0.93 (0.92-0.94)	0.71 (0.63-0.78)
Arthur et al., 2014 [22]	2	21	1	71	NA	0.67 (0.09-0.99)	0.77 (0.67-0.85)	0.73 (0.60-0.83)
Wang et al., 2014 [20]	6	8	1	27	>4.60	0.86 (0.42-1.00)	0.77 (0.60-0.90)	0.83 (0.70-0.98)
Torregrosa et al., 2015 [27]	5	30	2	156	>1.70	0.71 (0.29-0.96)	0.84 (0.78-0.89)	0.71 (0.55-0.88)
Metzger et al., 2016 [29]	3	56	2	58	>2.10	0.60 (0.15-0.95)	0.51 (0.41-0.60)	0.57 (0.47-0.67)
Elmedany et al., 2017 [26]	4	7	2	32	>10.00	0.67 (0.22-0.96)	0.82 (0.66-0.92)	0.70 (0.54-0.87)
Wybraniec et al., 2017 [25]	3	6	1	85	>0.40	0.75 (0.19-0.99)	0.93 (0.86-0.98)	0.81 (0.42-0.94)
Nadkarni et al., 2017 [23]	27	478	5	709	>0.17	0.84 (0.67-0.95)	0.60 (0.57-0.63)	0.70 (0.48-0.81)
Dong et al., 2017 [24]	5	45	1	99	>0.09	0.83 (0.36-1.00)	0.69 (0.61-0.76)	0.76 (0.53-0.87)
Gist et al., 2018 [16]	10	21	2	65	>0.53	0.83 (0.52-0.98)	0.76 (0.65-0.84)	0.60 (0.46-0.74)
Wybraniec et al., 2018 [28]	2	8	0	85	>0.18	1.00 (0.16-1.00)	0.91 (0.84-0.96)	0.73 (0.51-0.86)

Abbreviations: AKI, acute kidney injury; TP, true positive; FP, false positive; FN, false negative; TN, true negative; KIM-1, kidney injury molecule 1; NA, not applicable; AUROC, areas under the receiver operating characteristic (ROC) curve; CI, confidence interval.

Evidence synthesis

The aim of this study was to investigate the accuracy of uKIM-1 levels in predicting AKI. True-positive, false-positive, false-negative, true-negative, and corresponding cut-off values, sensitivities, and specificities, for each study, are shown in **Table 3**. Furthermore, HSROC was used to summarize ROC curves. It was found that the diagnostic odds ratio (DOR) of uKIM-1 was 2.4, with a sensitivity of 0.76 and specificity of 0.84 (**Figure 2**). The AUROC was 0.71. In addition, levels of uKIM-1 in adults (DOR: 3.7, AUROC: 0.79) [12-14, 20, 22, 23, 25-29] and children (DOR: 2.6, AUROC: 0.76) [24] were predicted to be more accurate than those in infants (DOR: 1.5, AUROC: 0.60) [16]. Studies by Liang et al. [15] and Parikh et al. [21] were excluded

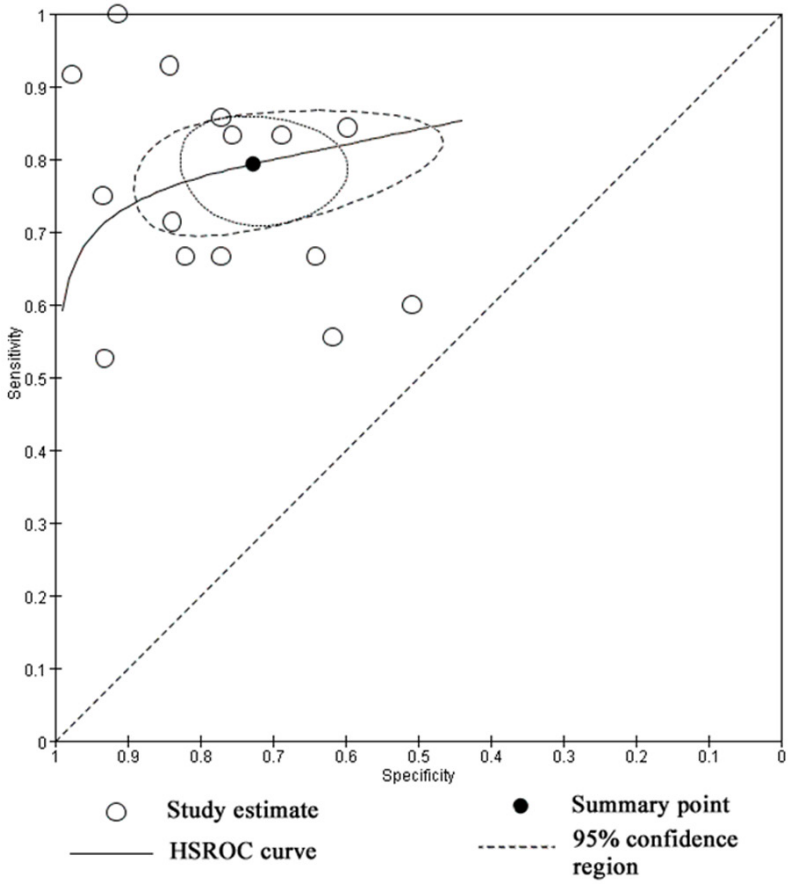

Figure 2. Hierarchical summary receiver operating characteristic (HSROC) plot of urinary kidney injury molecule-1 (uKIM-1) to predict acute kidney injury after cardiac surgery. Based on combined sensitivity (95% confidence interval [CI]) and specificity (95% CI) weighted for sample size of each data set reflected by the size of the circles, showing average sensitivity and specificity estimate of the study results (solid square) and a 95% confidence region around it.

because they included adults and children. It was difficult to obtain valid data by calculations.

To rule out limitations of different assays on uKIM-1 levels, this study compared the accuracy of uKIM-1 levels in standardized assays and research-based assays for predicting AKI associated with cardiac surgery. Results showed that the accuracy of using standardized detection of uKIM-1 (DOR: 2.5, AUROC: 0.78) was significantly higher than that of research-based assays (DOR: 1.8, AUROC: 0.71). The degree of consistency of standardized detection of uKIM-1 was also significantly higher than that of research-based assays. Although there were some deviations in results of the studies included, the values obtained after meta-analysis were broadly consistent, indicating that most studies supported KIM-1 levels for diagnosis of AKI after cardiac surgery.

Discussion

In recent years, incidence and mortality rates of acute kidney injuries (AKI) have continuously increased, due to various reasons [1, 2]. Early diagnosis and timely intervention are keys to treatment of AKI patients. Finding accurate and effective biomarkers has become a hot topic in the field of AKI research. However, due to the many drawbacks of clinical pathological diagnosis of AKI (Kidney Puncture Pathology), related study progress has been slow [30]. In clinical practice, serum creatinine (Scr) and urea nitrogen (BUN) levels are the most commonly used and popularized test items. However, they have large heterogeneity for different genders, ages, and even ethnic groups, limiting clinical diagnosis [5].

Some studies have proposed a method for assessment of renal function using radioisotope labeling. However, the research is only permitted in animal experiments because of its invasiveness and the likelihood of causing cause renal damage [1, 31]. Regarding related biomarkers of AKI, urinary kidney injury molecule-1 (uKIM-1) is a hot spot, highly praised in recent years [8]. With the improvement of laboratories in medical centers around the world, the rapid standardization of detection of uKIM-1 has arisen. However, results of different clinical studies have varied widely. Therefore, the accuracy of uKIM-1 as an important biomarker for future diagnosis of AKI remains controversial.

In present study, a systematic review and meta-analysis was conducted, aiming to clarify the

accuracy of uKIM-1 in predicting AKI associated with cardiac surgery. This study systematically reviewed published clinical observational studies. Studies concerning post-cardiac AKI were included, with the study population including adults, children, and infants. This study also analyzed the accuracy of different methods for detection of uKIM-1 in the diagnosis of AKI, as well as its sensitivity and specificity in early diagnosis of AKI after cardiac surgery. Results suggest that uKIM-1 is an effective biomarker for early diagnosis of AKI after cardiac surgery and that standardized detection of uKIM-1 is more sensitive and specific.

In different studies, the definition of AKI was different. Times to collect urine samples from patients were also different, making it difficult to evaluate levels of uKIM-1 in diagnosing AKI. The International Health Organization and Society of Nephrology have not yet proposed a clear cut-off value of uKIM-1 for diagnosis of AKI. HO et al., [32], for the first time, conducted a meta-analysis of the accuracy of uKIM-1 in the diagnosis of postoperative cardiac AKI. A total of 6 studies were included in the analysis. However, their results did not clearly indicate cut-off values of uKIM-1 and AUROC values. The current study included a total of 15 clinical observation studies. A more systematic meta-analysis of the accuracy of uKIM-1 in post-cardiac AKI was performed. Cut-off values and AUROC values of uKIM-1 were clarified, providing reference value for future research and guidance.

The current meta-analysis also assessed uKIM-1 using a uniform AKI definition and standardized time. This method could be used directly in the clinic. Results suggest that uKIM-1 is a valuable biomarker for diagnosis of post-cardiac AKI, with high sensitivity and specificity. It could be used in adults and children, but with a lower diagnostic value for infants. The reason might be that the organs of infants are not yet well developed. In all included studies, they clearly defined inclusion and exclusion criteria. All patients with chronic kidney disease were excluded. Thus, data quality was relatively high. However, due to different clinical circumstances of each institute, normal and critical values of uKIM-1 were different. Therefore, further international large-scale multicenter randomized controlled trials are necessary to confirm present results.

There were 5 studies [20-21, 23, 26] with unspecified sample storage times. There was a certain heterogeneity in the detection of uKIM-1 levels, but the data obtained was broadly consistent. Therefore, these studies were not excluded. Of these studies, 8 (53.3%) were from the United States [12-14, 16, 21-24], 4 (26.7%) were from Europe [25, 27-29], 3 (20%) were from China [15, 20, 24], and 1 (6.7%) was from Egypt [26]. Thus, whether levels of uKIM-1 are universal requires further study. In addition, if uKIM-1 levels are measured using uniform normalization, it is believed that the diagnostic accuracy of AKI assessments could be made more comparable.

The current study had five limitations. First, many of the studies included used AKI definitions differently and uKIM-1 levels were measured at different times. There may be some errors in data acquisition and calculations. Second, AKI occurred at different times in these studies. Urine collection, processing, and storage criteria were also different. Therefore, resulting values were heterogeneous. Third, in the standardized form developed, the urine quantity definition of AKI was not used. However, the AKIN standard was to evaluate the AKI, indicating the need to recalculate the original data and achieve data integration. Fourth, there was insufficient data to assess the impact of uKIM-1 levels on patient mortality and RRT. This study did not conduct a comprehensive analysis of these results. Fifth, none of these studies used radiolabeling or inulin clearance to assess renal function and verify the performance of uKIM-1. Therefore, accuracy of uKIM-1 levels for diagnosis of AKI and the predictive ability of renal function recovery were limited.

In summary, a total of 15 studies (4120 patients) from 7 countries were included in the current meta-analysis. Results suggest that uKIM-1 levels are highly sensitive and specific for diagnosis of AKI after cardiac surgery. However, due to heterogeneity, large multicenter clinical randomized controlled trials are necessary to validate present conclusions.

Disclosure of conflict of interest

None.

Address correspondence to: Dong Cen, Department of Laboratory Test, Yinzhou Second Hospital, No.

998 Qianhe North Road, Ningbo, Zhejiang Province, China. E-mail: cendong2002@163.com

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