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The diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for acute kidney injury in adults

A PRISMA-compliant meta-analysis

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Abstract

Introduction: Early diagnosis of acute kidney injury (AKI) remains a challenge. Recently, [TIMP-2]·[IGFBP7], which is a combination of urine tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor (IGF) binding protein 7 (IGFBP7), has been identified as a potential biomarker of AKI. We performed this meta-analysis to assess the diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for AKI in adult patients.

Methods: We searched the PubMed, Embase, and Cochrane Library databases from database inception to March 2017. Two authors independently screened articles based on inclusion and exclusion criteria and assessed the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies 2 criteria. Review Manager and STATA were used for all statistical analyses.

Results: Nine studies (n = 1886) satisfied the inclusion criteria. Pooled analyses demonstrated that urinary [TIMP-2]·[IGFBP7] exhibited fair diagnostic accuracy for AKI (sensitivity [SEN] 0.83 [95% CI 0.75–0.89], specificity [SPE] 0.72 [95% CI 0.56–0.84], and area under the summary receiver operating characteristic [SROC] curve 0.86 [95% CI 0.82–0.88]) and AKI stage ≥ 2 (according to the 2012 Kidney Disease: Improving Global Outcomes [KDIGO] 2012 classification system; SEN 0.92 [95% CI 0.81–0.96], SPE 0.63 [95% CI 0.49–0.74], and area under the SROC curve 0.88 [95% CI 0.85–0.91]) in adult patients.

Conclusion: Our findings indicate that urinary [TIMP-2]·[IGFBP7] may be a reliable biomarker for the early detection of AKI. However, given the significant heterogeneity among the included studies, clinicians should be aware of the utility and limitations of this biomarker in clinical practice. Additional high-quality studies examining a larger sample of patients are required.

Abbreviations: AKI = acute kidney injury, AUC = area under curve, CKD = chronic kidney disease, DOR = diagnostic odds ratio, FDA = Food and Drug Administration, FP = false positive, IGFBP7 = insulin-like growth factor binding protein 7, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2, RRT = renal replacement therapy, SEN = sensitivity, SPE = specificity, SROC = summary receiver operating characteristic, TIMP-2 = tissue inhibitor of metalloproteinase 2.

Keywords: [TIMP-2]·[IGFBP7], acute kidney injury, biomarker, diagnosis, insulin-like growth factor binding protein 7, meta-analysis, tissue inhibitor of metalloproteinase 2

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The datasets analyzed during the present study are available in the PubMed, Embase, and Cochrane Library databases.

CL and XL contributed equally to this work.

CL and XL contributed equally to this work. CL participated in the design, selected trials, extracted data, performed the statistical analyses, and drafted the manuscript. XL participated in the design, selected trials, performed the statistical analyses, and drafted the manuscript. ZM helped draft the manuscript and assessed the risk of bias of the trials. HK helped draft the manuscript and assisted with interpretation of the data. HL contributed to data collection. LP participated in the analysis and interpretation of data. LW helped draft the manuscript and assessed the risk of bias of the trials. FZ collected the data, performed the statistical analyses, and supervised the study. All authors read and approved the final manuscript.

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1. Introduction

Acute kidney injury (AKI) is a common but complex clinical syndrome that often occurs in critically ill or postoperative patients, is difficult to predict, and is inevitably associated with adverse clinical outcomes. In addition, AKI significantly increases hospital costs and the incidences of dialysis and chronic kidney disease (CKD).[1–5] As understanding of the etiology and pathology of AKI has advanced, various biomarkers have been evaluated for the early and preclinical detection of AKI in different patients. These biomarkers include plasma and urine neutrophil gelatinase-associated lipocalin,[6] urine interleukin 18,[7] urine liver-type fatty acid-binding protein,[8] and urine kidney injury molecule 1.[9] However, none of these potential markers has been widely used in clinical practice because they do not exhibit acceptable accuracy for the early diagnosis of kidney injury and the early identification of at-risk patients.[10]

Fortunately, the novel AKI-related biomarker [TIMP-2]·[IGFBP7], which is a combination of urine tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor (IGF) binding protein 7 (IGFBP7), was approved by the US Food and Drug Administration (FDA) for AKI-related marketing.[11,12] TIMP-2 and IGFBP7 are biomarkers of G1 cell cycle arrest, and the levels of these proteins increase during the early period after renal tubular cell injury.[13,14] TIMP-2 is an important component in the pathophysiology of ischemia–reperfusion injury,[15] and IGFBP7 is a secreted protein that regulates the bioavailability of IGFs through direct low-affinity binding.[16] Therefore, [TIMP-2]·[IGFBP7] has potential value for the prediction of early AKI.

Recently, an increasing number of studies have evaluated the value of urinary [TIMP-2]·[IGFBP7] in the diagnosis of AKI. To fully understand the diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for AKI, we conducted this meta-analysis to assist physicians in making clinical decisions.

2. Methods

2.1. Search strategy

We searched the PubMed, Embase, and Cochrane Library databases from database inception to March 2017. The search terms were as follows: ("TIMP-2" or "tissue inhibitor metalloproteinase-2" or "IGFBP7" or "IGF-binding protein 7" or "insulin-like growth factor binding protein 7" or "cycle arrest biomarkers") and ("AKI" or "acute kidney injury"). The search was limited to human studies with no language restrictions. The reference lists of selected studies were searched by hand to identify potentially relevant citations. Ethical approval was not required because the meta-analysis was based on published articles.

2.2. Study selection

Two investigators (CL and ZM) independently conducted the study selection. Any disagreement was resolved by consultation with a third party (FZ). The inclusion criteria were as follows: a diagnostic value of urinary [TIMP-2]·[IGFBP7] for AKI morbidity in adult patients (≥18 years old) was reported; a 2×2 contingency table could be extracted; AKI was adjudicated using the RIFLE (risk, injury, failure, loss, and end-stage renal disease), Acute Kidney Injury Network (AKIN) or Kidney Disease: Improving Global Outcomes (KDIGO) consensus criteria (based on the RIFLE/AKIN definitions for AKI)[17]; and a prospective controlled design was used. The exclusion criteria were as follows: a review, letter, commentary, correspondence, case report, conference abstract, expert opinion, editorial, or animal experiment; a duplicated study; insufficient information to calculate accurate estimates; the involvement of pediatric patients; and the inclusion of patients with pre-existing chronic renal failure.

2.3. Data extraction and quality assessment

One investigator extracted details regarding the first author, year of publication, study design, inclusion criteria, definition of AKI, definition of a positive test result, number of patients, average age, time of marker detection, cut-off points, true positives, false positives (FPs), false negatives, true negatives, sensitivity (SEN), and specificity (SPE) from the included studies.

Two investigators (CL and ZM) independently assessed the methodological quality of each included study using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) criteria and evaluated each of these studies in 4 domains: patient selection; index test; reference standard; and patient flow and test timing.[18] Any disagreements in the quality assessment were resolved by discussion and consensus.

2.4. Statistical analysis

All statistical analyses were conducted using Review Manager, version 5.1.2 (RevMan; The Cochrane Collaboration, Oxford, UK) and STATA, version 12.0 (Stata Corporation, College Station, TX). A bivariate random-effects regression model was used to calculate the pooled SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (CIs). We also constructed a summary receiver operating characteristic (SROC) curve by plotting individual and summary points for SEN and SPE to assess the overall diagnostic accuracy.[19,20] Between-study heterogeneity was assessed using the I^2 index, with an $I^2 \geq 50\%$ regarded as indicative of substantial heterogeneity among studies. P values $< .05$ were considered significant. In addition, sensitivity and subgroup analyses were conducted to investigate potential sources of between-study heterogeneity. Fagan nomo-

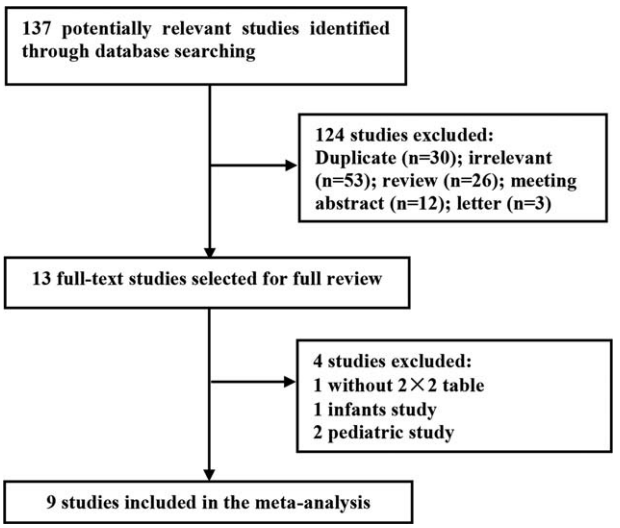

Figure 1. Flow chart depicting the study selection procedure.

Table 1

Characteristics of the included studies.

Study	Population	Definition of AKI	AKI threshold	No. of patients/ male/No. of patients with AKI	Mean age, y	Severity	Time of markers detection	Cutoff, ng/mL^2 / 1000	TP	FP	FN	TN	SEN, %	SPE, %
Kashani et al[21] (2013; North America and Europe)	Critically ill adult patients (≥21 y) within 24 h of admission to an ICU	KDIGO	AKI stage ≥2 within 12 h	728/449/101	AKI (≤1): 64 (52–73)* AKI (≥2): 65 (57–77)*	AKI (≤1): APACHE III 67 (51–88)* AKI (≥2): APACHE III 85 (59–106)*	At enrollment	0.3	90	313	11	314	89	50
								2	42	31	59	596	42	95
Hoste et al[22] (2014; USA)	Critically ill adult patients (≥21 y) within 24 h of admission to an ICU	KDIGO	AKI stage ≥2 within 12 h	153/87/27	AKI (≤1): 65 (54–78)* AKI (≥2): 64 (54–75)*	NR	At enrollment	0.3	24	59	3	67	89	53
								2	12	13	15	113	44	90
Bihorac et al[23] (2014; USA)	Critically ill adult patients within 24 h of admission to an ICU	KDIGO	AKI stage ≥2 within 12 h	408/219/71	63 ± 17†	APACHE III 58 (44–78)*	At enrollment	0.3	65	182	6	155	92	46
								2	26	17	45	320	37	95
Meersch et al[24] (2014; Germany)	Patients undergoing cardiac surgery with CPB	KDIGO	AKI stage ≥1 within 72 h	50/33/26	71 ± 12†	AKI (=0): APACHE 8 ± 3† AKI (≥1): APACHE 12 ± 5†	4 h after CPB	0.3	21	4	5	20	80	83
							12 h after CPB		22	12	4	12	85	50
							24 h after CPB		19	10	7	14	73	58
Gocze et al[25] (2015; Germany)	Patients (≥18 y) received major noncardiac surgery and transported to the ICU	KDIGO	AKI stage ≥1 within 48 h	107/NR/45	60 ± 14.8†	SAPS II 22.1 ± 9.6†	At enrollment	0.315	39	17	6	45	86.7	72.6
			AKI stage ≥2 within 48 h	107/NR/24				0.315	24	32	0	51	100	61.4
Pilarczyk et al[26] (2015; Germany)	Patients (≥18 y) scheduled for elective on-pump CABG	KDIGO	AKI stage ≥2 within 48 h	60/48/6	AKI (≤1): 68.8 ± 9.1† AKI (KI8: 76.2 ± 3.9†	AKI (≤1): SAPS 24.9 ± 13.8† AKI (≥K): SAPS 30.8 ± 11.6†	4 h after surgery	0.3	4	13	2	41	67	76
								2.0	2	1	4	53	33	98
							24 h after surgery	0.89	5	10	1	44	80	81
								0.3	6	18	0	36	100	67
								2.0	2	3	4	51	40	95
Wetz et al[27] (2015; Germany)	Patients (≥18 y) undergoing CABG surgery with CPB	KDIGO	AKI stage ≥1 within 2 post-operative days	42/NR/16	72 (65–76)*	NR	End of surgery	0.41	6	2	10	24	36	92
								0.3	6	4	10	22	36	84
								2.0	1	1	15	25	7	96
							24 h after surgery	1.065	8	1	8	25	47	96
								0.3	8	12	8	14	53	54
								2.0	5	0	11	26	33	100

Study	Population	Definition of AKI	AKI threshold	No. of patients/ male/No. of patients with AKI	Mean age, y	Severity	Time of markers detection	Cutoff, ng/mL^2 / 1000	TP	FP	FN	TN	SEN, %	SPE, %
Kimmel et al[28] (2016; Germany)	Patients (≥18 y) admitted to the ED	KDIGO	AKI stage ≥2 within 12 h	298/216/46	63 ± 14†	NR	Within 12 h	0.3	35	118	11	134	76	53
								2	14	15	32	237	30	94
Dusse et al[29] (2016; Germany)	Patients undergoing TAVI	KDIGO	AKI stage ≥2 within 48 h	40/16/8	81.2 ± 5.6†	AKI (≤1): SAPS 27.0 ± 6.7† AKI (≥2): SAPS 33.8 ± 9.7†	4 h after surgery	0.3	3	11	5	21	38	67
								2.0	1	0	7	32	13	100
							24 h after surgery	1.03	8	3	0	29	100	90
								0.3	8	14	0	18	100	55
								2.0	5	2	3	30	67	95

AKI = acute kidney injury, APACHE = Acute Physiology and Chronic Health Evaluation, CABG = coronary artery bypass surgery, CPB = cardiopulmonary bypass, ED = emergency department, FN = false negative, FP = false positive, ICU = intensive care unit, KDIGO = Kidney Disease: Improving Global Outcomes, NR = not report, SAPS = Simplified Acute Physiology Score, SEN = sensitivity, SPE = specificity, TAVI = transcatheter aortic valve implantation, TN = true negative, TP = true positive.

* Median (interquartile range).

† Mean ± standard error.

gram was used to calculate the post-test probability (PTP), and Deek funnel plot was employed to detect publication bias.

3. Results

3.1. Search results and study characteristics

The literature flow diagram (Fig. 1) summarizes the search for and selection of studies. In total, 9 studies satisfied the inclusion criteria.[21–29] One valuable study was excluded from this meta-analysis due to an inability to extract a 2×2 contingency table from the available data,[30] and 3 other studies were excluded due to the inclusion of infants[31] and pediatric patients.[32,33] Details regarding all 9 studies are presented in Table 1. All these studies were published between 2013 and 2016, and a total of 1886 patients were included in this meta-analysis. Six of the included studies were conducted in Germany,[24–29] 2 were conducted in the United States,[22,23] and the remaining study was conducted in North America and Europe.[21] Four studies focused on patients who had undergone cardiac surgery,[24,26,27,29] 1 study included noncardiac surgery patients,[25] 4 studies included critically ill patients,[21–23,25] and 1 study included emergency department patients.[28] All studies defined AKI based on the KDIGO criteria,[17] and urinary [TIMP-2]·[IGFBP7] was measured using the commercially available and FDA-approved NephroCheck Test.

3.2. Study quality and publication bias

The QUADAS-2 tool was used to assess the risk of bias in the 9 included studies (Fig. 2). The results revealed that 1 study[24] had a high risk in patient selection, and 2 studies[26,27] had a high risk in flow and timing. Deek funnel plot is shown in Fig. 3. Significant publication bias was observed ($P = .04$).

3.3. Diagnostic value of urinary [TIMP-2]·[IGFBP7] for AKI prediction

The pooled SEN and SPE values were 0.83 (95% CI 0.75–0.89) and 0.72 (95% CI 0.56–0.84), respectively (Fig. 4). The PLR and NLR were 3.0 (95% CI 1.9–4.7) and 0.24 (95% CI 0.17–0.33), respectively (Fig. 5). The DOR was 12 (95% CI 7, 22). The area under the SROC curve for urinary [TIMP-2]·[IGFBP7] was 0.86 (95% CI 0.82, 0.88; Fig. 6). Fagan nomogram was applied to estimate the diagnostic value of urinary [TIMP-2]·[IGFBP7] for AKI (Fig. 7). When 50% was selected as the pretest probability of AKI, the results indicated that the use of [TIMP-2]·[IGFBP7] for the detection of AKI increased the post-test probability to 75% when the [TIMP-2]·[IGFBP7] results were positive; the observed PLR of 3 indicated that a person with AKI was 3 times more likely to have a positive diagnosis than a healthy individual. By contrast, when the [TIMP-2]·[IGFBP7] results were negative, the post-test probability decreased to 19%; the NLR was 0.24, suggesting that the combination of TIMP-2 and IGFBP7 was a useful biomarker for the diagnosis of AKI.

The I^2 values for the pooled SEN and SPE were 79.87% (95% CI 67.33–92.41; $P < .01$, Fig. 4) and 95.38% (95% CI 93.49–97.27; $P < .01$; Fig. 4), respectively. The overall I^2 result for the bivariate model was 94% (95% CI 89–99). The proportion of heterogeneity likely caused by the threshold effect was small ($P = .86$). Some of the observed heterogeneity was likely caused by population differences and the use of different definitions of positive test results, different cut-off values, or

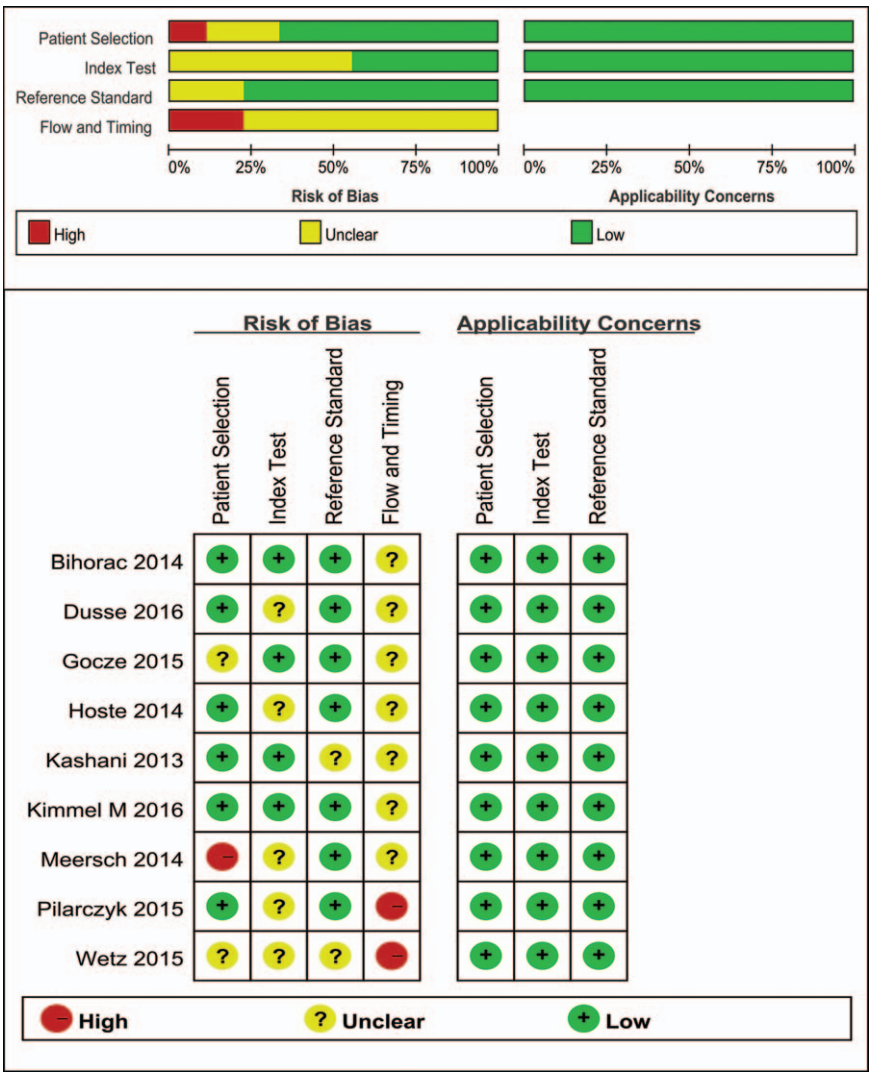

Figure 2. Summary of the methodological quality of the studies according to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria.

different assessment times. Therefore, we performed a sensitivity analysis and a subgroup analysis to explore the sources of potential heterogeneity in the SEN and SPE (Table 2). However, due to the limited number of included studies, significant heterogeneity was observed among those groups. The results suggested that the cardiac surgery group and the elderly group (mean age > 65 years) had a higher area under curve (AUC 0.91), although these 2 groups included the same studies. Patients who will develop moderate and severe AKI (stage 2 and 3 AKI, respectively, according to the 2012 KDIGO classification)[17] also have a higher AUC (SEN 0.92 [95% CI 0.81–0.96], SPE 0.63 [95% CI 0.49–0.74], and area under the SROC curve 0.88 [95% CI 0.85–0.91]).

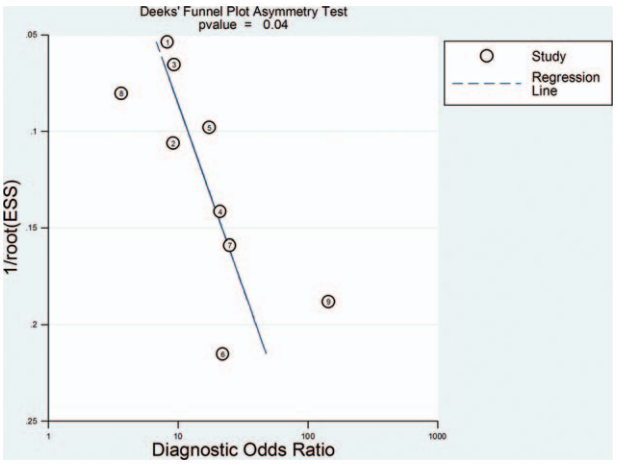

Figure 3. Deek funnel plot asymmetry test for publication bias.

4. Discussion

This meta-analysis evaluated the diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for AKI in adult patients. Overall, [TIMP-2]·[IGFBP7] exhibited fair diagnostic accuracy for AKI (AUC = 0.86, SEN = 0.83, and SPE = 0.72) and AKI ≥ stage 2 (according to the 2012 KDIGO classification[17]; AUC = 0.88, SEN = 0.92, and SPE = 0.63), suggesting that [TIMP-2]·[IGFBP7] is a valuable biomarker for the early detection of AKI. However, current evidence indicates that early recognition cannot prevent the progression of AKI or reduce AKI-associated costs; moreover, FPs may increase unnecessary expenditures.[34]

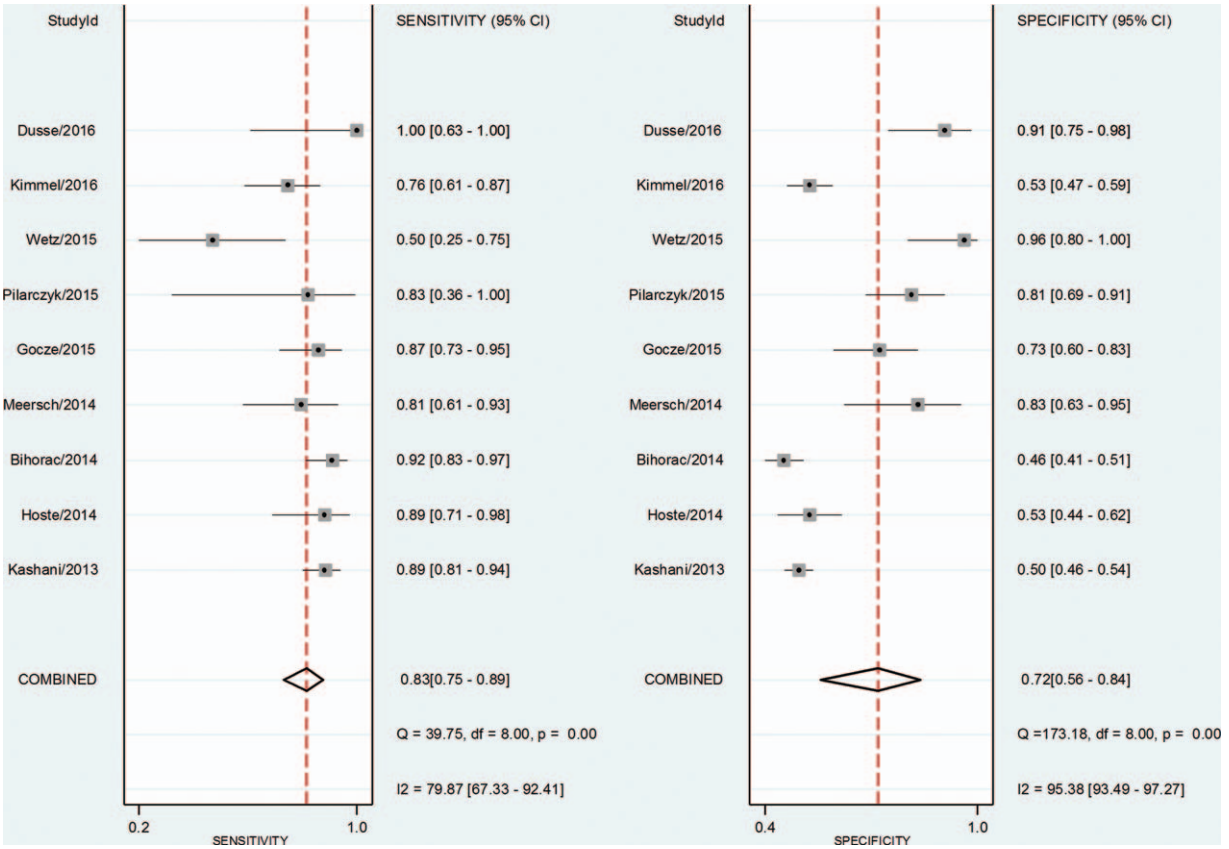

Figure 4. Forest plot of the sensitivity and specificity of urinary [TIMP-2]·[IGFBP7] for the diagnosis of acute kidney injury.

A previous meta-analysis[35] focused on this topic included 10 full-text prospective studies showing that the estimated sensitivity of urine [TIMP-2]·[IGFBP7] for the early diagnosis of AKI was 0.84 (95% CI 0.80–0.88) and the SPE was 0.57 (95% CI 0.55–0.60). The SROC analysis showed an AUC of 0.88.[35] The results from our meta-analysis were similar, but this meta-analysis included a subgroup analysis[36] of the enrolled studies,[21,23] which might influence the accuracy of the analysis results. We also performed more sensitivity analyses to explore the sources of heterogeneity and collected more data in Table 1 to enable the readers to acquire more valuable information. Furthermore, we used the STATA software to

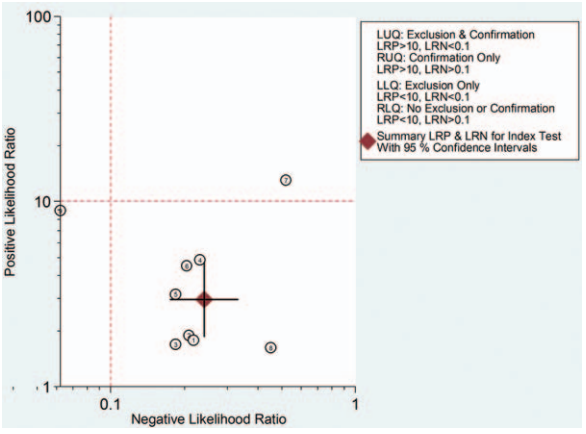

Figure 5. Likelihood ratio scattergram of urinary [TIMP-2]·[IGFBP7] for the diagnosis of acute kidney injury. The positive likelihood ratio and negative likelihood ratio were 3.0 (95% CI 1.9–4.7) and 0.24 (95% CI 0.17–0.33), respectively. CI = confidence interval, LLQ = left lower quadrant, LRN = likelihood ratio negative, LRP = likelihood ratio positive, LUQ = left upper quadrant, RLQ = right lower quadrant, RUQ = right upper quadrant.

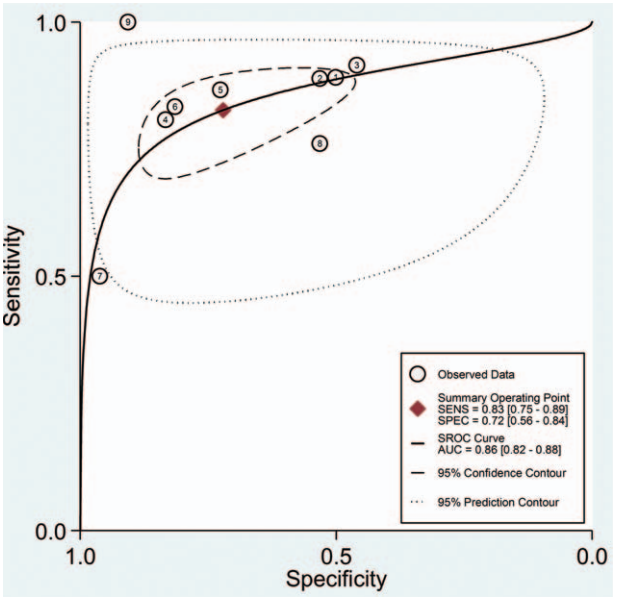

Figure 6. Summary receiver operating characteristic graph for the included studies. AUC = area under curve, SEN = sensitivity, SPE = specificity.

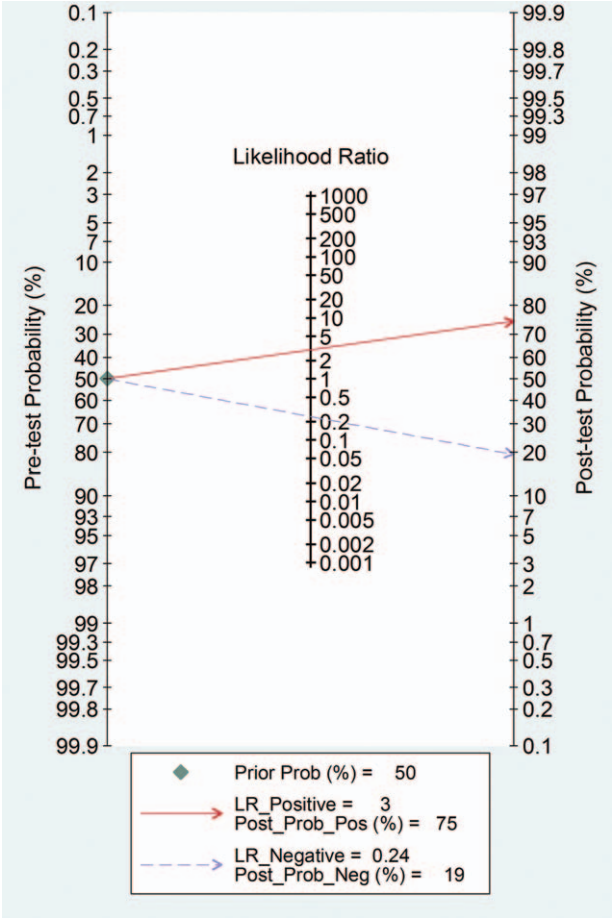

Figure 7. Fagan nomogram of urinary [TIMP-2]·[IGFBP7] for the diagnosis of acute kidney injury.

draw Fagan nomogram (Fig. 7) to analyze the index tests and draw a likelihood ratio scattergram (Fig. 5) to evaluate the clinical utility.

AKI is a common complication among hospitalized patients and is associated with significant morbidity and mortality.[37] Early identification of AKI can provide better opportunities for preventive interventions.[38] TIMP-2 and IGFBP7 are novel urinary G1 cell cycle biomarkers released by cellular stress during the early phase of tubular cell injury[39] and have potential value for the early recognition of AKI.[39] However, the product of [TIMP-2]·[IGFBP7] showed a small reverse correlation with age,[40] and diabetes was independently associated with higher [TIMP-2]·[IGFBP7] levels.[30] Therefore, clinicians should be aware of both the utility and limitations of this biomarker in clinical practice.

In this meta-analysis, significant between-study heterogeneity was observed. Although we performed sensitivity and subgroup analyses to explore the sources of potential heterogeneity, the between-study heterogeneity was not significantly decreased. Additional high-quality studies examining a larger sample of patients are required. In addition to its predictive value for AKI, urinary [TIMP-2]·[IGFBP7] has potential for the prediction of the use of renal replacement therapy (RRT) in high-risk patients. One study[25] included in this meta-analysis revealed that the AUC for the use of RRT was 0.83.

Our meta-analysis excluded patients with pre-existing chronic renal failure. However, 1 study compared the reference intervals (inner 95%) for [TIMP-2]·[IGFBP7] in apparently healthy subjects with those for chronic comorbid subjects without AKI (including patients with stable CKD) and found no significant difference ($P = .42$).[40] Therefore, an analysis of the urinary [TIMP-2]·[IGFBP7] results for CKD patients would be interesting.

Several limitations of this meta-analysis should be considered. First, only 9 studies with marked between-study heterogeneity were included in this meta-analysis; additional subgroup analyses could not be performed to reduce and interpret the heterogeneity. This issue will limit the widespread clinical use of urinary [TIMP-2]·[IGFBP7]. Second, differences in sample collection times may have affected the detection results and led to bias in the findings of this analysis. Third, publication bias was produced because several valuable studies were excluded from this meta-analysis due to an inability to extract a 2×2 contingency table from the available data. Fourth, most of the patients were associated with 2 authors (J.A. Kellum and A. Bihorac), most of whom were from German studies; this issue could also have influenced the publication bias. Further research addressing the diagnostic accuracy of the examined biomarker in patients of other ethnicities and regions may be required.

Table 2

Results of sensitivity analysis and subgroup analysis.

	Categories	Number of studies	Sensitivity (95% CI)/I^2	Specificity (95% CI) /I^2	AUC (95% CI)	DOR (95% CI)	PLR/NLR
All studies		9 [21–29]	0.83 (0.75, 0.89)/79.87	0.72 (0.56, 0.84)/95.38	0.86 (0.82, 0.88)	12 (7, 22)	3.0/0.24
Sensitivity analysis	Participants more than 100	5 [21–23, 25, 28]	0.87 (0.82, 0.91)/41.41	0.53 (0.47, 0.59)/75.30	0.79 (0.76, 0.83)	7 (5, 11)	1.8/0.25
	Assessment blinded	6 [21–23, 26, 28, 29]	0.89 (0.79, 0.94)/72.90	0.63 (0.47, 0.77)/95.77	0.89 (0.86, 0.91)	14 (5, 40)	2.4/0.18
	AKI stage ≥2	7 [21–23, 25, 26, 28, 29]	0.92 (0.81, 0.96)/73.45	0.63 (0.49, 0.74)/94.70	0.88 (0.85, 0.91)	18 (5, 62)	2.4/0.13
	AKI stage ≥2 within 12 h	4 [21–23, 28]	0.87 (0.80, 0.92)/55.58	0.50 (0.47, 0.54)/18.60	0.60 (0.55, 0.64)	7 (4, 11)	1.8/0.25
	From Germany	6 [24–29]	0.78 (0.66, 0.87)/71.76	0.82 (0.66, 0.91)/94.30	0.86 (0.82, 0.88)	16 (7, 38)	4.2/0.27
	Mean age > 65 y	4 [24, 26, 27, 29]	0.79 (0.56, 0.92)/65.45	0.88 (0.79, 0.93)/24.43	0.91 (0.88, 0.93)	26 (9, 77)	6.4/0.24
	Cutoff value = 0.3	8 [21–24, 26–29]	0.76 (0.60, 0.87)/85.17	0.62 (0.52, 0.71)/84.94	0.72 (0.68, 0.76)	5 (3, 8)	2.0/0.39
	Cutoff value = 2	8 [21–24, 26–29]	0.37 (0.32, 0.43)/0.00	0.94 (0.93, 0.95)/57.69	0.83 (0.79, 0.86)	10 (7, 14)	6.7/0.66
Subgroup analysis	Cardiac surgery	4 [24, 26, 27, 29]	0.79 (0.56, 0.92)/65.45	0.88 (0.79, 0.93)/24.43	0.91 (0.88, 0.93)	26 (9, 77)	6.4/0.24
	ICU and ED	5 [21–23, 25, 28]	0.87 (0.82, 0.91)/41.41	0.53 (0.47, 0.59)/75.30	0.79 (0.76, 0.83)	7 (5, 11)	1.8/0.25

AKI = acute kidney injury, AUC = area under curve, CI = confidence interval, DOR = diagnostic odds ratio, ED = emergency department, ICU = intensive care unit, NLR = negative likelihood ratio, PLR = positive likelihood ratio.

5. Conclusions

Despite the aforementioned limitations, the results of this meta-analysis indicated that urinary [TIMP-2]·[IGFBP7] may be a reliable biomarker for the early detection of AKI. However, given the significant heterogeneity among the included studies, clinicians should be aware of the utility and limitations of this biomarker in clinical practice. Additional high-quality studies examining a larger sample of patients are required.

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