Diagnostic prediction of urinary [TIMP-2] x [IGFBP7] for acute kidney injury: A meta-analysis exploring detection time and cutoff levels

Zhenzhu Song1, Zhongchao Ma2, Kai Qu3, Sinan Liu3,4, Wenquan Niu5 and Ting Lin3,4

1Department of Clinical Laboratory, Liaocheng People’s Hospital, Taishan Medical College, Liaocheng 252000, China
2Department of Nephrology, Hemodialysis Center, Liaocheng People’s Hospital, Taishan Medical College, Liaocheng 252000, China
3Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an 710061, China
4Department of Surgical Intensive Care Unit, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an 710061, China
5Project and Data Management Office, Institute of Clinical Medicine, China-Japan Friendship Hospital, Beijing 100029, China

Correspondence to: Ting Lin, email: 947119451@qq.com
Wenquan Niu, email: niuwenquan_shcn@163.com

Keywords: [TIMP-2] x [IGFBP7], acute kidney injury, meta-analysis, prediction

Received: May 01, 2017 Accepted: September 21, 2017 Published: October 13, 2017

ABSTRACT

Acute kidney injury (AKI) most commonly occurs in critically ill and postoperative patients. Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are two newly-identified urinary biomarkers that can help to detect early AKI, yet their predictive accuracies range widely. Here, we conduct a systematic meta-analysis to evaluate the diagnostic values of [TIMP-2] x [IGFBP7] for AKI at different detection times and cutoff levels. Ten studies were meta-analyzed on 1606 patients. Overall, urinary [TIMP-2] x [IGFBP7] had a pooled sensitivity of 58% and specificity of 79%. Subgroup analysis showed that the sensitivity and specificity were 0.72 and 0.58 with a cutoff value of 0.3 (ng/mL)^2/1000, and 0.38 and 0.94 with a cutoff value of 2.0 (ng/mL)^2/1000, respectively. Moreover, when 0.3 was chosen as the cutoff value, restricting analysis to patients who were tested within 4 hours showed a sensitivity of 0.71 and specificity of 0.73, with the AUROC of 0.75. When 2.0 was chosen as the cutoff value, the sensitivity and specificity were 0.43 and 0.93, respectively in patients who were tested within 24 hours, with the AUROC of 0.70. In summary, urinary [TIMP-2] x [IGFBP7] can predict the occurrence of AKI with moderate diagnostic accuracy. In the earlier administrative periods (less than 4 hours), 0.3 (ng/mL)^2/1000 is recommended to be used; whereas for patients who were administrated more than 24 hours, 2.0 (ng/mL)^2/1000 is more appropriate.

INTRODUCTION

Acute kidney injury (AKI) is a chief public health concern worldwide, and it is projected to affect 5% of patients admitted to the hospital and up to 50% of patients in intensive care units (ICU) [1]. Clinically, dehydration and sepsis combined with nephrotoxic drugs, especially following major surgeries, were considered the most common causes of AKI [2]. Currently, a growing concern has been paid to AKI, as it can precipitate the development of chronic kidney disease (CKD) and end-stage renal disease, and is associated with prolonged hospitalization and an increased mortality [3].

AKI ranks as one of the most expensive conditions, and in the United States the aggregative costs reached nearly $5−10 billion per year [1, 4]. Given that AKI is generally reversible and several therapies in animal models were proposed [5], to extend anti-AKI therapies from bench...
to bedside still has a long way to go. In view of the high prevalence of AKI and its deleterious consequences, it is clinically practical to identify certain accurate and reliable biomarkers to predict the occurrence of AKI.

Over the past decade, several urinary and blood biomarkers have been postulated for the early detection of AKI, including neutrophil gelatinase associated lipocalin (NGAL), kidney injury marker 1 (KIM-1) and interleukin-18 (IL-18), with inherent limitations [5, 6]. In pursuit of ideal biomarkers for AKI diagnosis, two cell-cycle arrest proteins, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) have come to our sight. TIMP-2 and IGFBP7 were firstly identified in 2013 by Kashani et al. [7] and subsequently validated in the United States and European countries [8]. Afterwards, a growing number of studies have showed that the product of urinary TIMP-2 and IGFBP7, termed as [TIMP-2] × [IGFBP7] is a promising early indicator of AKI [9, 10]. However, when to detect this biomarker and how to select cutoff values thus far remains confused. To clear up this confusion, we attempted to evaluate the diagnostic value of urinary [TIMP-2] × [IGFBP7] for AKI through a meta-analysis based on recent clinical investigations.

RESULTS

Literature search

Figure 1 is a flow diagram that schematizes the selection of qualified articles in this meta-analysis. The initial literature search found 103 potentially relevant articles, and among them, 24 articles that seemingly met our inclusion and exclusion criteria were downloaded for further perusal. Finally, a total of 10 articles written in English and published between 2014 and 2016 were considered in this meta-analysis [11–20].

Characteristics of included studies

The basic characteristics of 10 qualified studies with 1648 participants are shown in Table 1. There were three multicenter trials and five clinical trials that recruited more than 100 participants. Nine of ten studies (n = 1597) were conducted in adult participants, and one study (n = 51) in children [14]. Six studies (n = 350) were conducted to evaluate the diagnostic value of urinary [TIMP-2] × [IGFBP7] for AKI after major surgeries (5 cardiac surgery [13, 14, 16–18] and 1 non-cardiac surgery [15]), and four studies (n = 1298) were conducted among ICU patients [11, 12, 19, 20]. The definition of AKI in eight studies accorded with the Kidney Disease: Improving Global Outcomes classification (KDIGO) criteria. There was one study defining AKI according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [14] and the U-score [20], respectively.

The widely chosen time points of collecting urine samples were 4 h, 12 h and 24 h after surgery or ICU admission. All studies employed the commercial NephroCheck kit to measure TIMP-2 and IGFBP7 in urine samples. Cutoff values for urinary [TIMP-2] × [IGFBP7] varied across studies. The widely used cutoff values were 0.3 and 2.0 (ng/mL)/1000. Time of measurement, cutoff point and diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] in each individual study for AKI diagnosis, including true positive (TP), true negative (TN), false positive (FP) and false negative (FN), sensitivity, specificity and the area under the summary receiver operating characteristic (AUROC) values are listed in Table 2.

Comparison of diagnostic accuracies of different cutoff values and detection time

The diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] for AKI was also assessed across different subgroups. Table 3 summarizes the diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] for AKI at cutoff values and detection times. At the cut-off values of 0.3 (ng/mL)/1000, the summary sensitivities, specificities and AUROC were 0.72 (95% CI: 0.57–0.84), 0.58 (95% CI: 0.48–0.68) and 0.68 (95% CI: 0.64–0.73), respectively. Meanwhile, at the cut-off values of 2.0 (ng/mL)/1000, the summary sensitivities, specificities and AUROC were 0.38 (95% CI: 0.19–0.42), 0.94 (95% CI: 0.93–0.95) and 0.75 (95% CI: 0.60–0.89), respectively (Table 3 and Figure 2). It is clearly shown that 0.3 (ng/mL)/1000 had a relatively higher sensitivity and a lower specificity in diagnosing AKI, whereas, 2.0 (ng/mL)/1000 had a lower sensitivity and a relatively higher specificity.

In addition, with prolonged sampling time, the sensitivity increased yet the specificity decreased. When 0.3 (ng/mL)/1000 was chosen as the cutoff value of urinary [TIMP-2] × [IGFBP7] to predict AKI, the sensitivity and specificity were respectively 0.76 and 0.72 and the AUROC was 0.74 (95% CI, 0.70–0.78) in patients who were tested within 4 hours post-operatively (Table 4). When 2.0 (ng/mL)/1000 was chosen as the cutoff value, the sensitivity and specificity were respectively 0.49 and 0.93 and the AUROC was 0.70 (95% CI, 0.51–0.89) in patients who were tested within 24 hours post-operatively (Table 4).

Diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] for adverse kidney events

Adverse kidney events, including death, need for RRT, or persistence of renal dysfunction at 30 days were reported by only three studies [15, 21, 22]. In spite of inconsistent cutoff values in each study, we did not perform meta-analysis but only list their diagnostic accuracies of (Table 4). Data from those three studies
showed that when detected urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) on ICU admission, the lower cutoff values (less than 0.6) can be selected, with a high sensitivity (mean: 100%) and moderate specificity (mean: 61%).

**DISCUSSION**

AKI is a common, complex disorder featured by a high mortality and costly complications. Previously, serum creatinine (Scr) and urine output are regarded as two “gold-standard” functional markers for the early detection of kidney injury, yet their diagnoses were later proven to be insensitive. In addition, Scr and urine output were also subject to confounding impact of muscle volume, diets and diuretics usage, which limited their further clinical application. To look for more sensitive and specific markers for renal injury, several clinical trials on AKI have been conducted and suggested some promising biomarkers, including NGAL, KIM-1, IL-18, liver-type fatty acid-binding protein (L-FABP) and cystatin C [6]. There is compelling evidence that NGAL was affected by age, renal function and severity of AKI, and NGAL and IL-18 can stimulate inflammation response [23]. Considering the fact that TIMP-2 and IGFBP7 are cell-cycle arrest proteins expressed in renal tubular cells

---

**Figure 1:** Forest plots of pooled sensitivities and specificities of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) for diagnosis of AKI at different cutoff values and detection times. (A) When the cutoff value of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) was 0.3, the pooled sensitivities and specificities were calculated at 4 h, 12 h and 24 h, respectively. (B) When the cutoff value of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) was 2.0, the pooled sensitivities and specificities were calculated at 4 h, 12 h and 24 h, respectively.
during the periods of cellular stress or injury [8], it is tempting to speculate that urinary TIMP-2 and IGFBP7 are involved in the early pathological changes of AKI and carry the diagnostic probability of early renal injury. Now, several AKI cohort studies have evaluated the diagnostic value of the product of urinary TIMP-2 and IGFBP7, termed as \([\text{TIMP-2}] \times [\text{IGFBP7}]\) for AKI, whereas their detection times and cutoff values differed considerably. To fill this void in knowledge, we attempted to conduct a meta-analysis to quantify the appropriate detection time and cutoff value of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) for the early detection of AKI.

Via pooling the results of 10 clinical studies, our findings indicated that the performance of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) for predicting AKI was suboptimal, with a lower sensitivity (0.63; 95% CI, 0.49-0.76) and a moderate specificity (0.76; 95% CI, 0.62-0.86). Moreover, the AUC of 0.75 further suggested that the overall predictive accuracy was moderate.

It is a general practice to determine the optimal cutoff value of a continuous predictive marker. There are two widely used cutoff points for urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) in the literature, viz. 0.3 and 2.0 (ng/mL)/1000 in the assessment of AKI. In the Gunnerson’s study,}

![Figure 2: SROC curves of urinary \([\text{TIMP-2}] \times [\text{IGFBP7}]\) for diagnosis of AKI at different cut off values (0.3 or 2.0) and detection times (4 h, 12 h or 24 h).](image-url)
| Author (year)          | Time of measurement | [TIMP-2] | [IGFBP7] | TP  | TN  | FP  | FN  | Sensitivity | Specificity | AUROC (95% CI) |
|-----------------------|---------------------|----------|----------|-----|-----|-----|-----|-------------|-------------|----------------|
| Bihorac (2012)        | within 12 h of ICU  | 0.30     | 65       | 155 | 182 | 6   | 92.0% | 46.0%       | 0.82 (0.76–0.88) |
|                       | admission           | 2.00     | 30       | 320 | 17  | 41  | 37.0% | 95.0%       |             |
| Hoste (2014)          | within 12 h of ICU  | 0.30     | 3        | 59  | 67  | 24  | 11.1% | 46.8%       | 0.80 (0.74–0.84) |
|                       | admission           | 2.00     | 12       | 114 | 12  | 15  | 44.4% | 90.5%       |             |
| Meersch (2014)A       | 4 h after surgery   | 0.30     | 21       | 20  | 4   | 5   | 80.0% | 83.0%       | 0.81 (0.68–0.93) |
|                       |                     | 0.40     | 16       | 21  | 3   | 10  | 62.0% | 88.0%       |             |
|                       |                     | 0.50     | 14       | 22  | 2   | 12  | 54.0% | 92.0%       |             |
|                       |                     | 0.60     | 12       | 22  | 2   | 14  | 46.0% | 92.0%       |             |
|                       | 12 h after surgery  | 0.30     | 22       | 12  | 12  | 4   | 85.0% | 50.0%       |             |
|                       |                     | 0.40     | 20       | 18  | 6   | 6   | 77.0% | 75.0%       |             |
|                       |                     | 0.50     | 13       | 20  | 4   | 13  | 65.0% | 83.0%       |             |
|                       |                     | 0.60     | 15       | 22  | 2   | 11  | 58.0% | 92.0%       |             |
|                       |                     | 0.70     | 12       | 24  | 0   | 14  | 46.0% | 100.0%      |             |
| Meersch (2014)B       | 4 h after surgery   | 0.30     | 10      | 25  | 14  | 2   | 83.0% | 64.0%       | 0.85 (0.72–0.94) |
|                       |                     | 0.40     | 10      | 26  | 13  | 2   | 83.0% | 67.0%       |             |
|                       |                     | 0.50     | 10      | 27  | 12  | 2   | 83.0% | 69.0%       |             |
|                       |                     | 0.60     | 10      | 29  | 10  | 2   | 83.0% | 74.0%       |             |
|                       |                     | 0.70     | 10      | 30  | 9   | 2   | 83.0% | 77.0%       |             |
| Meersch (2014)B       | 24 h after surgery  | 0.30     | 6       | 21  | 18  | 6   | 50.0% | 54.0%       |             |
|                       |                     | 0.40     | 6       | 26  | 13  | 6   | 50.0% | 67.0%       |             |
|                       |                     | 0.50     | 6       | 30  | 9   | 6   | 50.0% | 77.0%       |             |
|                       |                     | 0.60     | 6       | 31  | 8   | 6   | 50.0% | 79.0%       |             |
|                       |                     | 0.70     | 6       | 31  | 8   | 6   | 50.0% | 79.0%       |             |
| Gocze (2015)          | On ICU admission    | 0.30     | 21      | 60  | 23  | 3   | 86.7% | 72.6%       | 0.85 (0.78–0.93) |
| Pilarczyk (2015)      | 4 h after surgery   | 0.15     | 5       | 36  | 18  | 1   | 83.0% | 66.7%       | 0.86 (0.72–1.00) |
|                       |                     | 0.30     | 4       | 41  | 13  | 2   | 67.0% | 76.0%       |             |
|                       |                     | 2.00     | 2       | 53  | 1   | 4   | 33.0% | 98.0%       |             |
| Wetz (2015)           | End of surgery      | 0.30     | 6       | 22  | 4   | 10  | 36.0% | 84.0%       |             |
|                       |                     | 2.00     | 1       | 25  | 1   | 15  | 7.0%  | 96.0%       |             |
| Dusse (2016)          | 4 h after surgery   | 0.19     | 6       | 18  | 14  | 2   | 75.0% | 56.0%       | 0.65 (0.38–0.92) |
|                       |                     | 0.30     | 3       | 21  | 11  | 5   | 38.0% | 67.0%       |             |
|                       |                     | 2.00     | 1       | 32  | 0   | 7   | 13.0% | 100.0%      |             |
|                       | 24 h after surgery  | 0.30     | 4       | 18  | 14  | 4   | 55.0% | 55.0%       | 0.87 (0.72–1.00) |
|                       |                     | 1.00     | 8       | 29  | 3   | 0   | 100.0% | 90.0%       |             |
the [TIMP-2] × [IGFBP7] > 0.3 (ng/mL)^2/1000 had a sensitivity of 92% for moderate or severe AKI within the next 12 hours, and was associated with approximately 7 times risk compared with the [TIMP-2] × [IGFBP7] ≤ 0.3 (ng/mL)^2/1000 [19]. However, the specificity of this cutoff point to detect AKI was only 46%. Therefore, it is not uncommon to encounter a false-positive finding if the test is used inappropriately in low-risk patients. The [TIMP-2] × [IGFBP7] value > 0.3 (ng/mL)^2/1000 will have a greater predictive value in patients at high risk for AKI, but will be less useful in patients at low risk for AKI. A cutoff value of 2.0 (ng/mL)^2/1000 for urinary [TIMP-2] × [IGFBP7] was associated with the specificity for moderate to severe AKI of 94%, although the sensitivity decreased to 38%.

In addition, we compared the diagnostic value of urinary [TIMP-2] × [IGFBP7] at different times for different cutoff value. It is of interest to note that with prolonged sampling time, the sensitivity increased yet the specificity decreased. It is reasonable to speculate that

| Author (year) | Adverse events | kidney No of events/total patients | Time measurement of | Cutoff value | TP | FP | FN | TN | Sensitivity | Specificity | AUROC (95% CI) |
|---------------|----------------|----------------------------------|---------------------|--------------|----|----|----|----|-------------|-------------|----------------|
| Dewitte (2015) | Death, need for RRT, or persistent of renal dysfunction at 30 days | 16/57 | On ICU admission | 2.6 | 13 | 12 | 3 | 29 | 81% | 71% | 0.79 (0.66–0.88) |
| Gocze (2015) | Need for RRT | 10/107 | On ICU admission | 0.43 | 10 | 32 | 0 | 65 | 100% | 67% | 0.83 (0.75–0.92) |
| Westhoff (2015) | Need for RRT | 16/46 | On ICU admission | 4.99 | 7 | 2 | 9 | 28 | 43.8% | 93.6% | 0.67 (0.50–0.84) |
|               | Death in 28 days | 10/107 | On ICU admission | 0.415 | 10 | 34 | 0 | 63 | 100% | 64.9% | 0.77 (0.67–0.86) |
|               | Death in 30 days | 6/46 | On ICU admission | 0.56 | 6 | 20 | 0 | 20 | 100% | 50% | 0.79 (0.61–0.97) |

Abbreviations: RRT, renal replacement therapy; TIMP-2, tissue inhibitor of metalloproteinase-2; IGFBP7, insulin-like growth factor binding protein 7; TP, true positive; TN, true negative; FP, false positive; FN, false negative; AUROC, area under receiver operating characteristic curve; NA, not available.

*aThe definition of adverse kidney events was according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) guideline [24].

Table 3: Diagnostic accuracies of urinary [TIMP-2] × [IGFBP7] for AKI at different cutoff values and time points

| Time of measurement | No. of studies | Sensitivity (95% CI) | Specificity (95% CI) | DOR(95% CI) | AUROC (95% CI) |
|---------------------|---------------|----------------------|----------------------|-------------|----------------|
| [TIMP-2] × [IGFBP7] = 0.3 | | | | | |
| Within 4 h | 6 | 0.71 (0.60–0.80) | 0.73 (0.67–0.79) | 6.44 (2.72–15.2) | 0.75 (0.71–0.79) |
| Within 12 h | 4 | 0.76 (0.69–0.82) | 0.84 (0.44–0.51) | 2.65 (0.42–16.7) | 0.48 (0.44–0.52) |
| Within 24 h | 6 | 0.67 (0.56–0.77) | 0.55 (0.50–0.59) | 2.30 (0.94–5.63) | 0.64 (0.60–0.68) |
| Overall | 16 | 0.72 (0.57–0.84) | 0.58 (0.48–0.68) | 3.57 (1.77–7.21) | 0.68 (0.64–0.72) |
| [TIMP–2] × [IGFBP7] = 2.0 | | | | | |
| Within 4 h | 3 | 0.13 (0.04–0.31) | 0.98 (0.94–1.00) | 8.59 (1.55–47.72) | 0.99 (0.99–1.00) |
| Within 12 h | 3 | 0.42 (0.34–0.51) | 0.94 (0.92–0.95) | 11.10 (7.02–17.6) | 0.55 (0.48–0.63) |
| Within 24 h | 4 | 0.43 (0.29–0.58) | 0.93 (0.90–0.95) | 8.33 (3.80–18.23) | 0.70 (0.51–0.89) |
| Overall | 10 | 0.38 (0.32–0.45) | 0.94 (0.93–0.95) | 10.2 (6.96–15.0) | 0.75 (0.60–0.89) |

Abbreviations: AKI, acute kidney injury; TIMP-2, tissue inhibitor of metalloproteinase-2; IGFBP7, insulin-like growth factor binding protein 7; TP, true positive; TN, true negative; FP, false positive; FN, false negative; AUROC, area under receiver operating characteristic curve; ICU, intensive care units; NA, not available.

Table 4: The diagnostic sensitivity and specificity of urinary [TIMP-2] × [IGFBP7] to predict adverse kidney events

The definition of adverse kidney events was according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) guideline [24].
as the time went on, the secretion level of TIMP-2 and/or IGFBP7 increased gradually. So urinary [TIMP-2] × [IGFBP7] was low at the earlier time; if we choose a lower cutoff value at this time, we will derive a high specificity and a low sensitivity (compared at the same cutoff value). Further, the [TIMP-2] × [IGFBP7] becomes higher with prolonged time; if we choose a higher cutoff value at this time, we can derive a high sensitivity and a low specificity (compared at the same cutoff value). As such, we therefore developed a working hypothesis that if we set a low cutoff value, we should do the test earlier; if we set a high cutoff value, we should do the test later.

Several possible limitations in the present study merit serious consideration. First, with the purpose of avoiding low-quality studies, only published English articles were retrieved and articles in other languages was not covered, publication bias might be possible. Second, the types of participants in each study were various. Among of them, six studies were conducted among post-operative patients (5 studies cardiac surgery and 1 non-cardiac surgery), and four studies were conducted among ICU patients. It might cause significant heterogeneity between the selected studies. Therefore, the jury must refrain from drawing a conclusion until large, multi-center and well-performed clinical trials confirm or refuse our findings.

In summary, this meta-analysis provided evidence that urinary [TIMP-2] × [IGFBP7] can predict the occurrence of AKI with moderate diagnostic accuracy. In the earlier administrative periods (less than 4 hours), 0.3 (ng/mL)^2/1000 is recommended to be used; whereas for patients who were administered more than 24 hours, 2.0 (ng/mL)^2/1000 is more appropriate. Nonetheless, it still remains an open question to determine the optimal time for urinary TIMP-2 and IGFBP7 measurement and the optimal cutoff value of [TIMP-2] × [IGFBP7] for the diagnosis of AKI. We hope further clinical trials with larger sample sizes and high-quality evidence are designed to clear away the clouds of these controversial issues convincingly.

**MATERIALS AND METHODS**

**Data sources and search strategy**

Two investigators (Ting Lin and Kai Qu) systematically and independently searched PubMed, EMBASE, Scopus and Web of Sciences databases for articles published before October 1, 2016 that provided data on the diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] on the early identification of AKI in ICU patients. The conduct of this meta-analysis accorded with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary PRISMA checklist). Subject terms used for literature search embraced [“TIMP-2” OR “tissue inhibitor of metalloproteinase-2”] AND [“IGFBP7” OR “insulin-like growth factor binding protein 7”] AND [“acute kidney injury” OR “AKI”] AND [“diagnosis” or “diagnostic”]. Search spectrum was also extended to the reference lists of retrieved original and review articles. Only studies with a prospective design and articles published in the English language were retained for analysis.

**Data extraction and synthesis**

Two investigators (Ting Lin and Kai Qu) independently evaluated the study eligibility and quality according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) score system. The data of interest were extracted on the first author, year of publication, population, study design, clinical setting, age, gender, history of CKD, AKI definition, time of measurement, urine sample storage and detection method. Diagnostic accuracy estimates included TP, FN, FN, TN. In addition, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each reported test threshold were evaluated accordingly.

**Assessment of diagnostic test accuracy**

The diagnostic test accuracy of the [TIMP-2] × [IGFBP7] for AKI diagnosis was quantified by the area under the summary receiver operating characteristic (SROC), summary diagnostic odds ratios (DORs) and summary sensitivities/specificities, respectively. Different SROC curves for the [TIMP-2] × [IGFBP7] were depicted and differences in SROC values were justified. The SROC curve delineates the relationship of the sensitivity against the specificity of different studies. Further summary DORs using a Der-Simonian and Laird random-effects model were computed, as well as between-study heterogeneity.

**Assessment of heterogeneity and publication bias**

Between-study heterogeneity was represented by the Q-F statistic, which denotes the percentage of varied estimates accruing from heterogeneity rather than from sample errors. Significant heterogeneity was reported if the Q-F statistic is 50% or over. Potential contributing factors responsible for significant heterogeneity in the diagnostic accuracy of the [TIMP-2] × [IGFBP7] for AKI were sought by a meta-regression analysis. Also, heterogeneity was explored further by subgroup analyses across different clinical settings. In addition, the possibility of publication bias was visually inspected by the asymmetry of a Deek’s funnel plot in the prediction of urinary [TIMP-2] × [IGFBP7] for AKI.

Pooled sensitivity and specificity, DORs, and relevant 95% CIs were calculated on the basis of a bivariate normal model with log-transformed sensitivities and specificities. In the case of multiple cutoff points for
the \([\text{TIMP-2}] \times [\text{IGFBP7}]\) provided in a single study, the point with the maximum overall accuracy entered into the overall analysis.

All statistical tests were two sided, and \(P < 0.05\) was considered significant unless otherwise indicated. Above statistical analyses were completed with Stata 12.0.

Author contributions

Ting Lin and Kai Qu: Designed the research and rafted the manuscript; Wenquan Niu and Chang Liu: Revised the paper; Zhenzhu Song, Ting Lin and Kai Qu: Performed meta-analysis; Sinan Liu: Participated in literature search and study selection; Ting Lin and Kai Qu: Analyzed data and constructed figures.

CONFLICTS OF INTEREST

There is no competing financial interest among the authors.

FUNDING

This study was supported by National Science Foundation of China (No. 81201549), the Natural Science Basic Research Plan in Shaanxi Province of China (No. 2017JM8039), the Fundamental Research Funds for the Central Universities (no. 2016pgz05), the Clinical Research Award of the First Affiliated Hospital of Xi’an Jiaotong University, China (No. XJTU1AF-CRF-2015–011), and the Hospital Fund of the First Affiliated Hospital of Xi’an Jiaotong University (No. 2014YK11).

REFERENCES

1. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, Wu J, Ye C, Mei C, Dai B. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. American journal of kidney diseases. 2013; 62:1058–1067.
2. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury: an increasing global concern. Lancet. 2013; 382:170–179.
3. Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. Critical care. 2016; 20:188.
4. Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD).
5. Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, Gill K, Walker S, MacDonald K, Hiebert BM, Arora RC, Rigatto C. Urinary, Plasma, and Serum Biomarkers' Utility for Predicting Acute Kidney Injury Associated With Cardiac Surgery in Adults: A Meta-analysis. American journal of kidney diseases. 2015; 66:993–1005.
6. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. Clin J Am Soc Nephrol. 2015; 10:147–155.
7. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihoraoc A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Critical care. 2013; 17:R25.
8. Endre ZH, Pickering JW. Acute kidney injury: cell cycle arrest biomarkers win race for AKI diagnosis. Nature reviews Nephrology. 2014; 10:683–685.
9. Jia HM, Huang LF, Zheng Y, Li WX. Diagnostic value of urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 for acute kidney injury: a meta-analysis. Critical care. 2017; 21:77.
10. Su Y, Gong Z, Wu Y, Tian Y, Liao X. Diagnostic Value of Urine Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 for Acute Kidney Injury: A Meta-Analysis. PLoS One. 2017; 12:e0170214.
11. Bihoraoc A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, Fitzgerald R, Gong MN, Graham DD, Gunnerson K, Heung M, Jortani S, Kleerup E, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014; 189:932–939.
12. Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, Feldkamp T, Uettwiller-Geiger DL, McCarthy P, Shi J, Walker MG, Kellum JA, Sapphire I. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. Nephrol Dial Transplant. 2014; 29:2054–2061.
13. Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, Gorlich D, Kellum JA, Zarbock A. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS One. 2014; 9:e93460.
14. Meersch M, Schmidt C, Van Aken H, Rossaint J, Gorlich D, Stege D, Malec E, Januszewska K, Zarbock A. Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery. PLoS One. 2014; 9:e110865.
15. Gocze I, Koch M, Renmer P, Zeman F, Graf BM, Dahlke MH, Nerlich M, Schlitt HJ, Kellum JA, Bein T. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. PLoS One. 2015; 10:e0120863.
16. Pilarczyk K, Edadayidyl-Dudasova M, Wendt D, Demircioglu E, Benedik J, Dohle DS, Jakob H, Dusse F. Urinary [TIMP-2]*[IGFBP7] for acute kidney injury: a meta-analysis. Reviews Nephrology. 2014; 10:683–685.
17. Wetz AJ, Richardt EM, Wand S, Kunze N, Schotola H, Quintel M, Brauer A, Moerer O. Quantification of urinary TIMP-2 and IGFBP-7: an adequate diagnostic test to predict acute kidney injury after coronary artery bypass surgery. Ann Intensive Care. 2015; 5:50.
18. Dusse F, Edadayidyl-Dudasova M, Thielmann M, Wendt D, Kahlert P, Demircioglu E, Jakob H, Schaefer ST, Pilarczyk
K. Early prediction of acute kidney injury after transapical and transaortic aortic valve implantation with urinary G1 cell cycle arrest biomarkers. BMC Anesthesiol. 2016; 16:76.

19. Gunnerson KJ, Shaw AD, Chawla LS, Bihorac A, Al-Khafaji A, Kashani K, Lissauer M, Shi J, Walker MG, Kellum JA, Sapphire Topaz I. TIMP2*IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. J Trauma Acute Care Surg. 2016; 80:243–249.

20. Kimmel M, Shi J, Wasser C, Biegger D, Alscher MD, Schanz MB. Urinary [TIMP-2].[IGFBP7] - Novel Biomarkers to Predict Acute Kidney Injury. Am J Nephrol. 2016; 43:375–382.

21. Dewitte A, Joannes-Boyau O, Sidobre C, Fleureau C, Bats ML, Derache P, Leuillet S, Ripoche J, Combe C, Ouattara A. Kinetic eGFR, Novel AKI Biomarkers to Predict Renal Recovery. Clin J Am Soc Nephrol. 2015; 10:1900–1910.

22. Westhoff JH, Tonshoff B, Waldherr S, Poschl J, Teufel U, Westhoff TH, Fichtner A. Urinary Tissue Inhibitor of Metalloproteinase-2 (TIMP-2) * Insulin-Like Growth Factor-Binding Protein 7 (IGFBP7) Predicts Adverse Outcome in Pediatric Acute Kidney Injury. PLoS One. 2015; 10:e0143628.

23. Soto K, Papoila AL, Coelho S, Bennett M, Ma Q, Rodrigues B, Fidalgo P, Frade F, Devarajan P. Plasma NGAL for the diagnosis of AKI in patients admitted from the emergency department setting. Clin J Am Soc Nephrol. 2013; 8:2053–2063.

24. Palevsky PM, Molitoris BA, Okusa MD, Levin A, Waikar SS, Wald R, Chertow GM, Murray PT, Parikh CR, Shaw AD, Go AS, Faubel SG, Kellum JA, et al. Design of clinical trials in acute kidney injury: report from an NIDDK workshop on trial methodology. Clin J Am Soc Nephrol. 2012; 7:844–850.