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Review Article

REVIEW ARTICLE

Predictive value of cell cycle arrest biomarkers for cardiac surgery-associated acute kidney injury: a meta-analysis

L.-J. Su[1,3], Y.-M. Li[1,3], J. A. Kellum[2] and Z.-Y. Peng[1,2,*]

[1]Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China and [2]Center of Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

*Corresponding author. E-mail: pengzy5@hotmail.com

[3] Contributed equally for this manuscript.

Abstract

Background: A biomarker test based on a combination of urine tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) has been used as a potential biomarker of acute kidney injury (AKI). Our meta-analysis aimed to evaluate the predictive value of this biomarker for cardiac surgery-associated acute kidney injury (CSA-AKI). We searched MEDLINE, PubMed, Cochrane, and EMBASE for studies.

Methods: We evaluated the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies 2 criteria. Meta-DiSc and STATA were used for all statistical analyses.

Results: A total of 10 studies (747 patients) were included in this meta-analysis. Pooled sensitivity and specificity with corresponding 95% confidence intervals (CI) were 0.77 (95% CI: 0.70–0.83, I^2=40.7%) and 0.76 (95% CI: 0.72–0.79, I^2=69.1%), respectively. Pooled positive likelihood ratio (LR), negative LR, and diagnostic odds ratio were 3.26 (95% CI: 2.51–4.23, I^2=50.7%), 0.32 (95% CI: 0.24–0.41, I^2=6.7%), and 10.08 (95% CI: 6.85–14.84, I^2=6.7%), respectively. The area under the curve estimated by summary receiver operating characteristics was 0.83 [standard error (SE) 0.023] with a Q* value of 0.759 (SE 0.021). There was no heterogeneity amongst the 10 studies from both threshold and non-threshold effects. Subgroup analysis showed that the diagnostic value was related to the severity of AKI and time measurement.

Conclusions: This study shows that urinary [TIMP-2]·[IGFBP7] is an effective predictive test for cardiac surgery associated acute kidney injury with good diagnostic accuracy within 24 h. Studies examining use of biomarker-guided care bundles are indicated.

Keywords: acute kidney injury; cardiac surgery; cell cycle arrest; insulin-like growth factor-binding protein 7; tissue inhibitor of metalloproteinase-2

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common complication and is associated with increased morbidity and mortality.[1] As the second leading cause of AKI,[2] CSA-AKI requiring renal replacement therapy (RRT) occurs in about 6% of cardiac surgery patients and is associated with significantly worse survival.[3,4] It is also a risk factor for ensuing chronic kidney disease, even when renal function completely recovers after surgery.[5] The early diagnosis of AKI

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Editor's key points

- The authors systematically reviewed the literature for evidence of urinary [TIMP-2]·[IGFBP7] as an effective predictor of acute kidney injury after cardiac surgery.
- Meta-analysis confirmed its predictive usefulness. Further studies are indicated to examine the impact of biomarker-guided therapy.

is essential for early implementation of preventive strategies in order to prevent the development of severe kidney damage. Therefore, it is of great importance to find potential markers exhibiting acceptable accuracy for the early diagnosis of kidney injury after cardiac surgery. Fortunately, a biomarker test based on a combination of urine tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), was recently approved by the US Food and Drug Administration for AKI risk stratification.[6] TIMP-2 and IGFBP7 have been linked to cell-cycle arrest, which is known to be involved in the pathogenesis of AKI.[7] Several studies have reported that [TIMP-2]·[IGFBP7] can be used to predict AKI after cardiac surgery.[8–12] Previous meta-analyses have evaluated the diagnostic value of [TIMP-2]·[IGFBP7] for AKI, but were underpowered to examine CSA-AKI specifically.[13,14] Recently, five new studies have evaluated the value of urinary [TIMP-2]·[IGFBP7] in the diagnosis of CSA-AKI, and the threshold values of the biomarkers for predicting CSA-AKI remains somewhat controversial.[15–19] We included these new data and conducted this meta-analysis to assess the predictive value of urinary [TIMP-2]·[IGFBP7] as an early biomarker for CSA-AKI.

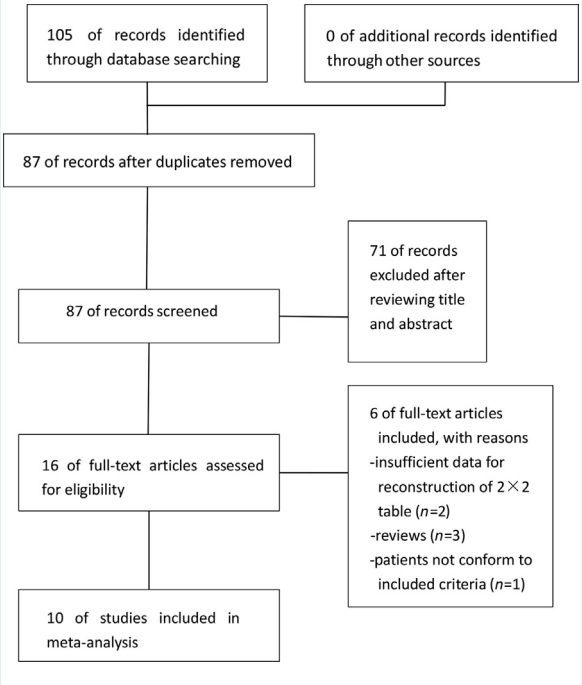

Fig 1. Flow chart of study selection.

Methods

Search strategy

We searched MEDLINE, PubMed, Cochrane and EMBASE (before November 1, 2017) for studies that investigated the diagnostic value of urinary [TIMP-2]·[IGFBP7] of CSA-AKI, without language restrictions. The clinical trial.gov website was also searched for trials that were registered as completed but not yet published. We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary PRISMA checklist). The search terms were as follows: ('TIMP-2' or 'tissue inhibitor metalloproteinases-2' or 'IGFBP7' or 'IGF-binding protein 7' or 'insulin-like growth factor binding protein 7' or 'cycle arrest biomarkers') and ('CSA-AKI' or 'cardiac surgery-associated acute kidney injury'). The search strategy was manually adapted according to the citation lists of retrieved articles for sensitivity (SEN). The reference lists of selected studies were searched by hand to identify potentially relevant citations. The searches were performed independently by two investigators.

Study selection

Two investigators independently conducted the study selection. Any disagreement was resolved by consultation with a third investigator. Studies included met the following criteria: (1) original study; (2) patients undergoing cardiovascular surgery; (3) urinary [TIMP-2]·[IGFBP7] as biomarkers for CSA-AKI diagnosis; and (4) sufficient information to calculate SEN and specificity (SPE). Exclusion criteria were as follows: (1) studies from conference abstracts, guidelines, letters, editorials, or reviews; and (2) studies without sufficient data for analysis, even after contacting the authors.

Data extraction and quality assessment

Data on patient and study characteristics were collected and entered into a database for assessment of study eligibility. If eligible, we extracted relevant data, using a standardised data extraction form. The following information was extracted from each study: first author, publication data, study design, patient setting, age, sample size, test method, timing at measurement, AKI definition, true positive rate, false positive rate, false negative rate, true negative rate, SEN, SPE, and area under the curve (AUC). We assessed the methodologic quality by using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[20] Both data extraction and quality assessment were performed independently by two reviewers and discussed with a third assessor when discrepancies were present.

Statistical analysis

Meta-DiSc 1.4 software (Zamora J, Muriels A, Abraira V, Madrid, Spain) was used for statistical analysis. A random-effects model (DerSimonian and Laird method) or fixed-effects model (Mantel–Haenszel method) was constructed to estimate pooled SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (CI). Model selection was based on the heterogeneity of included studies.[21] The analysis of diagnostic accuracy accords with summary receiver operating characteristics (SROC) curve and the AUC of the SROC. Heterogeneity induced by the threshold effect was reflected by a

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