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ORIGINAL RESEARCH

Predictive Value of Urinary KIM-1, TIMP-2 and sTREM-1 for Contrast-Induced Acute Kidney Injury in Elderly Patients After Percutaneous Coronary Intervention

Wu Huang, Rong Wang, Ping Zhang

Department of Geriatric Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, People's Republic of China

Correspondence: Rong Wang, Department of Geriatric Medicine, The Second Xiangya Hospital of Central South University, 139 Renmin Middle Road, Changsha, Hunan, 410011, People's Republic of China, Tel +86-0731-85295173, Email Wangrong5913@163.com

Objective: We aimed to address the predictive value of urinary kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) for contrast-induced acute kidney injury (CI-AKI) in elderly patients after percutaneous coronary intervention (PCI).

Methods: One hundred thirty-six patients who underwent PCI were separated into the CI-AKI group (n = 36) and the non-CI-AKI group (n = 100) based on CI-AKI occurrence after operation, and their general data were collected. Blood and urine specimens were collected before operation (at the time of admission) and 6 h, 12 h, 24 h and 48 h after the operation and preserved for future use. Serum creatinine (Scr) levels were tested and an estimated glomerular filtration rate (eGFR) was counted. Urinary KIM-1, TIMP-2 and sTREM-1 levels were assessed and the preoperative and general data as well as postoperative urinary KIM-1, TIMP-2 and sTREM-1 levels were compared. The early diagnostic value of urinary KIM-1, TIMP-2 and sTREM-1 at 6 hours postoperatively for CI-AKI was analyzed by receiver operating characteristic (ROC) curve.

Results: After 48 h of operation, Scr in the CI-AKI group was higher versus the non-CI-AKI group. At 24 h and 48 h postoperatively, eGFR in the CI-AKI group was lower versus the non-CI-AKI group; urinary KIM-1 and sTREM-1 in the CI-AKI group were higher in contrast to the non-CI-AKI group; TIMP-2 in the CI-AKI group was higher versus that in the non-CI-AKI group. ROC curve analysis showed that the areas under the curve (AUCs) for urine KIM-1, TIMP-2, and sTREM-1 in diagnosing CI-AKI at 6 hours postoperatively were 0.852 (95% CI: 0.768–0.936), 0.810 (95% CI: 0.723–0.898), and 0.874 (95% CI: 0.804–0.943), and the cut-off values were 45.93 ng/L, 1.63 ng/mL, and 61.48 ng/L, respectively, with sensitivities of 66.70%, 58.30%, and 72.20%, and specificities of 95.00%, 93.00%, and 91.00%, respectively (all $P < 0.05$).

Conclusion: Urinary KIM-1, TIMP-2 and sTREM-1 can respond to early changes in renal function after PCI and have good application value in the early diagnosis of CI-AKI.

Keywords: percutaneous coronary intervention, kidney injury molecule-1, tissue inhibitor of metalloproteinases-2, soluble triggering receptor expressed on myeloid cells-1, contrast-induced acute kidney injury

Introduction

Contrast-induced acute kidney injury (CI-AKI), alternatively referred to as contrast-induced nephropathy (CIN), ranks as the third most common cause of AKI resulting from medical interventions.[1] As an iatrogenic disease, CI-AKI can be defined as an elevation in serum creatinine (Scr) by at least 0.5 mg/dl or 25% from baseline in the first 48 hours after contrast administration, without other reasons for renal function impairment.[2] CI-AKI is a main complication caused by percutaneous coronary intervention (PCI), characterized by acute or sub-acute renal function deterioration owing to exposure to iodinated contrast medium that is linked to raised morbidity and mortality.[3] CI-AKI incidence stands out in patients with higher age, systemic arterial hypertension, diabetes mellitus, the volume of contrast infused and

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osmolarity.[4] The consequences of CI-AKI can range from mild renal function worsening to renal failure that needs renal replacement treatment.[5] The occurrence of this disease is associated with the number of contrast administrations,[6] and CI-AKI is involved in prolonged hospitalization and elevated cardiovascular, renal, and all-cause mortality. Several risk factors might predict the incidence of CI-AKI, and novel biomarkers might offer a diagnosis of CI-AKI at an early stage.[7]

According to reports, kidney injury molecule-1 (KIM-1) is one of the urine biomarkers that is utilized in the early prediction of CI-AKI and improves outcomes of these patients.[8] KIM-1, also known as HAVcr-1, is a transmembrane glycoprotein. TIM-1, another glycoprotein, belongs to the T-cell immunoglobulin and mucin domain (TIM) protein family, which is found on immune cells and plays a role in regulating immune responses. Unlike other TIM family members, KIM-1 is expressed not only by immunocompetent cells but also by epithelial cells. The cellular and humoral effects of KIM-1 are involved in numerous physiological and pathophysiological processes.[9] Prior to the utilization of contrast-relevant procedures, high concentrations of KIM-1, a kidney-specific molecule, are demonstrated to allow estimation of kidney vulnerability to contrast-induced acute kidney injury (CI-AKI), which can have the potential in the prediction of cardiovascular events and overall mortality.[10] Urine KIM-1 levels in those after implantation of coronary stents have the ability to reflect renal function changes at an early stage, thereby offering a certain basis for early CI-AKI diagnosis.[11] Moreover, matrix metalloproteinases and their inhibitors (tissue inhibitor of metalloproteinase, TIMPs) are of great importance in atherosclerosis and remodeling after acute myocardial infarction.[12] TIMP-2 belongs to the TIMPs family and serves a crucial role in modulating the activity of MMPs in diverse tissues, including those within the reproductive system.[13] Additionally, TIMP-2 has been reported to identify patients at risk for AKI,[14] and urinary TIMP-2 is also demonstrated to serve as a predictive marker for AKI.[15] According to another report, the soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) refers to a soluble form of TREM-1 released within the inflammatory process.[16] As an innate immune receptor, TREM-1 is present on the surface of several immune and non-immune cells,[17] which can be upregulated in inflammatory diseases.[18] Baseline sTREM-1 levels after cardiac surgery can be utilized to identify patients with a high risk of postoperative complications and prolonged hospital stay.[19] Moreover, sTREM-1 is reported to act as a novel diagnostic biomarker of AKI and urine sTREM-1 can be utilized as a diagnostic and predictive biomarker for AKI in critically ill sepsis patients.[20] Considering the above research, we realize that the predictive value of urinary KIM-1, TIMP-2 and sTREM-1 in CI-AKI is rarely discussed. Therefore, this study was aimed at ascertaining the predictive value of urinary KIM-1, TIMP-2 and sTREM-1 for CI-AKI in elderly patients after PCI.

Materials and Methods

Ethics Statement

The study was ratified by the Medical Ethics Committee of The Second Xiangya Hospital of Central South University (approval number: 20200118) and the patients had signed the written informed consent form. Additionally, this study was conducted in accordance with the Declaration of Helsinki.

Study Subjects

One hundred and thirty-six CI-AKI patients who underwent PCI in the Cardiology Department of The Second Xiangya Hospital of Central South University from April 2020 to April 2022 were categorized into the CI-AKI group (n = 36) and the non-CI-AKI group (n = 100) according to CI-AKI occurrence. CI-AKI diagnostic criteria: Scr levels were increased by > 25% from the basal value within 48–72 h after contrast application, or absolute Scr was increased by ≥ 5 mg/L (44 μmol/L) while excluding acute renal impairment caused by other reasons. Inclusion criteria: (1) patients with PCI indication, including unstable angina, acute myocardial infarction (proposed elective PCI), and first-time PCI; (2) those with complete clinical data; (3) those given informed consent. Exclusion criteria: (1) those with iodine contrast allergy; (2) those with a history of renal transplantation, renal surgery, renal insufficiency, acute renal failure, hemodialysis treatment, and massive proteinuria; (3) those with acute myocarditis, acute left heart failure, uncontrollable severe heart failure, acute myocardial infarction in parallel with acute surgery, and pulmonary edema; (4) those with coagulation dysfunction; (5) those combined with malignant neoplasms; (6) those employed contrast media within 1 week.

Methods

Patient history and related information, including gender, age, body mass index (BMI), smoking history, underlying diseases (hypertension, hyperlipidemia, diabetes), and New York Heart Association (NYHA) functional classification, were collected from the patients' hospital records before surgery.

Blood and urine samples were obtained from patients before and at 6h, 12h, 24h, and 48h after PCI, and stored at −20°C for spare use. Scr levels were tested by immunoturbidimetric method with a 7600–020 fully automatic biochemical analyzer (Hitachi (China) Ltd.) and estimated glomerular filtration rate (eGFR) was counted according to the modification of diet in renal disease formula. Urinary KIM-1, TIMP-2 and sTREM-1 contents were tested by enzyme-linked immunosorbent assay, and the kits were obtained from Amyjet Scientific Inc (Wuhan, China).

Observation Indicators

The general data and Scr, eGFR, urine KIM-1, TIMP-2, and sTREM-1 levels at different time points were compared between CI-AKI and non-CI-AKI patients to assess the diagnostic efficacy of urine KIM-1, TIMP-2, and sTREM-1 for CI-AKI.

Statistics

SPSS20.0 statistical software was applied for data analysis. Numeration data were depicted as [case (%)] with the χ^2 test or Fisher's exact test. Measurement data were depicted as ($\bar{x}\pm$ s), with independent samples *t*-test for comparison between the two groups. The diagnostic sensitivity and specificity of urine KIM-1, TIMP-2, and sTREM-1 for CI-AKI were analyzed using the receiver operating characteristic (ROC) and areas under the curve (AUC). $P < 0.05$ was implemented to indicate that the difference was statistically significant.

Results

General Data

There were 61 males and 39 females in the non-CI-AKI group, aged 53–67 years, with an average age of 60.31 ± 3.07 years old and a BMI of 23.39 ± 2.80 kg /m^2. There were 16 males and 20 females in the CI-AKI group, aged 55–67 years old, with an average age of 60.27 ± 3.22 years old and a BMI of 23.55 ± 2.69 kg/m^2. General data including age, gender, BMI, smoking history, hypertension, hyperlipidemia, diabetes mellitus, and NYHA classification of both groups were compared, and the difference was not statistically significant ($P > 0.05$) (Table 1).

Table 1 General Data Between the Two Groups

Indicators	The Non-CI-AKI Group (n=100)	The CI-AKI Group (n = 36)	*P* Value
Age (years)	60.31 ± 3.07	60.27 ± 3.22	0.946
Gender			0.116
Male	61 (61.00)	16 (44.44)	
Female	39 (39.00)	20 (55.56)	
BMI (kg/m^2)	23.39 ± 2.80	23.55 ± 2.69	
Smoking history	29 (29.00)	10 (27.78)	> 0.999
Hypertension	53 (53.00)	13 (36.11)	0.119
Hyperlipidemia	38 (38.00)	15 (41.67)	0.696
Diabetes mellitus	27 (27.00)	13 (36.11)	0.394
NYHA classification			0.119
I	46 (46.00)	11 (30.56)	
II	54 (54.00)	25 (69.44)	

Note: In the table, measurement data are expressed as (mean ± standard deviation), and numeration data are expressed as n (%). Numeration data were analyzed using Fisher's exact test, and measurement data were compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; BMI, body mass index; NYHA, New York Heart Association.

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Pre- and Postoperative Scr of Patients

Prior to operation and 6 h, 12 h and 24 h after the operation, no statistically significant difference in Scr between the two groups was found ($P > 0.05$), and at 48 h after surgery, Scr of CI-AKI patients was higher relative to non-CI-AKI patients ($P < 0.05$) (Table 2).

Pre- and Postoperative eGFR of Patients

Prior to operation and 6 h and 12 h after the operation, no statistically significant difference in eGFR between the two groups was found ($P > 0.05$), and at 24 h and 48 h after the operation, eGFR of patients in the CI-AKI group was lower in contrast to the non-CI-AKI group ($P < 0.05$) (Table 3).

Pre- and Postoperative Urinary KIM-1 of Patients

Preoperatively, there were no differences in urinary KIM-1 between the two groups ($P > 0.05$); at 6 h, 12 h, 24 h, and 48 h postoperatively, higher urinary KIM-1 was found in CI-AKI patients versus non-CI-AKI patients ($P < 0.05$) (Table 4).

Pre- and Postoperative Urinary TIMP-2 of Patients

Prior to surgery and at 6 h, 12 h, 24 h, and 48 h after the surgery, TIMP-2 of CI-AKI patients was higher in comparison to non-CI-AKI patients ($P < 0.05$) (Table 5).

Table 2 Pre- and Postoperative Blood Creatinine Between the Two Groups of Patients (μmol/L)

Grouping	Before surgery	6 h after surgery	12 h after surgery	24 h after surgery	48 h after surgery
The non-CI-AKI group (n = 100)	63.03 ± 7.27	65.03 ± 8.12	65.42 ± 8.29	66.85 ± 8.92	63.31 ± 7.11
The CI-AKI group (n = 36)	65.32 ± 8.36	62.44 ± 7.28	65.79 ± 8.74	67.85 ± 9.22	89.62 ± 12.15
P value	0.122	0.094	0.821	0.569	< 0.001

Note: In the table, measurement data are expressed as (mean ± standard deviation) and compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury.

Table 3 Pre- and Postoperative eGFR Between the Two Groups of Patients [$mL \cdot min^{-1} \cdot (1.73m^2)^{-1}$]

Grouping	Before Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	48 h After Surgery
The non-CI-AKI group (n = 100)	110.68 ± 22.23	108.45 ± 22.36	109.62 ± 22.74	110.35 ± 22.36	112.50 ± 22.17
The CI-AKI group (n = 36)	111.33 ± 22.38	109.08 ± 22.71	102.69 ± 20.69	96.04 ± 18.51	76.37 ± 17.31
P value	0.881	0.886	0.111	< 0.001	< 0.001

Note: In the table, measurement data are expressed as (mean ± standard deviation) and compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate.

Table 4 Pre- and Postoperative Urinary KIM-1 Between the Two Groups of Patients (Ng/L)

Grouping	Before Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	48 h After Surgery
The non-CI-AKI group (n = 100)	28.74 ± 4.22	35.41 ± 6.78	39.20 ± 9.57	41.07 ± 7.11	39.20 ± 5.73
The CI-AKI group (n = 36)	28.38 ± 4.47	47.93 ± 9.52	74.93 ± 11.12	72.33 ± 9.68	55.14 ± 7.59
P value	0.666	< 0.001	< 0.001	< 0.001	< 0.001

Note: In the table, measurement data are expressed as (mean ± standard deviation) and compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; KIM-1, kidney injury molecule-1.

Table 5 Pre- and Postoperative Urinary TIMP-2 Between the Two Groups of Patients (Ng/mL)

Grouping	Before Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	48 h After Surgery
The non-CI-AKI group (n = 100)	0.84 ± 0.12	1.20 ± 0.29	1.81 ± 0.37	2.62 ± 0.47	3.39 ± 0.54
The CI-AKI group (n = 36)	1.38 ± 0.34	1.76 ± 0.55	5.89 ± 0.61	6.44 ± 0.62	7.27 ± 0.74
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: In the table, measurement data are expressed as (mean ± standard deviation) and compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; TIMP-2, tissue inhibitor of metalloproteinases-2.

Pre- and Postoperative Urinary sTREM-1 of Patients

Preoperatively, no difference in sTREM-1 between the two groups was found ($P > 0.05$); at 6 h, 12 h, 24 h, and 48 h postoperatively, sTREM-1 in the CI-AKI group was elevated versus that of the non-CI-AKI group ($P < 0.05$) (Table 6).

ROC Curve Analysis of Urinary KIM-1, TIMP-2 and sTREM-1 in CI-AKI Diagnosis

ROC curve analysis revealed that at 6 h postoperatively, the area under the curve (AUC) of KIM-1, TIMP-2 and sTREM-1 for diagnosing CI-AKI patients were 0.852, 0.810 and 0.874, respectively, with cut-off values of 45.93ng/L, 1.63ng/mL and 61.48ng/L, sensitivity of 66.70%, 58.30%, and 72.20%, and specificity of 95.00%, 93.00%, and 91.00%, respectively. Urinary KIM-1, TIMP-2 and sTREM-1 possessed high efficacy in diagnosing CI-AKI (Table 7 and Figure 1).

Discussion

CI-AKI refers to a common complication of PCI.[21] As previously reported, CI-AKI, or CI-AKI, refers to an acute renal function impairment with the manifestation of increased Scr, and a variety of serum and urinary proteins have been intensively studied as potential biomarkers for the early diagnosis of AKI.[22] This study focused on the predictive value of urinary KIM-1, TIMP-2 and sTREM-1 for CI-AKI in elderly patients after PCI.

It is also reported that SCr and eGFR changes on the day following cardiac catheterization can predict CI-AKI development.[23] Scr levels ≤ 60 μmol/L are an independent risk factor of CI-AKI in patients undergoing PCI.[24] In our paper, we found that at 48 h after the surgery, Scr of patients in the CI-AKI group was elevated versus the non-CI-AKI group. In a previous study, it is demonstrated that CI-AKI patients possessed higher age and lower eGFR during PCI.[25] In

Table 6 Pre- and Postoperative Urinary sTREM-1 Between the Two Groups of Patients (Ng/L)

Grouping	Before Surgery	6 h After Surgery	12 h After Surgery	24 h After Surgery	48 h After Surgery
The non-CI-AKI group (n = 100)	45.21 ± 11.28	47.96 ± 11.39	48.26 ± 11.63	49.27 ± 12.45	45.06 ± 11.17
The CI-AKI group (n = 36)	46.86 ± 11.74	69.74 ± 15.16	116.55 ± 26.35	123.53 ± 27.85	134.84 ± 28.68
P value	0.458	< 0.001	< 0.001	< 0.001	< 0.001

Note: In the table, measurement data are expressed as (mean ± standard deviation) and compared using the independent samples *t*-test.
Abbreviations: CI-AKI, contrast-induced acute kidney injury; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

Table 7 ROC Curve Analysis of Urinary KIM-1, TIMP-2 and sTREM-1 in CI-AKI Diagnosis

Indicators	AUC	Cut-off	Sensitivity/%	Speciality/%	Youden index	*P* value	95% CI
KIM-1	0.852	45.93ng/L	66.70	95.00	0.617	< 0.001	0.768~0.936
TIMP-2	0.810	1.63ng/mL	58.30	93.00	0.513	< 0.001	0.723~0.898
sTREM-1	0.874	61.48ng/L	72.20	91.00	0.632	< 0.001	0.804~0.943

Abbreviations: ROC, receiver operating characteristic; CI-AKI, contrast-induced acute kidney injury; KIM-1, kidney injury molecule-1; TIMP-2, tissue inhibitor of metalloproteinases-2; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; AUC, area under the curve.

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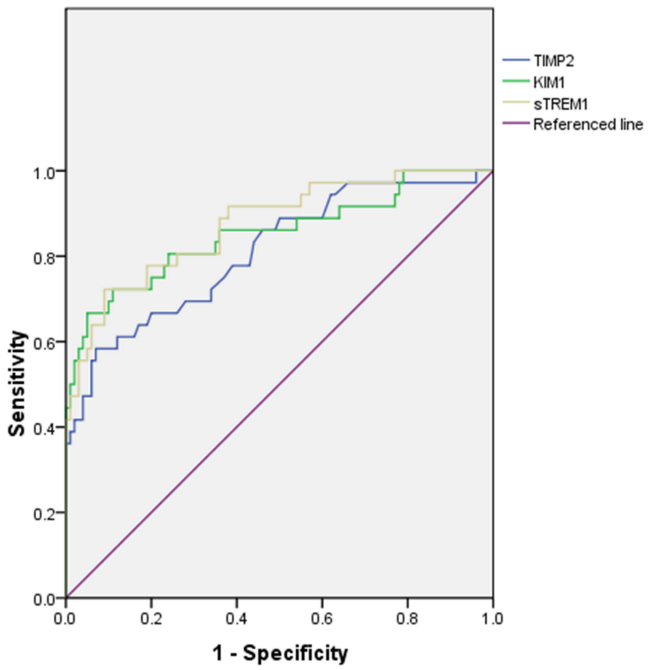

Figure 1 ROC curve analysis of KIM-1, TIMP-2 and sTREM-1 in CI-AKI diagnosis.

our paper, it was found that at 24 h and 48 h after surgery, eGFR of patients in the CI-AKI group was lower in contrast to the non-CI-AKI group.

KIM-1 is reported to be a novel marker of AKI.[26] CI-AKI onset is demonstrated to have an association with higher urinary KIM-1.[27] It is also demonstrated that serum KIM-1 concentration is an independent predictor of CI-AKI in non-ST-segment elevation myocardial infarction elderly patients, and serum KIM-1 is higher in CI-AKI patients versus in non-CI-AKI patients.[28] In addition, urinary KIM-1 is reported to be able to reflect renal function changes after contrast injection earlier than SCr and it might be a good biomarker for the diagnosis of CI-AKI at an early stage. Urinary KIM-1 concentrations in CI-AKI patients are raised versus those in non-CI-AKI patients p at 24 h after PCI.[29] In our paper, it was found that at 6 h, 12 h, 24 h, and 48 h postoperatively, urinary KIM-1 of patients in the CI-AKI group was higher versus the non-CI-AKI group. It is reported in a previous study that TIMP-2 is highly expressed in human coronary thrombi.[12] TIMP-2 serves as an unspecific marker in AKI detection at an early stage.[30] In our study, it was found that prior to surgery and at 6 h, 12 h, 24 h, and 48 h after surgery, TIMP-2 of CI-AKI patients was higher in contrast with that of non-CI-AKI patients. Serum sTREM-1 concentrations are raised in patients with in-stent restenosis. sTREM-1 is independently involved in in-stent restenosis incidence.[31] Urinary sTREM-1 concentrations are elevated in patients with IgA nephropathy.[32] sTREM-1 is also up-regulated in sepsis-associated AKI and it is predicted to function as a potential biomarker.[33] In our study, it was found that at 6 h, 12 h, 24 h, and 48 h postoperatively, sTREM-1 in the CI-AKI group was elevated versus that of the non-CI-AKI group. Moreover, it was found that urinary KIM-1, TIMP-2 and sTREM-1 possessed high efficacy in diagnosing CI-AKI.

Combining the literature and the results of this study, it can be seen that urinary KIM-1 exhibits high sensitivity and specificity in assessing early kidney injury. TIMP-2 undergoes changes during kidney injury, and its level variations may be associated with the occurrence and progression of CI-AKI, thus possessing potential predictive value. Additionally, sTREM-1 demonstrates high sensitivity and is upregulated during inflammatory responses, with its level changes potentially reflecting kidney injury earlier. Therefore, this study further explores the high efficacy of urinary KIM-1, TIMP-2, and sTREM-1 in the early diagnosis of CI-AKI, which is a strength of this research. However, the concentration of KIM-1 and the level of TIMP-2 in urine may be influenced by multiple factors, which may affect their accuracy in predicting CI-AKI. Furthermore, the detection methods and clinical application standards for sTREM-1 need further

refinement and unification, and more clinical data and long-term observations are required to verify its accuracy and reliability.

Conclusion

In summary, this research demonstrates that urinary KIM-1, TIMP-2 and sTREM-1 can respond to early changes in renal function after PCI and have good application value in the early diagnosis of CI-AKI. This study lays a foundation to explore the predictive value of urinary KIM-1, TIMP-2 and sTREM-1 for CI-AKI in elderly patients after PCI. Our study is on the basis of limited clinical data, and further exploration is needed to further convince our findings.

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Disclosure

The authors declare no competing interests in this work.

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