Serum cystatin C: A potential predictor for hospital-acquired acute kidney injury in patients with acute exacerbation of COPD

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Abstract
Hospital-acquired acute kidney injury (HA-AKI) is associated with poor prognosis. In this study, we evaluated whether serum cystatin C on admission could predict AKI in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The retrospective study was conducted using data on adult inpatients with AECOPD from January 2014 to January 2017. A total of 1035 patients were included, among which 79 (7.6%) with HA-AKI were identified. Univariate and multivariate logistic regression analyses were used to investigate predictors of HA-AKI in patients with AECOPD. HA-AKI was associated with poor prognosis, and patients with HA-AKI had higher inpatient mortality (34.2% vs. 2.6%, \( p < 0.001 \)). Furthermore, after adjusting for confounders, HA-AKI was an independent risk factor for inpatient mortality for patients with AECOPD (odds ratio (OR) 11.02; 95% confidence interval (CI) 4.77–25.45; \( p < 0.001 \)). Four independent risk factors for HA-AKI (age, levels of urea and cystatin C, and platelet count on admission) were identified in patients with AECOPD. Cystatin C (OR 5.22; 95% CI 2.49–10.95; \( p < 0.001 \)) was a significant independent predictor of AKI in patients with AECOPD. HA-AKI in patients with AECOPD could be identified with a sensitivity of 73.5% and a specificity of 75.9% (area under the curve (AUC) = 0.803, 95% CI 0.747–0.859) by cystatin C level (cutoff value = 1.3 mg/L) and with a sensitivity of 75.9% and a specificity of 82.0% (AUC = 0.853, 95% CI 0.810–0.896) using a model comprising all significant predictors. Serum cystatin C has the potential for use to predict the risk of HA-AKI in patients with AECOPD.

Keywords
Cystatin C, exacerbation, chronic obstructive pulmonary disease, hospital-acquired acute kidney injury, predictor

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Introduction
Acute kidney injury (AKI) is a common condition in countries worldwide, regardless of economic development. AKI can result in the development of chronic kidney disease or end-stage renal disease, and the incidence of AKI is increasing.¹ Further, the impacts of AKI on long-term health and the related costs are far greater than formerly acknowledged.¹² AKI occurs in...
1.9–21.3% of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and it is a predictor of poor outcome in patients with this condition. Our team reported that approximately three-quarters of AKI in patients with AECOPD is community-acquired AKI (CA-AKI), while one-quarter is hospital-acquired AKI (HA-AKI); however, compared with patients with CA-AKI, patients with HA-AKI had worse outcomes.

Early detection and timely intervention can improve outcomes for patients with AKI. The diagnosis of AKI is based on a rise in serum creatinine (SCr) from baseline or a decrease in urine output, with even a slight increase in SCr being associated with a significant reduction in survival rate and poor outcomes; however, the increase in SCr during AKI is delayed, leading to late diagnosis, treatment, and prevention of AKI complications. Moreover, a true fall in glomerular filtration rate (GFR) could not be adequately reflected by SCr in patients with muscle wasting, sepsis, or liver disease. Depletion of muscle and fat mass is relatively common in patients with chronic obstructive pulmonary disease (COPD) with reported prevalence rates ranging from 20% in stable outpatients to 50% in patients hospitalized for COPD exacerbations. Therefore, SCr has limitations for the diagnosis of AKI in patients with AECOPD.

In view of the importance of early detection and treatment of AKI, recently, novel biomarkers for the diagnosis of AKI at an early stage have been focused on. Serum cystatin C is a promising marker for early diagnosis of AKI; however, it has not been evaluated in patients with AECOPD. In this study, we evaluated whether serum cystatin C on admission could predict HA-AKI in patients with AECOPD.

**Patients and methods**

**Patient selection**

This retrospective study was conducted at Nanjing First Hospital, Nanjing, Jiangsu, China, using records from January 2014 to January 2017. The diagnosis of AECOPD was supported by spirometric evidence of airflow obstruction (forced expiratory volume in 1 s/forced vital capacity < 0.70) when clinically stable. Exacerbations were defined as cough, dyspnea, or sputum purulence sufficiently severe to warrant hospitalization. The inclusion criterion was COPD exacerbation requiring hospitalization. The exclusion criteria were patients with CA-AKI, patients without full records, patients with a history of chronic kidney disease stage 5, patients undergoing dialysis before admission, and patients with urinary tract infection (Figure 1). No patients were lost to
follow-up. This study protocol was approved by the Regional Human Research Ethics Committee of Nanjing First Hospital (Nanjing, China). Due to the retrospective analysis, individual patient consent was waived on condition that all patient data were deidentified before analysis.

**Definitions of CA-AKI and HA-AKI**

AKI was defined by the increase in SCr using Kidney Disease Improving Global Outcomes (KDIGO) criteria: increase in SCr ≥26.5 μmol/L (0.3 mg/dL) within 48 h or increase in SCr ≥1.5 times baseline in 7 days. Patients admitted to hospital with AKI apparent from their first SCr measurement (within 24 h of admission) were denoted as having CA-AKI. Conversely, patients were categorized as having HA-AKI if no AKI was apparent on admission, but AKI developed during hospitalization. Baseline SCr for patients was defined as the lowest recorded during the preceding 12 months or hospitalization. According to KDIGO criteria, the definition of AKI was based on the change of measurements with SCr or urine output. Due to the retrospective nature of the study, urine output in most patients was not monitored, and related data could not be obtained, and hence, this study did not consider the urine output standard.

**Data collection**

All data of baseline characteristics were extracted from electronic records: age, sex, complications (acute respiratory failure and hypercapnic encephalopathy), and preexisting clinical conditions (chronic cor pulmonale, hypertension, coronary artery disease, diabetes, pulmonary arterial hypertension, chronic liver disease, atrial fibrillation, anemia, cerebrovascular disease, and cancer). Clinical examinations conducted on admission included low-density lipoprotein, high-density lipoprotein, total cholesterol, triglyceride, urea, uric acid, cystatin C, chloride, sodium, potassium, albumin, neutrophil ratio, hematocrit, red blood cell distribution width, and platelet count. Data on previous drugs taken included data on statins, β-receptor blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

**Data analysis**

Categorical variables are presented as percentages. Continuous variables are presented as means ± standard deviation or medians (25th–75th percentile), as appropriate. For categorical variables, comparisons between two groups were conducted using the χ² and Fisher’s exact tests, when appropriate. The unpaired t-test was used to compare means between two groups and the Mann–Whitney U-test was used to compare medians. To develop the risk factors of inpatient death, univariate binary logistic regression analysis for each predicting variable (sex, age, complications, comorbid conditions, laboratory tests, and treatment) was carried out. Variables that were found to be significant (p < 0.05) on univariate logistic regression analysis were entered into the multivariable binary logistic regression analysis. Similarly, univariate and multivariate binary logistic regression analyses were performed to evaluate potential risk factors associated with HA-AKI. Receiver operating characteristic (ROC) curves were plotted and the corresponding area under the curve (AUC) values were calculated for prediction of HA-AKI in patients with AECOPD. AUC values for all significant independent categorical predictors of HA-AKI and cystatin C for HA-AKI were compared. The p values <0.05 were considered to indicate statistically significant differences. Data were analyzed using SPSS software (v22.0, SPSS, Inc., Chicago, Illinois, USA).

**Results**

**HA-AKI incidence**

There were 1035 patients with AECOPD included in this study. The mean age at admission was 76.5 years old (standard deviation 9.2 years) and 77% were male patients. Overall, 79 (7.6%) patients developed HA-AKI.

**Comparison of outcomes between patients with HA-AKI and without AKI**

Compared with patients without AKI, AECOPD patients with HA-AKI were associated with more requiring mechanical ventilation (51.9% for HA-AKI vs. 20.9% for non-AKI, p < 0.001), invasive mechanical ventilation (17.7% for HA-AKI vs. 3.6% for non-AKI, p < 0.001), noninvasive mechanical ventilation (34.2% for HA-AKI vs. 17.4% for non-AKI, p < 0.001), renal replacement therapy (3.8% for HA-AKI vs. 0% for non-AKI, p < 0.001), and intensive care unit (ICU) admission (44.3% for HA-AKI vs. 16.0% for non-AKI, p < 0.001). Moreover, patients with HA-AKI were hospitalized for longer periods (15 days for HA-AKI vs. 10 days for non-AKI, p < 0.001) and had
higher 30-day (31.6% for HA-AKI vs. 2.6% for non-AKI, \( p < 0.001 \)) and inpatient mortality rates (34.2% for HA-AKI vs. 2.6% for non-AKI, \( p < 0.001 \)). Although the differences in duration of mechanical ventilation and length of ICU stay were not significant, both of these variables were higher in patients with HA-AKI than those without AKI. (Table 1).

**Risk factors for inpatient mortality**

After adjusting for confounders, risk factors for inpatient mortality were age (odds ratio (OR) 1.05; 95% confidence interval (CI) 1.01–1.10; \( p = 0.041 \)), acute respiratory failure (OR 2.49; 95% CI 1.06–5.86; \( p = 0.037 \)), albumin (OR 0.88; 95% CI 0.81–0.95; \( p = 0.002 \)), neutrophil ratio (OR 1.05; 95% CI 1.01–1.09; \( p = 0.020 \)), ICU admission (OR 3.07; 95% CI 1.39–6.77; \( p = 0.006 \)), and HA-AKI (OR 11.02; 95% CI 4.77–25.45; \( p < 0.001 \)) (Online Supplemental Table).

**HA-AKI characteristics**

The demographic differences between patients without AKI and those with HA-AKI are presented in Table 2. The numbers of men and women in the non-AKI and HA-AKI groups were similar; however, there was a significant difference in age between the non-AKI and HA-AKI groups (78 vs. 83 years, respectively; OR 1.06; 95% CI 1.05–1.11; \( p < 0.001 \)). Patients with HA-AKI were more prone to have acute respiratory failure (48.1% vs. 29.4%; OR 2.23; 95% CI 1.40–3.54; \( p = 0.001 \)) and hypercapnic encephalopathy (10.1% vs. 2.9%; OR 3.73; 95% CI 1.64–8.50; \( p = 0.004 \)) on admission. Nevertheless, comparison of the prevalence of various comorbidities in patients without AKI and those with HA-AKI revealed approximately equal proportions of hypertension, diabetes mellitus, pulmonary arterial hypertension, chronic liver disease, anemia, cerebrovascular diseases, and cancer. The only three significant differences were higher prevalence in patients with HA-AKI of chronic cor pulmonale (62.0% vs. 39.9%; OR 2.45; 95% CI 1.53–3.94; \( p < 0.001 \)), coronary artery disease (36.7% vs. 25.0%; OR 1.74; 95% CI 1.08–2.81; \( p = 0.022 \)), and atrial fibrillation (16.5% vs. 9.4%; OR 1.90; 95% CI 1.01–3.57; \( p = 0.045 \)). In addition, patients with HA-AKI had a higher creatinine, urea, uric acid, cystatin C, red blood cell distribution width, and neutrophil ratio on admission, while they had lower platelet counts (Table 2).

**Risk factors for HA-AKI**

After adjusting for confounders, factors predicting the development of HA-AKI were age (OR 1.06; 95% CI 1.02–1.10; \( p = 0.005 \)), urea (OR 1.10; 95% CI 1.01–1.20; \( p = 0.034 \)), cystatin C (OR 5.09; 95% CI 2.41–10.75; \( p < 0.001 \)), and platelet count (OR 0.995; 95% CI 0.990–0.999; \( p = 0.023 \)) on admission (Table 3).

**Diagnostic efficiency of cystatin C for HA-AKI in patients with AECOPD**

Figure 2 and Table 4 showed the diagnostic efficiencies of age, urea, cystatin C, and platelet count for HA-AKI in patients with AECOPD. Figure 3 showed a comparison of the diagnostic efficiency of cystatin C and a model comprising all significant predictors. ROC curve analysis revealed AUC values of 0.803 (95% CI 0.747–0.859; \( p < 0.001 \)) and 0.853 (95% CI 0.810–0.896; \( p < 0.001 \)) for cystatin C and the model including all significant predictors, respectively.
AKI is common in patients with AECOPD, and it is associated with poor prognosis in this context. 3,4,15 Our team previously reported that among patients with AECOPD, approximately three-quarters of AKI is CA-AKI, while one-quarter is HA-AKI. 4 In comparison to patients with CA-AKI, patients with HA-AKI are more prone to require noninvasive mechanical ventilation and have a higher inpatient mortality rate, longer hospitalization, and longer duration of mechanical ventilation. Even after adjustment for other significant factors, HA-AKI (compared with CA-AKI) remains an independent risk factor for inpatient mortality.4 In this study, we confirmed that HA-AKI was associated with poor prognosis and found that it is an independent risk factor for inpatient mortality among patients with AECOPD. Furthermore, patients with HA-AKI had worse outcomes than those without AKI.

Table 2. Demographics, complications, comorbidities, medication use, and clinical features in patients without and with HA-AKI.

| Variable                          | Non-AKI (n = 956) | HA-AKI (n = 79) | OR    | 95% CI        | p Value |
|-----------------------------------|-------------------|----------------|-------|--------------|---------|
| Age (years)                       | 78 (70–83)        | 83 (76–86)     | 1.08  | 1.05–1.11    | <0.001  |
| Men n (%)                         | 732 (76.6)        | 63 (79.7)      | 1.21  | 0.68–2.13    | 0.520   |
| Complications, n (%)              |                   |                |       |              |         |
| Acute respiratory failure         | 281 (29.4)        | 38 (48.1)      | 2.23  | 1.40–3.54    | 0.001   |
| Hypercapnic encephalopathy       | 28 (2.9)          | 8 (10.1)       | 3.73  | 1.64–8.50    | 0.004   |
| Comorbid conditions, n (%)        |                   |                |       |              |         |
| Chronic cor pulmonale             | 381 (39.9)        | 49 (62.0)      | 2.45  | 1.53–3.94    | <0.001  |
| Hypertension                      | 488 (51.0)        | 49 (62.0)      | 1.57  | 0.98–2.51    | 0.061   |
| Coronary artery disease           | 239 (25.0)        | 29 (36.7)      | 1.74  | 1.08–2.81    | 0.022   |
| Diabetes mellitus                 | 133 (13.9)        | 13 (16.5)      | 1.22  | 0.65–2.27    | 0.532   |
| Pulmonary arterial hypertension   | 34 (3.6)          | 6 (7.8)        | 1.50  | 0.98–2.42    | 0.128   |
| Chronic liver disease             | 41 (4.3)          | 4 (5.1)        | 1.19  | 0.42–3.41    | 0.771   |
| Atrial fibrillation               | 90 (9.4)          | 13 (16.5)      | 1.90  | 1.01–3.57    | 0.045   |
| Anemia                            | 256 (26.8)        | 28 (35.4)      | 1.50  | 0.93–2.43    | 0.097   |
| Laboratory tests                  |                   |                |       |              |         |
| Low-density lipoprotein (mmol/L)  | 2.38 (1.85–2.97)  | 2.28 (1.79–2.96) | 0.93  | 0.70–1.24    | 0.445   |
| High-density lipoprotein (mmol/L) | 1.17 (0.96–1.39)  | 1.15 (0.92–1.40) | 0.94  | 0.48–1.87    | 0.758   |
| Total cholesterol (mmol/L)        | 3.96 (3.35–4.67)  | 3.91 (3.29–4.57) | 1.02  | 0.81–1.29    | 0.783   |
| Triglyceride (mmol/L)             | 0.79 (0.63–1.08)  | 0.88 (0.67–1.13) | 1.51  | 1.03–2.22    | 0.034   |
| Creatinine (μmol/L)               | 71 (60–84)        | 88 (68–105)    | 1.04  | 1.03–1.05    | <0.001  |
| Urea (mmol/L)                     | 6.11 (4.80–7.53)  | 8.26 (6.06–10.68) | 1.28  | 1.20–1.37    | <0.001  |
| Uric acid (μmol/L)                | 269 (200–350)     | 364 (261–490)  | 1.006 | 1.005–1.008  | <0.001  |
| Cystatin C (mg/L)                 | 1.13 (0.96–1.35)  | 1.71 (1.34–2.10) | 14.79 | 8.42–25.98   | <0.001  |
| Chloride (mmol/L)                 | 100 (96–104)      | 99 (95–103)    | 0.96  | 0.93–0.99    | 0.068   |
| Sodium (mmol/L)                   | 139 (136–142)     | 139 (135–142)  | 0.98  | 0.94–1.03    | 0.596   |
| Potassium (mmol/L)                | 3.79 (3.40–4.10)  | 3.87 (3.34–4.20) | 1.35  | 0.90–2.03    | 0.221   |
| Albumin (g/L)                     | 35.1 (32.7–37.9)  | 34.6 (31.8–37.1) | 0.93  | 0.88–0.99    | 0.058   |
| Neutrophil ratio (%)              | 77.8 (68.4–85.1)  | 79.6 (74.9–86.7) | 1.03  | 1.01–1.06    | 0.007   |
| Hematocrit (%)                    | 39.5 (36.3–42.9)  | 39.2 (33.7–42.5) | 0.96  | 0.93–1.01    | 0.137   |
| Red blood cell distribution width (%) | 13.6 (13.0–14.4)  | 14.0 (13.3–14.9) | 1.26  | 1.11–1.43    | 0.006   |
| Platelet count (10^9/L)           | 188 (147–231)     | 160 (125–201)  | 0.992 | 0.988–0.999  | <0.001  |
| Drug, n (%)                       |                   |                |       |              |         |
| Statins                           | 141 (14.7)        | 18 (22.8)      | 1.71  | 0.98–2.97    | 0.057   |
| β-Receptor blocker                | 64 (6.7)          | 4 (5.1)        | 0.74  | 0.26–2.10    | 0.812   |
| AECI/ARB                          | 132 (13.8)        | 15 (19.0)      | 1.46  | 0.81–2.64    | 0.205   |

AKI: acute kidney injury; HA-AKI: hospital-acquired acute kidney injury; AECI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Table 3. Risk factors for HA-AKI.

| Variable                          | OR (95% CI) | p Value |
|-----------------------------------|-------------|---------|
| Age                               | 1.06 (1.02–1.10) | 0.005 |
| Urea                              | 1.10 (1.01–1.20) | 0.034 |
| Cystatin C                        | 5.09 (2.41–10.75) | < 0.001 |
| Platelet count (10^9/L)           | 0.995 (0.990–0.999) | 0.023 |

HA-AKI: hospital-acquired acute kidney injury; OR: odds ratio; CI: confidence interval.

Discussion

AKI is common in patients with AECOPD, and it is associated with poor prognosis in this context. 3,4,15 Our team previously reported that among patients with AECOPD, approximately three-quarters of AKI is CA-AKI, while one-quarter is HA-AKI. 4 In comparison to patients with CA-AKI, patients with HA-AKI are more prone to require noninvasive mechanical ventilation and have a higher inpatient mortality rate, longer hospitalization, and longer duration of mechanical ventilation. Even after adjustment for other significant factors, HA-AKI (compared with CA-AKI) remains an independent risk factor for inpatient mortality.4 In this study, we confirmed that HA-AKI was associated with poor prognosis and found that it is an independent risk factor for inpatient mortality among patients with AECOPD. Furthermore, patients with HA-AKI had worse outcomes than those without AKI.
Early detection and timely intervention could improve outcomes for patients with AKI. Multiple novel biomarkers have been reported to discriminate AKI in patients at an early stage. Urinary liver fatty acid-binding protein and plasma fibroblast growth factor-23 are new and highly predictive early biomarkers for AKI following cardiac surgery.\(^{16,17}\) Further, urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary kidney injury molecule-1 could efficiently predict vancomycin-associated AKI earlier than SCr.\(^{18}\) Cystatin C, measured on day 3 of life, can predict AKI earlier than SCr and estimated GFR in neonates with respiratory distress syndrome\(^{19}\); however, which biomarkers can predict AKI in patients with AECOPD remains unclear.

This study may be the first to explore novel biomarker to predict AKI in patients with AECOPD. In this study, all data were collected on patient admission to

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**Table 4.** Diagnostic efficiency of age, urea, cystatin C, and platelet count for HA-AKI in patients with AECOPD.

| Variable          | Cutoff value | Sensitivity | Specificity | AUC (95% CI)       |
|-------------------|--------------|-------------|-------------|--------------------|
| Age (years)       | 80.5         | 0.620       | 0.627       | 0.669 (0.610–0.728) |
| Urea (mmol/L)     | 8.1          | 0.810       | 0.570       | 0.711 (0.647–0.775) |
| Cystatin C (mg/L) | 1.3          | 0.759       | 0.735       | 0.803 (0.747–0.859) |
| Platelet count (10^9/L) | 170         | 0.628       | 0.620       | 0.638 (0.575–0.700) |

HA-AKI: hospital-acquired acute kidney injury; AECOPD: acute exacerbations of chronic obstructive pulmonary disease; AUC: area under the curve; CI: confidence interval.
hospital. The results of univariate and multivariate binary logistic regression demonstrated that four variables (cystatin C, urea, age, and platelet count) were significant indicators of HA-AKI in patients with AECOPD and that cystatin C was an important predictor of HA-AKI. Currently, SCr is used to evaluate kidney function; however, it is extremely limited for the early prediction of AKI. In our study, we also found that SCr was not a sensitive predictor of AKI in patients with AECOPD. There are two possible explanations for these findings: (1) the role of SCr as a marker of renal function is limited by the fact that its half-life increases from 4 h to 24–72 h if GFR is decreased\(^{20}\) and (2) creatinine production is determined by the amount generated in the liver, pancreas, and kidneys, ingested creatinine (i.e. intake of red meat), and muscle function.\(^{9}\)

Depletion of muscle and fat mass is common in patients with AECOPD\(^{12}\) and a genuine fall in GFR may not be adequately reflected by SCr in patients with muscle wasting.\(^{20}\) Unlike SCr, cystatin C is a representative marker of kidney function and is not influenced by muscle mass, age, sex, or protein intake.\(^{21}\) Cystatin C is a cysteine proteinase inhibitor, which has a half-life of approximately 50% that of creatinine; hence, serum cystatin C levels change earlier than those of creatinine.\(^{22,23}\) On even mild kidney injury, serum cystatin C begins to increase at 24–48 h before SCr and gradually increases during disease progression.\(^{24}\)

Further, the performance of serum cystatin C for the diagnosis of AKI is superior to that of SCr in various clinical settings.\(^{23,25}\)

NGAL has also been reported as a novel biomarker for AKI\(^{26,27}\); however, plasma NGAL is unlikely to be specific for AKI in patients with COPD, as it can also be increased in patients with COPD without AKI,\(^ {28}\) which may limit the utility of plasma NGAL for prediction of AKI in patients with AECOPD. In our study, cystatin C level (cutoff value = 1.3 mg/L) could be used to identify HA-AKI in patients with AECOPD with a sensitivity of 73.5% and a specificity of 75.9% (AUC = 0.803, 95% CI 0.747–0.859). Hence, our findings suggest that cystatin C on admission could be used as a biomarker for HA-AKI in patients with AECOPD. If our results are confirmed by other studies, this marker could be applied in clinical practice to predict the occurrence of HA-AKI in patients with AECOPD.

Our study had several limitations. Firstly, this is a single-center, retrospective study. In the future, a multicenter prospective study is needed to confirm our results. Secondly, the data of respiratory characteristics (such as, prior forced expiratory volume in 1 second (FEV\(_1\)), Medical Research Council dyspnea scale (MRC) score, partial pressure of oxygen (PaO\(_2\)), and partial pressure of arterial carbon dioxide (PaCO\(_2\)), congestive cardiac failure, medications (such as non-steroidal anti-inflammatory medications and diuretics), and radiography may be potential variables associated with HA-AKI in patients with AECOPD, which are lacking in this investigation. Thirdly, there are several other novel biomarkers for AKI,\(^{29}\) and we have not compared cystatin C with those biomarkers for predicting HA-AKI in patients with AECOPD. Fourthly, due to the retrospective nature of the study, urine output in most patients is not monitored, and related data could not be obtained, and hence, this study does not consider the urine output standard.

**Conclusion**

In conclusion, serum cystatin C on admission is associated with HA-AKI in patients with AECOPD and is a potential biomarker for predicting HA-AKI in patients with this condition.

**Author contributions**

The authors DC and CC contributed equally to this work.
DC takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis. XW, DC, and CC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. JL, YT, HY, MM, HZ, BP helped conduct the study, and collect and analyze the data.

Declaration of conflicting interests
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