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Iron metabolism indexes as predictors of the incidence of cardiac surgery-associated acute kidney surgery

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Abstract

Background Acute kidney injury (AKI) is a major complication following cardiac surgery. We explored the clinical utility of iron metabolism indexes for identification of patients at risk for AKI after cardiac surgery.

Methods This prospective observational study included patients who underwent cardiac surgery between March 2023 and June 2023. Iron metabolism indexes were measured upon admission to the intensive care unit. Multivariable logistic regression analyses were performed to explore the relationship between iron metabolism indexes and cardiac surgery-associated AKI (CSA-AKI). Receiver operating characteristic (ROC) curve was used to assess the predictive ability of iron, APACHE II score and the combination of the two indicators. Restricted cubic splines (RCS) was used to further confirm the linear relationship between iron and CSA-AKI.

Results Among the 112 recruited patients, 38 (33.9%) were diagnosed with AKI. Multivariable logistic regression analysis indicated that APACHE II score (odds ratio [OR], 1.208; 95% confidence interval [CI], 1.003–1.455, $P=0.036$) and iron (OR 1.069; 95% CI 1.009–1.133, $P=0.036$) could be used as independent risk factors to predict CSA-AKI. ROC curve analysis showed that iron (area under curve [AUC] = 0.669, 95% CI 0.572–0.757), APACHE II score (AUC = 0.655, 95% CI 0.557–0.744) and iron and APACHE II score combination (AUC = 0.726, 95% CI 0.632–0.807) were predictive indicators for CSA-AKI. RCS further confirmed the linear relationship between iron and CSA-AKI.

Conclusions Elevated iron levels were independently associated with higher risk of CSA-AKI, and there was a linear relationship between iron and CSA-AKI.

Keywords Iron metabolism indexes, Cardiac surgery-associated acute kidney injury, Receiver operating characteristic, Restricted cubic splines

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Introduction

More than two million heart surgeries are performed worldwide each year [1]. Acute kidney injury (AKI) is a common and serious complication after cardiac surgery with cardiopulmonary bypass (CPB). The incidence of cardiac surgery-associated AKI (CSA-AKI) ranges from 20 to 40%, which is the second leading cause of AKI in intensive care unit (ICU) [2, 3]. Patients with severe CSA-AKI are confronted with a 3-8-fold higher perioperative mortality, prolonged length of ICU and hospital stay, and an increased expenses [4]. Approximately 25% of CSA-AKI patients develop chronic kidney disease (CKD) after three years [5].

The exact pathophysiology of CSA-AKI is multifactorial, complex, and incompletely understood. However, animal and human studies have shown that these factors interact before, during, and after cardiac surgery, including genetic susceptibility, nephrotoxicity, CPB-induced haemolysis, ischemia–reperfusion injury, complexity of cardiac surgery, oxidative stress, and inflammation [6, 7].

Although the specific mechanism linked to the occurrence and development of CSA-AKI has yet to be identified, release of free heme and iron during CPB is likely to play an important role [8]. During CPB, red blood cells are exposed to nonphysiologic surfaces, shear forces may injure red blood cells, leading to the release of free hemoglobin and catalytic iron [9]. During ischemia–reperfusion period, a decrease in pH or superoxide-induced reduction of Fe^{3+} may cause dissociation of protein-bound intracellular iron, thereby increasing the levels of catalytic iron, which could contribute to oxidative stress and cellular damage, resulting in tubular necrosis [10]. Some studies have shown that iron metabolism-related indicators (serum ferritin, transferrin, urine catalytic iron) can be used as predictors of the incidence of CSA-AKI [11–13].

There are no effective treatment measures for CSA-AKI, so it is necessary to identify risk factors associated with CSA-AKI to allow that preventive and early diagnosis measures to be taken, thereby reducing the incidence of CSA-AKI. However, at present, serum creatinine and urine have a lag in the diagnosis of CSA-AKI. Many other well-known biomarkers for CSA-AKI such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) have been identified based on their known biology [14]. Nevertheless, the ideal biomarker for predicting CSA-AKI remains controversial. Therefore, we conducted a prospective, single center cohort study in patients undergoing cardiac surgery to evaluate the predictive performance of iron metabolism indexes for CSA-AKI.

Methods and materials

Study design and participants

This is a single-center, prospective, and observational study. This study included adult patients (≥18 years old) who underwent cardiac surgery at a university-affiliated hospital between March 2023 and June 2023. Patients were excluded if they met any of the following criteria: (1) pre-existing AKI, end-stage renal disease, or dialysis; (2) emergency cardiac surgery; (3) kidney or heart transplantation; (4) recent urinary tract infection or obstruction; (5) pregnant women. This study was approved by the Ethics Committee of our hospital (KY20220518-KS-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of our hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Participants or their legal representatives provided written informed consent.

Data collection

The study data were collected from electronic medical record databases of our hospital. Demographic information was recorded for further analyses (e.g., age, gender, EuroSCORE, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, body mass index (BMI), and co-morbidities as well as iron metabolism indexes). In addition, types of operation, surgery time, CPB time and Cross-clamp time were collected. Moreover, outcome variables (e.g., AKI, hospital mortality, length of hospital stay) were recorded for further comparison.

Measurement of iron metabolism indexes

To conduct iron metabolism indexes analysis, serum concentration of iron (S-Fe), serum unsaturated iron binding capacity (UIBC), serum total iron binding capacity (TIBC), transferrin (TRF), ferritin, soluble transferrin receptor (sTfR), transferrin saturation (TS) were determined from blood samples of the patients when they were transferred to the Cardiovascular Intensive Care Unit postoperatively. Iron metabolism indexes was detected with immunonephelometry method (C16000, Abbott, America). In addition, the reference values of the hospital of the authors included: S-Fe: 9.00–27.00umol/L, UIBC: 31.00–51.00umol/L, TIBC: 45.00–75.00umol/L, TRF: 2.00–4.00 g/L, ferritin: 4.63–204.00 ng/ml, sTfR: 0.76–1.76 mg/L, TS: 20–55%.

Main outcome

The main outcome was the development of AKI. According to the newest consensus-based KDIGO criteria, postoperative AKI was defined as (1) small changes in serum creatinine (≥0.3 mg/dl or 26.5 mmol/l)

when they occurred within 48 h; (2) a maximal change in serum creatinine ≥ 1.5 times the baseline value until postoperative day 7 compared with preoperative baseline values; (3) urine volume < 0.5 ml/kg/h for 6 h. In our study, we did not take urine volume into consideration owing to its inaccuracy, as done in the previous study [15]. The serum creatinine levels measured before surgery were used as the baseline value [16].

Statistical analysis

Descriptive statistics were reported as numbers and percentages for categorical variables and means (SD) or medians (IQR) for continuous variables. Statistical differences between categorical or continuous variables were carried out using Student's t test, Mann Whitney U test, chi-square test, or Fisher's exact probability method as appropriate. We performed the multivariable binary logistic regression models to evaluate the association of S-Fe and AKI with a statistically signifcant association at $P < 0.05$ in univariate regression analysis. For a long time, the APACHE II score was reported to be good indicator of prognosis in critically ill patients. Some studies have shown that iron metabolism indexes can be used as predictors of the incidence of CSA-AKI, so we combined S-Fe and APACHE II score to predict CSA-AKI. The receiver operating characteristics curve (ROC) analysis was used to assess the overall discriminative ability of S-Fe, APACHE II score, the combination of the two indicators to predict CSA-AKI. Restricted cubic splines (RCS) was used to explore the relationship between S-Fe and CSA-AKI. All statistical tests were conducted with SPSS version 25.0 (SPSS Inc, Chicago, IL, USA) and R statistical software version 4.0.0 (R Foundation, Vienna, Austria). In all analyses, differences were considered statistically significant with a P value < 0.05.

Results

On the whole, 134 patients admitting to the center of the authors and having undergone cardiac surgery were screened, and 22 patients were excluded (Fig. 1), leaving 112 patients included and analyzed in this study. Patients fell to the AKI group (n = 38) and no AKI group (n = 74).

The baseline characteristics exhibited by patients and patients's poor outcomes were listed in Table 1. Significant differences between the two groups were described as follows: age ($P = 0.028$), CPB time ($P = 0.037$), cross-clamp time ($P = 0.048$), APACHE II score ($P = 0.003$), S-Fe ($P = 0.011$).

Table 2 illustrated the results of the logistic regression for CSA-AKI. Age, CPB time, cross-clamp time, APACHE II score and S-Fe were enrolled in the multivariable logistic regression analysis. The results showed that APACHE II score (OR 1.208; 95% CI 1.003–1.455,

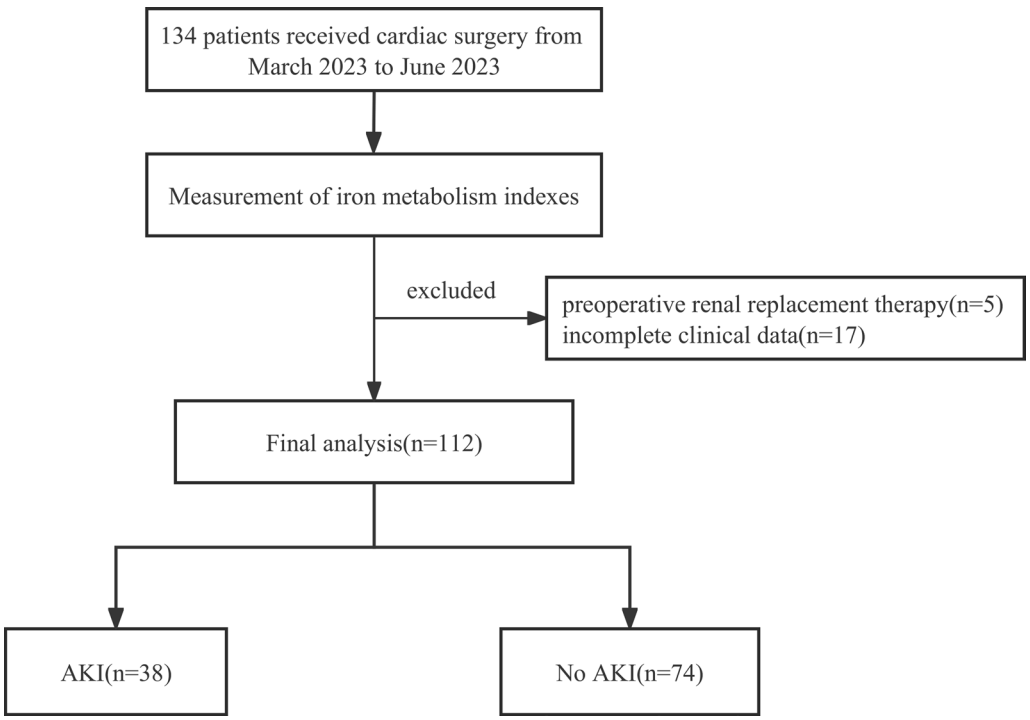

Fig. 1 The flowchart of participants selection

Table 1 Baseline characteristics of patients undergoing cardiac surgery according to acute kidney injury status

Demographics	Total(n = 112)	No AKI(n = 74)	AKI(n = 38)	*P* value
Female, n (%)	46(41.1)	33(44.6)	13(34.2)	0.290
Age, yrs	61.6 ± 11.7	59.9 ± 12.3	65.0 ± 9.7	0.028
BMI, kg/m2	23.7 ± 3.3	23.7 ± 3.1	23.7 ± 3.6	0.999
Smoke, n (%)	20(17.9)	11(14.9)	9(23.9)	0.249
Hypertension, n (%)	58(51.8)	35(47.3)	23(60.5)	0.185
Diabetes, n (%)	17(15.2)	11(14.9)	6(15.8)	0.897
COPD, n (%)	5(4.5)	4(5.4)	1(2.6)	0.501
Previous myocardial infarction, n (%)	2(1.8)	1(1.4)	1(2.6)	0.999
Preoperative hemoglobin, g/dL	130.5 ± 16.1	131.0 ± 17.2	129.6 ± 13.8	0.660
Operative variables				
Surgery type, (n%)				0.502
CABG alone	26(23.2)	19(25.7)	7(18.4)	
Valve alone	69(61.6)	42(56.8)	27(71.1)	
CABG and valve surgery	7(6.3)	5(6.8)	2(5.3)	
Others	10(8.9)	8(10.8)	2(5.3)	
Surgery time, h	4.1(3.7–4.7)	4.1(3.7–4.7)	4.1(3.7–4.7)	0.868
CPB time, min	110.5 (85.0–135.0)	103.5 (81.3–129.3)	126 (100.0–140.5)	0.037
Cross-clamp time, min	78.7 ± 28.0	75.0 ± 27.7	86.0 ± 27.4	0.048
Intraoperative intravenous fluid infusion(mL/kg/h)	9.4(7.9–11.1)	9.8 (7.9–11.1)	8.8 (8.0–10.4)	0.667
Intraoperative estimated blood loss(mL/kg/h)	4.7 ± 1.5	4.7 ± 1.5	4.8 ± 1.5	0.728
Intraoperative urine output (mL/kg/h)	3.6 (2.6–4.6)	3.3 (2.6–4.5)	3.9 (2.8–5.1)	0.277
pRBC transfusion during surgery(units)	2.50 (1.9–3.8)	2.50 (2.5–3.8)	2.50 (1.3–3.8)	0.984
Clinical scores				
EuroScore	6(5–6)	5(4–6)	6(5–6)	0.054
APACHE-II Score	10(8–13)	9(8–12)	12(9–13)	0.003
Iron metabolism indexes				
Iron, umol/L	19.8(12.9–28.3)	18.2(12.2–26.7)	25.5(15.8–30.9)	0.011
UIBC, umol/L	14.8(6.1–28.3)	15.8(7.5–23.4)	12.2(4.2–24.8)	0.363
TIBC, umol/L	36.3 ± 8.1	35.1 ± 6.9	38.5 ± 9.7	0.065
TRF, g/l	1.4 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	0.158
Ferritin, ng/ml	209.9 (110.6–318.8)	201.8 (107.6–292.7)	234.1 (123.0–431.0)	0.150
sTfR, mg/L	0.6(0.5–0.8)	0.6(0.5–0.8)	0.6(0.5–0.8)	0.951
TS (%)	58.9(38.8–80.7)	56.5(38.2–78.5)	64.8(42.5–87.2)	0.139
Poor outcomes				
Hospital stay, d	17(15–20)	17(14–2)	19(16–21)	0.126
In-hospital death, n (%)	2(1.8)	1(1.4)	1(2.6)	0.999

AKI, Acute kidney injury; *BMI*, Body Mass Index; *COPD*, Chronic obstructive pulmonary disease; *CABG*, Coronary artery bypass grafting; *CPB*, Cardiopulmonary bypass; *pRBC*, Packed Red Blood Cell; *EuroSCORE*, European system for cardiac operative risk evaluation; *APACHE II*, Acute physiology and chronic health evaluation II; UIBC, Unsaturated iron binding capacity; *TIBC*, Total iron binding capacity; *TRF*, Transferrin; sTfR, Soluble transferrin receptor; *TS*, Transferrin saturation

$P = 0.047$) and S-Fe (OR 1.069; 95% CI 1.009–1.133, $P = 0.024$) might be able to predict CSA-AKI.

ROC curve analysis showed that S-Fe (area under curve[AUC] = 0.669, 95% CI 0.572–0.757), APACHE II score (AUC = 0.655, 95% CI 0.557–0.744) and S-Fe and APACHE II score combination (AUC = 0.726, 95% CI 0.632–0.807) might be predictive indicators for CSA-AKI (Fig. 2). As shown in Fig. 3, a linear association was observed between the S-Fe and CSA-AKI (Fig. 3). The OR increased evidently when the S-Fe reached approximately 19.92umol/L.

Discussion

In this prospective study we reported the comprehensive analysis of iron metabolism indexes after cardiac surgery. We found that levels of S-Fe, unlike other iron related metabolism indicators, rose in AKI group. we also examined the ability of S-Fe to predict postoperative

Table 2 Multivariate regression analysis for cardiac surgery associated acute kidney injury

Variables	Regression coefficient	SE	OR(95%CI)	*P* Value
Age, yrs	0.018	0.026	1.018(0.968–1.070)	0.490
CPB time, min	0.005	0.014	1.005(0.977–1.033)	0.750
Cross-clamp time, min	−0.004	0.018	0.996(0.962–1.031)	0.816
APACHE-II Score	0.189	0.095	1.208(1.003–1.455)	0.047
Iron, umol/L	0.067	0.030	1.069(1.009–1.133)	0.024

CPB, Cardiopulmonary bypass; *APACHE II*, Acute physiology and chronic health evaluation II

AKI by ROC curve. Furthermore, we combined S-Fe and APACHE II score to plot ROC curve to predict CSA-AKI. These findings support the notion that S-Fe levels may be an indicator of poor outcomes after cardiac surgery.

Iron is an essential microelement for the human body, which plays an active role in maintaining physiolo gical functions. During CPB, red blood cells are exposed to nonphysiologic surfaces, shear forces may injure red blood cells, leading to the release of free hemoglobin and catalytic iron [9]. During aortic cross-clamp and reperfusion period, the levels of catalytic iron increase, which could contribute to oxidative stress and cellular damage, resulting in tubular necrosis [10]. After cardiac surgery, a large amount of catalytic iron is released, which may trigger AKI and mediate death [8]. Some studies found that elevated plasma catalytic iron levels are independently associated with increased prevalence of AKI after cardiac surgery [9, 17]. We found that patients who developed CSA-AKI had longer CPB time, longer aortic cross-clamp time. Adding to these findings, in this study we reported that patients who developed AKI had elevated serum catalytic iron levels upon admission to the ICU.

Ferritin is the primary tissue iron-storage protein, and may release iron in the presence of superoxide produced under conditions of inflammation [18]. Ferritin consists of 24 subunits of heavy (FtH) and light (FtL) chains. FtH can convert ferrous iron into ferric iron, which is stored within the ferritin shell subsequently [19]. The level of serum ferritin can indirectly reflect the level of FtH in the body. Nora Choi et al. found that patients with higher baseline serum ferritin levels have a low probability of developing CSA-AKI [12]. It is further suggested that high serum ferritin levels can reflect the body's immunoregulatory capacity and ability to process catalytic iron release during CPB. We found no significant difference in the serum ferritin levels between the AKI group and non-AKI group.

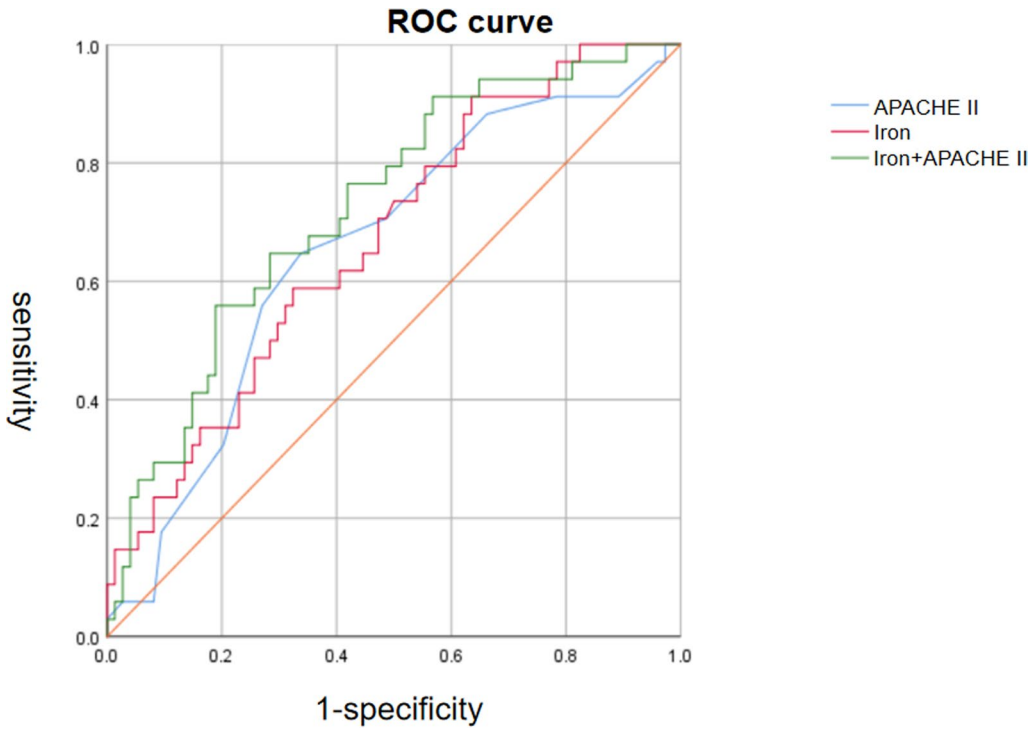

Fig. 2 Receiver operating characteristics curve of serum concentration of iron, acute physiology and chronic health evaluation II score and the combination of the two indicators for predicting cardiac surgery-associated acute kidney surgery

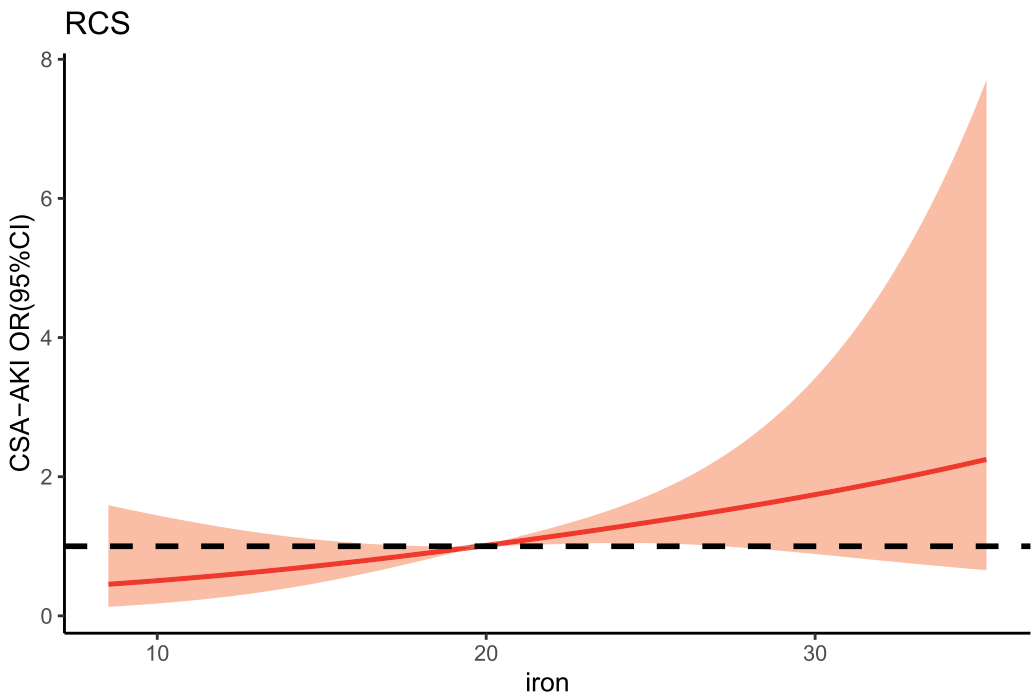

Fig. 3 Restricted spline curves for the relationship between serum concentration of iron and the incidence of cardiac surgery-associated acute kidney surgery. The red bold line denotes the odds ratio, while the shaded area represents the 95% confidence intervals

Because we only included data at the time of ICU admission, we did not collect the data of preoperative serum ferritin levels.

TRF is produced in the liver and binds one or two Fe^{3+} atoms in the circulation, and therefrom endocytosed by a variety of cells through specific plasma membrane receptors (TfR1 and TfR2). TRF is known to be filtered through the glomerular filtration barrier, and reabsorbed in the proximal tubule [20]. Increased urinary excretion of TRF results from decreased tubular uptake. Some studies show that urinary TRF can be further explored as a wider biomarker of renal damage induced by insults causing subclinical tubular alterations, which means that high levels of TRF may predict a higher incidence of AKI [20]. Iron binding capacity is the capacity of TRF to bind with iron. There are two types of iron binding capacity, TIBC and UIBC. As only one-third of TRF is saturated with iron, so the TRF present in serum has an extra binding capacity (67%), which is called UIBC. TIBC was calculated as the sum of the serum iron plus the UIBC [21]. TS was calculated as the percentage of iron to total iron binding capacity. Choi N et al. found that TS elevated at 1 h after CPB, which can be used as an independent predictor of the incidence of AKI after cardiac surgery [12]. sTfR is derived from proteolysis of the membrane transferrin receptor, it can be used to assess iron status. sTfR has been widely used in cardiopulmonary disease research [22]. Frise et al. found that when defined using sTfR rather than ferritin, non-anemic iron deficiency predicts prolonged hospitalisation following surgical aortic valve replacement [23]. Choi N et al. found that lower serum ferritin and higher transferrin saturation at 1 h CPB were independent predictors of acute kidney injury [12]. Lower intraoperative iron-binding proteins are inversely associated with postoperative AKI development, suggesting an impaired capacity to rapidly handle free iron release during CPB leading to AKI. However, we found no statistically significant difference in TRF, UIBC, TIBC, TS and sTfR between the two groups.

There are several limitations in our study. First, the sample size of our study is relatively small, so the level of evidence provided by our study is not high enough. However, Nora Choi, et al. conducted a study, the base clinical prediction model (Thakar score) demonstrated good discrimination for CSA-AKI (AUC, 0.72; 95% CI, 0.62–0.81), the intraoperative model (Thakar score, serum ferritin, and TS) is better clinical prediction alone (AUC, 0.76; 95% CI, 0.67–0.85) [12]. Second, we did not take urine volume into consideration as done in the previous study, because some patients were treated with diuretics and the urine volume is inaccurate, which may result in bias. Third, we did not study the relationship between the patient's preoperative iron

metabolism indexes and CSA-AKI. However, we found no difference in preoperative haemoglobin between the two groups. We plan to study the role of preoperative and postoperative iron metabolism indexes in the more crowds and explore the mechanism between ferroptosis and CSA-AKI in the future.

The results of our study and other researches highlight the importance of iron homeostasis in human ischemia–reperfusion injury and suggest it is a potentially modifiable risk during cardiac surgery [12]. Given that ferroptosis is extensively involved in the occurrence and development mechanisms of CSA-AKI, targeting the ferroptosis pathway may be a novel strategy for preventing and treating AKI. This strategy mainly includes iron chelation therapy, targeting iron metabolism-related proteins, lipophilic antioxidants, and direct inhibitors of ferroptosis [24]. What is more, further researches are required to verify these results.

Conclusions

In summary, our study showed that S-Fe levels upon admission to the ICU were associated with CSA-AKI. Meanwhile, S-Fe and APACHE II score combination was predictive indicator for CSA-AKI. What is more, the relationship between the S-Fe and CSA-AKI is a linear relationship. Further investigations will be required to verify the results of iron metabolism indexes for CSA-AKI.

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Author contributions
Wenxiu Chen wrote the main manuscript text and prepared the figures and tables. Hao Zhang, Xiao Shen, Liang Hong, Hong Tao, Jilai Xiao, Shuai Nie, Meng Wei and Ming Chen collected the data. Cui Zhang and Wenkui Yu were involved in study design, data interpretation, and manuscript preparation.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
In accordance with the Declaration of Helsinki, this study was approved by the Ethics Committee of Nanjing First Hospital (KY20220518-KS-01). Informed consent was obtained from participants or their legal representatives. All the methods were carried out in accordance with relevant guidelines and regulations in the declaration.

Consent for publication
All the authors agree to publish.

Competing interest
The authors declare no competing interests.

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