## **Original research**

# **BMJ Open** Effects of hyperuricaemia, with the superposition of being overweight and hyperlipidaemia, on the incidence of acute kidney injury following cardiac surgery: a retrospective cohort study

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## ABSTRACT

**Objectives** Acute kidney injury (AKI) is a common complication of cardiac surgery. This study aimed to explore the effects of hyperuricaemia, being overweight and hyperlipidaemia as risk factors for AKI in patients following cardiac surgery (cardiac surgery-associated acute kidney injury (CSA-AKI)).

Design Retrospective observational study.

**Setting** University teaching, grade-A tertiary hospital in Shanghai, China.

**Participants** Patients who underwent cardiac surgery from July 2015 to December 2015 in Zhongshan Hospital, Fudan University.

**Main outcome measures** We investigated the effect of hyperuricaemia, in combination with being overweight and hyperlipidaemia, on the risk of CSA-AKI.

Results A total of 1420 patients were enrolled. The AKI incidence in the highest uric acid group was 44.4%, while that in the lowest uric acid group was 28.5% (p<0.001). Patients in the higher uric acid guartiles were more likely to be overweight and hyperlipidaemic at the same time (p<0.001). Multivariate logistic regression analysis showed that hyperuricaemia was an independent risk factor for AKI (OR=1.237, 95% CI 1.095 to 1.885; p=0.009); being overweight or hyperlipidaemia alone was not an independent risk factor, but the combination of being overweight and hyperlipidaemia was (OR=1.544, 95% CI 1.059 to 2.252; p=0.024). In the final model, the OR value increased to 3.126 when hyperuricaemia was combined with being overweight and hyperlipidaemia, and the Hosmer-Lemeshow test showed that all three models fit well (p=0.433, 0.638 and 0.597, respectively). Conclusions The combination of being overweight and having hyperlipidaemia was an independent risk factor, but being overweight or having hyperlipidaemia alone was not. The combination of hyperuricaemia, being overweight and hyperlipidaemia further increased the risk of CSA-AKI.

# BACKGROUND

Acute kidney injury (AKI) is a common complication of cardiac surgery. The cardiac

# Strengths and limitations of this study

- This article offers an exploration of the combination of risk factors on the incidence of acute kidney injury (AKI) in patients following cardiac surgery.
- Appropriate statistical methods were used to analyse the findings of the study.
- This was a retrospective and observational study, which may limit the generalisation of the conclusions.
- Further research needs to be conducted on whether reducing the combination of risk factors can reduce the risk of AKI.

surgery-associated acute kidney injury (CSA-AKI) rate is approximately 20%-40%, and the mortality rate is up to 30%, which affects the long-term prognosis.<sup>1 2</sup> CSA-AKI has many non-modifiable risk factors, including age, race and pre-existing comorbidities such as hypertension and chronic kidney disease g (CKD); there are some potentially modifiable risk factors such as nephrotoxic medications, anaemia and fluid administration.<sup>3</sup> Studies have shown that hyperuricaemia and increased body mass index (BMI) are independent risk factors for CSA-AKI<sup>4-6</sup> that are modifiable for elective surgery. Interventions to control modifiable risk factors may be the main way to prevent CSA-AKI.<sup>7</sup>

Uric acid is the end product of purine metabolism and is excreted by the kidneys. While the kidneys excrete approximately 70% of uric acid, 90%–95% is reabsorbed in the renal tubule after being filtered by the glomerulus. Therefore, serum uric acid levels depend on glomerular filtration capacity and renal tubular reabsorption. Previous studies have confirmed that preoperative

**To cite:** Su Y, Li H, Li Y, *et al.* Effects of hyperuricaemia, with the superposition of being overweight and hyperlipidaemia, on the incidence of acute kidney injury following cardiac surgery: a retrospective cohort study. *BMJ Open* 2022;**12**:e047090. doi:10.1136/ bmjopen-2020-047090

Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/ bmjopen-2020-047090).

YS and HL contributed equally. JT and JX contributed equally.

Received 20 November 2020 Accepted 23 November 2021

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Acute kidney injur cn complication of card hyperuricaemia is an independent risk factor for CSA-AKI.<sup>8-10</sup> A meta-analysis including 18 cohort studies with 75200 patients found that patients with hyperuricaemia have a significantly higher risk of AKI compared with the control group (OR 2.24, 95% CI 1.76 to 2.86; p<0.01). The mechanism of AKI caused by hyperuricaemia is related to the crystallisation of uric acid, which may also activate an epithelial-mesenchymal proinflammatory response.

Hyperuricaemia is often associated with metabolic disorders, such as being overweight and hyperlipidaemia. Studies have confirmed that serum uric acid level is positively correlated with serum total cholesterol (TC), triglycerides and low-density lipoprotein (LDL) levels and negatively correlated with high-density lipoprotein (HDL) levels.<sup>11</sup> Other studies have suggested that hyperlipidaemia is a risk factor for AKI after surgery.<sup>12</sup> In addition, the incidence of AKI can increase with increasing BMI.<sup>13 14</sup> Previous studies also confirmed that preoperative serum creatinine (SCr) and uric acid levels increased with an increase in BMI, which was an independent risk factor for AKI.<sup>6</sup>

With economic development and changes in lifestyle and diet patterns, the risk factors for AKI in the Chinese population have increased rapidly in recent years. An increasing number of people tend to be obese or have hypertension, diabetes, hyperuricaemia and hyperlipidaemia. Considering that many risk factors might have additive effects and to provide a reference for clinicians, this study explored the relationship between hyperuricaemia, being overweight and hyperlipidaemia, and the effect of these factors on the risk of CSA-AKI.

## **MATERIALS AND METHODS Patient selection**

We retrospectively analysed data from patients who underwent cardiac surgery between July 2015 and December 2015 in our hospital. Patients were excluded if they were <18 years of age, had pre-existing end-stage renal disease, had kidney transplantation, intended to receive heart transplantation or had missing data

## **Definitions**

AKI was defined according to the following Kidney Disease: Improving Global Outcomes (KDIGO) criteria<sup>15</sup>: (1) increase in SCr by  $\geq 26.5 \,\mu \text{mol/L}$  within 48 hours; (2) increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; and (3) urine volume of <0.5 mL/kg/hour for 6 hours and staged according to the SCr and urine output. Severe AKI was defined as having KDIGO stage 2 or 3. Hypertension was defined as having a systolic blood pressure (BP) of  $\geq 140$  mm Hg or a diastolic BP of  $\geq 90$  mm Hg or an individual currently using antihypertensive drugs.<sup>16</sup>Hyperuricaemia was defined as having serum uric acid levels of  $>360 \mu mol/L$  (women) and  $>420 \mu mol/L$  (men and postmenopausal women). Hyperlipidaemia was defined as having levels of triglyceride of ≥1.70 mmol/L and data min

high-density lipoprotein cholesterol (HDL-c) and of <1.04 mmol/L (and/or) TC of  $\geq 5.18 \text{ mmol/L}$ . Being overweight was defined as having a BMI of  $\geq 24 \text{ kg/m}^{2.17}$ High-risk surgery was defined as either aortic surgery, macrovascular surgery or combined surgery. CKD was defined as having an estimated glomerular filtration rate (eGFR) of  $<60 \text{ mL}/((min/1.73 \text{ m}^2))$ .

## **Data collection and groups**

Preoperative information of all patients was collected, including sex, age, preoperative comorbidities (hypertension and diabetes), New York Heart Association (NYHA) cardiac function classification grade, SCr, eGFR, blood glucose and blood lipid levels. Intraoperative data included surgical type, extracorporeal circulation time and aortic clamping time. Postoperative data included length of hospital stay, length of intensive care unit (ICU) stay and mechanical ventilation days. Patients were divided into AKI versus non-AKI groups, and hyperuricaemia versus normal uric acid groups. The uric acid levels were categorised into four groups according to the quartiles of gender-specific distribution: for men: Q1, <311 µmol/L; Q2, 311–366 µmol/L; Q3, 366–442 µmol/L; uses rela Q4, >442µmol/L; for women: Q1, <246µmol/L; Q2, 246-304 µmol/L; Q3, 304-369 µmol/L; Q4, >369 µmol/L. Poor short-term outcomes include death during hospitalatec isation or discharge from the hospital automatically after abandoning treatment. to text

## Patient and public involvement

The patients and the public were not involved in the design, conduct, reporting or dissemination plans of this research.

# Statistical analysis

Statistical analysis was performed using SPSS V.20.0. The d independent sample t-test or the Mann-Whitney test was > used to compare continuous variables, and dichotomous variables were analysed using the  $\chi^2$  test or Fisher's exact test. Pearson's correlation was used to analyse the relationship between uric acid, blood lipid and BMI. A logistic മ regression model was used to analyse the risk factors for AKI. We first performed univariate analysis of all variables, then the backward stepwise selection method was used for multiple regression analysis, with a p value of <0.05 as the inclusion criterion and p value of  $\geq 0.10$  or higher as nologi the exclusion criterion. The Hosmer-Lemeshow test was used to verify the goodness of fit of the models. Statistical lles significance was set at a p value of <0.05.

# RESULTS

## **Baseline characteristics**

We identified 1420 patients who underwent cardiac surgery with a mean age of 57.1±12.2 years. The baseline demographic and medical characteristics for all patients, as divided by the uric acid quartiles, are shown in table 1. A history was documented for hypertension in 532

Table 1         Baseline characteristics of the study population according to uric acid quartiles						
	All (=1420)	Q1 (n=351)	Q2 (n=360)	Q3 (n=353)	Q4 (n=356)	P value
Gender (male), n (%)	833 (58.7)	127 (36.2)	207 (57.5)	231 (65.4)	272 (76.4)	<0.001
Age (years)	57.1±12.2	56.7±12.5	56.9±12.3	56.9±12.4	57.7±11.5	0.877
Body mass index (kg/m²)	23.6±3.3	22.9±3.2	23.2±3.2	24±3.2	24.4±3.4	<0.001
Overweight, n (%)	601 (42.3)	108 (30.8)	131 (36.4)	170 (48.2)	192 (53.9)	<0.001
Hypertension, n (%)	532 (37.5)	113 (32.2)	127 (35.3)	141 (39.9)	151 (42.4)	0.023
Diabetes, n (%)	221 (15.6)	56 (15.9)	55 (15.3)	57 (16.1)	53 (14.9)	0.228
Blood glucose (mmol/L)	5.2±0.7	5.4±1.8	5.3±1.7	5.3±1.4	5.3±1.4	0.788
Glycosylated haemoglobin (%)	5.8±0.5	6.1±0.7	5.6±0.2	5.8±0.5	5.7±0.5	0.735
Blood urea nitrogen (mmol/L)	6.0±2.0	5.2±1.5	5.7±1.5	6±1.8	7.2±2.6	<0.001
Serum creatinine (µmol/L)	80.8±22.4	67.7±15.3	76.6±14.6	82.1±16.6	96.6±29.1	<0.001
eGFR (mL/(min/1.73 m <sup>2</sup> ))	86.4±20.6	97.3±20.1	89.1±18.1	84.7±18.5	74.7±19.3	<0.001
eGFR <60 mL/(min/1.73 m²), n (%)	117 (8.2)	7 (2.0)	13 (3.6)	27 (7.6)	70 (19.7)	<0.001
Albuminuria, n (%)	109 (7.7)	20 (5.7)	21 (5.8)	28 (7.9)	40 (11.2)	<0.001
Cholesterol (mmol/L)	4±0.9	4±0.9	4±0.9	4±0.9	4±0.9	0.073
Triglyceride (mmol/L)	1.3±0.8	1.1±0.6	1.3±0.7	1.5±1	1.5±0.9	< 0.001
Low-density lipoprotein cholesterol (mmol/L)	2.3±0.8	2.2±0.8	2.2±0.8	2.4±0.8	2.3±0.8	0.132
High-density lipoprotein cholesterol (mmol/L)	1.2±0.3	1.3±0.4	1.2±0.3	1.1±0.3	1.1±0.4	< 0.001
Hyperlipidaemia, n (%)	292 (20.6)	36 (10.3)	68 (18.9)	86 (24.4)	102 (28.7)	<0.001
Albumin (g/L)	40.8±3.9	39.1±3.4	39.7±3.3	40.1±3.6	40.4±3.8	<0.001
Urolithiasis	76 (5.4)	15 (4.3)	22 (6.1)	20 (5.7)	19 (5.3)	0.287
Urinary tract infection	30 (2.1)	7 (2.0)	7 (1.9)	8 (2.3)	8 (2.2)	0.766
Nephrotoxic drugs	141 (9.9)	32 (9.1)	32 (8.9)	37 (10.5)	40 (11.2)	0.021
Low cardiac output syndrome	178 (12.5)	33 (9.4)	36 (10.0)	46 (13.0)	63 (17.7)	< 0.001
Results presented as mean±SD or number (percentage). eGFR, estimated glomerular filtration rate.						

patients (37.5%) and diabetes in 221 patients (15.6%). When analysed by the quartile of the uric acid level, the patients with higher uric acid levels were more likely to be older, with more occurrences of hypertension, higher BMI and levels of blood urea nitrogen, SCr, albumin and triglycerides. There were no significant differences in cholesterol, low-density lipoprotein cholesterol (LDLc), glycosylated haemoglobin and blood glucose levels among the four groups. Moreover, patients in the higher uric acid quartiles were more likely to be overweight and to have hyperlipidaemia (all p<0.001). In contrast, the patients in the higher uric acid quartiles showed lower levels of eGFR and HDL-c (all p<0.001) (table 1). We also found significant differences between the AKI group and the non-AKI group for male sex, age, diabetes, NYHA grade >II, hyperuricaemia, preoperative SCr and uric acid levels (all p<0.001) (online supplemental table 1). A total of 117 patients (8.2%) were diagnosed with CKD. Compared with the non-AKI group, the AKI group also had a higher proportion of patients with CKD (11.8% vs 6.2%, p<0.001). The AKI group had a higher proportion of being overweight (47.9% vs 39.1%, p=0.006) and higher BMI (24.1±3.5 vs 23.4±3.1, p<0.001). There

were no significant differences in levels of cholesterol, AI training triglycerides and LDL-c between the two groups (online supplemental table 1). There was no significant difference in extracorporeal membrane oxygenation support and the use of inotropic agents between the two groups, but the AKI group had a higher proportion of using nephrotoxic drugs (20.3% vs 4%, p<0.001), diuretics (97.1% vs <u>0</u> 93.2%, p=0.002) and vasoactive agents (93.2% vs 89.4%, p=0.015). The AKI group also had a higher proportion of 24-hour fluid balance (1.2 vs 0.3, p<0.001) and the inciechnologies dence of low cardiac output syndrome (LCOS; 19.7% vs 8.4%, p<0.001; online supplemental table 1).

## **AKI incidence and short-term outcomes**

When analysed by quartile of the uric acid level, the AKI incidence correlated with higher uric acid levels (p<0.001). The patients in the higher uric acid quartiles displayed longer lengths of hospital stay and ICU stay (all p<0.001) (table 2). However, the incidence of severe AKI, renal replacement therapy (RRT) treatment and poor short-term prognosis showed no statistical differences among the uric acid quartiles (all p>0.05) (table 2).

Table 2         Comparison of AKI incidence and short-term outcomes according to uric acid quartiles					
	Q1 (n=351)	Q2 (n=360)	Q3 (n=353)	Q4 (n=356)	P value
AKI, n (%)	100 (28.5)	116 (32.2)	144 (40.8)	158 (44.4)	<0.001
Severe AKI, n (%)	21 (6.0)	26 (7.2)	28 (7.9)	33 (9.3)	0.094
Renal replacement therapy, n (%)	6 (1.7)	5 (1.4)	4 (1.1)	12 (3.4)	0.143
Length of hospital stay (days)	13.5±15.8	13.2±6.9	13.2±5.1	14.2±6.8	< 0.001
Length of intensive care unit stay (hours)	46.6±80.3	46.4±76.4	53.1±74.7	64.3±116	<0.001
Poor short-term prognosis, n (%)	6 (1.7)	3 (0.8)	2 (0.6)	8 (2.2)	0.613

Results presented as mean±SD or number (percentage).

AKI, acute kidney injury.

When grouped by AKI and non-AKI, the patients with AKI required longer ICU and hospital stays (all p<0.001, online supplemental table 1); the incidence of poor short-term outcomes in the AKI group was significantly higher than that in the non-AKI group (3.3% vs 0.2%, p<0.001; online supplemental table 1).

When grouped by hyperuricaemia, the incidence of AKI, severe AKI and RRT treatment in the hyperuricaemia group was significantly higher than that in the normal uric acid group (44.2% vs 33%, p<0.001;10.7% vs 6.2%, p=0.003; and 3.2% vs 1.4%, p=0.027) (online supplemental table 2).

The length of ICU stay in the hyperuricaemia group was significantly higher than that in the normal uric acid group (p<0.001) (online supplemental table 2).

## Correlation analysis between uric acid, lipids, BMI and qlucose

Pearson correlation analysis showed the uric acid level is positively correlated with the triglyceride level (r=0.221, p<0.001) and BMI (r=0.157, p<0.001), respectively. There was a negative correlation between uric acid and HDL-c levels (r=0.190, p<0.001). There was no correlation between the uric acid level and the level of cholesterol (r=0.014, p=0.603), LDL-c (r=0.044, p=0.095) or blood glucose (r=-0.016, p=0.549) (figure 1). The AKI incidence in different subgroups showed that the combination of hyperuricaemia, hyperlipidaemia and being overweight had the highest AKI incidence (56.7%); this was followed by hyperuricaemia combined with being overweight, and hyperuricaemia acid combined with hyperlipidaemia, with AKI incidences of 50.5% and 49.2%, respectively (figure 2).

## Logistic regression analysis of risk factors for CSA-AKI

Univariate logistic analysis was conducted and screened out several risk factors for AKI, including male sex (OR=1.524, 95% CI 1.219 to 1.905), age (OR=1.022, 95% CI 1.013 to 1.032), being overweight (OR=1.403, 95% CI 1.100 to 1.790), diabetes (OR=1.353, 95% CI 1.011 to 1.811), preoperative coronary angiography (OR=1.290, 95% CI 1.039 to 1.602), NYHA grade >II (OR=1.375, 95% CI 1.043 to 1.812), preoperative eGFR <60 mL/  $(min/1.73 m^2)$  (OR=2.016, 95% CI 1.379 to 2.949),

Protected by copyright albuminuria (OR=1.394, 95% CI 1.024 to 2.203), hyperuricaemia (OR=1.696, 95% CI 1.275 to 2.022), high-risk surgery (OR=2.065, 95% CI 1.538 to 2.772), extracorporeal cardiopulmonary bypass (CPB) time (OR=1.010, inc 95% CI 1.007 to 1.014), LCOS (OR=2.241, 95% CI 1.183 uding to 3.576) and aortic occlusion time (OR=1.015, 95% CI 1.010 to 1.020) (table 3).

₫ Multiple logistic regression analysis showed that hyperuricaemia was an independent risk factor for CSA-AKI (OR=1.237, 95% CI 1.095 to 1.885; p=0.009) in model 1, after adjusting for the confounding factors of male sex, ē age, being overweight, diabetes, angiography, NYHA >II, preoperative eGFR <60 min/1.73 m<sup>2</sup>, high-risk surgery, 5 extracorporeal CPB time and aortic occlusion time. When the combination of being overweight and hyperlipidaemia was included in model 2, it became a risk factor ല for AKI (OR=1.544, 95% CI 1.059 to 2.252; p=0.024), while hyperuricaemia became insignificant. In model 3, adjusting for confounding factors, we found that the combination of hyperuricaemia, being overweight and hyperlipidaemia further increased the risk of postoperative AKI (OR=3.126, 95% CI 1.731 to 5.646; p<0.001). The ⊳ Hosmer-Lemeshow test showed that all models fit well training, and (p=0.433, 0.638 and 0.597, respectively) (table 4).

# DISCUSSION

sim This study found that patients with higher uric acid levels had a higher incidence of AKI, and these patients were more commonly overweight and hyperlipidaemic at the same time. Hyperuricaemia was positively correlated with 0 triglycerides and BMI; it was negatively correlated with HDL-c. Hyperuricaemia was an independent risk factor 🖁 for CSA-AKI (OR=1.237, 95% CI 1.095 to 1.885; p=0.009); the combination of being overweight and having hyperlipidaemia was an independent risk factor, but being overweight or having hyperlipidaemia alone were not. The combination of hyperuricaemia, being overweight and hyperlipidaemia further increases the risk of AKI.

The incidence of AKI increased according to the uric acid quartile, and patients with higher uric acid levels displayed longer lengths of hospital stay and ICU stay. The level of uric acid is related to blood lipids and BMI,







Figure 2 Comparison of acute kidney injury incidence among different subgroups.

respectively. The mechanism of hyperuricaemia caused by AKI is related to the crystallisation of uric acid. Urate crystals have a proinflammatory effect, which can cause renal tubular damage. Moreover, elevated serum uric acid may lead to endothelial dysfunction, oxidative stress and elevated C reactive protein.<sup>11 18-22</sup> Multiple studies have confirmed that hyperuricaemia is an independent risk factor for AKI. A retrospective study of 18444 hospitalised patients divided into four groups according to uric acid levels showed that blood uric acid of >6.7 mg/dL(men) or >5.4 mg/dL (women) correlated with a higher risk of AKI compared with blood uric acid of <4.5 mg/dL(men) and <3.6 mg/dL (women) with ORs of 3.2 (95%) CI 2.55 to 4.10) in men (p<0.001) and 3.1 (95% CI 2.40 to 4.19) in women (p<0.001).<sup>8</sup> Another retrospective study including 1536 patients with rheumatic heart disease showed that uric acid was independently associated with in-hospital (OR=1.21, 95% CI 1.06,1.37; p=0.004) and 1-year (HR=1.17, 95% CI 1.05,1.29; p=0.003) mortality after valve replacement surgery.<sup>10</sup> A prospective study by Gaipov et al showed that uric acid seemed to predict the progression of AKI and RRT requirement in patients who underwent cardiac surgery better than neutrophil gelatinase-associated lipocalin.<sup>9</sup> A meta-analysis including 18 cohort studies with 75200 patients found that the hyperuricaemia group had a significantly higher risk of AKI compared with the controls (OR 2.24, 95% CI 1.76 to 2.86; p<0.01). The risk rate after percutaneous coronary intervention (PCI) was much higher in the hyperuricaemia group than in the control group (16.0% vs 5.3%, OR 3.24, 95% CI 1.93 to 5.45; p<0.01).<sup>4</sup> Similar findings on AKI and in-hospital mortality have been reported in Asian populations.<sup>23</sup> Previous studies have confirmed that hyperuricaemia is a solution of the provided of the pr

Previous studies have confirmed that hyperuricaemia is closely related to lipid metabolism.<sup>24</sup> Ali *et al* found that serum uric acid level was positively correlated with serum levels of TC, triglycerides and LDL.<sup>25</sup> A study involving 536 patients undergoing radical gastrectomy concluded that age, BMI, hypertension, hyperlipidaemia and preoperative cystatin C level were independent risk factors for AKI.<sup>12</sup> The results of our study showed that the incidence of hyperlipidaemia in the AKI group was higher than that in the non-AKI group (36.5% vs 34%, p=0.351). In addition, there was a positive correlation between uric

Table 3         Univariate logistic analysis of risk factors for cardiac surgery-associated acute kidney injury					
	OR (95% CI)	P value			
Gender (male/female)	1.524 (1.219 to 1.905)	<0.001			
Age (1 year added)	1.022 (1.013 to 1.032)	<0.001			
Overweight	1.403 (1.100 to 1.790)	0.006			
Hypertension	1.197 (0.959 to 1.495)	0.113			
Diabetes	1.353 (1.011 to 1.811)	0.042			
Glycosylated haemoglobin	1.208 (0.779 to 1.983)	0.365			
Coronary angiography	1.29 (1.039 to 1.602)	0.021			
New York Heart Association grade >II	1.375 (1.043 to 1.812)	0.024			
Preoperative estimated glomerular filtration rate (<60 mL/(min/1.73 m <sup>2</sup> ))	2.016 (1.379 to 2.949)	<0.001			
Albuminuria	1.394 (1.024 to 2.203)	0.020			
Hyperuricaemia	1.696 (1.275 to 2.022)	<0.001			
Hyperlipidaemia	1.257 (0.896 to 1.636)	0.098			
High-risk surgery	2.065 (1.538 to 2.772)	<0.001			
Cardiopulmonary bypass time (1 min added)	1.01 (1.007 to 1.014)	<0.001			
Aortic occlusion time (1 min added)	1.015 (1.010 to 1.020)	<0.001			
Nephrotoxic drugs	1.368 (0.889 to 1.958)	0.064			
Low cardiac output syndrome	2.241 (1.183 to 3.576)	<0.001			

acid and triglyceride levels (r=0.221, p<0.001) and a negative correlation between uric acid and HDL-c levels (r=0.190, p<0.001). The possible mechanisms may be as follows: first, both purine synthesis and lipid metabolism are carried out in the liver, and hyperuricaemia causes increased glucose-6-phosphate activity, resulting in increased blood lipid synthesis from liver fatty acids; second, insulin resistance may lead to simultaneous elevation of uric acid and blood lipid (triglyceride and cholesterol) levels; third, long-term dyslipidaemia involves the afferent and efferent arterioles, impairs the glomerular filtration function and leads to hyperuricaemia due to the reduction of renal uric acid clearance.<sup>26 27</sup>

In this study, there was a positive correlation between uric acid levels and BMI (R=0.157, p<0.001); in univariate regression analysis, being overweight was an independent risk factor for AKI (OR=1.314, 95% CI 1.031 to 1.675; p=0.027). Obesity is significantly related to insulin resistance and hyperinsulinaemia, and obesity can activate the renin-angiotensi- aldosterone system; these can cause glomerular haemodynamic changes, such as glomerular hyperperfusion and hyperfiltration, lead to further glomerular injury and reduce the number of functional nephrons in obese patients, which can cause glomerulosclerosis.<sup>28-31</sup> In addition, adipocytes may act as sites for activated inflammatory cytokines and oxidative stress,<sup>30 32</sup> which may damage the kidneys. A single-centre cohort study involving 15470 critically ill patients found that each  $5 \text{ kg/m}^2$  increase in BMI was associated with a 10% risk (95% CI 1.06 to 1.24, p<0.001) of more severe AKI.<sup>14</sup> Previous studies have shown that the incidence of postoperative AKI in obese patients (BMI ≥28) increased significantly, and that BMI was an independent risk factor for

AKI. Another analysis involving 445 patients after cardiac surgery found that BMI was associated with an increased risk of AKI within 30 days, with the risk of AKI increasing by 26.5% for every  $5 \text{ kg/m}^2$  increase in BMI.<sup>33</sup>

text In the current study, multivariate logistic regression analysis found that hyperlipidaemia alone was not an independent risk factor for AKI, but the coexistence of hyperlipidaemia and being overweight was identified as đ a new risk factor. In the final model, the combination of hyperuricaemia, hyperlipidaemia and being overweight further increased the risk. The results show that hyper-≥ lipidaemia alone does not increase the risk of AKI, but in combination with other risk factors, such as being overweight or hyperuricaemia, it greatly increases the AKI risk. This means that controlling a single risk factor might not be effective, but controlling for multiple risk factors simultaneously may be sufficient to prevent AKI.

This study had several limitations. First, this was a single-centre retrospective analysis based on prospectively collected data. Second, the degree of hyperuricaemia was not graded, and the effect of uric acid-lowering treatment on the occurrence of CSA-AKI was not clear. Third, prospective studies should be conducted in the future to generation the effects of urate-lowering therapy, fat reduction and weight loss therapy on the risk of AKI.

## CONCLUSIONS

The incidence of AKI increased according to the uric acid quartiles, and patients with higher uric acid levels had higher proportions of hypertension, being overweight and hyperlipidaemia. The level of uric acid is related to blood lipids and BMI, respectively. Hyperuricaemia was

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Table 4         Multivariate regression analysis of risk factors for cardiac surgery-associated acute kidney injury					
	OR (95% CI)	P value	Hosmer-Lemeshow test (P value)		
Model 1*			0.433		
Male	1.797 (1.378 to 2.344)	<0.001			
Age	1.026 (1.014 to 1.038)	<0.001			
Diabetes	1.681 (1.188 to 2.378)	0.003			
NYHA grade >II	1.120 (1.064 to 1.437)	0.023			
Preoperative eGFR (<60 mL/(min/1.73m <sup>2</sup> ))	1.668 (1.071 to 2.598)	0.024			
High-risk surgery	1.749 (1.117 to 2.380)	<0.001			
Extracorporeal circulation time	1.046 (1.012 to 2.362)	<0.001			
Hyperuricaemia	1.237 (1.095 to 1.885)	0.009			
Model 2 (model 1+overweight×hyperlipidaemia)†			0.638		
Male	1.892 (1.415 to 2.531)	<0.001			
Age	1.032 (1.019 to 1.046)	<0.001			
Diabetes	1.490 (1.002 to 2.215)	0.047			
Preoperative eGFR (<60 mL/(min/1.73m <sup>2</sup> ))	1.741 (1.150 to 2.635)	0.029			
High-risk surgery	1.698 (1.134 to 2.459)	0.013			
Extracorporeal circulation time	1.009 (1.006 to 1.013)	<0.001			
Overweight×hyperlipidaemia	1.544 (1.059 to 2.252)	0.024			
Model 3 (model 1+hyperuricaemia×overweight×hyperlipidaemia)‡			0.597		
Male	1.658 (1.303 to 2.110)	<0.001			
Age	1.029 (1.017 to 1.040)	<0.001			
Preoperative eGFR (<60 mL/(min/1.73 m <sup>2</sup> ))	1.739 (1.165 to 2.595)	0.007			
High-risk surgery	1.779 (1.128 to 2.673)	0.017			
Extracorporeal circulation time	1.011 (1.007 to 1.015)	<0.001			
Hyperuricaemia×overweight×hyperlipidaemia	3.126 (1.731 to 5.646)	< 0.001			

\*Covariates adjusted for in model A: male, age, overweight, diabetes, angiography, NYHA grade >II, preoperative eGFR <60 mL/(min/1.73 m<sup>2</sup>), high-risk surgery, extracorporeal CPB time and aortic occlusion time.

†Covariates adjusted for in model B: male, age, overweight, diabetes, angiography, NYHA grade >II, preoperative eGFR <60 mL/(min/1.73 m<sup>2</sup>), high-risk surgery, extracorporeal CPB time and aortic occlusion time.

‡Covariates adjusted for in model C: male, age, overweight, diabetes, angiography, NYHA grade >II, preoperative eGFR <60 mL/(min/1.73 m<sup>2</sup>), high-risk surgery, extracorporeal CPB time and aortic occlusion time.

CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

an independent risk factor for CSA-AKI; the combination of being overweight and having hyperlipidaemia was an independent risk factor, but being overweight or having hyperlipidaemia alone was not. The combination of hyperuricaemia, being overweight and hyperlipidaemia further increases the risk of AKI. Therefore, reducing combinations of risk factors might reduce the risk of AKI. Continued studies are needed to focus on the early detection of, and intervention for, these and other risk factors.

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Acknowledgements We express our sincere gratitude to our colleagues whose names do not appear on the paper but contributed diligently to the research. We thank Xin Chen, Yanting Shi, Zhihong Chen, Xueping Lin, Man Su and Yunlu Zhang for data collection.

**Contributors** JX, YS and HL designed the study; YS, YL, BS, WJ, CW, ZL, XD, JT and YW participated in the acquisition of data; YS, JX, YF and HL researched and evaluated the literature; YS, XX and JX undertook the statistical analysis; HL wrote the first draft of the manuscript; YS, HL, JX, JT and YW made substantial contributions to the interpretation of data. JX is responsible for the overall content as guarantor. All authors approved the final manuscript for publication.

**Funding** The study was funded by Shanghai Municipal Hospital Frontier Technology Project, supported by Shanghai ShenKang Hospital Development Center (number SHDC12018127), National Natural Science Foundation of China (81901939), Xiamen Science and Technology Plan in 2018 (3502Z20184009) and Dynamic Alert System for Acute Kidney Injury and Multidisciplinary standard (3502Z20199179).

#### Competing interests None declared.

Patient consent for publication Not applicable.

**Ethics approval** This study involves human participants and was approved by the ethical committee of Zhongshan Hospital, Fudan University (number B2017-039). The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request via email to the corresponding author (xu.jiarui@zs-hospital.sh.cn).

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	All (n=1420)	Non-AKI group (n=902)	AKI group (n=518)	P-value
	(	(	(11 010)	
Preoperative				
Gender (male) [n(%)]	833(58.7%)	496(55%)	337(65.1%)	< 0.001
Age	57.1±12.2	55.9±12.8	59.1±10.8	< 0.001
BMI(kg/m <sup>2</sup> )	23.6±3.3	23.4±3.1	24.1±3.5	< 0.001
Overweight [n(%)]	601(42.3%)	353(39.1%)	247(47.9%)	0.006
Hypertension [n(%)]	532(37.5%)	324(35.9%)	208(40.2%)	0.113
Diabetes[n(%)]	221(15.6%)	127(14.1%)	94(18.1%)	0.042
NYHA>II [n(%)]	872(61.4%)	504(55.9%)	368(71.0%)	< 0.001
Echocardiographic data:				
LVEF(%)	61.3±8.8	61.7±8.5	60.4±9.2	0.077
LAD(mm)	43.2±8.2	42.8±8.5	43.8±7.7	0.240
LVEDD(mm)	48.6±7.5	48.7±6.9	48.5±8.3	0.860
LVESD(mm)	34.6±8.0	35.3±8.1	33.4±7.8	0.424
LVST (mm)	10.6±2.4	10.3±2.1	11.2±2.7	0.003
RAD enlargement (%)		24(2.7%)	18(3.5%)	0.383
PAP (mmHg)	33.6±7.2	33.2±7.0	34.0±7.6	0.296
Urea nitrogen (mmol/L)	$6.0{\pm}2.0$	5.7±1.9	6.4±2.1	< 0.001
Scr (µmol/L)	80.8±22.4	78.7±20.1	84.5±25.5	< 0.001
Uric acid(µmol/L)	356.6±22.4	345.9±106.4	375.2±107.2	< 0.001
Hyperuricemia [n(%)]	439(30.9%)	245(27.2%)	194(37.5%)	< 0.001
eGFR [ml/(min/1.73m <sup>2</sup> )]	86.4±20.7	87.9±20.1	83.8±21.3	< 0.001
eGFR<60ml/(min/1.73m <sup>2</sup> ) [n(%	b)] 117(8.2%)	56(6.2%)	61(11.8%)	< 0.001
Cholesterol (mmol/l)	4.0±0.9	4.0±0.9	4.0±0.9	0.675
Triglyceride (mmol/l)	$1.3{\pm}0.8$	$1.3 \pm 0.8$	$1.4{\pm}0.9$	0.129
LDL-c(mmol/l)	$2.3 \pm 0.8$	2.3±0.8	$2.3 \pm 0.8$	0.348
HDL-c(mmol/l)	1.1±0.3	1.2±0.3	1.1±0.3	0.042
Hyperlipidemia [n(%)]	292(20.6%)	173(19.2%)	119(23.0%)	0.089
Blood glucose(mmol/L)	5.3±1.6	5.2±1.5	5.4±1.8	0.059
Coronary angiography[n(%)]	691(48.7%)	418(46.3%)	273(52.7%)	0.021
Intraoperative				
Type of operation [n(%)]				
- valve	822(57.9%)	519(57.6%)	303(58.5%)	
-CABG	250(17.6%)	184(20.4%)	66(12.7%)	
- Aorta or great vessels	95(.6.7%)	64(7.1%)	31(6.0%)	
- Combined surgery	46(3.2%)	28(3.1%)	18(3.5%)	
- others	207(14.6%)	107(11.9.%)	100(19.3%)	
High-risk operation [n(%)]	422(29.7%)	158(17.5%)	264(51.0%)	

Table S1.	Baseline	characteristics	of	patients	with	and	without A	ΚI
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CPB time (min)	99.1±52.6	91.7±56.7	111.0±42.9	< 0.001
Aortic occlusion time (min)	59.7±35	54.4±26.7	$68.5 \pm 45.0$	< 0.001
Postoperative				
Medications (%)				
diuretic	1344(94.6%)	841(93.2%)	503(97.1%)	0.002
inotropic agents	1264(89.0%)	797(88.4%)	467(90.2%)	0.297
vasoactive agents	1289(90.8%)	806(89.4%)	483(93.2%)	0.015
IABP (%)	25(1.8%)	11(1.2%)	14(2.7%)	0.040
ECMO support, n (%)	7(0.7%)	2(0.2%)	5(1.0%)	0.055
24h Fluid balance (%)	0.5 [-0.6, 1.8]	0.3 [-0.8, 1.3]	1.2 [-0.1, 2.5]	< 0.001
Nephrotoxic drugs (%)	141(9.9%)	36(4.0%)	105(20.3%)	< 0.001
LCOS (%)	178(12.5%)	76(8.4%)	102(19.7%)	< 0.001
Length of hospital stay (d)	13.5±7.1	12.5±4.7	15.3±14.4	< 0.001
Length of ICU stay (h)	26[19,66]	24[18,48]	42[21,87]	< 0.001
Poor short-term outcomes [n(%)]	19(0.1%)	2(0.2%)	17(3.3%)	< 0.001

Note: BMI: Body mass index; NYHA: New York Heart Association classification; LVEF: Left ventricular ejection fraction; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; IVST: interventricular septum thickness; RAD: right atrial diameter; PAP: pulmonary arterial pressure; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; LCOS: low cardiac output syndrome; SCr : Serum creatinine; eGFR: Estimation of glomerular filtration rate; LDL-c: Low-density lipoprotein -c; HDL-c: High-density lipoprotein–c ; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; ICU: Intensive care unit

	normal uric acid group (n=981)	hyperuricemia group (n=439)	Р
AKI [n(%)]	324(33%)	194(44.2%)	<0.001
Sever AKI [n(%)]	61(6.2%)	47(10.7%)	0.001
RRT treatment [n(%)]	14(1.4%)	14(3.2%)	0.027
Length of hospital stay (d)	13.3±10.6	14.0±6.5	0.220
Length of ICU stay (h)	30[21, 67]	43[22, 76]	< 0.001
Poor short-term prognosis [n(%)]	11(1.1%)	8(1.8%)	0.288

Table S2. Comparison of AKI incidence and short-term outcomes in hyperuricemia and normal uric acid group

AKI: Acute kidney injury; RRT: Renal replacement therapy; ICU: Intensive care unit