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ORIGINAL ARTICLE

Uric acid and acute kidney injury in high-risk patients for developing acute kidney injury undergoing cardiac surgery: A prospective multicenter study

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KEYWORDS
Acute kidney injury;
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Uric acid

Abstract
Purpose: It is unclear whether preoperative serum uric acid (SUA) elevation may play a role in the development of acute kidney injury (AKI) associated with cardiac surgery (CSA-AKI). We conducted a cohort study to evaluate the influence of preoperative hyperuricemia on AKI in patients at high risk for developing SC-AKI.
Design: Multicenter prospective international cohort study.
Setting: Fourteen university hospitals in Spain and the United Kingdom.
Participants: We studied 261 consecutive patients at high risk of developing CSA-AKI, according to a Cleveland score $\geq$ 4 points, from July to December 2017.
Interventions: None.
Measurements and main results: AKIN criteria were used for the definition of AKI. Multivariable logistic regression models and propensity score-matched pairwise analysis were used to determine the adjusted association between preoperative hyperuricemia ($\geq$7 mg/dL) and AKI. Elevated preoperative AUS ($\geq$7 mg/dL) was present in 190 patients (72.8%), whereas CSA-AKI occurred in 145 patients (55.5%). In multivariable logistic regression models, hyperuricemia was not associated with a significantly increased risk of AKI (adjusted Odds Ratio [OR]: 1.58; 95% confidence interval [CI]: 0.81–3; P = .17). In propensity score-matched analysis of 140 patients, the hyperuricemia group experienced similar adjusted odds of AKI (OR 1.05, 95%CI 0.93–1.19, P = .37).
Conclusions: Hyperuricemia was not associated with an increased risk of AKI in this cohort of patients undergoing cardiac surgery at high risk of developing CSA-AKI.

PALABRAS CLAVE
Daño renal aguda;
Cirugía cardiaca;
Pacientes de alto riesgo;
Hiperuricemia;
Factores de riesgo;
Ácido úrico

Ácido úrico y daño renal agudo en pacientes con alto riesgo de desarrollar daño renal agudo sometidos a cirugía cardiaca: cohorte prospectiva multicéntrica

Resumen
Objetivo: No está claro si la elevación de ácido úrico sérico (AUS) preoperatorio puede desempeñar un papel en el desarrollo de daño renal agudo (DRA) asociado a cirugía cardiaca (DRA-CS). Se realizó un estudio de cohortes para evaluar la influencia de la hiperuricemia en el DRA en pacientes de alto riesgo para desarrollar DRA-CS.
Diseño: Estudio de cohortes prospectivo multicéntrico.
Entorno: Catorce hospitales universitarios en España y en Reino Unido.
Participantes: Se estudiaron a 261 pacientes consecutivos con alto riesgo de desarrollar DRA-CS, según una puntuación de Cleveland $\geq$ 4 puntos, de julio a diciembre de 2017.
Intervenciones: Ninguna.
Mediciones y resultados principales: Se utilizaron los criterios AKIN para la definición de DRA. Para determinar la asociación ajustada entre hiperuricemia ($\geq$7 mg/dL) e DRA se utilizaron modelos de regresión logística multivariable y análisis de pares emparejados por puntuaje de propensión.

El AUS preoperatorio elevado (≥7 mg/dL) estaba presente en 190 pacientes (72,8%), mientras que la DRA-CS se produjo en 145 pacientes (55,5%). En los modelos de regresión logística multivariable, la hiperuricemia no se asoció con un aumento significativo del riesgo de DRA (Odds Ratio [OR] ajustado: 1,58; intervalo de confianza [IC] 95%: 0,81–3; *P* = ,17). En el análisis de emparejamiento por puntaje de propensión de 140 pacientes, el grupo de hiperuricemia experimentó probabilidades ajustadas similares de DRA (OR 1,05; IC 95%: 0,93–1,19; *P* = ,37).
Conclusiones: La hiperuricemia no se asoció con un mayor riesgo de DRA en esta cohorte de pacientes con alto riesgo de desarrollar DRA-CS.

Introduction

Acute kidney injury (AKI) is a common complication after cardiac surgery, and is associated with worse clinical outcomes and short- and long-term survival, and high care costs.[1–3] Cardiac surgery-associated AKI is a major health problem, given the large number of cardiac surgeries performed annually worldwide (more than one million interventions).[4] Predictive models that estimate the patient's risk of AKI may be useful for optimizing perioperative care and preventing AKI.

There is increasing epidemiological and clinical evidence that hyperuricemia, even at low concentrations that do not cause intratubular precipitation of crystals, may play a role in the pathogenesis of AKI.[5] Serum uric acid (SUA) may be involved in many of the proposed mechanisms underlying AKI, such as renal vasoconstriction,[6] inflammation, antiangiogenesis, and impaired autoregulation,[7] and it plays an important role in both the adaptive and innate immune response.[8,9]

In a recent study evaluating the association between elevated preoperative SUA and postoperative AKI in a cohort of patients undergoing cardiac surgery,[10] the authors found that preoperative hyperuricemia was associated with postoperative AKI in patients undergoing coronary artery bypass surgery.

In our study, we aimed to determine the association between preoperative hyperuricemia and AKI in patients at high risk (Cleveland score ≥ 4) of cardiac surgery-associated acute kidney injury.

Methods

Study design

This multicentre prospective cohort study in 14 Spanish and British hospitals included all consecutive patients aged 18 years or older with a Cleveland score ≥ 4 that underwent cardiac surgery between July and December 2017 (Fig. 1). The Cleveland score is a validated scale for identifying patients at risk for severe AKI after cardiac surgery.[11] All cardiac surgery procedures (including major aortic surgery requiring cardiopulmonary bypass [CPB]) were included, except pericardiectomy and heart transplantation. Patients with severe preoperative kidney failure (defined as need for dialysis or estimated glomerular filtration rate [eGFR] < 15 ml/min/1.73 m^2) and pregnant women were excluded.

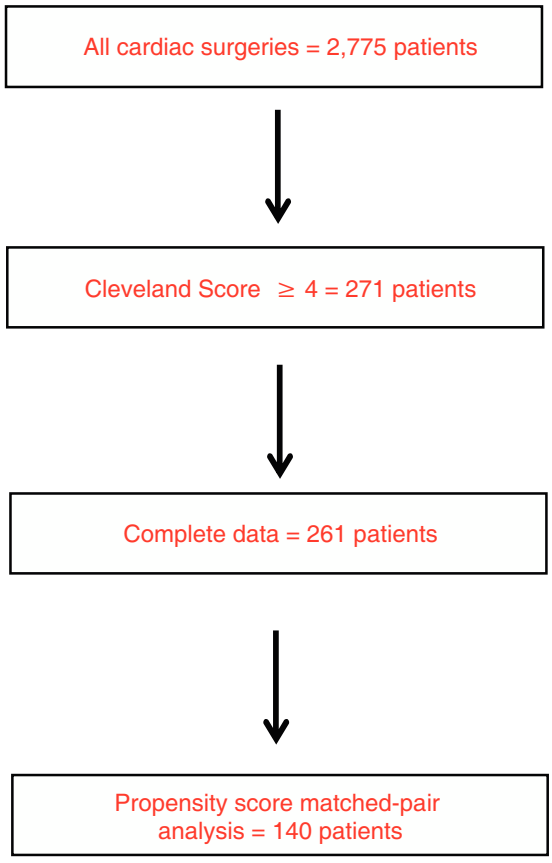

Figure 1 Study flowchart.

This study was approved by the Ethics Committees of each local institution and complied with the Declaration of Helsinki. All patients or a surrogate with perioperative decision-making capacity signed the informed consent form.

Exposure of interest

The cohort was divided into 2 groups, patients with preoperative SUA ≥ 7 mg/dL (n = 190) and those with SUA < 7 mg/dL (n = 71). SUA was measured in all patients, on the same

day, before surgery. Since uric acid has an oxidising affect at serum concentrations of ≥5.5 mg/dL,[12] a categorical instead of a continuous variable was used. The threshold of ≥7 mg/dL was based on previous studies.[12,13]

Primary dependent variable

The primary dependent variable was AKI defined according to AKIN criteria (stages I, II or III).[14] To apply these criteria, creatinine was measured at 6, 12, 24 and 48 h postoperatively.

Statistical analysis

STATA Version 13.0 (Stata-Corp. 2013. Release 13. College Station, TX: Stata Corp LP) was used for all statistical analyses. A 2-tailed *P* value of less than .05 defined statistical significance.

Descriptive statistics were initially used to stratify patients according to their preoperative SUA levels (i.e., SUA ≥ 7 vs. SUA < 7) and the development of postoperative AKI (AKI vs. no AKI). Categorical variables were described as percentages and continuous variables as mean with standard deviation or median with interquartile range. We used the Shapiro-Wilk test to test the variables for normal distribution.

We then used a multivariate logistic regression model to estimate the adjusted correlation between hyperuricemia and the postoperative outcomes of interest.

The covariates included were demographic data (age, sex), body surface area, reintervention, baseline eGFR, New York Heart Association (NYHA) class, comorbidities (diabetes mellitus, chronic obstructive pulmonary disease [COPD], heart failure [CHF], and chronic kidney disease), left ventricular ejection fraction (LVEF), baseline Cleveland Score, and cardiopulmonary bypass (CPB) time.

All the results are expressed as odds ratio (OR) and 95% confidence interval (CI). The performance of these regression models was evaluated using several different approaches: (a) discrimination was evaluated using the c statistic, (b) internal validation was evaluated using bootstrapping with 1000 replications, (c) the amount of multicollinearity was evaluated using the variance inflation factor, and (d) sensitivity was evaluated by repeating regression analyses after excluding covariates that could exist in the causal pathway between hyperuricemia and AKI.

We also used propensity score matching (70 matched pairs) to compare outcomes in patients with and without hyperuricemia. The propensity score was estimated using Stata's pscore package, which uses a probit regression model with hyperuricemia as the independent variable. The clinically important predictor variables included in the probit model were demographics (age, sex), body surface area, reintervention, baseline eGFR, NYHA class, comorbidities (diabetes mellitus, COPD, CHF, chronic kidney disease), LVEF, baseline Cleveland Score, CPB time, and aortic cross-clamping time.

We also performed 1:1 nearest neighbour matching using Stata's teffects psmatch algorithm based on the estimated propensity score. The mean treatment effects among treated individuals were calculated using the Stata teffects package. All the results were expressed as odds ratio (OR) and 95% confidence interval (CI).

The sample size was determined by the number of eligible patients who underwent surgery during the time period of interest. As recommended, we did not perform a post-hoc power calculation because it would be methodologically inappropriate; instead, the estimated 95% confidence intervals were used to help interpret the results of the analysis.[15]

Results

Descriptive data

Our cohort included 261 consecutive cardiac surgery patients with a Cleveland score ≥ 4, which indicates a high risk of cardiac surgery associated acute kidney injury. A total of 190 (72.8%) patients in our cohort presented preoperative hyperuricemia (≥7 mg/dL); 145 (55.5%) developed postoperative AKI; and 41 (15.7%) died in hospital. Patients in the hyperuricemia group had a greater comorbidity burden (e.g., greater weight, lower eGFR, higher preoperative creatinine, and slightly higher Hb A1C) (Table 1). No differences were observed between groups in terms of intraoperative characteristics and postoperative complications, except for a lower percentage of patients using dobutamine and use of higher doses of tranexamic acid in the hyperuricemia group (Table 2).

Results

Univariate logistic regression models

No statistically significant differences were observed between groups in terms of the unadjusted odds of developing AKI (OR 1.05; 95% CI: 0.6–1.8; *P* = .86).

Propensity score matched-pair analysis

Propensity score matched-pair analysis showed that the preoperative and intraoperative characteristics of both groups were similar (Table 3).

Primary dependent variable: postoperative AKI. In the propensity score-matched-pairs analysis, there were no significant differences between sub-groups with elevated SUA levels vs normal SUA levels with respect to the odds of developing AKI (OR 1.05; 95% CI: 0.93–1.19; *P* = ,37) (Table 4).

Multivariate logistic regression models

Primary dependent variable: postoperative AKI. After risk adjustment based on the multivariate logistic regression model, preoperative hyperuricaemia (≥7 mg/dL) was not associated with a significantly increased risk of AKI (adjusted OR 1.58; 95% CI: 0,81–3; *P* = ,17) (Table 4) in our cohort of high-risk patients. The internal ''bootstrap'' validation showed that the regression model was stable, with no significant multicollinearity and good discrimination (c-statistic 0.74). To evaluate sensitivity, a risk-adjusted analysis was performed using a multivariate logistic regression model that included the covariates intraoperative dobutamine use and tranexamic acid dose. No differences were observed in our primary outcome of AKI - OR 1.72, (95% CI 0.84–3.5); *P* = .13 (Table 4).

Table 1 Baseline characteristics.

	SUA < 7 (n = 71)	SUA ≥ 7 (n = 190)	*P*-value
Age (median [IQR]) years	67 [64–77]	71 [65–78]	.93
Women, n (%)	33 (46.4%)	67 (35.2%)	.09
Weight (median [IQR]) kg	74 [64–82]	75 [65–85]	.30
Height (mean ± SD) cm	163 ± 9	164 ± 9.2	.49
Body surface area (mean ± SD) m^2	1.79 ± 0.17	1.80 ± 0.18	.71
Degree of surgical urgency			.15
Scheduled surgery, n (%)	54 (76%)	118 (62.1%)	
Urgent surgery, n (%)	12 (16.9%)	41 (21.5%)	
Emergency surgery, n (%)	5 (7%)	29 (15.2%)	
Previous cardiac surgery, n (%)	17 (23.9%)	36 (18.9%)	.39
Preoperative Hb (mean ± SD) mg/dL	12 ± 2	12.1 ± 2	.72
Preoperative creatinine (median [IQR]) mg/dL	1.38 [0.9–1.6]	1.41 [1.24–1.86]	.05
eGFR, (median [IQR]) ml/min	45 [35–67]	42 [30–55]	,049
CKD stage III–V, n (%)	47 (68.7%)	127 (66.8%)	.08
Recent MI < 90 days, n (%)	5 (7%)	31 (16.3%)	.06
NYHA III–IV, n (%)	50 (70%)	124 (65.2%)	.6
Preoperative IABP, n (%)	5 (7%)	13 (6.8%)	1
Congestive heart failure, n (%)	42 (59.1%)	101 (53.1%)	.38
LVEF (median[IQR]) %	55 [40–64]	55 [45–64]	.90
LVEF < 35%, n (%)	11 (15.5%)	17 (9%)	.17
Preoperative statins, n (%)	51 (71.8%)	130 (70.2%)	.80
ACE inhibitor/ARA-2, n (%)	35 (49.3%)	104 (55.3%)	.38
Diabetes, n (%)	34 (47.9%)	83 (43.6%)	.50
Glycated Hb, (median[IQR]) %	5.9 [5.2–7.1]	6.2 [5.8–7.1]	.08
HBP, n (%)	56 (79%)	158 (83%)	.47
COPD, n (%)	19 (26.7%)	58 (30.5%)	.55
Peripheral artery disease, n (%)	9 (12.6%)	27 (14.2%)	.84
Cleveland Score, (median [IQR])	5 [5–6]	5 [5.5–7]	.45
Intraoperative urine output (median [IQR]) ml/kg/h	1.2 [1–2]	1.2 [0.8–2.3]	.76
Use of dobutamine, n (%)	41 (57%)	79 (41.5%)	.02
Use of norepinephrine, n (%)	43 (60%)	135 (71%)	.10
Use of noradrenaline > 0.2 mcg/kg/min, n (%)	25 (35%)	62 (32%)	.35

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, estimated glomerular filtration rate; Hb, haemoglobin; HBP, high blood pressure; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; UCI, Intensive care unit; SUA, serum uric acid.

Discussion

Several epidemiological studies have suggested that hyperuricemia is associated with hypertension, cardiovascular diseases, diabetes mellitus, and the progression of chronic kidney disease.[16–18] Hyperuricemia has also been associated with AKI in different clinical scenarios.[19,20] In recent years, several studies have been performed to determine whether hyperuricemia is an independent risk factor for increasing the incidence and/or worsening the prognosis of AKI in the general population. One such study is the meta-analysis published by Xu et al.,[12] in which the authors observed a significant difference in the incidence of AKI between patients with and without hyperuricemia. The causal correlation between hyperuricemia and AKI in the general population widely debated. Two large randomized clinical trials have recently shown that treating hyperuricemia with allopurinol does not modify disease progression in patients with early to moderate diabetic kidney disease.[21,22] This suggests that hyperuricemia is associated with an increase in comorbidities but is not independently correlated with progression of chronic kidney disease (CKD).

Patients undergoing cardiac surgery present high levels of uric acid due to the coexistence of CHF,[23] chronic kidney disease,[24,25] ischaemia-reperfusion injury, and diuretic therapy. After cardiac surgery, uric acid levels may increase further in the immediate postoperative period in response to tissue ischaemia or kidney injury.[26] In this respect, elevated SUA levels could reflect the presence of oxidative stress, tissue ischaemia, or renal vasoconstriction.[27]

These results are consistent with those reported in other studies evaluating the effect of hyperuricemia on kidney function in the cardiac surgery population.[10,13,28–30]

Data from a retrospective cohort study in 2185 patients[10] showed that hyperuricemia was associated with an increased rate of AKI. However, in this study the patient population included patients at lower risk of developing AKI, important clinical variables such as CHF, reintervention, and LVEF were not included in the logistic regression model, and the authors did not use propensity score matching to confirm the accuracy of the multivariate regression

Table 2 Intraoperative characteristics and postoperative complications.

	SUA < 7 (n = 71) (n = 71)	SUA ≥ 7 (n = 190)	*P* value
Aortic clamping time (median [IQR]) min	91 [63–116]	91 [65–128]	.49
CPB time (median [IQR]) min	120 [91–162]	124 [90–170]	.65
Type of surgery			.84
Cardiac, n (%)	6 (8.4%)	22 (11.6%)	
Heart valve, n (%)	22 (31%)	50 (26.4%)	
Combined/aorta/others, n (%)	43 (61%)	117 (62%)	
Crystalloid volume, (median[IQR]) ml	1.000 [1.500–2.000]	1.000 [1.500–2.000]	.3
Nadir Hb, (median ± SD), mg/dL	8 ± 1.4	7.9 ± 1.3	.54
Intraoperative urine output (median [IQR]) ml/kg/h	1.2 [1–2]	1.2 [0.8–2.3]	.76
Use of dobutamine, n (%)	41 (57%)	79 (41.5%)	.02
Use of norepinephrine, n (%)	43 (60%)	135 (71%)	.10
Use of noradrenaline > 0.2 mcg/kg/min, n (%)	25 (35%)	62 (32%)	.35
Intraoperative blood transfusion, (median [IQR]) units	1 [0–3]	1.5 [0–3]	.75
Intraoperative blood transfusion, n (%)	41 (57.7%)	117 (65.3%)	.26
Use of tranexamic acid, n (%)	66 (92.9%)	172 (91%)	.63
Tranexamic acid dose, (median [IQR]) mg/kg	24 [15–33]	30 [20–42]	,005
Preoperative IABP, n (%)	7 (9.9%)	23 (12.1%)	.82
LCOS, n (%)	7 (9.9%)	31 (16.3%)	.23
Reintervention within 48 h, n (%)	3 (4.2%)	18 (9.5%)	.20
Intraoperative or postoperative stroke, n (%)	4 (5.7%)	12 (6.3%)	1
New atrial fibrillation, n (%)	21 (29.6%)	48 (25.3%)	.52
Preoperative MI, n (%)	3 (4.2%)	15 (7.9%)	.41
Acute kidney injury	41 (57.7%)	112 (58.9%)	.07
Stage 1, n (%)	22 (31%)	49 (25.8%)	
Stage 2, n (%)	12 (16.9%)	20 (10.5%)	
Stage 3, n (%)	7 (9.8%)	43 (22.6%)	

CPB, cardiopulmonary bypass; Hb, haemoglobin; IABP, intra-aortic balloon pump; LCOS, low cardiac output syndrome; MI, Acute myocardial infarction; UCI, Intensive care unit; SUA, serum uric acid.

Table 3 Characteristics after propensity score matching.

Initial characteristics	SUA ≥ 7 (n = 70)	SUA < 7 (n = 70)	*P* value
Age, mean years	68	71	.06
Women	36	41	.33
Body surface area, mean m^2	1.85	1.81	.07
Estimated GFR, mean ml/min	50	45	.08
MYHA, mean	2.7	2.9	.08
Congestive heart failure, %.	55	65	.13
Mean Cleveland score	5.7	5.9	.08
Chronic kidney disease, %.	49	54	.15
Reintervention, %	24	20	.48
Baseline LVEF, mean %.	52	51.5	.82
Diabetes	62	68	.12
COPD, %	39	32	.13
Intraoperative characteristics			
Aortic clamping, mean min	90	95	.44
CPB time, mean min	121	132	.26

COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SUA, serum uric acid.

analysis. Furthermore, the discrimination capacity of the model measured by the c statistic did not improve significantly when uric acid was included in the multivariate model.

Ahsan-Ejaz et al.[28] suggested that uric acid could be a new risk factor for AKI in patients undergoing certain cardiac surgeries, such as thoracic aneurysm repair and aortic or mitral valve surgery. However, these authors performed a

Table 4 Risk-adjusted differences for the primary dependent variable.

Results	SUA < 7 vs SUA ≥ 7 Risk-adjusted OR (95% CI)	*P* value
Acute kidney injury	Multivariate logistic regression model*: OR 1.58 (0.81–3)	*P* = .17
	Multivariate logistic regression model**: OR 1.72 (0.84–3.5)	*P* = .13
	Propensity score matching: OR 1.05 (0.93–1.19)	*P* = .37

SUA, serum uric acid.

* Adjusted for the following covariates: age, sex, body surface area, reintervention, baseline eGFR, New York Heart Association, diabetes mellitus, chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease, left ventricular ejection fraction, baseline Cleveland Score, and CPB time.

** Adjusted for the following covariates: age, sex, body surface area, reintervention, baseline eGFR, New York Heart Association, diabetes mellitus, chronic obstructive pulmonary disease, heart failure, chronic kidney disease, left ventricular ejection fraction, baseline Cleveland Score, time of CPB, use of dobutamine, and tranexamic acid dose.

cohort study with a small sample of 58 patients and only 18 cases of AKI.

Another retrospective observational study in 190 patients observed that a J-shaped relationship appears to exist between preoperative SUA levels and AKI.[13] However, this cohort included very low-risk patients, and 87% of patients with AKI were AKIN grade I. Furthermore, the results were not confirmed by a propensity score matched-pairs analysis.

Data from a recent large observational retrospective study of 1420 patients showed that patients with higher uric acid levels had a higher incidence of AKI.[29] However, the cohort included different patient populations, with patients at lower risk of developing AKI. Furthermore, important clinical variables such as CHF, reintervention, and LVEF were not included in the logistic regression model, hyperuricemia was not associated with severe AKI, and the authors did not use propensity score matching to confirm the results of the multivariate regression analysis.

Data from a retrospective cohort study in 1019 patients showed that hyperuricemia (≥6.5 mg/dL) was associated with AKI.[30] However, important clinical variables, such as CHF, reintervention, diabetes mellitus, type of surgery, emergency surgery, COPD, and peripheral artery disease were not included in the logistic regression model. Furthermore, the c statistic showed that discrimination did not improve significantly when uric acid was included in the multivariate model (AUROC 0.780 vs 0.783 vs 0.782), and the authors did not use propensity score matching to confirm the results of the multivariate regression analysis.

Unlike most of the foregoing studies, our multicentre cohort study of 261 consecutive patients at high risk of cardiac surgery-associated AKI showed that preoperative hyperuricemia (≥7 g/dL) compared to uric acid < 7 g/dL was not associated with a significantly higher risk of postoperative AKI.

Our study has some limitations. First, there were significant baseline differences between the hyperuricemia and non-hyperuricemia groups. To compensate for these differences, we used 2 different methods - regression models and propensity score matching - to analyse our data. Second, we cannot exclude the possibility of unmeasured confounding, as is the case in most observational studies. Third, the 95% CIs of our adjusted estimates were wide. Therefore, although the point estimate is reassuring, more studies are needed to confirm the impact of hyperuricemia on kidney function in high-risk patients undergoing surgery. Fourth, we used the AKIN criteria for AKI (acute changes in serum creatinine within 48 h), but this may be too short compared to the 7-day changes included in the KDIGO definition. Finally, data on the number of patients in our cohort that were receiving treatment for hyperuricemia were unavailable.

The strengths of this study include its pragmatic, real-world, high-risk cardiac surgery population recruited from 14 hospitals, and our use of different risk-adjustment methods (propensity score matching and multivariate regression models).

Conclusion

Preoperative hyperuricemia in high-risk patients was not associated with an increased risk of AKI after cardiac surgery in this multicentre prospective cohort study.

Key points

- The association between preoperative hyperuricemia and cardiac surgery-associated acute kidney injury is controversial.
- After performing an adjusted analysis using multivariate logistic regression and propensity score matching, no association was observed between preoperative hyperuricemia and acute kidney injury in our cohort.

Declaration of authorship

All authors have participated in the following: (1) Study conception and design, or data acquisition, or data curation, (2) writing (original draft) or review and editing for important intellectual content, (3) approval of final version, and 4) all authors agree to be accountable for all aspects of the work, such that questions related to its accuracy or integrity are appropriately investigated and resolved.

Declarations of interest

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