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The preoperative plasma histamine level as a possible protective biomarker for postoperative acute kidney injury

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Abstract

Acute kidney injury (AKI) is a life-threatening complication of acute type A aortic dissection (ATAAD) patients. Increasing evidence suggests that histamine ameliorates the pathology of renal injury. However, data on the association between histamine levels and postoperative AKI in ATAAD patients are limited. The purpose of our study was to explore the incidence and independent risk factors of postoperative AKI, with special emphasis on the relationship between preoperative plasma histamine levels and the severity of postoperative ATAAD-AKI. This retrospective single-center study evaluated 160 patients with ATAAD admitted to the Beijing Anzhen Hospital aortic surgery database between April 2020 and December 2021. Univariate and multivariate logistic regression analyses were performed to determine the potential risk factors for postoperative ATAAD-AKI. A subgroup analysis was performed to investigate the association between preoperative plasma histamine levels and the severity of postoperative ATAAD-AKI or continuous renal replacement therapy (CRRT). ATAAD-AKI occurred in 84 of 160 patients (52.5%), including 32 with stage 1 (38.1%), 14 with stage 2 (16.7%), 38 with stage 3 (45.2%), and 34 (21.3%) received postoperative CRRT. The in-hospital mortality rate was 19.0% (16/84) in the AKI group and 2.6% (2/76) in the non-AKI group (P = .02). Preoperative lower plasma histamine levels (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.10–1.52; P = .004) were an important factor related to postoperative ATAAD-AKI in multivariate logistic regression analysis. Subgroup analysis revealed that low preoperative plasma histamine level was independently associated with postoperative ATAAD-AKI (stage 3) (OR, 1.38; 95% CI, 1.10–1.73; P = .005) and CRRT (OR, 1.44; 95% CI, 1.13–1.79; P = .008). Low preoperative plasma histamine level was an independent prognostic indicator of postoperative AKI in patients with ATAAD, especially for postoperative AKI (stage 3) and CRRT. Preoperative plasma histamine levels may serve as potential protective biomarkers of postoperative ATAAD-AKI.

Abbreviations: AKI = acute kidney injury, ATAAD = acute type A aortic dissection, AUC = area under the curve, BMI = body mass index, CI = confidence interval, CPB = cardiopulmonary bypass, CRRT = continuous renal replacement therapy, eGFR = estimated glomerular filtration rate, ELISA = enzyme-linked immunosorbent assay, FET = frozen elephant trunk, HCA = hypothermic circulatory arrest, ICU = intensive care unit, KDIGO = Kidney Disease: Improving Global Outcomes, OR = odds ratio, ROC = receiver operating characteristic, sCr = serum creatinine, TAR = total arch replacement.

Keywords: acute kidney injury (AKI), acute type A aortic dissection (ATAAD), body mass index (BMI), continuous renal replacement therapy (CRRT), histamine

1. Introduction

Acute type A aortic dissection (ATAAD) is one of the most challenging medical emergencies associated with high mortality and morbidity.[1,2] Although improvements in surgical techniques and perioperative management have evolved over the last few decades, acute kidney injury (AKI) after total arch replacement (TAR) combined with a frozen elephant trunk (FET) implant in patients with ATAAD still results in a low survival rate and poor prognosis.[3,4] Compared with other cardiovascular surgeries,

XLG and LL contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study complied with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Anzhen Hospital (Institutional Review Board File No. 2018004), and all experimental procedures were performed in accordance with relevant guidelines and regulations.

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the incidence of ATAAD-AKI and continuous renal replacement therapy (CRRT) is relatively higher.[5–7] Thus, there is an urgent need to explore simple and readily available biomarkers to identify high-risk patients and assess the prognosis of patients with ATAAD.

Notably, inflammatory responses play a key role in the occurrence and development of AKI.[8,9] In the past several years, we have investigated inflammatory factors and vital organ protection in patients with ATAAD. However, plasma histamine level, as the key component of the inflammatory system is very likely to possess a prospective predictive and protective ability against AKI.[10,11] As mentioned above, we aimed to examine the incidence and risk factors of AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria among patients with ATAAD after emergency aortic surgery, with a special emphasis on the relationship between preoperative histamine levels and different stages of ATAAD-AKI or CRRT.

2. Methods

This was a single-center retrospective study conducted at Beijing Anzhen Hospital, Capital Medical University, China. The acute aortic syndrome cooperation network (AASCN) database contains >2500 data of patients with aortic syndrome and >11000 specimens at 10 cardiovascular surgery centers in China. This database was dominated by Beijing Anzhen Hospital, Capital Medical University, and was approved by the hospital ethics committee in April 2018 (No. 2018004). The Chinese Clinical Trial Registry number is ChiCTR1900022637. The requirement for informed consent was waived because this was a retrospective study used clinical data. This study was performed in accordance with the Declaration of Helsinki (revised in 2013).

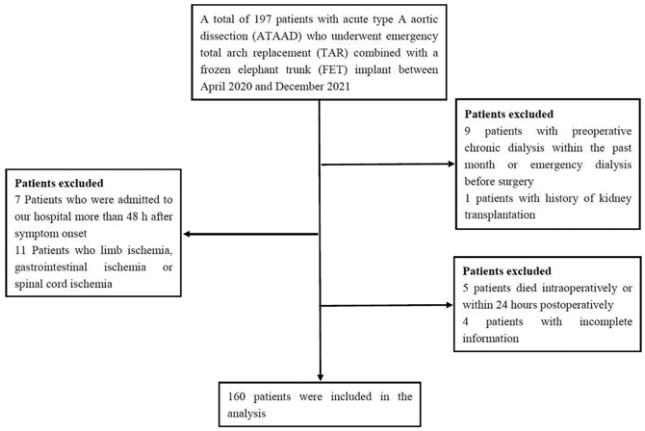

Figure 1. Flowchart of the study cohort.

3. Patient population

We included all patients with ATAAD from the AASCN database who underwent emergency TAR combined with FET implantation and cardiopulmonary bypass (CPB) between April 2020 and December 2022. Patients with ATAAD were excluded if they met the exclusion criteria (Fig 1). Ultimately, 160 patients diagnosed with ATAAD according to the Stanford classification were selected from the AASCN database for further analysis at the Institute of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, China. Patient data, including patient characteristics, perioperative outcomes, and postoperative mortality or complications, were obtained from the electronic medical records system of our medical center.

3.1. Measurements and variable definitions

Postoperative AKI was defined according to the updated KDIGO criteria. In line with the KDIGO criteria, the patients were subsequently categorized into 2 groups: AKI group (n = 84) and non-AKI group (n = 76) (Table 1). We did not consider urine output criteria for defining AKI because of its inaccuracy in our study. The decision to implement CRRT was based on the physician's judgment of the severity of AKI in the intensive care unit (ICU). Blood specimens from the AASCN database were assayed using monoclonal antibody-mediated sandwich enzyme-linked immunosorbent assay (ELISA). All ELISA were performed in duplicate, and the mean values were used for analysis. The preoperative serum creatinine (sCr) value was defined as the first sCr level available at the emergency department or the lowest sCr level in 2 days in other hospitals. ATAAD was diagnosed using enhanced computed tomography based on the Stanford classification. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Regardless of whether the renal function was normal, renal malperfusion was defined based on imaging evidence using the Penn classification.

3.2. Surgical procedures

Standard median sternotomy was performed under general anesthetic management. After systemic heparinization, CPB was routinely established through the right axillary artery, innominate artery, femoral artery, and right atrium cannulation drainage. Emergency aortic surgery with TAR using a tetra-furcate vascular graft in combination with FET implantation into the descending aorta was performed under moderate hypothermic circulatory arrest (HCA). The patients were cooled to a nasopharyngeal temperature of approximately 26°C to 28°C. The right axillary artery or innominate artery was used for selective antegrade cerebral perfusion [5–15 mL/(kg·min)] during HCA. Proximal aortic root operations, such as aortic valve replacement or ascending aorta replacement, were performed based on lesions of the aortic root during the cooling period. The

Table 1

Kidney disease: Improving global outcomes stages of acute kidney injury according to serum creatinine levels and urine output.

Stage	sCr	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dL (≥26.5 mmol/L) increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	>3.0 times baseline or increase in sCr to ≥4.0 mg/dL (≥353.6 mmol/L) or initiation of RRT or in patients <18 yr, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

eGFR = estimated glomerular filtration rate, RRT = renal replacement therapy, sCr = serum creatinine.

sequence of aortic arch reconstruction was as follows: proximal descending aorta, left carotid artery, ascending aorta, left subclavian artery, and innominate artery. After distal aortic reconstruction was completed, the CPB was restarted and gradually rewarmed. Concomitant cardiac procedures were performed, if necessary. After completion of the repair and adequate rewarming, the patient was weaned from CBP. All the patients were admitted to ICU for routine postoperative monitoring.

3.3. Statistical analysis

The normality of the data distribution was tested using the Kolmogorov–Smirnov test. Continuous variables are expressed as mean ± standard deviation or median (25th and 75th percentiles), and categorical variables are expressed as n (%). Differences between the 2 groups were analyzed using independent sample *t* tests or Wilcoxon rank sum tests for continuous variables and the chi-squared test or Fisher exact test for categorical variables. Univariate logistic regression analysis was used to compare the baseline characteristics between the 2 groups. The multivariate logistic regression model included variables that were considered significant ($P < .05$) in the univariate analysis to identify possible risk factors for different stages of ATAAD-AKI and CRRT. In addition, a receiver operating characteristic (ROC) curve was used to further evaluate the predictive ability of the risk factors for ATAAD-AKI and CRRT. For all analyses, a 2-tailed value of $P < .05$ was considered statistically significant.

4. Results

4.1. Incidence of postoperative ATAAD-AKI

According to the KDIGO criteria, the incidence of postoperative ATAAD-AKI in our patient population was 52.5% (84/160), including 32 stage 1 (38.1%), 14 stage 2 (16.7%), and 38 stage 3 (45.2%) patients. Postoperative CRRT was required in 34 (21.3%) patients. The mean age of the patients with AKI was 46.7 ± 11.2 years, and the data comprised 60 men (71.4%) and 24 women (28.6%) in the AKI group. Most patients with ATAAD had chest pain (94.4%) as their predominant preoperative symptom. Hypertension was present in 121 of the 160 patients. Marfan syndrome was present in 10.6% of the patients (Table 2).

4.2. Patient and surgical characteristics

Among the preoperative characteristics, Table 2 showed that body mass index (BMI) were higher in AKI group when compared to non-AKI group ($P = .005$). Notably, no significant differences in medical history were observed between the 2 groups. On admission, a clotted false lumen was found on enhanced computed tomography in 112 patients. One hundred twenty-six patients received dissections that extended below the diaphragm, while for 34, the dissection terminated above the diaphragm. Renal malperfusion was present preoperatively in 22 patients (13.8%), and 27.3% (6/22) of the patients developed postoperative AKI.

No significant differences were observed between the 2 groups with respect to preoperative imaging tests. The preoperative laboratory test results of the 2 groups are summarized in Table 2. The neutrophil ratio, fibrinogen degradation products and D-dimer levels were higher in the AKI group than in the non-AKI group ($P = .02$, $P = .008$, $P = .01$, and $P = .003$, respectively). Other standard laboratory tests, such as eGFR and white blood cell count, did not differ markedly between the 2 groups. Preoperative ELISA revealed that plasma histamine levels were lower in the AKI group than in the non-AKI group ($P = .002$).

The operational details are presented in Table 2. Although the surgical techniques were similar in the 2 groups, patients with AKI required a longer operation time than those without AKI ($P = .02$). The nasopharyngeal temperature and rectal temperature values were not significantly different between the 2 groups. Moreover, with regard to the intraoperative volume of transfusion and drainage volume, there were no obvious discrepancies between the 2 groups.

4.3. The in-hospital outcomes

The in-hospital mortality rate was 19.0% (16/84) in the AKI group and 2.6% (2/76) in the non-AKI group ($P = .02$). Postoperative clinical outcomes were also complicated in patients with AKI, with a higher rate of complications, such as longer ICU stay, severe hypoxemia, low cardiac output syndrome, multi-organ failure, sepsis, and CRRT ($P = .001$, $P < .001$, $P = .03$, $P = .001$, $P = .002$ and $P < .001$, respectively).

4.4. Univariate and multivariate logistic regression analysis associated with independent risk factors for postoperative ATAAD-AKI

In the univariate analysis, preoperative characteristics associated with a higher risk of postoperative AKI included BMI, neutrophil ratio, fibrinogen degradation products, D-dimer level, and plasma histamine level. In terms of operative variables, a longer operation time might be linked to postoperative AKI in univariate logistic regression analysis. The risk factors for postoperative AKI, identified using multivariate logistic regression analysis are shown in Table 3. After adjusting for potential confounders, plasma histamine level (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.10 to 1.52; $P = .004$) and BMI (OR, 1.19; 95% CI, 1.03 to 1.37; $P = .04$) were identified as independent risk factors for postoperative AKI in patients with ATAAD in the multivariate logistic regression analysis.

4.5. Subgroup analysis

The overall postoperative in-hospital mortality was 11.3% (18/160). The in-hospital mortality rates were 19.0% (16/84) in the AKI group and 2.6% (2/76) in the non-AKI group ($P = .02$), and increased with the stratification of the KDIGO criteria (stage 0, 2.6% [2/76]; stage 1, 6.3% [2/32]; stage 2, 28.6% [4/14]; stage 3, 26.3% [10/38]). Among patients with ATAAD, the AKI group had a higher in-hospital mortality rate than the non-AKI group (11.3% vs 2.6%; $P = .02$). The mortality in the AKI stage 2 and 3 group is higher at 28.6% and 26.3% comparison with the AKI stages 1 group (6.3%).

There was a significant difference in preoperative plasma histamine levels among the AKI groups according to the AKI stages in the overall trend analysis ($P < .001$) (Fig. 2). Similar to the overall analysis, the preoperative plasma histamine levels were lower in the postoperative AKI stage 1, stage 2, and stage 3 groups than in the normal kidney function group ($P = .011$, $P = .018$, and $P < .001$, respectively). Additionally, there was a significant difference in BMI among the AKI groups in the overall trend analysis ($P = .035$) (Fig. 3). However, there was only a small difference in the BMI between AKI stage 0 and AKI stage 1/3 ($P = .014$ and $P = .021$, respectively). Importantly, subgroup analysis revealed that preoperative plasma histamine levels were independently associated with the occurrence of severe postoperative AKI (stage 3) (OR, 1.38; 95% CI, 1.10–1.73; $P = .005$) and CRRT (OR, 1.44; 95% CI, 1.13–1.79; $P = .008$) after adjusting for confounding factors (Table 4).

4.6. Risk prediction for postoperative ATAAD-AKI

As shown in Figure 4, the preoperative plasma histamine level (cutoff, 344.6; area under the curve [AUC], 0.773; sensitivity,

Table 2

Characteristics of the study patients with acute type A aortic dissection at baseline.

Characteristics	Non-AKI (n = 76)	AKI (n = 84)	*P* value
Demographic data			
Age, yr	49.1 ± 11.1	46.7 ± 11.2	.34
Male, %	54 (71.1)	60 (71.4)	.62
BMI, kg/m^2	27.4 ± 3.6	24.8 ± 4.3	.005
Medical history			
Hypertension, %	58 (76.3)	64 (76.2)	.99
Diabetes mellitus, %	2 (2.6)	4 (4.8)	.62
Cerebrovascular disease, %	6 (7.9)	4 (4.8)	.56
Coronary artery disease, %	6 (7.9)	6 (7.1)	.90
Smoking history, %	26 (34.2)	40 (47.6)	.22
Drinking history, %	14 (18.4)	12 (14.3)	.62
Marfan syndrome, %	4 (5.3)	8 (9.5)	.47
Preoperative condition			
Alanine amino transaminase, U/L	34.0 ± 3.6	31.9 ± 5.5	.75
sCr, umol/L	82.1 ± 33.0	90.3 ± 29.3	.24
eGFR, mL/(min·1.73m^2)	85.8 ± 12.4	84.7 ± 13.2	.36
White blood cells, ×10^3/mm^3	10.4 ± 3.8	11.8 ± 3.9	.11
Neutrophil ratio, %	76.8 ± 8.4	81.4 ± 8.4	.02
Hemoglobin, g/dL	137.2 ± 20.4	137.9 ± 16.5	.87
Platelet counts, ×10^3/mm^3	193.3 ± 84.2	166.1 ± 62.5	.11
Fibrinogen level, g/L	3.9 ± 1.5	3.3 ± 1.8	.08
FDP, μg/mL	10.8 (5.8, 10.8)	22.5 (12.9, 43.8)	.008
D-dimer, ng/mL	993 (534, 2456)	2044 (790, 3072)	.01
Histamine, pg/mL	339.9 ± 33.1	317.9 ± 26.7	.002
LVEF, %	61.6 ± 6.7	62.8 ± 5.8	.38
Aortic root size, mm	41.4 ± 8.8	40.55 ± 7.2	.65
Ascend aorta size, mm	46.6 ± 7.2	44.3 ± 7.0	.15
Aortic regurgitation, %	34 (44.7)	42 (50.0)	.64
Renal malperfusion, %	16 (21.1)	6 (7.1)	.08
Operation details			
Bentall + TAR + FET, %	24 (31.6)	34 (40.5)	.41
Combined with CABG, %	6 (7.9)	6 (7.1)	.90
The duration of operation, h	7.5 ± 1.4	8.4 ± 1.8	.02
CPB time, min	199.0 ± 47.2	220.5 ± 60.0	.08
Aortic cross clamp time, min	121.7 ± 52.2	127.2 ± 36.0	.53
The duration of HCA, min	27.7 ± 10.6	28.1 ± 8.2	.87
Nasopharyngeal temperature, °C	23.2 ± 2.3	22.5 ± 1.5	.11
Rectal temperature, °C	25.8 ± 2.8	25.2 ± 2.1	.27
Intraoperative blood loss, mL	1287 ± 493	1459 ± 577	.16
Intraoperative amount of plasma, mL	400 (0, 400)	400 (0, 650)	.30
Intraoperative amount of RBC, mL	300 (0, 600)	150 (0, 600)	.50
Postoperative outcomes			
In-hospital mortality, %	2 (2.6)	16 (19.0)	.02
Length of hospital, d	15 (10, 19)	15 (12, 21)	.25
Length of ICU, d	2.0 (1.0, 3.5)	5.8 (1.5, 12.5)	.001
CRRT, %	0	34 (40.5)	<.001
Severe hypoxemia, %	12 (15.8)	46 (54.8)	<.001
Reoperation for bleeding, %	2 (2.6)	12 (14.3)	.07
Low cardiac output syndrome, %	2 (2.6)	10 (11.9)	.03
Cerebral infarction or bleeding, %	2 (2.6)	8 (9.5)	.20
Multi-organ failure, %	0	18 (21.4)	.001
Sepsis, %	2 (2.6)	24 (28.6)	.002

Results are expressed as n (%), mean ± standard deviation or median (interquartile range).

AKI = acute kidney injury, BMI = body mass index, CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass, CRRT = continuous renal replacement therapy, eGFR = estimated glomerular filtration rate, FDP = fibrinogen degradation products, FET = frozen elephant trunk, HCA = hypothermic circulatory arrest, ICU = intensive care unit, LVEF = left ventricular ejection fraction, RBC = red blood cell, sCr = serum creatinine, TAR = total arch replacement.

52.6%; specificity, 93.9%; P = .02) was a predictive value of the risk factor for postoperative AKI in patients with ATAAD in the ROC curve analysis. Subsequently, ROC curves were used to evaluate the predictive ability of preoperative plasma histamine levels in determining severe postoperative AKI (stage 3) (cutoff, 325.2; AUC, 0.789; sensitivity, 52.5%; specificity, 94.7%; P < .001) and CRRT (cutoff, 325.2; AUC, 0.772; sensitivity, 50.8%; specificity, 94.1%; P < .001) (Figs. 5 and 6).

5. Discussion

In summary, the main finding of the current study was that the preoperative plasma histamine level was an independent predictive indicator for ATAAD-AKI after TAR combined with FET but also emphasized its association with severe postoperative AKI (stage 3) and CRRT. To our knowledge, research on the relationship between preoperative plasma histamine levels and the severity of postoperative AKI in patients with ATAAD

Table 3

Risk factors for postoperative acute kidney injury in multivariate logistic regression analysis in patients with acute type A aortic dissection.

Risk factors	OR	95% CI	*P* value
BMI, kg/m^2	1.19	1.03–1.37	.04
Neutrophil ratio, %	1.04	0.96–1.13	.30
FDP, μg/mL	0.99	0.94–1.06	.98
D-dimer, ng/mL	1.00	1.00–1.01	.55
Histamine, pg/mL	1.31	1.10–1.52	.004
The duration of operation, h	1.26	0.87–1.83	.22

BMI = body mass index, CI = confidence interval, FDP = fibrinogen degradation products, OR = odds ratio.

is rare. Owing to the high incidence and complicated comorbidities of postoperative ATAAD-AKI, the preoperative plasma histamine level might be a possible protective biomarker for the early identification and categorization of high-risk populations in patients with ATAAD.

In recent years, ATAAD has become a complex aortic disease that is often complicated by multi-organ dysfunction.[2,12] Moreover, postoperative AKI is one of the most common organ injuries and an early serious complication after emergency ATAAD surgery, which can result in prolonged ICU and in-hospital stays and increased 30-day mortality.[5,13–16] Furthermore, a few recent studies[3,4,13] have shown that postoperative ATAAD-AKI obviously deteriorates the short- and long-term prognosis of patients along with high mortality and morbidity. In our study, the AKI group also had significantly higher in-hospital mortality and length of ICU stay than the non-AKI group (P = .02 and P = .001, respectively). Importantly, an association between the severity of postoperative AKI and long-term survival has been demonstrated in patients with ATAAD.[3,4,17] In our study, the overall postoperative in-hospital mortality rate increased with each ATAAD-AKI stage. However, to date, there is no clear and effective therapeutic treatment for preventing ATAAD-AKI before surgery. Thus, our results emphasize the importance of the early identification and prevention of AKI in the initial stages.

Owing to the use of different AKI definition criteria, diverse patient characteristics, and surgical options, the incidence and outcomes of postoperative AKI have been widely inconsistent among different studies. Several previous studies[18] demonstrated that the incidence of AKI associated with cardiovascular surgery usually varies from 4.2 to 36.0%, whereas other studies[5] found that postoperative AKI was deemed a more common complication, ranging from 17.7 to 71.9% after ATAAD surgery. Other previous studies[19,20] indicated a remarkably lower incidence of postoperative ATAAD-AKI (17.7–31.3%), perhaps because of different surgical procedure types and strict postoperative management. In contrast, Li et al[5] reported that 71.9% of the patients with ATAAD developed postoperative AKI. Previous studies have demonstrated that 71.9% of the patients had the highest incidence of ATAAD-AKI. Similarly, Zhao et al[6] reported an incidence of up to 66.7% after urgent aortic surgery in 108 obese patients but defined AKI according to the AKI Network criteria. However, Vekstein et al[21] and other studies[3,4,13,16] documented that the incidence of ATAAD-AKI ranges from 40 to 55%. Unsurprisingly, these results were similar to our findings (52.5%) in ATAAD patients who underwent emergent TAR combined with FET implantation.

The incidence of severe postoperative ATAAD-AKI (stage 3) in our study was 23.8% (38/160) and the required CRRT was 21.3% (34/160). A recent research[17] reported that 23.8% of patients developed severe postoperative ATAAD-AKI (stage 3) after ATAAD surgery, including 16.6% of patients who underwent CRRT. Similarly, Chen et al[7] demonstrated that 47.9% of patients developed severe postoperative AKI (AKI stages 2–3) and 14.6% of patients required CRRT. However, Ko et al[4] found that the incidence of severe AKI (AKI stage 3) after emergency aortic surgery was 14%, and only 9% of the patients received CRRT. The reason for the low incidence of severe AKI (AKI stage 3) may be partially because patients who underwent emergency aortic surgery were excluded from the study. Notably, in-hospital mortality gradually increased with each severity stratification of ATAAD-AKI in our subgroup analysis.

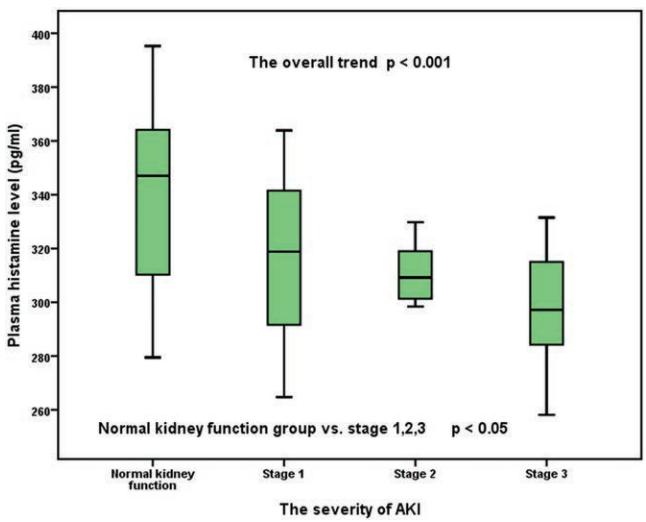

Figure 2. Changes in preoperative plasma histamine level among AKI groups. AKI = acute kidney injury.

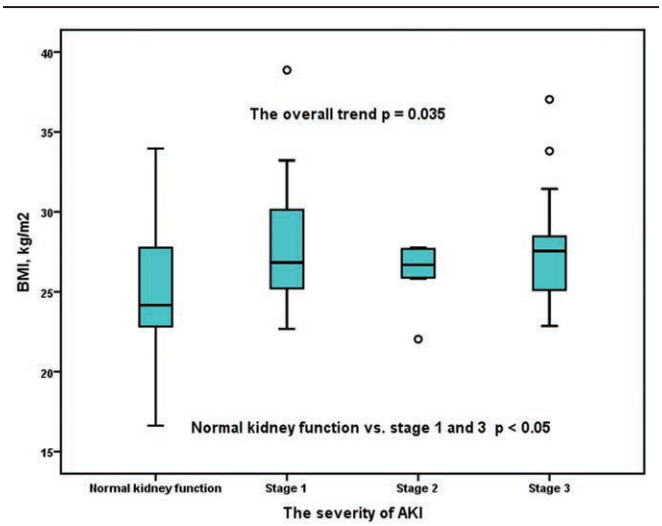

Figure 3. Changes in BMI among AKI groups. AKI = acute kidney injury, BMI = body mass index.

Table 4

Risk factors for severity of postoperative acute kidney injury and continuous renal replacement therapy in multivariate logistic regression analysis in patients with acute type A aortic dissection.

Risk factors	Severity of postoperative AKI									CRRT		
	Stage 1			Stage 2			Stage 3					
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
BMI, kg/m^2	1.16	0.99–1.36	.06	1.60	0.86–2.97	.14	1.29	0.94–1.79	.12	1.05	0.88–1.25	.58
Histamine, pg/mL	1.36	0.96–2.44	.37	1.30	0.98–1.33	.24	1.38	1.10–1.73	.005	1.44	1.13– 1.79	.008

AKI = acute kidney injury, BMI = body mass index, CI = confidence interval, CRRT = continuous renal replacement therapy, OR = odds ratio.

Owing to the high mortality rate of CRRT after ATAAD-AKI,[22] increasing evidence has shown that early identification of high-risk patients with severe postoperative ATAAD-AKI (stage 3) could substantially improve the overall prognosis.

Given the effect of the complexity of ATAAD or surgery itself and variable malperfusion syndromes, the details of the pathophysiological mechanism of ATAAD-AKI are more complex than those of other cardiovascular procedures and remain unclear. Recently, the inflammatory response was thought to be the underlying mechanism of postoperative AKI in non-cardiac surgery.[23,24] There is growing evidence that histamine, a biogenic amine, is more likely to have a protective effect against renal injury in animal models.[25] In addition, disease-induced reflective increased histamine levels have been reported in chronic renal disease and nephrotic syndrome.[26] Similarly, Noguchi et al[10] demonstrated that elevated histamine levels were protective reaction for kidney dysfunction in mouse model. Moreover, they identified that histamine deficiency resulted in more serious deterioration of renal abnormalities. Importantly, we have explored vital organ protection in patients with ATAAD who undergo emergency cardiac surgery all the time. To the best of our knowledge, this is the first study to investigate the association between baseline levels of histamine and postoperative AKI in patients with ATAAD. Our study revealed that the preoperative plasma histamine level was lower in the AKI group than in the non-AKI group, indicating that a lack of histamine accelerated renal injury. In addition, regulation of the histamine receptor H3 agonist for the inflammatory response has been previously described in the central nervous system. Furthermore, the insufficient antioxidative stress and anti-inflammatory effects of histamine may be a fundamental theory for the occurrence of postoperative AKI, which is similar to previous studies.[12,27] These results clearly demonstrate that histamine plays a protective role in renal injury through transcriptional regulation of anti-inflammatory gene expression. Therefore, histamine as a useful inflammatory biomarker may provide a new therapeutic strategy and insights into ATAAD-AKI.

Many studies[16,28,29] which have found advanced age to be an independent risk factor for developing postoperative ATAAD-AKI. Wang et al[17] also suggested that elderly patients with ATAAD may develop severe postoperative AKI (stage 3). Inconsistent with previous studies,[13,21] our study showed that advanced age was not an independent risk factor for AKI in ATAAD patients. This is probably because the patients in our study were relatively young. In addition, preoperative eGFR or baseline sCr level was not associated with risk factors for ATAAD-AKI in our study, unlike many other studies.[6,13] One possible explanation for this finding is that patients undergoing preoperative chronic or emergency dialysis were excluded from our study.

The incidence of renal malperfusion in our study was 13.8% (22/160), similar to that reported by Qian et al,[30] who reported an incidence of 22%, both of which were higher than the 5% reported by Helgason et al.[13] Recent studies[4,31] had shown that renal malperfusion might significantly lead to an increased incidence of AKI and poor prognosis in patients with ATAAD. Although renal malperfusion was obviously correlated with AKI, the majority of patients with AKI did not develop postoperative AKI, which may have resulted from the prevention of the progression of AKI and restoration of renal blood flow using surgery.[13]

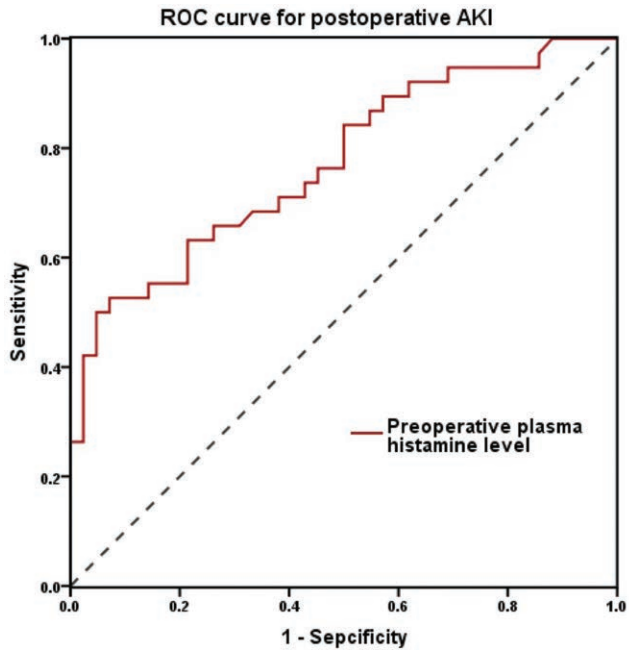

Figure 4. The preoperative plasma histamine level as predictive value of risk factor for postoperative AKI in patients with ATAAD by ROC curve analysis. AKI = acute kidney injury, ATAAD = acute type A aortic dissection, ROC = receiver operating characteristic.

Previous studies[4,5,13,21,32] concluded that prolonged CPB time is associated with an increased risk of postoperative ATAAD-AKI. Wang et al[17] also identified a longer CPB duration as an independent risk factor for severe postoperative ATAAD-AKI (stage 3). However, the operation time, but not the CPB time, was markedly higher in the AKI group than in the non-AKI group in the univariate analysis in our study. Similarly, other investigations[5] also discovered that CPB time was not recognized as a surgical risk factor for ATAAD-AKI in a multivariable analysis. In addition, HCA time is another well-documented independent risk factor for postoperative ATAAD-AKI.[28] However, this finding has not been confirmed in other clinical studies.[13] Indeed, renal ischemia or reperfusion injury during HCA largely contributes to the morbidity and mortality associated with ATAAD-AKI. However, these discrepant findings may be explained by the heterogeneous populations and different definitions of AKI.

Markers of massive bleeding included excessive perioperative blood products transfusion and drainage volume, both of which were identified as known independent risk factors for ATAAD-AKI.[5,13] However, no statistical difference was observed in the number of transfusions and drainage volumes between the 2

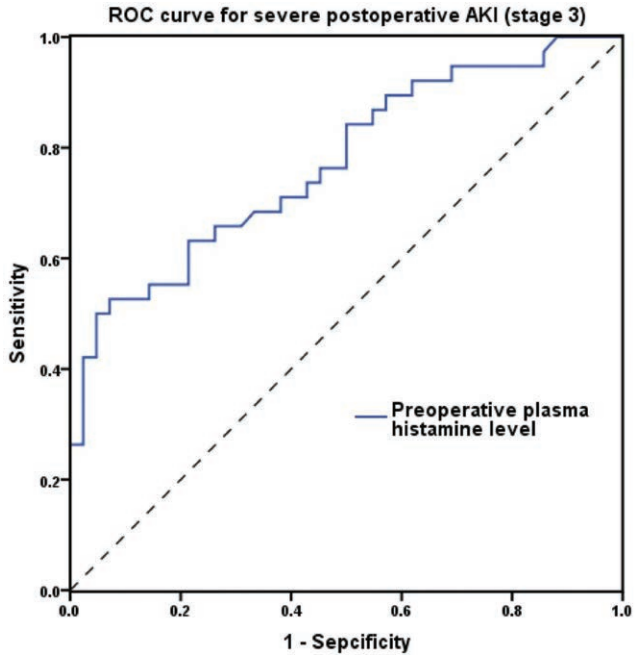

Figure 5. The preoperative plasma histamine level as predictive value of risk factor for severe postoperative AKI (stage 3) in patients with ATAAD by ROC curve analysis. AKI = acute kidney injury, ATAAD = acute type A aortic dissection, ROC = receiver operating characteristic.

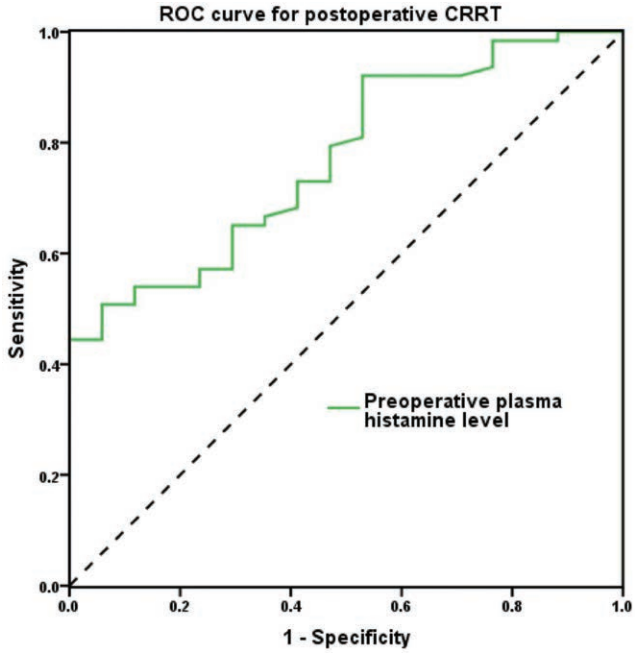

Figure 6. The preoperative plasma histamine level as predictive value of risk factor for postoperative CRRT in patients with ATAAD by ROC curve analysis. ATAAD = acute type A aortic dissection, CRRT = continuous renal replacement therapy, ROC = receiver operating characteristic.

groups in our study. Despite no definite relationship between bleeding and postoperative ATAAD-AKI in our study, no additional benefits were observed from unnecessary transfusions. The influence of obesity on the serious outcomes after emergency aortic surgery is complex. Previous reports[4,5,13] have demonstrated that an increased BMI is a well-documented risk factor for ATAAD-AKI. In the study by Zhao H and colleagues,[6] BMI $\geq 24\,kg/m^2$ was also supposed to be independently associated with AKI in obese patients with ATAAD. Consistently, we found that overweight patients were more likely to develop postoperative ATAAD-AKI.

5.1. Study limitations

Our study had several limitations. First, this was a nonrandomized retrospective analysis in a single-center series with a relatively young age, which limited its applicability in other areas. Second, another limitation of this study had a small sample size. This limited the power of our analysis to identify changes in the inflammatory system of patients with ATAAD. Third, although multivariate logistic regression was performed, our findings may have been affected by some potential confounding variables. Finally, the fundamental mechanism underlying the relationship between plasma histamine levels and AKI is not fully understood. With the experience gained in recent years, we designed a long-term follow-up clinical trial and animal experiment to focus on the role of preoperative plasma histamine levels in postoperative ATAAD-AKI.

6. Conclusions

In conclusion, low preoperative plasma histamine levels were significantly associated with the risk of AKI in patients with ATAAD and had a prospective predictive value for severe postoperative AKI (stage 3) and CRRT in the present study. Thus, we recommend that preoperative plasma histamine levels serve as a protective biomarker for risk factors for postoperative AKI in patients with ATAAD.

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