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Original Article

Ulinastatin in combination with aprotinin improves systemic inflammation in patients undergoing cardiac surgery with cardiopulmonary bypass

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Abstract: Objective: To investigate the impact of ulinastatin combined with protease inhibitors on serum inflammatory factors in patients undergoing cardiac surgery with cardiopulmonary bypass. Methods: A retrospective analysis was conducted on 86 patients who underwent cardiac surgery with cardiopulmonary bypass at Xi'an Gaoxin Hospital from May 2019 to June 2021. Based on the administration of drugs by a micro-infusion pump after anesthesia induction and before skin incision, the patients were divided into an observation group (receiving ulinastatin at a dose of 12,000 U/kg and protease inhibitors at a dose of 4 million units) with 46 cases and a control group (receiving protease inhibitors at a dose of 2 million units) with 40 cases. Peripheral blood leukocyte count, neutrophil percentage, interleukin (IL)-6, tumor necrosis factor (TNF)-α, serum creatine kinase isoenzyme (CK-MB), and serum cardiac troponin I (cTnI) levels were measured and compared between the two groups before surgery, 1 hour after surgery, and 24 hours after surgery. The positive inotropic drug usage, duration of postoperative mechanical ventilation, and incidence of complications were also compared between the two groups. Finally, an analysis was conducted to identify independent risk factors affecting patient prognosis. Results: The peripheral blood white blood cell (WBC) count, neutrophil percentage, serum inflammatory factor level, CK-MB, and cTnI of the two groups of patients at 1 h and 24 h after the operation were significantly higher than those before the operation. However, the observation group had significantly lower levels of peripheral blood WBC count, neutrophil percentage, serum inflammatory factors, CK-MB, and cTnI compared to the control group (all $P<0.05$). Additionally, the observation group had significantly lower dopamine dosage and a shorter duration of mechanical ventilation compared to the control group (all $P<0.05$). The incidence of complications was lower in the observation group compared to the control group ($P<0.05$). TNF-α, cTnI, and treatment regimen were identified as independent risk factors associated with adverse patient prognosis. Conclusion: The perioperative use of ulinastatin combined with protease inhibitors in patients undergoing cardiac surgery with cardiopulmonary bypass is beneficial in suppressing systemic inflammatory response, improving cardiopulmonary function, and reducing the incidence of complications. These findings suggest its clinical utility.

Keywords: Ulinastatin, protease inhibitors, cardiac surgery, serum inflammatory factors

Introduction

Extracorporeal circulation (ECC) is an important adjunctive technique in the surgical treatment of cardiac diseases [1]. With the continuous advancement in cardiac surgical technique and improvements in ECC equipment, the incidence of postoperative complications and mortality rate after ECC surgery have significantly decreased in recent years [2]. However, a multitude of factors, including ischemia-reperfusion injury, surgical trauma, endotoxin effects, and blood-ECC circuit interaction, can stimulate neutrophils, endothelial cells, and platelets, thereby eliciting the release of numerous pro-inflammatory mediators and initiating a complex cascade of events. This unbridled inflammatory response can give rise to a systemic inflammatory response syndrome (SIRS) [3, 4]. SIRS can significantly impact postoperative pulmonary and cardiovascular function and reduce long-term survival rates. Data have shown that

the mortality rate has been steadily increasing in the population affected by SIRS and sepsis in the past five years [5]. Therefore, improving the prognosis of patients undergoing cardiac surgery with ECC is a pressing issue that needs to be addressed.

Aprotinin is a nonspecific serine protease inhibitor derived from organs such as bovine lungs and pancreas. It can inhibit platelet activation, reduce neutrophil aggregation in the lungs, protect pulmonary surfactant, alleviate damage to alveolar epithelial cells, and inhibit the release of vasoactive peptides, kinins, and the complement system, thereby preventing reperfusion injury to lung tissues; However, the use of protease inhibitors may cause adverse reactions such as nausea and diarrhea in patients, necessitating dose adjustments that may reduce efficacy, hence the need for additional medications to complement its effects [6]. Ulinastatin is a type of protease inhibitor that targets pancreatic proteases, serine proteases, and fibrinolysins [7]. Both ulinastatin and aprotinin have demonstrated the ability to effectively suppress systemic inflammatory responses during cardiac surgery, rendering them indispensable as protective agents for vital organs and blood cells. Previous studies have highlighted the significant inhibitory effects of ulinastatin on neutrophil elastase elevation following extracorporeal circulation, thereby indirectly mitigating the release of other inflammatory factors [8]. Nonetheless, there remains a paucity of research on the concurrent administration of ulinastatin and aprotinin in patients undergoing cardiac surgery with extracorporeal circulation.

The main objective of this study was to observe the effects of ulinastatin combined with aprotinin on serum inflammatory factors in patients undergoing cardiac surgery with extracorporeal circulation to provide further insight into the selection of intraoperative medication for such patients.

Materials and methods

Clinical data

A retrospective analysis was conducted on 86 patients who underwent cardiac surgery with extracorporeal circulation at Xi'an Gaoxin Hospital from May 2019 to June 2021. The patients were divided into an observation group (n=46) and a control group (n=40) based on the administration of medication by a micro-pump after anesthesia induction and before skin incision. The observation group received ulinastatin at a dose of 12,000 U/kg and aprotinin at a dose of 4 million units, while the control group received only aprotinin at a dose of 4 million units. Inclusion criteria were as follows: (1) patients requiring cardiac surgery with extracorporeal circulation; (2) patients who were able to tolerate the surgery; (3) patients with complete clinical data. Exclusion criteria were as follows: (1) patients unable to tolerate the surgery; (2) patients with significant organ dysfunction, such as liver or kidney impairment; (3) patients with severe infectious diseases or immune dysfunction; (4) pregnant or lactating patients; (5) patients who refused to participate in the study. This study was approved by the hospital's ethics committee and complied with the principles of the Helsinki Declaration.

Surgical methods

All patients underwent endotracheal intubation and received general anesthesia. During the induction of anesthesia, intravenous administration of fentanyl at a dosage of (5-10) μg/kg, etomidate at a dosage of (0.3-0.4) mg/kg, and vecuronium bromide at a dosage of (0.1-0.2) mg/kg was performed. Anesthesia maintenance involved continuous propofol infusion, inhalation of isoflurane, and intermittent intravenous administration of pancuronium bromide in combination with fentanyl. Following the surgery, patients were transferred to the intensive care unit (ICU) and extubated once they regained spontaneous breathing and achieved hemodynamic stability.

In the observation group, patients received a slow intravenous infusion of ulinastatin at a dose of 12,000 U/kg (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., H1999-0134) from anesthesia induction to the start of extracorporeal circulation. Aprotinin at a dose of 4 million units (Shanxi Pude Pharmaceutical Co., Ltd., H14022653) was administered as a one-time preloading dose. In the control group, patients received a slow intravenous infusion of aprotinin at a dose of 2 million units from anesthesia induction to the start of extracorporeal circulation, and an additional 2 million

Table 1. Comparison of general data

Variable	Observation group n=46	Control group n=40	X^2	P
Gender			0.069	0.793
Male	24 (52.17)	22 (55.00)		
Female	22 (47.83)	18 (45.00)		
Age (years)			0.231	0.631
≥54	25 (54.35)	23 (57.50)		
<54	21 (45.65)	17 (42.50)		
BMI (kg/m^2)			0.053	0.817
≥23	23 (50.00)	21 (52.50)		
<23	23 (50.00)	19 (47.50)		
Smoking history			0.001	0.983
Yes	30 (65.22)	26 (65.00)		
No	16 (34.78)	14 (35.00)		
Hypertension			0.086	0.769
Yes	25 (54.35)	23 (57.50)		
No	21 (45.65)	17 (42.50)		
Type of surgery			0.057	0.972
Coronary artery bypass graft	17 (36.96)	15 (37.50)		
Valve replacement	16 (34.78)	13 (32.50)		
Hybrid surgery	13 (28.26)	12 (30.00)		

units of aprotinin was given as a one-time preloading dose. Dopamine and adrenaline were administered based on the patient's surgical condition.

Outcome measures

(1) Comparison of peripheral blood leukocyte count and neutrophil percentage before anesthesia induction, as well as at 1 hour and 24 hours after surgery. (2) Comparison of the usage of positive inotropic drugs between the two groups, including the use of dopamine and adrenaline. (3) Measurement and comparison of inflammatory markers, such as interleukin (IL)-6 (ThermoFisher, BMS213HS) and tumor necrosis factor (TNF)-α (Abcam, ab285312) before anesthesia induction, as well as at 1 hour and 24 hours after surgery using enzyme-linked immunosorbent assay (ELISA). (4) Measurement and comparison of serum levels of creatine kinase isoenzyme (CK-MB) and cardiac troponin I (cTnI) before anesthesia induction, as well as at 1 hour and 24 hours after surgery. (5) Comparison of the duration of mechanical ventilation after surgery between the two groups. (6) Comparison of the incidence of complications in both groups, including pulmonary infections, renal dysfunction, myocardial injury, and sepsis. (7) Analysis of the 1-year prognosis of the two patient groups, where patients experiencing adverse outcomes during the follow-up period were classified as the adverse prognosis group, while those without disease progression were classified as the good prognosis group. All patients underwent regular follow-up through hospital visits, telephone follow-ups, SMS messages, and home visits. Logistic regression was utilized to analyze the independent risk factors affecting patient prognosis.

Statistical methods

The collected data were processed and analyzed using SPSS 20.0 software and GraphPad Prism 8 software for visualization. Independent samples t-test was used for between-group comparisons, paired t-test was used for within-group comparisons before and after treatment. Comparisons among multiple time points were conducted using one-way analysis of variance. Chi-square test was used for comparison of categorical data. A significance level of $P<0.05$ indicated a significant difference.

Results

Comparison of general information between the two groups

There were no evident differences in gender, age, or BMI between the two groups, indicating that the two groups were comparable (all $P>0.05$, **Table 1**).

Comparison of peripheral blood WBC count and neutrophil percentage between the two groups

No significant difference in peripheral blood WBC count and neutrophil percentage was observed between the two groups before surgery (all $P<0.05$). At 1 hour after surgery, both

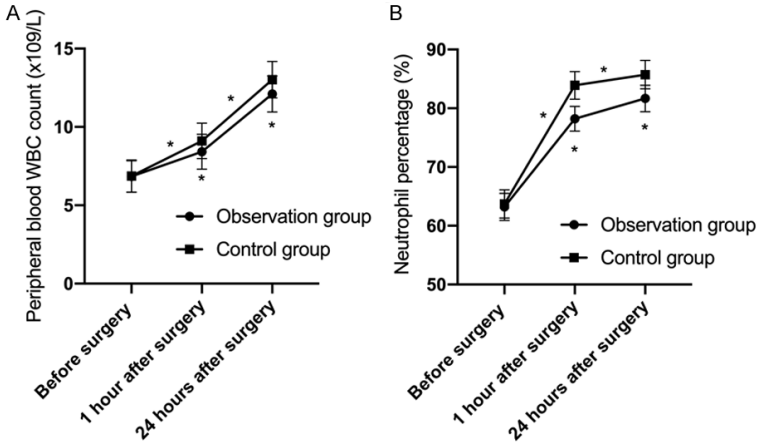

Figure 1. Comparison of the peripheral blood WBC count and neutrophil percentage between the two groups of patients. A: WBC count; B: Neutrophil percentage. *, P<0.05. WBC, white blood cells.

Table 2. Comparison of the dosage of inotropic drugs in the two groups of patients

Drug type	Observation group n=46	Control group n=40	t	P
Adrenaline	0.07±0.01	0.07±0.02	0.001	0.999
Dopamine	5.78±0.86	4.76±0.77	5.758	<0.001

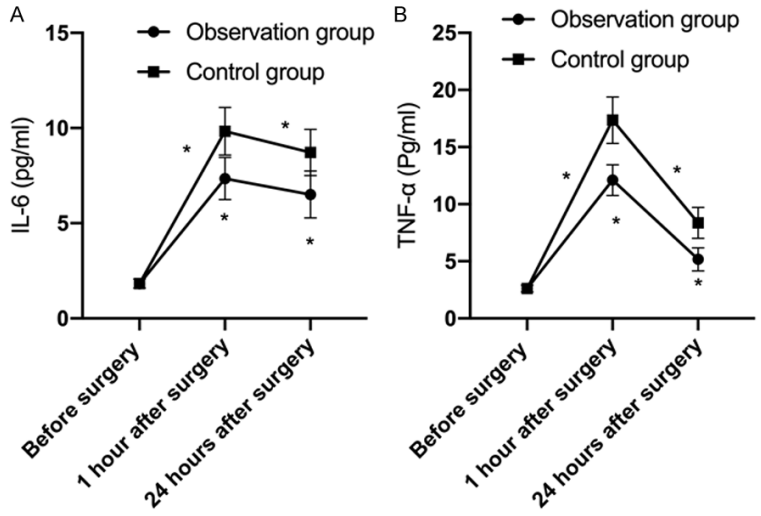

Figure 2. Comparison of serum inflammatory factors between two groups of patients. A: Serum IL-6; B: Serum TNF-α. *, P<0.05. IL-6, interleukin 6; TNF-α, tumor necrosis factor-α.

groups showed a significant increase in the levels of peripheral blood WBC count and neutrophil percentage, but the observation group was significantly lower than the control group (P<0.05). At 24 hours after surgery, the levels in both groups decreased compared to 1 hour postoperatively but remained higher than preoperative levels, with the observation group consistently lower than the control group (all P<0.05), as shown in **Figure 1**.

Comparison of the dosage of inotropic drugs in the two groups of patients

There was no significant difference in the dose of adrenaline used between the two groups (P>0.05). However, the observation group had a significantly lower dose of dopamine compared to the control group (P<0.05), as shown in **Table 2**.

Comparison of serum inflammatory factors in the two groups of patients

Compared to levels before surgery, both groups of patients showed significant increase in serum levels of IL-6 and TNF-α at 1 hour and 24 hours after surgery (all P<0.05). Specifically, the observation group had significantly lower levels of serum IL-6 and TNF-α at 1 hour and 24 hours postoperatively compared to the control group (both P<0.05), as shown in **Figure 2**.

Comparison of serum CK-MB and cTnI in two groups of patients

There were no significant differences in serum CK-MB and cTnI levels between the two groups of patients before surgery (both P>0.05). However, at 1 hour postoperatively, both groups of patients showed a significant increase in CK-MB and cTnI levels. At 24 hours postoperatively, the CK-MB levels gradually decreased in both groups, while the cTnI levels further increased and were higher than those before surgery. However, CK-MB and cTnI were significantly lower in the observa-

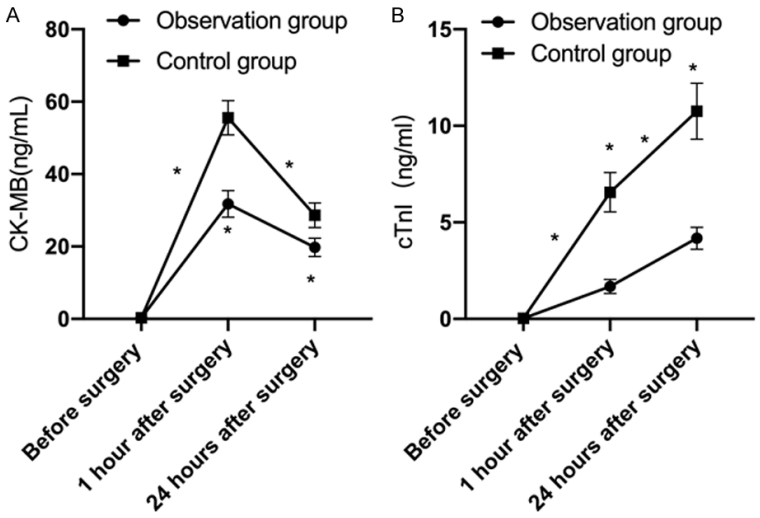

Figure 3. Comparison of serum CK-MB and cTnI between the two groups of patients. A: Serum CK-MB; B: Serum cTnI. *, P<0.05. TNF-α, tumor necrosis factor-α; cTnI, cardiac troponin I.

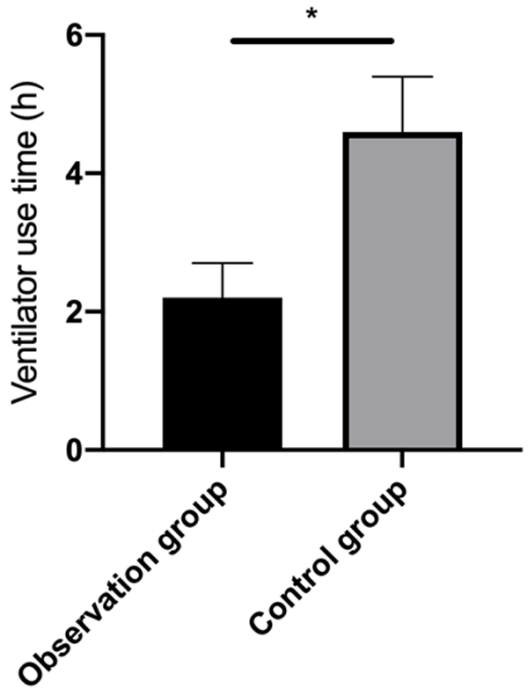

Figure 4. Comparison of ventilator usage time between two groups of patients. *, P<0.05.

tion group than in the control group at 1 hour and 24 hours after surgery, as shown in **Figure 3**.

Comparison of ventilator usage time between the two groups

The time of using a ventilator in the observation group was significantly shorter than that in the control group (P<0.05, **Figure 4**).

Comparison of the incidence of postoperative complications between the two groups

The incidence of adverse reactions in the observation group was 6.52%, which was significantly lower than that of the control group (27.50%) (P< 0.05), as shown in **Table 3**.

Analysis of risk factors affecting patients' prognosis

According to the patient's prognosis, they were divided into a good prognosis group (n=45) and a poor prognosis group (n=41). Single-factor analysis revealed that IL-6, TNF-α, CK-MB, cTnI, and treatment regimen were all factors influencing their prognosis (**Table 4**). Subsequently, logistic regression analysis was performed to further analyze the factors and identified TNF-α, cTnI, and treatment regimen as independent risk factors associated with poor patient prognosis (**Table 5**, all P<0.05).

Discussion

ECC is a highly invasive therapeutic modality that offers dependable support for open heart surgeries. Nevertheless, the utilization of ECC also induces an inflammatory response [9]. The inflammatory response is primarily instigated by the contact between blood and foreign surfaces, such as oxygenators and tubes, which subsequently triggers the activation of the complement system as well as monocytes or macrophages, leading to the release of an array of inflammatory mediators. Consequently, this cascade of events gives rise to systemic inflammatory response syndrome, characterized by cardiac and pulmonary dysfunction [10, 11]. Therefore, finding effective ways to improve intraoperative inflammatory response and patient outcomes is a crucial clinical challenge. In this study, we analyzed the impact of the combination of ustekinumab and aprotinin on the inflammatory response in patients undergoing cardiac surgery with cardiopulmonary bypass.

Ulinastatin, a glycoprotein derived from purified urine of healthy males, is comprised of 143

Table 3. Comparison of the incidence of postoperative complications between the two groups

Adverse reactions	Observation group n=46	Control group n=40	X^2	P
Lung infection	1 (2.17)	3 (7.5)	-	-
Renal impairment	2 (4.38)	3 (7.5)	-	-
Myocardial injury	0	4 (10.00)	-	-
Sepsis	0	1 (2.5)	-	-
Total incidence	3 (6.52)	11 (27.50)	6.909	0.009

amino acids and possesses a molecular weight of 66464U. As an acidic protein, it exhibits distinct pharmacological properties. It has a 100% bioavailability and a half-life of 40 minutes. Following administration, it rapidly attains peak concentrations in the kidneys and liver within approximately 5 minutes, subsequently undergoing excretion in the form of urine and feces over a period of 12 hours. Notably, it does not induce any detrimental effects on renal function [12, 13]. Pharmacological studies have shown that ulinastatin exhibits inhibitory effects on various hydrolytic enzymes such as trypsin, phospholipase A, and elastase. It can also inhibit the release of cell inflammatory mediators and suppress leukocyte transmigration across the endothelium [14]. On the other hand, aprotinin is a naturally occurring plasma protease inhibitor derived from bovine or porcine lungs. Its fundamental mechanism of action involves the formation of a complex structure between aprotinin and the active serine site of diverse proteases, including plasmin, trypsin, kallikrein, fibrinolytic enzymes, activated complement C, and coagulation factors [15, 16].

These proteases play vital roles in coagulation, fibrinolysis, inflammation, the complement system, and hemodynamics. IL-6 and TNF-α serve as early sensitive indicators of tissue damage in patients, and their levels are intricately linked to the inflammatory response within the patient's body. The perioperative inflammatory response during cardiac surgery is primarily characterized by pro-inflammatory cytokines (IL-6, TNF-α), peripheral blood leukocytes, and monocytes [17]. Therefore, we first compared the effects of combined use of ulinastatin and aprotinin with the use of aprotinin alone on the inflammatory response in patients. The results showed that after surgery, the serum levels of inflammatory factors (IL-6, TNF-α), the proportion of neutrophils, and peripheral blood leukocytes in both groups increased compared to preoperative levels, but the expression of these factors in the group receiving combined therapy was significantly lower than in the control group. This suggests that the combination of ulinastatin and aprotinin can better improve the postoperative inflammatory response in patients.

CK-MB and cTnI are important markers of myocardial enzymes, and their level changes are closely related to the extent of myocardial injury in patients [18]. To further analyze the treatment efficacy of combined use of ulinastatin and aprotinin, we also compared the levels of CK-MB and cTnI before and after surgery in both groups of patients. Although there was a decrease in CK-MB levels at 24 hours postoperatively compared to 1 hour postoperatively in both groups of patients, it was still higher than preoperative levels, indicating ulinastatin combined with aprotinin could reduce the levels of these indicators, exerting good control over myocardial enzyme indicators in perioperative patients, stabilizing cell membranes, and protecting organ function. Due to the higher sensitivity of cTnI to myocardial injury compared to CK-MB, this may be the reason why there is a decrease in CK-MB levels at 24 hours postoperatively, while cTnI continues to gradually increase [19]. A study [20] has indicated that ulinastatin, as a broad-spectrum serine protease inhibitor, not only inhibits the activity of various hydrolytic enzymes but also controls the release of inflammatory mediators induced by cardiopulmonary bypass (CPB), thereby exerting a preventive effect on postoperative cardiac dysfunction. Additionally, research has suggested that ulinastatin stabilizes lysosomal membranes in cells and inhibits the release of myocardial suppressive factors, which is crucial for the protection of cardiomyocytes during extracorporeal circulation [21].

Subsequently, we conducted a comparison of the duration of mechanical ventilation and the incidence of complications between the two patient groups. The results revealed that the observation group exhibited a significantly shorter duration of mechanical ventilation and a lower incidence of complications in comparison to the control group. Furthermore, no cases of sepsis were observed in the observation group.

Table 4. Univariate analysis of factors affecting patients' prognosis

Variable	Good prognosis group (n=45)	Poor prognosis group (n=41)	t/X^2	P
Gender			0.038	0.845
Male (n=46)	24 (53.33)	21 (51.22)		
Female (n=40)	21 (46.67)	20 (48.78)		
Age			0.148	0.701
≤54 years (n=48)	26 (57.78)	22 (53.66)		
>54 years (n=38)	19 (42.22)	19 (46.34)		
BMI (kg/m^2)			0.001	0.992
≤23 kg/m^2 (n=44)	23 (51.11)	21 (51.22)		
>23 kg/m^2 (n=42)	22 (48.89)	20 (48.78)		
Smoking history			1.088	0.297
Yes (n=56)	27 (60.00)	29 (70.73)		
No (n=30)	18 (40.00)	12 (29.27)		
IL-6	8.03±0.77	9.61±0.82	9.215	<0.001
TNF-α	7.74±0.84	8.97±0.73	7.216	<0.001
CK-MB	24.78±2.11	31.78±2.43	14.30	<0.001
cTnI	9.73±1.23	6.78±0.93	12.45	<0.001
Hypertension			0.003	0.960
Yes (n=48)	25 (55.56)	23 (56.10)		
No (n=38)	20 (44.44)	18 (43.90)		
Treatment regimen			0.214	0.643
Aprotinin (n=40)	22 (48.89)	18 (43.90)		
Ulinastatin combined with aprotinin (n=46)	23 (51.11)	23 (56.10)		

Note: IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; CK-MB, creatine kinase-MB; BMI, body mass index.

Table 5. Multivariate analysis of factors affecting patients' prognosis

Factors	B	S.E.	Wals	P	RR	95% C.I.	
						Lower limit	Upper limit
TNF-α	0.293	0.121	2.511	0.031	1.293	1.023	1.792
cTnI	0.231	0.072	2.982	0.033	1.083	1.461	1.263
Treatment regimen	0.514	0.093	2.964	0.015	1.637	1.318	1.973

Note: TNF-α, tumor necrosis factor-α; cTnI, cardiac troponin I.

These results indicate that the combined administration of ulinastatin and aprotinin exerts a favorable protective effect on the lungs and significantly reduces the occurrence of postoperative complications. Previous studies have indicated that ulinastatin regulates the generation and release of inflammatory factors during cardiac surgery with cardiopulmonary bypass, effectively inhibiting the activation of inflammatory factors and reducing endotoxin release [22], which is consistent with our observations. We also conducted an analysis of the independent risk factors influencing patient prognosis. The results revealed that TNF-α, cTnI, and treatment regimen were independent risk factors associated with poor patient prognosis.

In conclusion, the combination of ulinastatin and aprotinin can effectively improve the systemic inflammatory response in patients undergoing cardiac surgery with cardiopulmonary bypass. It exerts cardioprotective and pulmonary protective effects and significantly reduces the incidence of postoperative complications. Therefore, use of ulinastatin combined with aprotinin should be promoted in clinical practice. However, this study has certain limitations. First, due to our small sample size, our conclusions need further confirmation through

larger-scale studies. Second, we did not explore other anti-inflammatory drugs in our research, so whether the combination of ulinastatin and a protease inhibitor is the optimal regimen still remains worth further investigation.

Disclosure of conflict of interest

None.

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