

Effects of Ulinastatin on Postoperative Renal Function in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass: a Prospective Cohort Study

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Abstract

Background: Ulinastatin is a serine protease inhibitor with anti-inflammatory effects. Evidence for the effects of ulinastatin on renal outcomes remains sparse in patients receiving cardiac surgery with cardiopulmonary bypass (CPB).

Methods: This prospective cohort study evaluated 413 patients aged 18–70 years who underwent cardiac surgery with CPB, from Aug 2008 to Jul 2019 in Fuwai Hospital, Beijing, China. The ulinastatin group included 135 patients who received intravenous ulinastatin (1×10^6 U) after induction of anesthesia. The remaining 278 patients without ulinastatin served as the control group. The primary outcome was the rate of new-onset postoperative acute kidney injury (AKI). The secondary outcome was renal replacement therapy (RRT). Serum creatinine, plasma NGAL, and serum IL-6 levels were evaluated and the CSANGAL Score was calculated. In addition, in-hospital mortality, morbidity, adverse outcomes and 10-year follow-up the survival rate was analyzed.

Results: Rate of new-onset AKI was significantly lower in the ulinastatin group than in the control group (20.00% vs. 32.40%, $p=0.009$). There was no significant difference of RRT between the two groups (0.00% vs. 2.16%, $p=0.09$). In-hospital mortality, morbidity, and adverse outcomes were comparable between the two groups except for a significantly lower incidence of respiratory failure in the ulinastatin group compared with the control group (0.76% vs. 5.40%, $p=0.02$). The 10-year follow-up survival rates did not differ significantly between the two groups.

Conclusions: Ulinastatin significantly reduced postoperative AKI and respiratory failure in patients receiving cardiac surgery with CPB. But ulinastatin did not reduce ICU and hospital stay and mortality.

Clinical trial registration: NCT01060189

Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent and severe complication in adult patients undergoing cardiac surgery with cardiopulmonary bypass (CPB)[1] and the second most common cause of AKI in the intensive care unit (ICU). Notably, AKI is independently associated with the increased need for renal replacement therapy (RRT), length of hospital stay, hospitalization cost, and mortality[2]. However, to date, efficacious drugs that can reduce the incidence of AKI and the requirement for RRT remain limited [3]. Prior investigations indicated that CSA-AKI has associations with systemic inflammatory response syndrome (SIRS), renal ischemia-reperfusion injury, renal hypoperfusion, blood transfusion, and nephrotoxic drugs[4]. Moreover, CPB-induced inflammatory responses are associated with kidney dysfunction[4, 5]. CSA-AKI was defined according to the KDIGO criteria in the present study. The KDIGO criteria define AKI severity according to serum creatinine (SCr) and urinary output. However, SCr increases relatively late after the onset of kidney injury without specific symptoms, leading to limitations in the SCr-based definition of AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is one

AKI biomarker that shows promising for identifying acute tubular damage, especially in the subclinical AKI stage, and can represent acute tubular damage before the presence of clinical renal dysfunction[6].

Ulinastatin is a glycoprotein purified from healthy human urine as a broad spectrum protease inhibitor, which was demonstrated to reduce complications in patients undergoing cardiac surgery with CPB through its anti-inflammatory and antioxidant activities[7]. However, it remains controversial whether ulinastatin has benefits for renal function and can reduce morbidity and mortality associated with AKI in patients undergoing cardiac surgery procedures with CPB.

The present study aimed to determine the potential effects of ulinastatin on renal function and long-term survival in patients receiving cardiac surgery with CPB.

Patients And Methods

This single-center prospective cohort study was approved by the Ethics Committee of Fuwai Hospital, Patients aged 18–70 years who underwent cardiac surgery with CPB from Aug 2008 to Jul 2019 in Fuwai Hospital, Beijing, China were enrolled. Patients with preoperative renal dysfunction were excluded. For inclusion criteria, the patients required: diagnosis of coronary heart disease, valvular heart disease, congenital heart disease, or complex heart disease; cardiac surgery necessitating CPB; normal renal function with $GFR \geq 60 \text{ mL/min/1.73 m}^2$, calculated by the Chronic Kidney Disease Epidemiology Collaboration equation; and no kidney transplantation within the past 365 days. Finally, 413 patients were included in the study, and they were divided into the ulinastatin group ($n=135$) or the control group ($n=278$) (Figure 1), according to whether the ulinastatin was used during the surgery or not. The participants did not experience any events that resulted in AKI during the preoperative and intraoperative periods, including hypotension, shock, and use of nephrotoxic drugs, which will be excluded from the whole trials.

According to the routine practices in our institution, blood samples were taken before anesthesia induction (T0), on arrival at the ICU (T1), and at 6 (T2), 12 (T3), and 24 hours (T4) after surgery.

The primary outcome of the study was the rate of new-onset AKI, which was defined by the KDIGO criteria after surgery. The secondary outcome was the need for RRT. In-hospital mortality and morbidity and adverse outcomes were observed. The CSA-NGAL Score is a tubular damage score based on the level of NGAL and a clinical index for early prediction of subclinical AKI. SCr, pNGAL, and serum IL-6 concentrations were detected by ELISA for each sample, in which pNGAL and IL-6 were detected by emulsion enhanced immune turbidimetry assay and double antibody sandwich ELISA, separately.

A 10-year follow-up was achieved by telephone call, outpatient service, face-to-face visit, QQ, or WeChat. The data ascertained by the follow-up team were as follows: onset of death, loss to follow-up, and renal dysfunction; presence or absence of heart failure, hematosepsis, or re-hospitalization for renal dysfunction, RRT, intermittent hemodialysis, or potential nephrotoxic drugs; levels of blood glucose; and

results for renal function. All of these items were recorded. In death cases, information on the date and the primary and secondary causes of death were obtained.

Statistical Analysis

For continuous variables, the Shapiro–Wilk test was used to estimate the normal distribution assumption, and the Levene test was applied to assess the equal variance assumption. Differences in these characteristics between the two groups were evaluated by an independent two-sample t-test or one-way ANOVA. Categorical variables were summarized by frequency or percentage and compared by the chi-square test or Fisher’s exact test. Inter-group differences in serum IL-6, pNGAL, and SCr were assessed by two-way repeated-measures analysis of variance (ANOVA) with a Bonferroni post-hoc test. Survival analysis was performed using the Kaplan–Meier method and a log-rank test. All statistical analyses were performed using SPSS Version 18.0 software (SPSS Inc., Chicago, IL). Values of $p < 0.05$ were considered statistically significant.

Results

Demographic Data

There were no significant differences in the demographic characteristics between the two groups, Preoperative diagnoses comparable between the two groups (Table 1).

Table 1
Demographic and Preoperative Characteristics

	Ulinastatin Group (n=135)	Control Group (n=278)	<i>p</i> Value
Male, n (%)	56 (41.5)	133 (47.8)	0.22
Age, y	49.1±14.4	49.6±12.6	0.83
Body mass index	22.8 (20.3, 25.4)	22.4 (20.3, 25.2)	0.52
Hypertension, n (%)	30(22.2)	68 (24.5)	0.62
Diabetes, n (%)	5 (3.7)	10 (3.6)	0.96
Stroke, n (%)	7 (5.2)	5 (1.8)	0.06
Chronic pulmonary disease, n (%)	10 (7.4)	34 (12.2)	0.14
Liver dysfunction, n (%)	0 (0)	0 (0)	-
Diagnosis, n (%)	0.31		
Coronary heart disease	15 (11.1)	32 (11.5)	
Valvular heart disease			
Mitral valve lesion	69 (51.1)	128 (46.0)	
Aortic valve lesion	21 (15.6)	41 (14.8)	
Combined lesion	21 (15.6)	38 (13.7)	
Congenital heart disease			
Atrial septal defect	0 (0)	9 (3.2)	
Ventricular septal defect	4 (3.0)	10(3.6)	
Other	5 (3.7)	20 (7.2)	
NYHA class, n (%)	0.42		
I	9 (6.7)	34 (12.2)	
II	76 (56.3)	151 (54.3)	
III	40 (29.6)	70 (25.2)	
IV	10 (7.4)	23 (8.3)	
EuroSCORE II	2.4±1.9	2.6±1.7	0.34
Data for age and EuroSCORE II are shown as mean ± SD.			
NYHA class, New York Heart Association Functional Classification; EuroSCORE, European System for Cardiac Operative Risk Evaluation.			

Perioperative Data

The intraoperative and the postoperative data were comparable between the two groups (Table 2).

Table 2
Intraoperative and Postoperative Data

	Ulinastatin Group (n=135)	Control Group (n=278)	<i>p</i> Value
Aortic cross-clamp time, min	70.0 (50.0, 96.0)	63.0 (44.3, 92.0)	0.25
CPB time, min	97.0 (72.0,125.0)	87.0 (65.0,120.0)	0.27
Operation time, min	215.0 (175.0, 245.0)	195.0 (160.0, 240.0)	0.08
Operative mortality, n (%)	0 (0)	0 (0)	-
Surgical Type, n (%)			0.35
Coronary artery bypass grafting	16 (11.9)	32 (11.5)	
Mitral valvuloplasty or replacement	65 (48.1)	124 (44.6)	
Aortic valve replacement	20 (14.8)	39 (14.0)	
Mitral and aortic valve replacement	17 (12.6)	30 (10.8)	
CABG and valvular procedure	10 (7.4)	14 (5.0)	
Repair of atrial septal defect	0 (0)	9 (3.2)	
Repair of ventricular septal defect	4 (3.0)	10 (3.6)	
Other	5 (3.7)	20 (7.2)	
Postoperative data			
Mechanical ventilation, h	13.0 (11.0, 18.0)	13.0 (10.0, 17.0)	0.36
ICU stay, h	25.0 (18.0, 56.0)	25.5 (17.0, 58.3)	0.53
Hospital length of stay, h	7.0 (7.0, 8.0)	7.0 (7.0, 9.0)	0.39
The differences in these characteristics between the two groups were evaluated by an independent two-sample <i>t</i> -test or one-way ANOVA. Categorical variables were summarized as frequency or percentage and compared by the chi-square test or Fisher's exact test.			
CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; ICU, intensive care unit.			
There was no significant differences in the intraoperative and postoperative data (<i>p</i> >0.05).			

Renal Function Outcomes

The incidence of AKI in the ulinastatin group was significantly lower than that in the control group (20.00% vs. 32.37%, $p=0.009$). Furthermore, a significant difference was observed between the two groups ($p=0.002$) about the subclinical acute kidney injury, calculated by CSA-NGAL Scores (Table 3). Six of 278 patients in the control group and no patients in the ulinastatin group required RRT, but the difference was not significant ($p=0.09$).

Table 3
CSA-NGAL Scores and KDIGO Scores at 24 Hours Postoperatively

CSA-NGAL Score, n (%)	Ulinastatin Group (n=135)	Control Group (n=278)	
0	61 (45.2)	96(34.5)	
1	48 (35.6)	77(27.7)	
2	22 (16.3)	86(31.0)	
3	4 (3.0)	19(6.8)	
KDIGO Score, n (%)	Ulinastatin Group (n=135)	Control Group (n=278)	P value
0	108 (80.0)	188 (67.6)	
1	20 (14.8)	63 (22.7)	
2	5 (3.7)	18 (6.5)	
3	2 (1.5)	9 (3.2)	
AKI	27 (20.0)	90 (32.4)	0.009*
There was a significant difference between the two groups in the CSA-NGAL Scores at 24 hours postoperatively ($p=0.002$). There was no significant difference in the KDIGO Scores between the two groups and in comparisons of pairs ($p=0.07$).			
CSA-NGAL Score, cardiac surgery-associated NGAL score; NGAL, neutrophil gelatinase-associated lipocalin; KDIGO Score, Kidney Disease-Improving Global Outcomes score.			

On arrival at the ICU and at 6, 12, and 24 hours after surgery, the pNGAL levels in the ulinastatin group versus control group were 89.78 ± 114.23 vs. 129.41 ± 163.58 ng/mL ($p=0.005$), 135.20 ± 248.96 vs. 247.92 ± 445.87 ng/mL ($p=0.001$), 131.06 ± 208.67 vs. 212.16 ± 333.11 ng/mL ($p<0.001$), and 110.32 ± 147.00 vs. 159.78 ± 245.23 ng/mL ($p=0.04$), respectively. Moreover, the mean time between the end of CPB and the first measurement of NGAL between ulinastatin group and control group was 64.83704 ± 25.8575 min vs. 65.3777 ± 27.96383 min. The corresponding IL-6 levels were 0.37 ± 0.24 vs. 0.40 ± 0.25 pg/mL ($p=0.30$), 0.78 ± 0.51 vs. 0.93 ± 0.62 pg/mL ($p=0.02$), 0.83 ± 0.51 vs. 1.05 ± 0.74 pg/mL ($p=0.02$), and 0.58 ± 0.35 vs. 0.89 ± 0.65 pg/mL ($p<0.001$), respectively, and the corresponding SCr levels were 1.07 ± 0.30 vs. 1.08 ± 0.35 mg/dL ($p=0.86$), 1.46 ± 0.65 vs. 1.55 ± 0.69 mg/dL ($p=0.17$), 1.46 ± 0.72 vs. 1.57 ± 0.77 mg/dL ($p=0.14$), and 1.28 ± 0.43 vs. 1.32 ± 0.61 mg/dL ($p=1.00$) respectively.

The postoperative SCr levels did not differ significantly between the two groups ($p=0.23$; Figure 2a), while the postoperative pNGAL levels ($p=0.007$; Figure 2b) and IL-6 levels ($p=0.001$; Figure 2c) were significantly lower in the ulinastatin group than in the control group. The CSA-NGAL Score was significantly lower in the ulinastatin group than in the control group ($p=0.002$; Table 3), while the KDIGO Score did not differ significantly between the two groups ($p=0.07$; Table 3) during the first 24 hours after surgery.

Mortality and Other Adverse Outcomes

The in-hospital mortality rate was 1 case (0.74%) in the ulinastatin group and 1 case (0.36%) in the control group, with no significant difference between the two groups ($p=0.60$). In addition, length of ICU stay, length of mechanical ventilation, and length of hospital stay did not differ significantly between the two groups. The two groups also showed no significant differences in postoperative complications like stroke, postoperative myocardial infarction, cardiac arrest, deep sternal infection, ICU readmission, surgery-associated reoperation, and RRT, IABP, and ECMO ($p>0.05$; Tables 2 and 4). Notably, the incidence of respiratory failure was significantly lower in the ulinastatin group than in the control group ($p=0.02$; Table 4).

Table 4
Adverse Events

Adverse events, n (%)			
Mortality in-hospital	1 (0.7)	1 (0.4)	0.60
Stroke	0 (0)	3 (1.1)	0.23
Postoperative MI	0 (0)	3 (1.1)	0.23
Respiratory failure	1(0.7)	15 (5.4)	0.02*
Sudden cardiac arrest	0 (0)	3 (1.1)	0.23
Readmission to ICU	2 (1.5)	4 (1.4)	0.97
Reoperation for surgical cause	2 (1.5)	2 (0.7)	0.46
RRT	0 (0)	6 (2.2)	0.09
IABP	1 (0.7)	5 (1.8)	0.40
ECMO	0 (0)	0 (0)	–
Deep sternal infection	1(0.7)	1 (0.4)	0.60
*There were significant differences between the two groups in the incidences of AKI ($p=0.009$) and morbidity of respiratory failure ($p=0.022$). There were no significant differences between the two groups in mortality and other postoperative adverse events ($p>0.05$).			
AKI, acute kidney injury; MI, myocardial infarction; ICU, intensive care unit; RRT, renal replacement treatment; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation.			

Discussion

CSA-AKI is a severe complication in adult patients undergoing cardiac surgery with CPB, resulting in prolonged ICU stay and increased short-term and long-term morbidity[8]. Several processes to reduce CSA-AKI incidence have been established, and the efficacy of ulinastatin has been examined in recent years[3, 9]. In the present study, we found that ulinastatin significantly reduced the incidence of CSA-AKI diagnosed according to the KDIGO criteria. In our study, the incidences of AKI were 20.00% in the ulinastatin group and 32.40% in the control group, consistent with the findings in recent studies[3]. Nakanishi et al.[10] demonstrated that ulinastatin administered before CPB could decrease postoperative elevation of IL-6 and IL-8 in patients undergoing cardiac surgery with CPB, while Song et al.[11] found that ulinastatin has no effect on attenuation of IL-6, TNF- α , and improvements in renal function. Wang et al. [12]. Indicated that ulinastatin could reduce inflammation and dose dependently attenuate CPB-induced kidney injury in infant piglets. Wan et al.[13] performed a propensity score-matched study and showed that administration of ulinastatin during CPB is associated with a lower incidence of CSA-AKI. Other studies have indicated that ulinastatin can inhibit polymorphonuclear neutrophils, which is helpful to reduce the risk of bleeding and the requirement for blood transfusion after surgery[14, 15]. Although AKI is a complex pathophysiological process rather than a specific syndrome, especially following cardiac surgery[16], SIRS arising after cardiac surgery plays a pivotal role in AKI development[17, 18]. The pathogenesis of SIRS is associated with multiple factors, including surgical trauma, transfusion, hypothermia, blood loss, ischemia-reperfusion injury, immune system activation, and endotoxemia[19]. Ulinastatin has anti-inflammatory properties by inhibiting the activation of various inflammatory pathways[14, 20, 21]. Thus, serum IL-6 levels were evaluated in this study and found to be significantly lower in the ulinastatin group compared with the control group ($p=0.001$; Figure 2c). The effect of ulinastatin on reducing CSA-AKI is considered to involve the inhibition of inflammation.

Evidence suggests that the KDIGO criteria are superior to other criteria, but have less sensitivity to detect early-stage tubular damage. The KDIGO criteria are based on the SCr level for diagnosis of AKI, and changes in SCr often occur 48 hours to 7 days after the original damage. Furthermore, SCr levels are affected by many related factors, and rescue interventions may be too late to prevent early perioperative AKI. These limitations drive us to search for new biomarkers that reflect early AKI. In addition to the KDIGO criteria, pNGAL, a newly discovered biomarker, was tested to predict kidney injury and prove previous findings[22]. NGAL plays a role in the early detection of AKI and can be upregulated at an earlier stage than elevation of SCr to meet the KDIGO criteria. NGAL in plasma and urine is upregulated when acute tubular damage occurs, but pNGAL is detectable earlier than uNGAL when tubular damage occurs. In a previous study, pNGAL was used to predict AKI based on the CSA NGAL Score, and the results were proven to be similar to those based on the KDIGO Score[6]. According to the KDIGO criteria and CSA-NGAL Score criteria, the incidences of CSA-AKI were similar in the present study. However, according to the CSA-NGAL Score criteria, 48 (35.60%) patients in the ulinastatin group and 77 (27.70%) patients in the control group were in the region of possible tubular damage, so-called subclinical AKI that is a separate entity and provides a warning to trigger awareness and appropriate clinical therapeutic modifications[6].

Respiratory failure in the present study was defined as prolonged ventilation support for more than 48 hours. The findings demonstrated that ulinastatin could reduce the incidence of respiratory failure, consistent with previous studies[23]. Xu et al.[24] suggested that ulinastatin inhibits the release of proinflammatory cytokines and PMNE, reduces pulmonary injury, and improves pulmonary function after CPB, thereby shortening the intubation time and length of ICU stay. The lung-protective effect of ulinastatin is dose dependent and a lower-than-effective dose could lead to negative results.

The survival rate after ten years of follow-up did not differ significantly between the two groups. According to previous studies, the effect of ulinastatin may be diminished depending on the duration of administration[25], which is ascribed to the fact that ulinastatin is administered through a bolus injection rather than a continuous infusion[26]. Another reason is that the half-life of ulinastatin is about 40 minutes in healthy adults[27], while the duration of CPB is often longer than 40 minutes and the peak of IL-6 occurs at 4–6 hours postoperatively[28]. A meta-analysis showed that ulinastatin could reduce inflammatory cytokines but does not affect hospital mortality[29].

There are some limitations to the present study. First, the study was designed as a single-center prospective cohort design with less power than a randomized controlled trial. The rationale lay in the sparse evidence concerning the effect of ulinastatin on renal outcomes and the nature of a pilot study. It was in accordance with ethical considerations to conduct an observational study rather than an interventional study. Second, there were relatively high rates of loss to follow-up, comprising 14.20% (19/134) in the ulinastatin group and 14.10% (39/277) in the control group. It was a great challenge to achieve follow-up for as long as ten years. Nevertheless, the rates of loss to follow-up were comparable between the two groups and associated with less bias. Third, only SCr was evaluated for the AKI criteria in the present study. The urine output in the KDIGO criteria requires a state of oliguria or anuria lasting for more than 6, 12, or 24 hours, which was infeasible in postoperative ICU settings. For ethical considerations, oliguria and anuria would not be observed for such a long period and should be treated according to the institutional protocol promptly. Furthermore, assessment of AKI by SCr alone has been widely accepted in studies such as the BART study[30] and the ATACAS study[8].

In the present study, the SCr, pNGAL, and serum IL-6 were detected, and CSA-AKI incidences according to the KDIGO criteria and CSA-NGAL Score criteria were analyzed, of which differed significantly between the two groups, except for SCr. Meanwhile, respiratory failure in the ulinastatin group was considerably lower than that in the control group. In summary, ulinastatin can significantly reduce the incidence of early postoperative AKI during cardiac surgery with CPB without affecting the long-term survival rate.

Declarations

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Authors' contributions

Author Jia Shi and author Hong Lv, Huanran Lv, Yuda Fei, have given substantial contributions to the conception or the design of the manuscript, author Qian Li, Peng Zhang, Liang Cao, and author Lihuan Li to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, author Jia Shi revised it critically.

All authors read and approved the final version of the manuscript.

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There is no Conflict of Interest.

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Figures

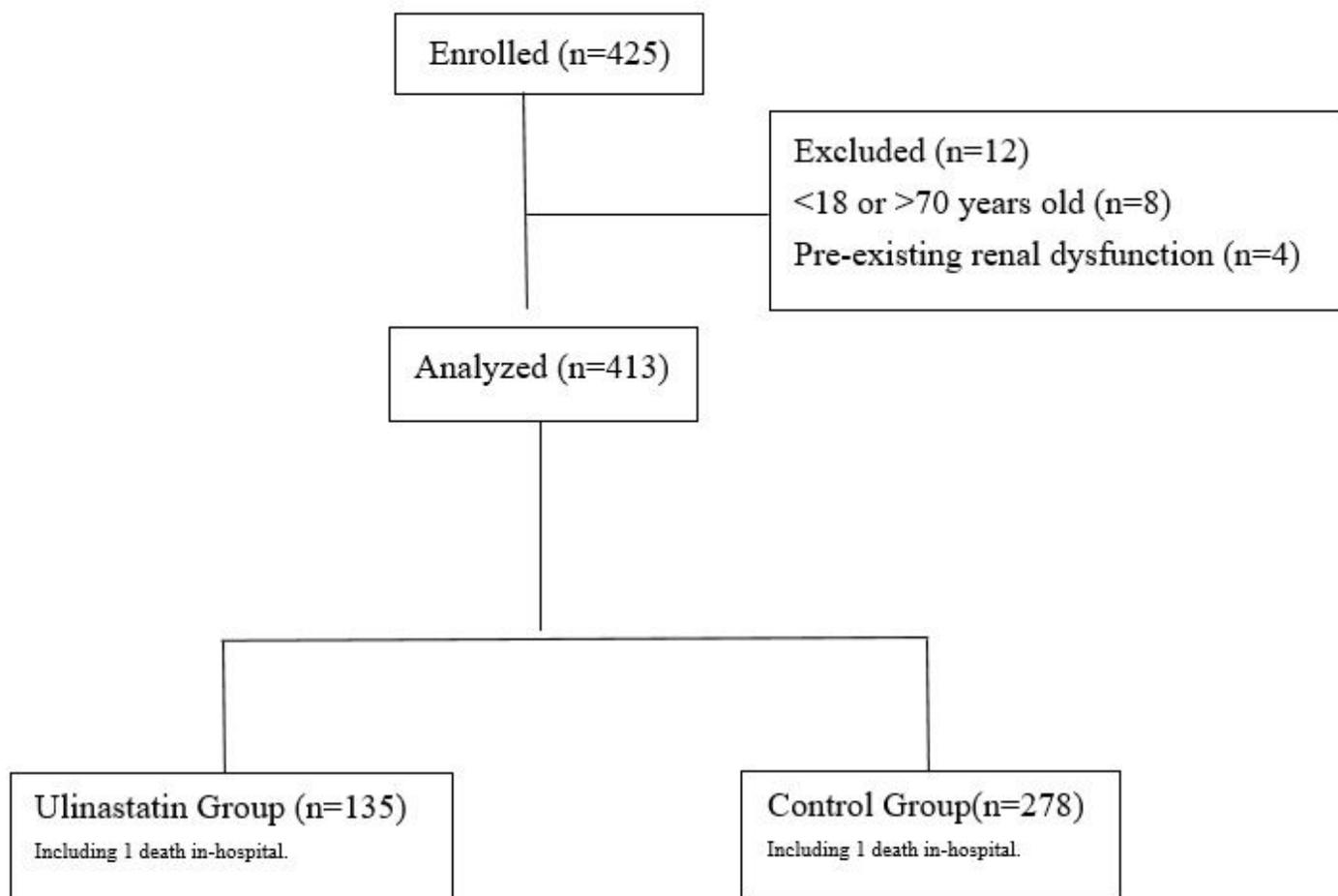
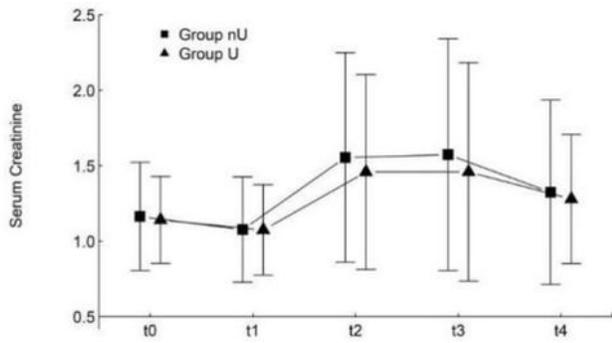


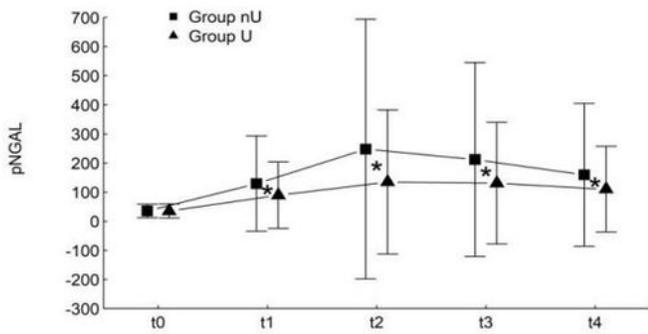
Figure 1

Scheme of patient recruitment. Ulinastatin group: patients with ulinastatin administration; Control group: patients without ulinastatin administration.

a. ■ Control group ▲ Ulinastatin



b.



c.

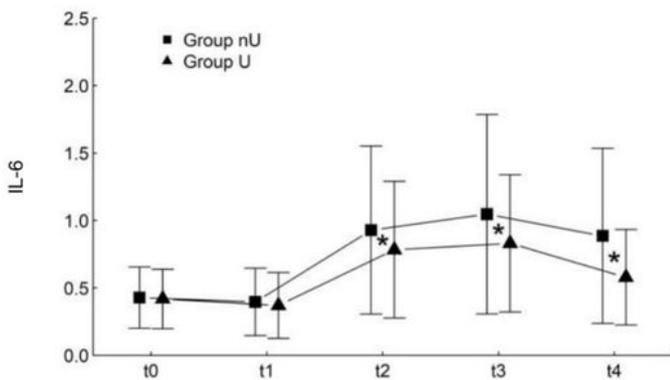


Figure 2

Changes in measured levels. (A) SCr levels. (B) pNGAL levels. (C) IL-6 levels. Data are expressed as mean \pm SD. There are significant differences in the levels of IL-6 and pNGAL between the two groups ($p < 0.05$). There is no significant difference in the levels of SCr between the two groups ($p = 0.23$). T0, before anesthesia induction; T1, on arrival at the ICU; T2, at 6 hours after surgery; t3, at 12 hours after surgery; T4, at 24 hours after surgery. * $p < 0.05$, significant difference between the two groups.

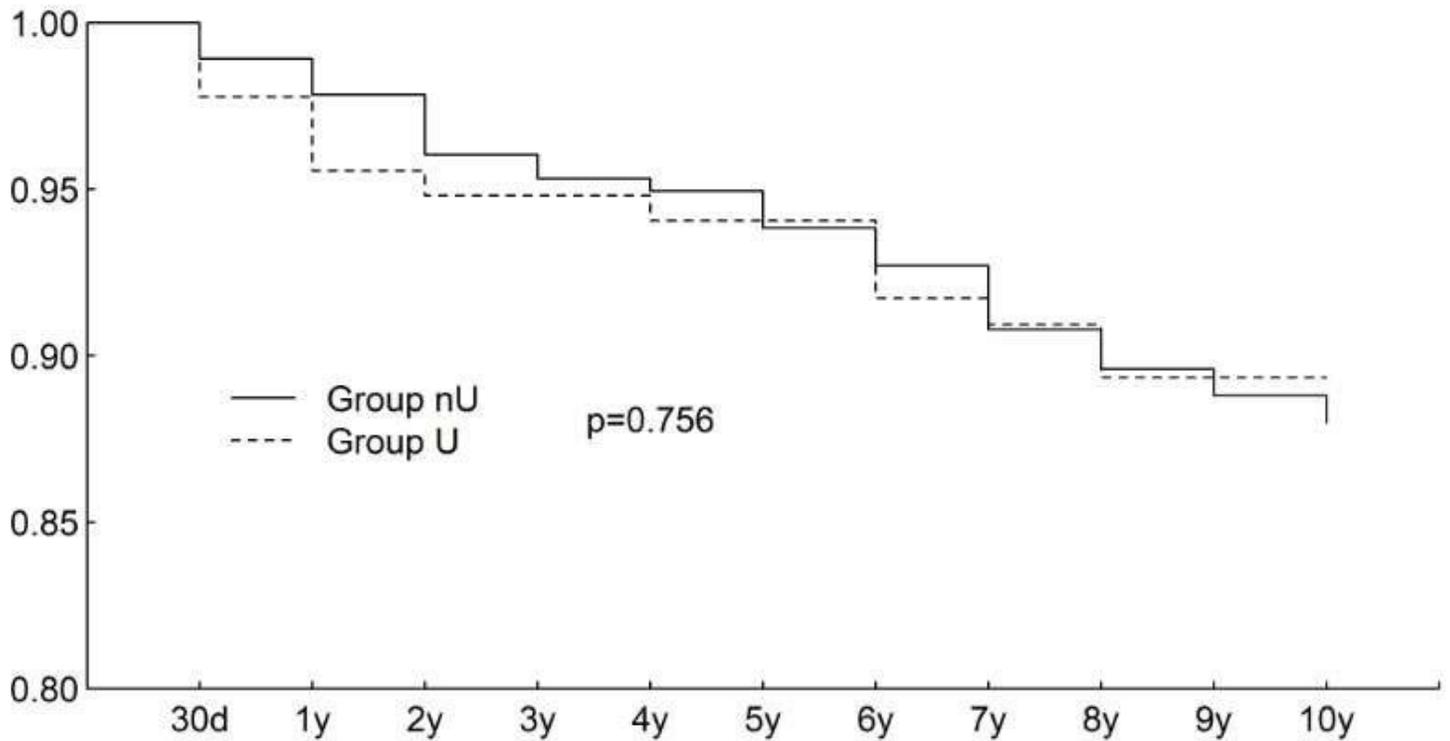


Figure 3

Survival rates. The survival rates did not differ significantly between the two groups (log-rank test, $p = 0.756$).