



# Use of ulinastatin was associated with reduced mortality in critically ill patients with sepsis

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**Contributions:** (I) Conception and design: Q Xu, S Chen; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: Q Xu, Q Yan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** Ulinastatin has anti-inflammatory properties and could potentially benefit critically ill septic patients. Nevertheless, clinical studies have yielded conflicting results. The present study examined the efficacy of ulinastatin in intensive care unit (ICU) patients with sepsis and/or septic shock.

**Methods:** All septic patients admitted to the ICU of Wuhu No. 2 People's Hospital between 2014 and 2017 were screened for potential eligibility for this retrospective study. The primary outcome was 28-day mortality, and its correlation with ulinastatin was assessed using multiple logistic regression models.

**Results:** The study included 263 patients, with an overall 28-day mortality of 38%. Patients receiving ulinastatin showed significantly lower mortality than the control patients (31% *vs.* 55%;  $P < 0.001$ ). Ulinastatin use was associated with significantly reduced risk of death (OR: 0.317, 95% CI: 0.158–0.621;  $P = 0.001$ ) after adjustment for age, Sequential Organ Failure Assessment score, vasopressor use, and patient type as determined with a multivariable regression model.

**Conclusions:** Treatment with ulinastatin was associated with a decrease in 28-day mortality in critically ill septic patients.

**Keywords:** Sepsis; effectiveness; mortality; critical care; multivariable logistic regression

Submitted Nov 20, 2018. Accepted for publication Apr 09, 2019.

doi: 10.21037/jtd.2019.05.03

**View this article at:** <http://dx.doi.org/10.21037/jtd.2019.05.03>

## Introduction

Sepsis is defined as a systemic organ dysfunction caused by an over-activation of the inflammatory response to infections. Severe sepsis and septic shock are leading causes of morbidity and mortality in the intensive care unit (ICU) (1,2) and hence efforts are continuously being made to develop novel interventions for sepsis treatment (3-6). Nonetheless, sepsis remains a major challenge for clinicians despite these advances.

Sepsis results from an over-activation of the inflammatory response that is characterized by excessive secretion of pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor-alpha, and IL-6. Therefore, pathways

mediating the release and clearance of these cytokines could present potential targets for sepsis treatment. Ulinastatin is a serine protease inhibitor found in the blood and urine of humans. Animal studies have demonstrated anti-inflammatory effects of ulinastatin (7,8) and identified potential benefits for the management of multiple organ dysfunction induced by sepsis (9). Ulinastatin achieved amelioration of inflammatory damage by modulating the quantity and function of regulatory T cells (Tregs) via the Toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF- $\kappa$ B) signaling pathway (10). Nonetheless, clinical studies have yielded conflicting results regarding the effectiveness of ulinastatin in the treatment of sepsis. While some studies could demonstrate beneficial effects, others

failed to corroborate such results (11), and these studies are often limited by the lack of an appropriate control of important confounders. We therefore set out to investigate the effectiveness of ulinastatin in the treatment of sepsis and hypothesized that this serine protease inhibitor reduces the mortality risk of critically ill septic patients.

## Methods

### *Study population*

This retrospective study was conducted between January 2014 and July 2017 in the Wuhu No. 2 People's Hospital in China. All patients admitted to the ICU were screened for potential eligibility. Medical charts were independently reviewed by two senior intensivists with more than 10 years of clinical experience in the ICU. We involved two investigators to ensure that no eligible patient was overlooked. Any disagreement was resolved by discussing the respective cases with a third investigator. Patients who had sepsis on day 1 of ICU entry were included in the study. Sepsis was defined as organ dysfunction plus infection according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (12). Organ dysfunction was defined as an increase in the Sequential Organ Failure Assessment (SOFA) score by two or more points. Infections were defined by the International Classification of Diseases (ICD-9) code (13). Information on organ dysfunction and infection was retrospectively extracted from the electronic healthcare records. Thus, we could apply the Sepsis-3 definition to patients that had been treated before the definition was issued. The following patients were excluded from the study: (I) pregnant women, (II) patients aged <18 years, (III) patients with contraindications for the use of ulinastatin such as allergy, (IV) terminally ill patients with a do-not-resuscitate (NDR) order, and (V) patients with sepsis that was treated in other hospitals for more than 3 days upon arrival in our hospital. The ethics committee of Wuhu No. 2 People's Hospital approved the study protocol (approval number: 201804). Informed consent was waived due to the retrospective design of the study. All individual patient data were de-identified and stored in an encrypted computer. The study was conducted in accordance with the Declaration of Helsinki.

### *Clinical variables*

Demographic data such as age and gender were included

in the analysis. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the SOFA score (14,15). We computed the APACHE II score by using variables obtained within 24 hours of ICU admission. If there were several measurements for a variable, the one associated with the maximum point score was employed. The types of patients included were emergency, surgical, and medical patients. Laboratory variables, such as procalcitonin (PCT), IL-6, C-reactive protein (CRP), platelet count, pro B-type natriuretic peptide (proBNP), and white blood cell (WBC) count, were recorded on day 0 and day 3 of ICU admission.

In terms of ulinastatin use, the dosage and times of initiation and discontinuation were recorded. There was no local practice guideline for the initiation of ulinastatin administration in our institution, and the decision was therefore left to the discretion of the attending physician. While there is no standard protocol for the dosage of ulinastatin, it was standardized in our institution to 200,000 U three times a day. We specified that vasopressors to assess were epinephrine, norepinephrine, and dopamine at a concentration of more than 5 µg/kg/min.

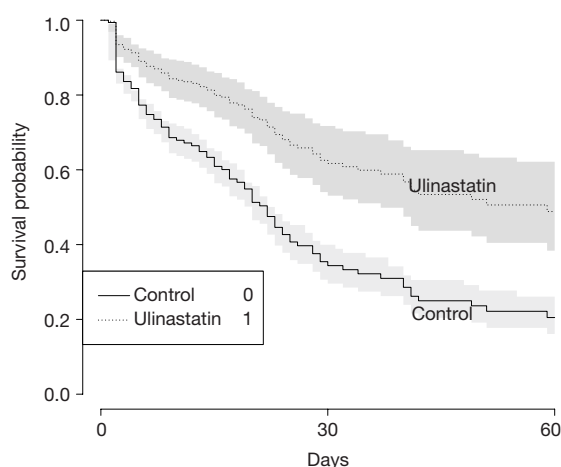
### *Outcomes*

The primary outcome was mortality at 28 days after ICU admission. Secondary outcomes included duration of mechanical ventilation (MV) and ICU length of stay. If a patient returned to the ICU within 48 hours after release, the ICU length of stay was computed as the sum of both ICU stays. Similarly, if a patient had to be re-intubated within 48 hours of weaning from MV, the MV duration was computed as the sum of both sessions.

### *Statistical analysis*

We assumed that the mortality rate was 0.5 in the control group and that the treatment could reduce the mortality rate to 0.34. The proportion of treated patients to control patients was 7:3. The type I error was 0.05, the type II error 0.2. The required sample size to reach statistical significance was 256. We included a total of 263 patients to account for potentially missing data.

Continuous variables were tested for their distribution (skewness and kurtosis). Data with normal distribution were expressed as mean and standard deviation and compared between survivors and non-survivors with the student's *t*-test. Skewed data were expressed as median



**Figure 1** Kaplan-Meier curves for the treatment and control groups.

and interquartile range (IQR) and were compared between groups by the Mann-Whitney U test. Qualitative variables were expressed as numbers and percentages and were compared between groups with the Chi-square test or Fisher's exact test, with p values reported for each comparison.

To adjust for confounding factors in this retrospective study, a multivariable logistic regression model was built with the binary mortality outcome as the response variable and vasopressor use, fluid balance, MV use, age, and SOFA score as potential confounders (16). Inflammatory biomarkers such as CRP, PCT, and WBC count have previously been associated with mortality outcome and were therefore considered as mediators of the effect of ulinastatin (17–19). Changes in these biomarkers on day 3 compared to day 1 were analyzed for both the treatment group and the control group. Model discrimination was determined by the area under the receiver operating characteristic (ROC) curve (20,21).

The R package Compare Baseline Characteristics Between Groups (CBCgrps) software was employed for all statistical analyses (version 3.4.3) (22). A two-tailed p value <0.05 was regarded as statistically significant (23).

## Results

A total of 297 patients fulfilling the definition of Sepsis-3.0 were screened by reviewing their medical charts. Thirty-four of these patients met the exclusion criteria and were omitted from the study (2 pregnant women, 4 patients

<18 years old, 13 patients with do-not-resuscitate orders, and 15 patients in a late stage of sepsis upon admission to our ICU, *Figure 1*). The remaining 263 patients included 162 survivors and 101 non-survivors, with an overall 28-day mortality of 38%.

All variables except for the type of patient were comparable between the treatment and control groups (*Table 1*). In the treatment group, patients received ulinastatin for a median of 5 days (IQR: 3–11 days). We further compared baseline characteristics between survivors and non-survivors. As expected, non-survivors had higher APACHE II and SOFA scores than survivors (APACHE II: 24 for non-survivors, 19 for survivors;  $P<0.001$ ; SOFA: 11 for non-survivors, 7 for survivors;  $P<0.001$ ). Survivors were younger (median age of survivors: 70 years, median age of non-survivors: 77;  $P<0.001$ ) and had a significantly higher WBC count on day 1 (survivors:  $11.52 \times 10^9/L$ , non-survivors:  $10.95 \times 10^9/L$ ;  $P=0.034$ ) than non-survivors. Other laboratory variables such as interleukin 6, PCT, CRP, proBNP, and platelet count did not significantly differ between both groups at baseline. Gender was not associated with mortality outcome ( $P=0.125$ ). Non-survivors were more likely to use vasopressors (proportion for non-survivors: 0.88, survivors: 0.57;  $P<0.001$ ), while the survivor group contained more surgical patients than the non-survivor group (survivors: 0.15, non-survivors: 0.08;  $P<0.001$ ).

*Table 2* shows the clinical outcomes of the treatment and control groups. There were 179 patients that received ulinastatin treatment during ICU stay and 84 control patients. Patients receiving ulinastatin showed a significantly lower mortality rate during the 28-day follow-up period (treatment group: 0.31, control group: 0.55;  $P<0.001$ ). Nevertheless, patients in the treatment group experienced a longer duration of MV [treatment group: 3 days (IQR: 1–7 days), control group: 0 days (IQR: 0–3 days) in the control group;  $P<0.001$ ], length of stay (LOS) in the ICU [treatment group: 5 days (IQR: 3–11 days), control group: 1 day (IQR: 0–6 days);  $P<0.001$ ], and hospital stay [treatment group: 16 days (IQR: 7–27 days), control group: 10 days (IQR: 2–21 days);  $P<0.001$ ] compared to the control group. The duration of vasopressor use did not significantly differ between both groups. Both CRP and PCT were significantly more reduced in the treatment group than in the control group.

After adjustment for age, SOFA, vasopressor use, patient type, and fluid balance, the multivariable regression model revealed a significantly reduced risk of death associated with

**Table 1** Comparison of baseline characteristics between the treatment and control groups

Variables	Total (n=263)	Control (n=84)	Ulinastatin (n=179)	P
Age, years (IQR)	72 (62 to 81)	73 (62 to 83)	72 (62 to 80)	0.567
Sex (male), n [%]	175 [67]	54 [64]	121 [68]	0.696
APACHE II score (IQR)	21 (17 to 26)	19 (16 to 26)	22 (17 to 26)	0.624
SOFA score (IQR)	9 (6 to 12)	9 (5 to 13)	9 (6 to 12)	0.719
Laboratory variables on day 1, median (IQR)				
WBC count ( $\times 10^9/L$ )	11.52 (7.25 to 17.29)	11.74 (7.2 to 15.92)	11.4 (7.25 to 18.52)	0.766
Neutrophil percent on day 1 (%)	88.07 (81.34 to 92.63)	88.41 (81.9 to 92.7)	87.40 (81.24 to 92.6)	0.897
Causes of sepsis, n [%]				0.840
Community-acquired infection	73 [28]	24 [29]	49 [27]	
Nosocomial infections	190 [72]	60 [71]	130 [73]	
Lactate (mmol/L)	3.45 $\pm$ 1.23	3.11 $\pm$ 1.33	4.23 $\pm$ 1.14	0.065
Serum creatinine (mg/dL)	1.98 $\pm$ 1.11	1.87 $\pm$ 1.22	2.02 $\pm$ 0.99	0.078
Platelet count ( $\times 10^9/L$ )	127 (69 to 173)	123 (62.25 to 167.5)	129 (70 to 173.5)	0.779
Interleukin 6 (pg/mL)	164.3 (46.61 to 959.4)	130.4 (62.44 to 947.1)	182.5 (39.83 to 958.2)	0.822
PCT (ng/mL)	6.39 (1.26 to 47.09)	8.41 (0.54 to 37.42)	6.25 (1.54 to 49.1)	0.726
CRP (mg/L)	133.3 (65.9 to 215)	138 (68.4 to 240)	122.5 (53.75 to 183)	0.198
proBNP (pg/mL)	5,142 (1,846 to 15,040)	4,854 (1,468 to 19,740)	5,215 (1,942 to 14,230)	0.822
Day 1 fluid balance, median (IQR)	2,314 (1,232 to 4,356)	2,219 (1,123 to 4,214)	2,412 (1,223 to 4,432)	0.053
Ventilator use, n [%]	97 [37]	36 [43]	61 [34]	0.169
Vasopressor use, n [%]	182 [69]	60 [71]	122 [68]	0.695
Type of patients, n [%]				0.004
Elective surgery	32 [12]	5 [6]	27 [15]	
Emergency surgery	41 [16]	7 [8]	34 [19]	
Medical	190 [72]	72 [86]	118 [66]	

Chi-square test or Fisher's exact test was employed for comparison of categorical variables. Mann-Whitney U test was used for continuous variables. APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; IQR, interquartile range; PCT, procalcitonin; proBNP, pro B-type natriuretic peptide; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

**Table 2** Comparison of outcomes between treatment and control groups

Clinical outcomes	Total (n=263)	Control (n=84)	Ulinastatin (n=179)	P
28-day mortality, n [%]	101 [38]	46 [55]	55 [31]	<0.001
Hospital LOS (days), median (IQR)	14 (6 to 26)	10 (2 to 21)	16 (7 to 27)	0.004
Duration of MV (days), median (IQR)	2 (0 to 6)	0 (0 to 3)	3 (1 to 7)	<0.001
ICU LOS (days), median (IQR)	4 (2 to 10)	1 (0 to 6)	5 (3 to 11)	<0.001
Antibiotics duration (days), median (IQR)	11 (6 to 20)	8 (3 to 19)	13 (7 to 20)	0.003
Duration of vasopressor (days), median (IQR)	2 (0 to 4)	2 (0 to 3)	2 (0 to 4)	0.603
Changes of CRP on day 3 (mg/L), median (IQR)	-23.3 (-54.3 to -11.2)	-18.1 (12.2 to -23.4)	-35.6 (-67.9 to -23.5)	0.002
Changes of WBC count on day 3 ( $\times 10^9/L$ ), median (IQR)	-3.1 (-4.5 to 3.4)	-2.2 (-3.5 to 4.5)	-3.5 (-5.4 to 3.2)	0.345
Changes of proBNP on day 3 (pg/mL), median (IQR)	-1,243 (-1,545 to 1,123)	-124 (-1,143 to 1,324)	-1,545 (-1,754 to 1,098)	0.445
Changes of PCT on day 3 (ng/mL), median (IQR)	-4.5 (-5.4 to -2.2)	-2.5 (-6.4 to -1.4)	-5.5 (-7.4 to -3.2)	0.031

ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; PCT, procalcitonin; proBNP, pro B-type natriuretic peptide; WBC, white blood cell.

ulinastatin use (OR: 0.317, 95% CI: 0.158–0.621;  $P=0.001$ ) (Table 3). Figure 1 shows the Kaplan-Meier curve for the treatment and control groups. The model discrimination was optimal as reflected by a C-index of 0.808.

## Discussion

The present study demonstrates that ulinastatin treatment is associated with decreased 28-day mortality in critically ill septic patients. This association remained robust even after adjustment for the severity of illness as determined by the SOFA score. Nonetheless, our study also showed that ulinastatin was associated with prolonged ICU and hospital stays. We suggest that ulinastatin treatment may help ICU patients to survive the critical phase of sepsis. This group of patients typically requires a longer recovery time before discharge from the hospital.

Our findings are consistent with those of previous studies assessing the effect of ulinastatin on sepsis patients. Karnad *et al.* investigated ulinastatin treatment of 122 sepsis patients with one or more organ failures (24) and discovered that the 28-day all-cause mortality in the ulinastatin group was 7.3 % (4 deaths) versus 20.3 % (12 deaths) in the placebo group ( $P=0.045$ ). The OR was 0.26 (95% CI: 0.07–0.95), which exceeds that reported in our study. Nevertheless, the results obtained in other studies do not agree with our observations. Uchida *et al.* found no association between ulinastatin treatment and 28-day mortality (OR: 1.22; 95% CI: 0.54–2.79) after adjustment for severity of illness and other confounding factors (11). These differences might reflect the higher age of the patients included in that particular study compared to those assessed in our study.

A proposed mechanism for the beneficial effect of ulinastatin is amelioration of the inflammatory response in sepsis patients. There is a large body of evidence from animal studies showing that ulinastatin treatment reduced inflammatory damage caused by sepsis (7,10,25,26). For example, Cao *et al.* reported that ulinastatin ameliorated inflammatory damage by modulating the quantity and function of Tregs via the TLR4/NF- $\kappa$ B signaling pathway (10); these biomarkers were not assessed in our clinical study. Nevertheless, we examined changes in inflammatory biomarkers such as CRP and PCT and observed that the levels of these biomarkers dropped to a greater extent in the treatment group than in the control group. Our findings therefore also support the previously observed anti-inflammatory properties of ulinastatin.

Zheng *et al.* performed a systematic review and meta-



**Table 3** Logistic regression model for analysis of an independent effect of ulinastatin on 28-day mortality

Variables	OR	95% CI	P
Age (for each 1-year increase)	1.025	1.001–1.050	0.051
SOFA (for each 1-point increase)	1.124	0.112–1.201	0.026
Fluid balance on day 1 (for each 1,000 mL increase)	1.231	1.123–1.424	0.034
Use of MV	2.121	1.089–2.454	0.021
Type of patients (elective surgery as reference)			
Emergency surgery	1.011	0.881–1.563	0.563
Medical	2.432	1.562–2.984	<0.001
Vasopressor use	3.846	1.775–8.771	0.001
Ulinastatin	0.317	0.158–0.621	0.001

OR corresponds to one unit increase for continuous variables. CI, confidence interval; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

analysis of 16 studies (27) and found that treatment with ulinastatin in combination with Xuebijing (a Chinese patent medicine for the symptomatic treatment of sepsis, promoting blood circulation and preventing blood stasis) reduced the mortality rate [relative risk (RR) 0.54, 95% CI: 0.41–0.70;  $P < 0.001$ ], APACHE II score on day 7 [standardized mean difference (SMD) = -1.21, 95% CI: -1.62 to -0.80,  $P < 0.01$ ], duration of MV (SMD = -1.21, 95% CI: -1.62 to -0.80;  $P < 0.01$ ), and length of stay in the ICU (SMD = -1.21, 95% CI: -1.62 to -0.80;  $P < 0.01$ ). While the effect on mortality outcome was consistent with our study, we could not replicate the effects on MV duration and ICU length of stay. The concomitant use of Xuebijing (i.e., another agent with anti-inflammatory effects) in the study by Zheng *et al.* may lead to a synergistic effect of ulinastatin and Xuebijing in the treatment of critically ill patients with sepsis and explain the differences with our results (28,29). Combination of ulinastatin with other inflammation modulatory agents such as thymosin  $\alpha 1$  that is known to restore immune function via enhancing cell-mediated immunity has proven promising in reducing mortality (30,31).

Several limitations of our study should be acknowledged. First, the retrospective design may result in selection bias. There might have been unmeasured confounders as patients receiving ulinastatin differed in many aspects from those in the control group. For example, we cannot exclude confounding by indication as the use of ulinastatin was at the discretion of the treating physician. The standard approach to adjust for such confounders is the use of a multivariable regression model, which we employed to

incorporate such potential confounding factors such as age, SOFA, vasopressor use, and MV use. The results remained robust despite these adjustments. Nonetheless, certain unmeasured confounders cannot be addressed in observational studies and thus randomized controlled trials are mandatory to issue any recommendations for routine ulinastatin use. The ongoing ADJUST trial, a randomized controlled trial assessing the efficacy of ulinastatin compared to placebo in improving mortality outcome, will provide important evidence for such recommendations (32). A second limitation of our study was the lack of other anti-inflammatory agents such as Xuebijing and thymosin  $\alpha 1$  that are not used in our hospital and we could therefore not determine any synergistic effects of these agents with ulinastatin.

## Conclusions

In conclusion, we discovered that treatment with ulinastatin was associated with a decreased 28-day mortality in critically ill septic patients. Future randomized controlled trials are required before recommendations on ulinastatin use in critically ill patients can be issued.

## Acknowledgments

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

**Ethical Statement:** The ethics committee of Wuhu No. 2 People's Hospital approved the study protocol (approval number: 201804). Informed consent was waived due to the retrospective design of the study.

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**Cite this article as:** Xu Q, Yan Q, Chen S. Use of ulinastatin was associated with reduced mortality in critically ill patients with sepsis. *J Thorac Dis* 2019;11(5):1911-1918. doi: 10.21037/jtd.2019.05.03