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Efficacy of Ulinastatin in the Treatment of COVID-19: A Retrospective Study

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Purpose: This retrospective study aimed to evaluate the efficacy of ulinastatin in the treatment of COVID-19 patients compared to conventional therapy.

Patients and Methods: A total of 437 COVID-19 patients admitted to the Respiratory Oncology Department of our hospital between December 31, 2022, and July 8, 2023, were included in the study. Patients were classified into the observation group (n=62) receiving ulinastatin in addition to standard treatment and the control group (n=347) receiving standard treatment only. Clinical information, laboratory results, and treatment outcomes were collected and analyzed.

Results: The observation group showed an improvement in lymphocyte count compared to the control group. The clinical improvement rate in patients receiving ulinastatin for 7 days or longer was 92.1%, significantly higher than that of patients treated for less than 7 days (62.5%) and those receiving standard treatment (71.0%). No significant difference in total length of hospitalization was observed between the two groups, and no related adverse events occurred in either group.

Conclusion: Ulinastatin treatment improves lymphocyte counts in severe COVID-19 patients, and the clinical improvement rate is significantly higher with treatment duration of 7 days or longer. Larger-scale randomized controlled trials are warranted to further explore the role of ulinastatin in the management of COVID-19.

Keywords: COVID-19, ulinastatin, severe cases, clinical improvement, radiographic findings

Introduction

The coronavirus disease-2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a widespread respiratory infection with high infectivity and rapid transmission, resulting in a global health crisis.[1–3] While the majority of COVID-19 patients exhibit mild to moderate symptoms, such as upper respiratory tract infections and mild pneumonia, a subset may progress to severe pneumonia with a higher mortality rate.[4] Antiviral therapy has become a standard treatment approach, but effective drugs targeting inflammation remain limited.[5,6] Severe COVID-19 cases are characterized by a cytokine storm, marked by significantly elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and IL-1β, which are believed to play a crucial role in disease progression, exacerbation, and even mortality.[7]

The urgent need for effective therapeutic options has prompted investigations into repurposing existing drugs. Ulinastatin, a natural pancreatic enzyme inhibitor, is an endogenous modulator of the human inflammatory response, capable of reducing levels of pro-inflammatory cytokines (IL-6, IFN-γ, TNF-α) and inflammatory biomarkers, such as C-reactive protein (CRP).[8] It is emerging as a promising therapeutic candidate for the treatment of severe COVID-19. Numerous studies, have confirmed the significant role of ulinastatin in the treatment of acute respiratory distress syndrome (ARDS) and acute lung injury.[8–11] Experts has pointed out that ulinastatin shares similar pathophysiological features with organ damage associated with COVID-19 and recommend daily administration of 1 million units of ulinastatin for the prevention and treatment of cytokine storms induced by COVID-19.[12] In a multicenter retrospective

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study, the addition of ulinastatin to standard therapy was associated with reduced 30-day mortality.[13] Potential mechanisms include immune modulation, anti-inflammatory effects, cytokine storm suppression, and prevention of the progression to new organ dysfunction.[13] However, whether ulinastatin can be recommended as a standard therapeutic agent for COVID-19 remains uncertain, as its clinical benefits have yet to be fully elucidated.[14] Based on these findings, we hypothesize that ulinastatin, due to its anti-inflammatory properties, may improve clinical outcomes in patients with severe COVID-19 by reducing inflammation. Thus, in this study, we aim to retrospectively compare cases treated with ulinastatin to those not receiving ulinastatin, summarizing the efficacy of ulinastatin in patients with COVID-19 pneumonia.

Materials and Methods

Ethical Statement

This study received approval from the Ethics Committee of Cangzhou Fifth Hospital (People's Hospital of Qingxian) (Approval Number 20240101) and adhered to the Helsinki Declaration, obtaining prior consent from the patients.

Study Design and Participants

This retrospective study focuses on patients admitted to the respiratory oncology department of our hospital from December 31, 2022, to July 8, 2023, for the treatment of COVID-19. The department was designated for the management of COVID-19 patients aged 18 and above. Inclusion criteria consisted of patients diagnosed with moderate to critical COVID-19, based on the clinical classification of COVID-19 severity as outlined in the Diagnosis and Treatment Plan for novel coronavirus Infection (Trial Version 10).[15] Moderate COVID-19 was defined as persistent fever lasting >3 days and/or symptoms such as cough or dyspnea, with a respiratory rate (RR) <30 breaths/min and an oxygen saturation (SpO_2) >93% on room air. Imaging should show characteristic features of COVID-19 pneumonia. Severe COVID-19 was defined by the presence of any of the following, not attributable to causes other than COVID-19 infection: 1) dyspnea with RR ≥30 breaths/min; 2) SpO_2 ≤93% on room air at rest; 3) a PaO_2/FiO_2 ratio ≤300 mmHg (1 mmHg = 0.133 kPa), with adjustment for high-altitude areas (altitudes >1000 meters) using the formula: PaO_2/FiO_2 × [760/atmospheric pressure (mmHg)]; 4) worsening clinical symptoms with significant lesion progression (>50%) on chest imaging within 24–48 hours. Critical COVID-19 was defined by one of the following: 1) respiratory failure requiring mechanical ventilation; 2) shock; 3) combined with other organ failure necessitating ICU monitoring. Exclusion criteria included age under 18 years old, incomplete medical records (including missing laboratory tests and chest CT scans), chronic moderate to severe hepatic dysfunction, need for chemotherapy, advanced malignant tumors, and mild COVID-19 cases. Pregnant patients were also excluded. The patient selection process is illustrated in Figure 1. Follow-up commenced from the day of confirmed COVID-19 hospital admission and concluded on the day of discharge if the patient did not return for further follow-up. The median follow-up period was 13 days, with an interquartile range (IQR) of 5 to 38 days.

Addressing Potential Selection Bias

To address the comparability of groups, we used a computer-generated random number system to randomly select moderate cases from the control group to match the number of the observation group. This ensured that the distribution of disease severity within the control group closely matched that of the observation group. To mitigate selection bias inherent to retrospective study designs, matching on baseline characteristics was performed to equalize distribution in disease severity and key demographic factors.

Intervention

All patients received standard treatment, including oxygen therapy, antiviral drugs, steroids, and antibiotics. Antiviral therapy included the standard doses of favipiravir and nirmatrelvir, administered for 5 days. Azvudine was given at a dose of 5 mg once daily for 7 days. The observation group received ulinastatin (Guangdong Tianpu Biochemical and Pharmaceutical Co., Ltd., 10,000 U with 10 mL of saline, intravenous injection three times a day for 3–10 days). The control group received conventional treatment.

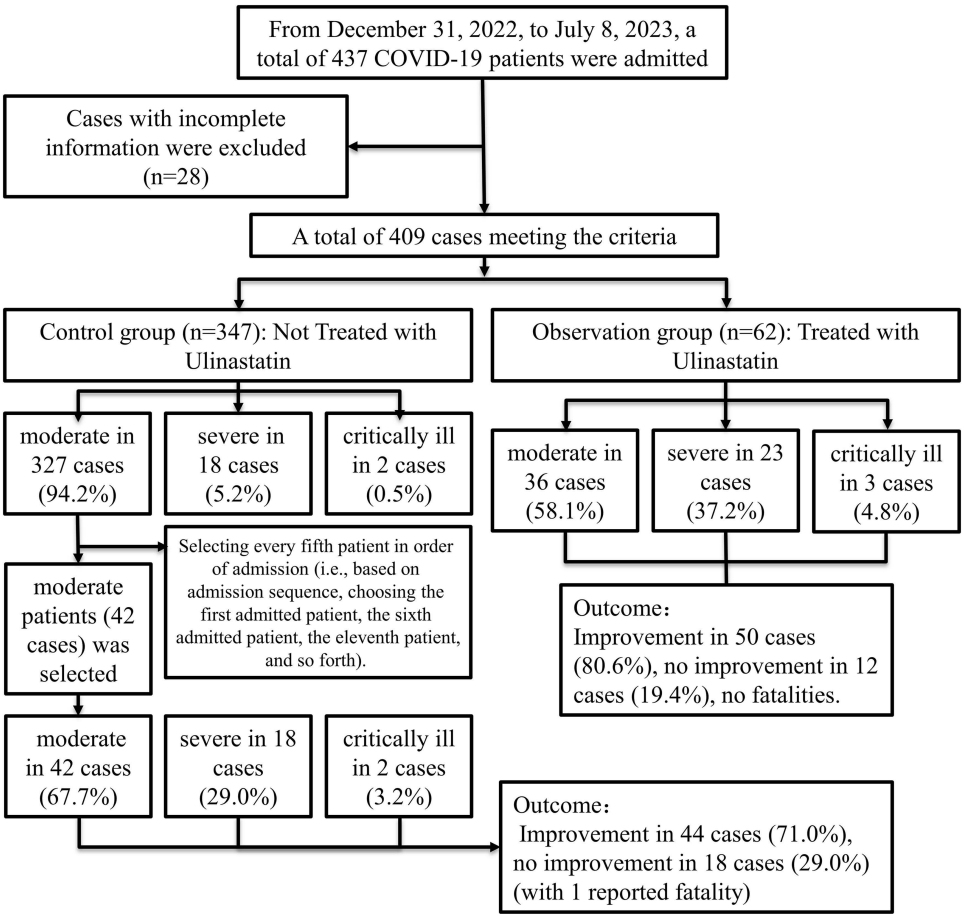

Figure 1 Flowchart of patient selection.

Data Collection

Clinical information for all patients was extracted from the hospital's electronic medical record system, encompassing electronic medical records, medication records, laboratory results, and radiological examinations. Data on patient characteristics, including age, gender, symptoms, and comorbidities such as hypertension, diabetes, cardiovascular diseases, and chronic obstructive pulmonary disease, were collected. Laboratory variables including white blood cell (WBC) count, lymphocyte count, erythrocyte sedimentation rate, C-reactive protein (CRP), total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, and creatinine were obtained upon admission.

Statistical Analysis

SPSS (PASW) 17.0 software was used for statistical analysis. As the Shapiro–Wilk normality test indicated that none of the continuous variables in this study followed a normal distribution, these variables were expressed as median with range. Categorical variables were presented as frequencies and percentages. Mann–Whitney *U*-test was used for comparing continuous variables, while chi-square or Fisher exact test was employed for evaluating categorical variables. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

From December 31, 2022, to July 8, 2023, a total of 437 cases of COVID-19 pneumonia were admitted. Cases with incomplete information and those treated with ulinastatin for less than 3 days (28 cases) were excluded, leaving 409 cases.

Among them, 62 cases received ulinastatin, with severity distribution as follows: moderate in 36 cases (58.1%), severe in 23 cases (37.2%), and critical in 3 cases (4.8%). All 26 patients with severe or critical conditions were monitored via electrocardiography. The control group, consisting of 347 cases not treated with ulinastatin, had a distribution of moderate in 327 cases (94.2%), severe in 18 cases (5.2%), and critical in 2 cases (0.5%). Electrocardiographic monitoring was provided to 20 patients with severe or critical conditions. Due to the preferential selection of ulinastatin for more severe cases and its lack of reimbursement, patients exhibited variability in its usage duration, resulting in a higher proportion of moderate cases in the control group. To address this, 42 moderate cases were randomly selected from the control group, yielding a final control group of 62 cases with a distribution of moderate in 42 cases (67.7%), severe in 18 cases (29.0%), and critical in 2 cases (3.2%) (Figure 1). A comparative analysis of these 124 cases was conducted, and detailed information is presented in Table 1. Gender, age, time from onset to admission, and baseline comorbidities showed no statistically significant differences between the observation and control groups, ensuring comparability.

Primary Symptoms and Signs

In the observation group, 58 cases (93.5%) presented with fever, with a temperature of 38.1 (36.7–39.4) °C, and 58 cases (93.5%) exhibited cough. Additionally, 43 cases (69.4%) reported chest tightness or shortness of breath, while other symptoms included muscle pain, fatigue, and sore throat. In the control group, 59 cases (96.7%) had fever, with a temperature of 38.2 (37–39.3) °C, and 55 cases (90.2%) had cough. Chest tightness or shortness of breath was reported in 36 cases (59.0%). Other symptoms included muscle pain, fatigue, and sore throat. In the observation group, 4 patients were readmitted due to COVID-19, while 3 patients in the control group experienced the same; all were treated and discharged after improvement. No statistically significant differences in major symptoms and signs were observed between the two groups, ensuring comparability (Table 1).

Antiviral Treatment

In the observation group, 56 cases (90.32%) received antiviral treatment, with 32 cases (51.6%) using favipiravir, 4 cases using nirmatrelvir, and 16 cases (25.8%) using azvudine. Four cases initially on oral azvudine with poor response switched to favipiravir, and 4 cases received oral nirmatrelvir. Six cases did not receive antiviral medications. In the control group, 55 cases underwent antiviral treatment, with 38 cases (61.2%) using favipiravir and 17 cases (27.4%) using azvudine, while 7 cases (11.3%) did not receive antiviral treatment. No statistically significant differences in antiviral treatment were observed between the two groups (Table 1).

Table 1 Patient Characteristics of Two Patient Groups

Characteristics	Observation Group (n=62)	Control Group (n=62)	Z/χ^2 Value	P-value Value
Sex			0.033	0.857
Men	35 (56.5%)	34 (54.8%)		
Women	27 (43.5%)	28 (45.2%)		
Age, Yrs	70 (29–87)	72.5 (36–86)	−1.25	0.211
Time from Onset to Admission, Days	6 (1–20)	6.5 (1–15)	−0.291	0.771
Fever	58 (93.5%)	59 (96.7%)	0.151	0.697
Body Temperature, °C	38.1 (36.7–39.4)	38.2 (37–39.3)	−1.439	0.150
Cough	58 (93.5%)	55 (90.2%)	0.898	0.343
Chest Tightness, Shortness of Breath	43 (69.4%)	36 (59.0%)	1.709	0.191
Comorbidities	50 (80.6%)	48 (78.7%)	0.195	0.659
Antiviral Treatment	56 (90.32%)	55 (88.71%)	0.334	0.563

Note: Values for categorical variables are presented as frequencies (percentages), and continuous variables are presented as medians (range). Z/χ^2 represents the statistical test used for comparison, and P-value indicates the level of significance.

Laboratory Parameters Comparison

Laboratory variables, including white blood cell (WBC) count, lymphocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total bilirubin (TB), alanine transaminase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), and creatinine (Cr), showed no statistically significant differences between the observation and control groups, indicating comparability (Table 2).

Clinical Efficacy

After treatment, CT images showed improvement in pneumonia absorption compared to previous scans. Pneumonia areas had reduced, indicating improvement, sometimes accompanied by decreased density; images without reduction or enlargement indicated no improvement, as depicted in Figure 2. In the observation group, 50 cases (80.6%) showed improvement, while 12 cases (19.4%) showed no improvement. There were no deaths. In the control group, 44 cases (71.0%) showed improvement, 18 cases (29.0%) showed no improvement (including 1 death), with no significant difference (P=0.294) (Figure 3A).

Comparison of Pre- and Post-Treatment Indicators

The lymphocyte counts showed no significant difference before treatment but exhibited a significant difference after treatment (*P*=0.04) (Figure 4A). Oxygen partial pressure and WBC count showed no significant difference between the two groups (Figure 4B and C).

Hospitalization Duration

Furthermore, we compared the hospitalization durations of the two groups (Figure 5). The observation group had a hospitalization duration ranging from 6 to 20 days, with a median of 8.5 days. The control group had a duration ranging from 6 to 34 days, with a median of 11.5 days. No significant differences were observed between the two groups (P=0.317) (Figure 5). Both groups had no relevant adverse events.

Subgroup Analysis

Subgroup analysis was conducted comparing patients treated with ulinastatin for 7 days or more (≥7 days) versus those treated for less than 7 days (<7 days). The results revealed a significant difference in improvement rates (P=0.011). In the <7-day treatment group, 15 patients (62.5%) showed improvement, while 12 patients (37.5%) did not. In the ≥7-day treatment group, 35 patients (92.1%) improved, and 3 patients (7.9%) did not (Figure 3B). Further comparative analysis

Table 2 Laboratory Test Results of Two Patient Groups

Laboratory Parameter	Observation Group (n=62)	Control Group (n=62)	Z/χ2 Value	P value
White Blood Cell Count (10^9/L)	7.56 (2.43–16.3)	6.18 (2.8–14.5)	−1.919	0.055
Lymphocyte Count (×10^9/L)	0.92 (0.18–5.89)	1.12 (0.19–20.2)	−0.775	0.439
C-reactive Protein (mg/L)	47 (4.6–147)	38.9 (1–193)	−1.922	0.055
Procalcitonin (ng/mL)	0.05 (0.02–0.62)	0.04 (0.01–0.67)	−1.786	0.074
Oxygen Partial Pressure (mmHg)	72 (50–99)	75.98 (44.71–95)	−0.935	0.350
Total Bilirubin (umol/L)	8.52 (4.05–23.2)	8.03 (5.35–17.88)	−0.102	0.918
ALT (U/L)	21 (9–84)	23 (4–358)	−1.32	0.187
AST (U/L)	24 (14–40)	26.5 (10–239)	−0.971	0.332
Blood Urea Nitrogen (mmol/L)	5.72 (3.21–17.3)	6.76 (3.7–18)	−1.566	0.117
Creatinine (umol/L)	69.7 (20–159)	69 (7.48–111)	−0.261	0.794
Erythrocyte Sedimentation Rate (mm/h)	55 (14–140)	46 (11–97)	−1.88	0.060

Note: Values are presented as median (range) for non-normally distributed data. Z/χ2 values and P values are calculated for the comparison between the Observation Group and the Control Group.

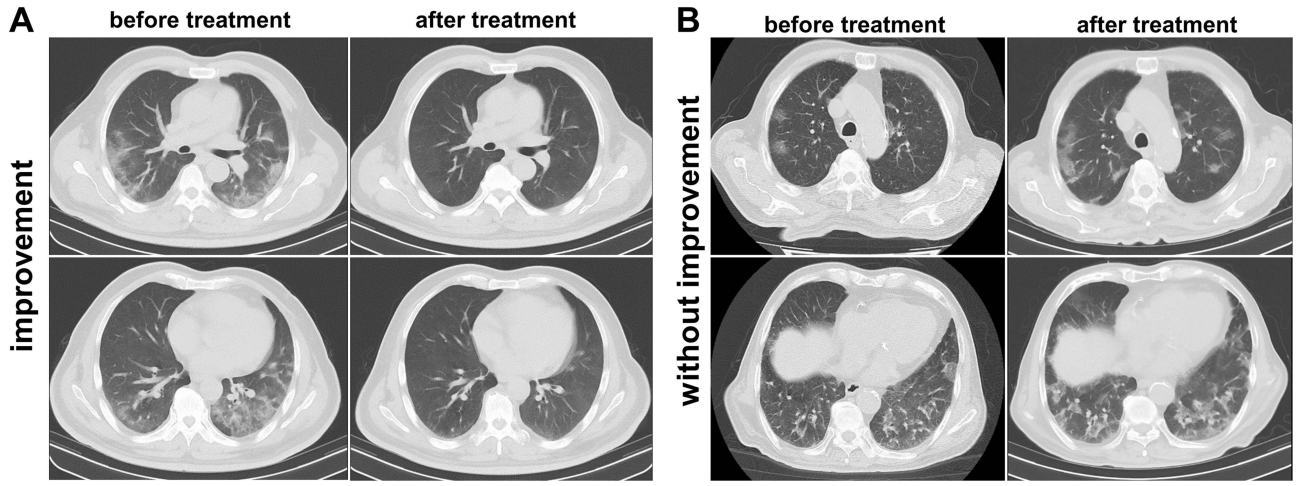

Figure 2 CT images depict the absorption status of pneumonia before and after treatment. (**A**) The pneumonia area has decreased, indicating a pronounced therapeutic effect and improvement in the condition. (**B**) The image of the pneumonia area does not show a reduction, and there is even a trend of enlargement, suggesting poor treatment efficacy and a lack of significant improvement in the condition.

was performed on the severity, ICU intubation rates, clinical response, and length of hospital stay between the control group and the ulinastatin ≥7-day treatment group. No significant differences were observed between the two groups in terms of COVID-19 severity, ICU intubation rates, and length of hospitalization (P>0.05, Table 3). However, the improvement rate in the ≥7-day ulinastatin group was 92.1%, which was significantly higher compared to the control group (P=0.012).

Discussion

SARS-CoV-2 emerged and rapidly disseminated globally, triggering a devastating pandemic with a substantial burden of severe cases and fatalities, profoundly impacting the global healthcare systems.[1–3] Despite the potential immunomodulatory role of ulinastatin, clinical evidence regarding its application in COVID-19 remains limited. Huang et al demonstrated potential beneficial effects of high-dose ulinastatin in treating COVID-19 patients.[16] Mehta et al concluded that early administration of ulinastatin may improve the prognosis of critically ill patients who do not require intubation.[13] Preliminary data in our study suggest superior outcomes in the ulinastatin observation group compared to the control group, particularly with a duration of ulinastatin application exceeding 7 days.

This article assesses the disparity in clinical improvement rates between ulinastatin and conventional treatment, observing a higher clinical improvement rate with ulinastatin. However, constrained by sample size, the final examination results failed to yield significant evidence. Similarly, Jain's study found no significant benefit of ulinastatin on ICU length of stay or overall mortality in COVID-19 patients.[14] Nevertheless, stratifying ulinastatin subgroups (>7 days and <7 days) revealed greater benefits in patients receiving ulinastatin for over 7 days. Notably, no conspicuous adverse reactions were observed in ulinastatin treatment, suggesting benefits with application for ≥7 days, with potential for dose escalation. This aligns with earlier preliminary research indicating the safety and potential beneficial effects of high-dose ulinastatin in COVID-19 patients.[16] Furthermore, while corticosteroids and IL-6 inhibitors have demonstrated efficacy in treating COVID-19, their widespread use has been associated with opportunistic infections, such as mucormycosis.[17,18] Ulinastatin's adverse reactions are rare, supported by a safety and tolerability study in adult healthy volunteers, demonstrating no severe adverse reactions with an 8,000,000 IU ulinastatin intravenous infusion within 2 h.[19] Although research on ulinastatin's application in COVID-19 is lacking, prior studies on other diseases have shown benefits, including shortened hospital stays and potential mortality reduction.[20–22] In this study, there was no significant difference in hospitalization duration between the two groups of patients, with no observed deaths in the ulinastatin group compared to 1 death in the control group. The safety profile of ulinastatin makes it a promising candidate for further investigation as an adjunctive therapy in similar clinical contexts.

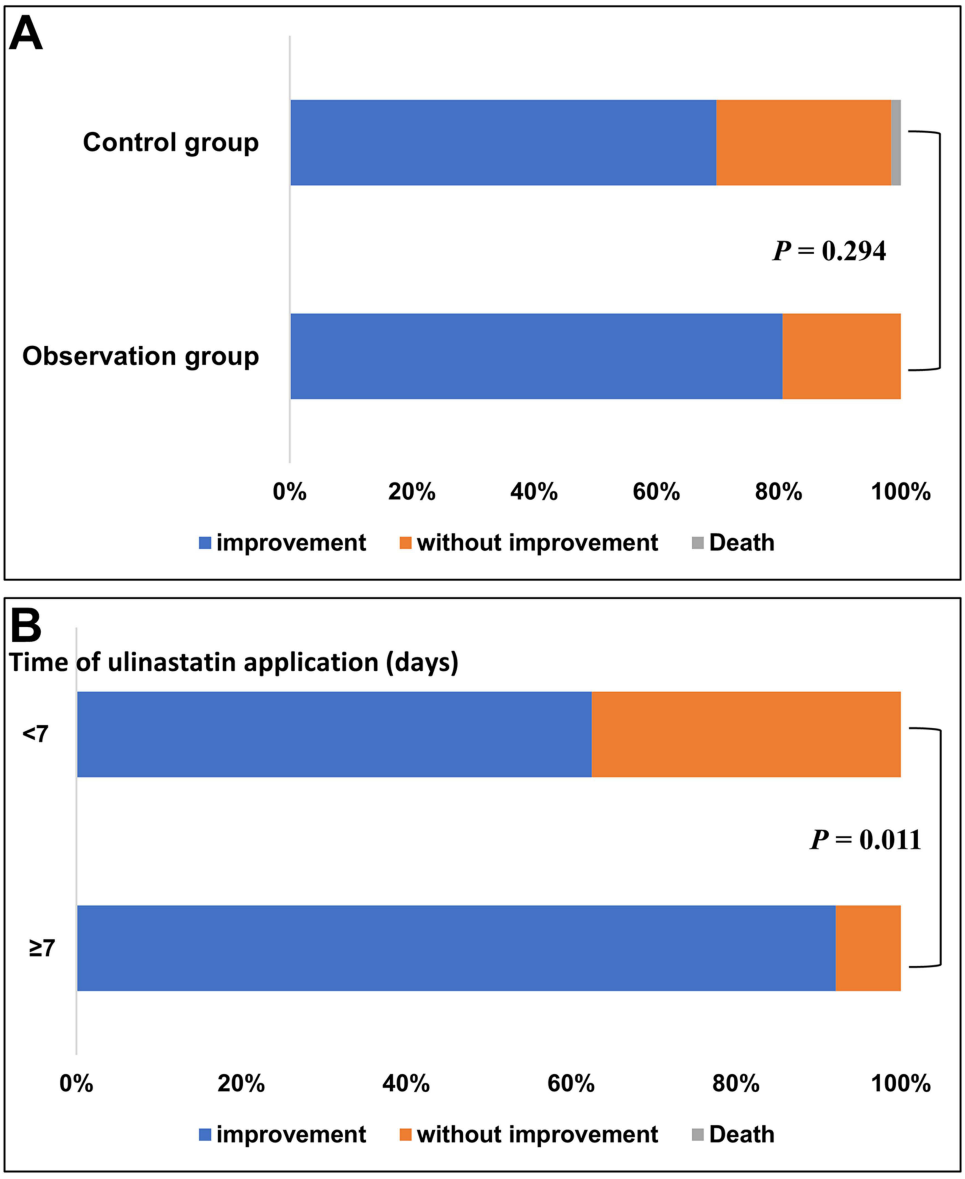

Figure 3 Therapeutic Efficacy Analysis. (**A**) Comparative assessment of therapeutic outcomes between the observation group and the control group. (**B**) Subgroup analysis comparing the efficacy of ulinastatin treatment for 7 days or more (≥7 days) and less than 7 days (<7 days) in patients.

Immunoregulatory imbalance has been identified as a primary pathogenic mechanism in COVID-19, involving decreased lymphocyte counts. Reports indicate that 63.0% to 82.1% of COVID-19 patients experience reduced circulating lymphocytes, with severe patients showing an 84.6% decrease, and mild patients a 4.4% decrease.[23] Lymphocyte level restoration serves as a prognostic indicator.[24] Ulinastatin regulates the binding of endothelial cells to monocytes, granulocytes, and lymphocytes, stabilizing lysosomal membranes and inhibiting the release of inflammatory factors.[16] In this study, ulinastatin treatment demonstrated a beneficial regulatory effect on lymphocyte counts in COVID-19 patients. A clinical study indicated that intravenous infusion of ulinastatin at 6×105 IU once daily, combined with non-invasive ventilation for one week, significantly reduced inflammation factors tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) levels in ARDS patients, improving blood gas parameters (arterial oxygen saturation, arterial oxygen pressure), exerting a lung-protective effect against ARDS.[25] Research findings suggest that ulinastatin significantly improves clinical symptoms in severe septic ARDS patients, reducing C-reactive protein, procalcitonin, and lactate concentrations, indicating effective infection control and anti-inflammatory effects in the

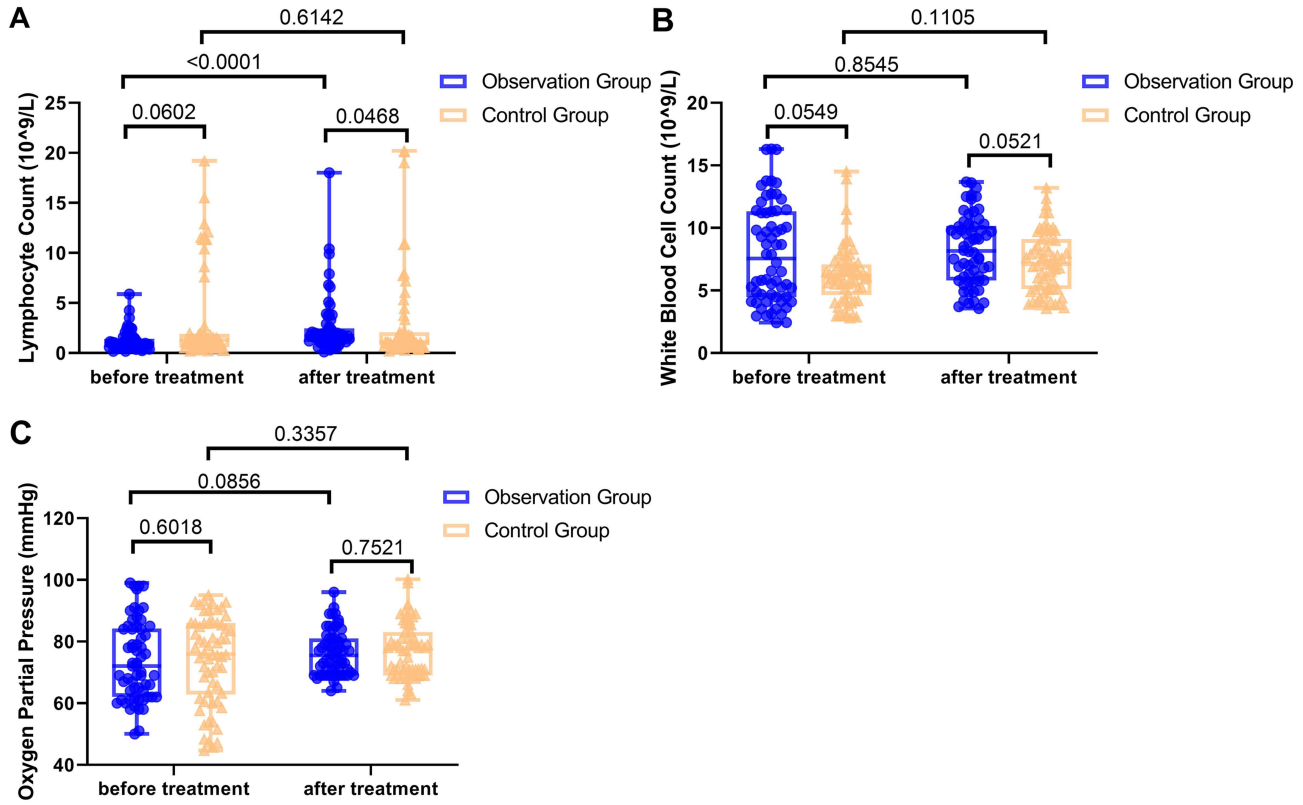

Figure 4 Comparative Analysis of Parameters Before and After Treatment. (**A**) Lymphocyte Count, (**B**) White Blood Cell Count, (**C**) Oxygen Partial Pressure.

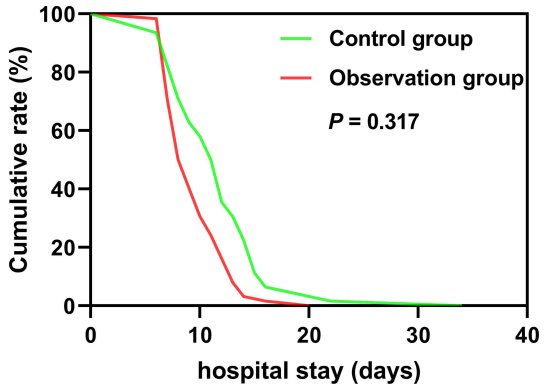

Figure 5 Compares the duration of hospitalization between two groups.

recovery process.[8,26] Unfortunately, due to limitations in hospital facilities, this study did not investigate changes in cytokines during treatment or compare differences in C-reactive protein before and after treatment.

This investigation faces several limitations. First, the single-center design may limit the generalizability of our findings, as patient demographics, treatment protocols, and healthcare resources can vary significantly between hospitals and regions. Moreover, our sample was relatively homogenous, lacking diversity in demographic backgrounds, which could affect the external validity of our results. Additionally, the absence of a multicenter design restricts our ability to confirm findings across varied clinical environments. Another limitation is the potential for confounding variables, as patient comorbidities and other concurrent treatments could influence outcomes. Though we adjusted for major factors in our analysis, the inherent observational nature of our study may not fully eliminate confounding, thus warranting cautious interpretation of the results. Future research should aim to expand on these findings in diverse and multicenter

Table 3 Comparison of Severity, ICU Intubation, Clinical Response, and Length of Hospitalization Between Patients Treated with Ulinastatin for ≥7 Days and the Control Group Characteristics

Characteristics	Ulinastatin Treatment ≥7 days (n=38)	Control Group (n=62)	Z/χ^2 Value	P-value
Sex			1.528	0.303
Men	22 (57.9%)	34 (54.8%)		
Women	16 (42.1%)	28 (45.2%)		
Age, Yrs	70.5 (44–85)	72.5 (36–86)	−1.507	0.132
Severity of Covid-19			1.361	0.531
Moderate	23 (60.5%)	42 (67.7%)		
Severe	12 (31.6%)	18 (29.0%)		
Critical	3 (7.9%)	2 (3.2%)		
Efficacy			6.345	0.012
Improvement	35(92.1%)	44(71.0%)		
Without improvement	3(7.9%)	18(29.0%)		
Intubated in ICU	3(7.9%)	2(3.2%)	1.081	0.365
Hospitalization Duration	12.0(7–20)	11.5(6–34)	−1.015	0.310

Note: Values are presented as median (range) for non-normally distributed data. Z/χ2 values and P values are calculated for the comparison between Ulinastatin Treatment ≥7 days Group and the Control Group.

populations to validate and refine our conclusions. Prospective trials assessing the optimal dosing, timing, and combination of ulinastatin with standard of care for COVID-19 patients would be particularly valuable. Additionally, we suggest further research on differential responses among varied patient demographics to establish broader applicability and refine treatment protocols across patient subgroups.

Conclusions

In conclusion, our findings suggest that ulinastatin treatment may offer notable benefits in managing severe COVID-19, particularly when administered for a duration of seven days or more. Specifically, patients who received ulinastatin demonstrated significant improvements in lymphocyte counts and alleviation of clinical symptoms, with no notable adverse reactions recorded. However, the study acknowledges its limitations, including a retrospective design, a small sample size, and a lack of population diversity, which may affect the generalizability of the findings. To further validate these results, future research should focus on randomized controlled trials and explore the long-term effects of ulinastatin across varying severity levels of COVID-19 in diverse populations. Additionally, the beneficial effects observed in COVID-19 may warrant investigation into ulinastatin's role in managing other conditions characterized by cytokine storms or severe inflammatory responses.

Data Sharing Statement

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

Ethical Approval

This study received approval from the Ethics Committee of Cangzhou Fifth Hospital (People's Hospital of Qingxian) (Approval Number 20240101) and adhered to the Helsinki Declaration. Written informed consent was obtained from the participant, who was fully informed about the purpose of the study.

Disclosure

Authors state no conflict of interest.

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