# High-dose vitamin C infusion for the treatment of critically ill COVID-19

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**Research**

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# Abstract

Background

No specific medication has been proven effective for the treatment of patients with severe coronavirus disease 2019 (COVID-19). Here, we tested whether high-dose vitamin C infusion was effective for severe COVID-19.

Methods

This randomized, controlled clinical trial was performed at 3 hospitals in Hubei, China. Patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the ICU were randomly assigned in as 1:1 ratio to either the high-dose intravenous vitamin C (HDIVC) or the placebo. HDIVC group received 12 g of vitamin C/50 ml every 12 hours for 7 days at a rate of 12 ml/hour, and the placebo group received bacteriostatic water for injection in the same way. The primary outcome was invasive mechanical ventilation-free days in 28 days(IMVFD28). Secondary outcomes were 28-day mortality, organ failure, and inflammation progression.

Results

Fifty-four critical COVID-19 patients were ultimately recruited. There was no difference in IMVFD28 between two groups. During the 7-day treatment period, patients in the HDIVC group had a steady rise in the $PaO_2/FiO_2$ (day 7: 229 vs. 151 mmHg, 95% CI 33 to 122, P = 0.01). Patients with SOFA scores ≥ 3 in the HDIVC group exhibited a significant reduction in 28-day mortality (P = 0.05) in univariate survival analysis. IL-6 in the VC group was lower than that in the placebo group (19.42 vs. 158.00; 95% CI -301.72 to -29.79; P = 0.04) on day 7.

Conclusion

The addition of HDIVC may provide a protective clinical effect without any adverse events in critically ill patients with COVID-19.

Clinicaltrial.gov identifer: NCT04264533


# Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become a global health issue, with more than 400,000 deaths worldwide [1, 2]. While the majority of patients presented with mild symptoms and did not even need hospitalization[3], nearly 30% of adult patients suffer from severe pneumonia and acute respiratory distress syndrome (ARDS), often associated with sepsis or septic shock, and multiple organ (kidney, liver, and heart) failure. Patients with ARDS and systemic complications require critical care and[4] complicate with a higher risk of death (28%)[5, 6] Due to the lack of effective medications against SARS-COV-2, the main management is supportive therapy.

Similar to the pathophysiology of severe acute respiratory syndrome (SARS), SARS-CoV-2 infection stimulates the innate immune system, causing numerous types of cytokine release, namely, a “cytokine storm”, inducing systemic inflammatory response[7, 8] and multiple organ failure[9, 10]. A retrospective study on SARS suggested that the worsening after 2 weeks was not related to uncontrolled viral replication but related to immunopathological damage[11]. Therefore, antiviral therapy alone may be insufficient to treat COVID-19 patients.

Vitamin C (ascorbic acid, ascorbate) functions as a potent water-soluble antioxidant by directly scavenging oxygen free radicals and acting as an essential co-factor for the production of catecholamines, vasopressin, and cortisol in the human body[12]. Vitamin C is also found in high concentrations in leukocytes and implicated in several immune responses and functions[13]. Emerging evidence in preclinical studies indicated that vitamin C played a crucial role in ameliorating the effects of inflammation by inhibiting proinflammatory cytokine production, assisting immunoregulation, neutralizing reactive oxygen species (ROS), and protecting host cells[14, 15]. Hypovitaminosis C was ubiquitous in critically ill patients, and approximately 40% of the patients had a severe deficiency[16], while the low vitamin C serum level cannot be corrected by oral supplementation due to the issue of pharmacokinetics[17]. Thus, high-dose intravenous vitamin C (HDIVC) was added to the standard therapy of critically ill patients in recent studies, such as sepsis[18–20], ARDS[20, 21], cardiac surgery[22], and burn[23]. The results showed that HDIVC was safe for critically ill patients and significantly reduced vasopressor support[24], limited organ injury[25], shortened the duration of mechanical ventilation[26] and ICU stay[27], and improved survival rates[18]. Additionally, vitamin C has direct nonspecific antiviral activity in vitro[28], although it is unclear whether this confers any protection to humans with COVID-19.

Therefore, we hypothesized that HDIVC together with conventional treatments would improve the outcomes for adult patients admitted to the ICU due to severe COVID-19 by preventing cytokine storms and reducing lung and other organ injuries. In this context, we conducted this multicenter, randomized, blind clinical trial to provide a therapeutic strategy for critically ill patients with COVID-19.

# Methods

This study is a multicenter, randomized trial that was approved by the ethics committee of Zhongnan Hospital of Wuhan University (#2020001). This study was conducted in the ICUs of Zhongnan Hospital of Wuhan University, Leishenshan (Thunder God Mountain) Hospital, and Taihe Hospital from February 14, 2020, to March 29, 2020. The ICUs specifically for COVID-19 from Zhongnan Hospital and Leishenshan Hospital were managed by the same team. The trial was registered on the website of ClinicalTrials.gov (ID: NCT04264533) before patient recruitment.

### Patient enrollment

Patients were screened and enrolled following admission to the three ICUs. The following inclusion criteria were met: (1) age ≥18 and <80 years; (2) RT-PCR positive for SARS-CoV-2[29]; (3) pneumonia

confirmed by chest imaging[29]; (4) $PaO_2/FiO_2$(P/F) <300 mmHg; and (5) admission to the ICU. Exclusion criteria were allergy to vitamin C, pregnancy or breastfeeding, expected survival duration <24 hours, and previous history of glucose-6-phosphate dehydrogenase deficiency or end-stage pulmonary disease. Patients who were already enrolled in other clinical trials were excluded as well. If these criteria were met within 48 hours of ICU admission, informed consent was obtained from the patients or their family members. When the patients' actual treatment time was less than 3 days due to death or discharge from the ICU, they were removed from this trial. The reason was because the efficacies of the treatments could not be evaluated with limited times of treatment.

### Randomization and allocation

Each ICU was assigned with an independent random numeric table generated by Microsoft Excel 2019 by the primary investigator alone. Each table had equal numbers of 1 and 2, which represented the placebo group (bacteriostatic water infusion) and treatment group (HDIVC), respectively. Participants were enrolled in the corresponding group in an orderly manner.

### Study interventions

Patients were randomized to receive vitamin C or placebo within 48 hours after admission to the ICU. To control the infusion rates accurately and not affect the fluid management of severe patients, we infused vitamin C or placebo via central vein catheterization controlled by a pump. The study groups in this trial were 1) HDIVC: 24 g vitamin C per day. Patients were infused with 12 g vitamin C diluted in 50 ml of bacteriostatic water every 12 hours at a rate of 12 ml/hour by infusion pump for 7 days. 2) Placebo: 50 ml of bacteriostatic water infused every 12 hours at the same rate. Study interventions were initiated on the same day as informed consent and randomization. The preparation, transportation, storage, and use of therapies (VC and bacteriostatic water for injection) were in line with the drug management protocol in each hospital. In addition, other general treatments followed the latest COVID-19 guidelines[29]. Adverse events related to HDIVC included (1) nausea or vomiting during or after infusion of VC; (2) electrolyte disturbance; and (3) acute kidney injury. If any adverse events were observed in HDIVC patients, drug infusion was stopped immediately, and the patient was removed from the study.

### Data collection and management

Baseline data, which included demographics, anthropometrics, comorbid conditions, vital signs, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, and Glasgow coma scale (GCS) scores, were obtained on the day of randomization. Laboratory data, sequential organ failure assessment (SOFA) scores, $PaO_2/FiO_2$, and other treatments used were monitored on days 1, 3, and 7 (day 1 was defined as the day of the first administration of vitamin C).

The primary outcome of the study was IMV- free days in 28 days (IMVFD28). Secondary outcomes included 28-day mortality, organ functions and inflammatory parameters, including white blood cell counts, neutrophil counts, lymphocyte counts, procalcitonin, interleukin-6 (IL-6), and C-reactive protein

(CRP). Multi-organ dysfunction was assessed using SOFA scores.Additionally, vasopressor days, respiratory support days, invasive mechanical ventilation (IMV)-free days, patient condition improvement rate, patient condition deterioration rate, length of ICU and hospital stay, ICU and in-hospital mortality were recorded as additional secondary outcomes of this research. IMV-free days were defined as the number of days a patient was extubated after recruitment to day 28. If the patient died with MV, a value of zero was assigned. Deterioration of the patient's condition was defined as the patient requiring HFNC or NIV on day 1 and requiring ECMO or IMV, or dying, after 7 days of treatment. Improvement of the patient's condition was defined as the patient requiring ECMO or IMV on day 1 and switching to HFNC, NIV, or discharged from the ICU after 7 days of treatment. The P/F was calculated based on the $PaO_2/FiO_2$, and we choose the lowest values recorded on the specific day. All the data were collected from the clinical information system of three ICUs.

### Statistical analysis

The sample size was calculated according to primary endpoint, with a one-sided error rate (α) of 2.5%, a power of 80%, and a withdrawal rate of 10%. With the control of the epidemic, this trial was stopped early, and the number of qualifying COVID-19 patients did not satisfy the anticipated sample size(140). Numerical variables are described as the mean with standard deviation (SD) or median with interquartile range (IQR) according to distribution and were compared with the t-test/Mann-Whitney U test. Category data are represented as frequencies and proportions and compared with the chi-square test and Fisher's exact test. For the outcome variables, the hazard ratio and 95% CI were estimated by the Cox proportional risk model for mortality, and odds ratios with 95% CI were calculated by binary logistic regression for the other variables. Kaplan-Meier analysis was used to estimate the 28-day mortality to reflect the early survival differences for the two groups, and survival curves were compared with the Wilcoxon test. Survival analyses were further performed in subgroup with SOFA score more than 3. The testing was 2-sided, and a P-value <0.05 was considered statistically significant. SPSS 20.0 and GraphPad Prism 8.0 were used to complete data processing and statistical analysis.

## Results

### Baseline Characteristics of the Patients

A total of 119 patients were identified, of whom 56 were finally included, as shown in Figure 1. Two patients (one in the HDIVC group and one in the placebo group) were excluded due to the treatment period of less than three days due to death. In total, 54 patients completed this study from February 14, 2020, to March 29, 2020. Patients were enrolled in the Leishenshan (Thunder God Mountain) Hospital (38 patients), Zhongnan Hospital of Wuhan University (10 patients), and Taihe Hospital of Hubei University of Medicine (6 patients). Of the 54 patients included in this analysis, 48 (88.9%) received the full 7-day treatment course and 6 (11.1%) only received 5 or 6 days of treatment due to death (2) or discharge from the ICU (4). Table 1 shows the baseline demographic and clinical characteristics of the 54 patients.

The average age of the study patients was 67.4 ±12.4 years, and 67% of the patients were male. The APACHE II score of all patients was 13.5 (IQR, 10.2- 15.7), with no differences between groups. The most common comorbidity was hypertension (44%), followed by diabetes (30%) and coronary heart disease (22%). The average time from symptom onset to starting HDIVC treatment was 17 (11-25) days. No significant differences in vital signs, laboratory results, disease severity, or treatments were observed between groups at baseline.

### Primary Outcome

The IMVFD28 was 26.5 days[1.5-28.0] in HDIVC, and 10.5 days[0.0-28.0] in placebo group, but this difference was not statistically significant ( (P=0.56, HR, 4.8[-2.3 to 11.9]) (Table 2).

### Secondary Outcomes

There was no statistically significant difference in the 28-day mortality between two groups (Figure 2).However, vitamin C infusion exhibited a significant reduction in 28-day mortality (P=0.05) in more severe patients (SOFA score ≥3) using univariate survival analysis, but the significance was lost after adjustment (P=0.06, HR, 0.32 [95% CI 0.10-1.06]) (Figure 2).

As shown in Figure 3, the median SOFA score increased from 2.00 to 6.00 in the placebo group while it slightly decreased from 3.50 to 3.00 in the HDIVC group on day 7. However, there was no statistically significant difference in SOFA scores between the two groups on days 3 and 7. During the 7-day treatment period, the P/F in the HDIVC group was better than that in the control group (day 7: 228.52 vs. 150.70 mmHg; 95% CI 33.17 to 122.47; P=0.01), and improved over time (Figure 3). IL-6 in the HDIVC group was lower than that in the placebo group (19.42 vs. 158.00 pg/ml; 95% CI -301.72, -29.79; P=0.04) on day 7. There was no significant difference in other anticipated infectious indicators and inflammation biomarkers between the two groups (Table 2). In addition, total bilirubin was also improved with HDIVC (HDIVC vs placebo: 8.40 vs. 14.85, 95% CI -18.33 to -0.59; P=0.03, Table 3). The ICU mortality of severe patients (baseline SOFA score ≥3) was improved in the HDIVC group (P=0.03, HR, 0.22 [95% CI 0.06-0.90]).

### The differences of other treatments

Table 1 demonstrates the differences in other treatments between the two groups. There were no significant differences in corticosteroids, antiviral agents or antibiotics.

### Adverse Events

During the 7-day infusion period, no study-related adverse events were reported, and no patients were withdrawn from the study due to these problems.

# Discussion

Our data provide evidence that the addition of high-dose (24 g per day for 7 days) intravenous vitamin C to the standard-of-care treatment for severe COVID-19 induced a significant beneficial effect, improving the P/F, IL-6 and even 28-day mortality. To our understanding, it was the first trial on a high dose of vitamin C infusion in patients with severe COVID-19.

High levels of IL-6 were observed in patients with COVID-19 and might serve as a predictive biomarker for disease severity[5, 30, 31]. Mechanistically, IL-6 acts as a critical cytokine in the systemic inflammatory response [32], leading to a myriad of biological effects that contribute to pulmonary infiltration and organ damage[33, 34]. In a recent trial, tocilizumab[35], a recombinant humanized anti-human IL-6 receptor antibody, improved clinical symptoms by attenuating inflammation in COVID-19. The findings of the decline in IL-6 in our cohort were consistent with basic research showing that vitamin C inhibited the production and release of proinflammatory cytokines from human monocytes (IL-1, IL-2, IL-6, and TNF-α) [36]. Previous animal studies on SARS-CoV also demonstrated that inhibiting NF-κB, together with reduced IL-6 levels, could increase the survival rate in infected animals[31].

In addition, this study was consistent with other studies that showed the protective role of vitamin C infusion in acute lung injury (ALI) and ARDS [20]. Moreover, the latest meta-analysis from eight vitamin C trials of a total of 685 patients indicated that vitamin C shortened the duration of mechanical ventilation in critically ill patients[26]. SARS-CoV-2 primarily affects the lung and causes pneumonia. Respiratory failure from ARDS is the leading cause of mortality from COVID-19[37]. Similar to sepsis-induced ALI/ARDS, the rapid increase in cytokines in COVID-19 causes neutrophil sequestration in the lung, which damages the alveolar capillaries[9, 10]. In sepsis modeling of mice, parenterally infused VC demonstrated a protective effect on the lung [38, 39]. The potential mechanisms included limiting cytokine surges, improving alveolar fluid clearance, preventing vascular injury, restoring endothelial and alveolar epithelial integrity, and augmenting lung barrier cell function. In our study, the P/F increased rapidly after the initiation of HDIVC, which was likely the result of pulmonary ventilation function improvement, based on the above mechanisms.

This finding was consistent with previous clinical trials showing that HDIVC reduced the extent of multiple organ failure and improved the short-term outcomes of sepsis. Additionally, plasma ascorbic acid levels were inversely correlated with the incidence of multiple organ failure and the risk of mortality[40]. We suspected that patients with worse organ dysfunction may have a more severe vitamin C deficiency, while high-dose intravenous VC effectively improved the deficiency and subsequently improved organ function [16]. Thus, the survival improvement was more significant in more severe COVID-19 patients with a higher baseline SOFA score in our study.

This study has several limitations. First, the study was started in the second half of the epidemic outbreak, and the number of qualifying COVID-19 patients decreased with the control of the epidemic so that we had to stop our trial before reaching the predefined sample size. Secondly, the initiation of vitamin C occurred more than 10 days after the first symptom, which may affect the efficacy of HDIVC. However, SARS-CoV-2 infection was characterized by mild symptoms initially, followed one week later by

a rapid deterioration leading to hospitalization, and ARDS always occurred at the day 8 after the first symptom [4]. As in other trial, administration of vitamin C was initiated shortly after the onset of ARDS[20], which started a couple of days earlier than our trial. Third, the absence of data on the monitoring of serum ascorbic acid concentration and viral loading made it unclear whether vitamin C has direct antiviral activity against SARS-CoV-2. Fourth, we did not measure the anti-oxidative variables due to the complexity of the blood sample treatment, which was also an important feature for vitamin C. Finally, the imbalance in the patient gender

distribution between the groups at baseline may have slightly influenced the outcomes.

# Conclusion

In summary, we found that the addition of HDIVC may provide a protective clinical effect without any adverse events in critically ill patients with COVID-19. HDIVC provided one of the alternative treatment options, as there was no effective drug or treatment to cure COVID-19 at the present. Nevertheless, further studies are still needed to confirm our understanding of the effect of HDIVC therapy on critically ill patients with COVID-19.

# Declarations

### Ethics approval and consent to participate

This study is a multi-center, randomized trial, which was approved by the ethic committee of Zhongnan Hospital of Wuhan University (#2020001).It was registered on the website of ClinicalTrials.gov (ID: NCT04264533) before patient recruitment. Informed consents were obtained from the patients or family members.

### Consent for publication

Not applicable.

### Availability of data and materials

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

### Competing interests

The authors declare no competing interests.

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### Authors' contributions

Concept and design: Zhang, Rao, Li.

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Drafting of the manuscript: Zhang, Rao, Li, Backer, Peng.

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Statistical analysis: Zhang, Zhu, Liu.

Obtained funding: Xiang, Peng.

Administrative, technical, or material support: Xiang, Rao, Peng.

Supervision: Xiang, Backer, Peng.

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Zhang, Xiang, and Peng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Zhang, Rao and Li contributed equally and share first authorship. Xiang and Peng are the co- corresponding author.

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# Tables

**Table 1 Baseline Characteristics of All Patients**

| Variable | All Patients(n=54) | Vitamin C(n=26) | Placebo(n=28) | P Value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, years | 67.4±12.4 | 67.1±10.6 | 67.7±14.0 | 0.86 |
| Gender, male, n, % | 36(66.7) | 14(53.8) | 22(78.6) | 0.08 |
| Height, cm | 168.8±6.6 | 167.0±6.9 | 170.8±5.8 | 0.08 |
| Weight, kg | 62.0±10.5 | 59.7±11.2 | 64.4±9.4 | 0.16 |
| **Centres** | | | | |
| Zhongnan Hospital of Wuhan University, n, % | 10(18.5) | 5(19.2) | 5(17.9) | - |
| Leishenshan (Thunder God Mountain) Hospital, n, % | 38(70.4) | 18(69.2) | 20(71.4) | - |
| Taihe Hospital, n, % | 6(11.1) | 3(11.5) | 3(10.7) | - |
| **General condition on randomization day** | | | | |
| Highest temperature, ℃ | 37±1.0 | 37.3±0.8 | 37.4±1.1 | 0.65 |
| Highest Heart rate, times/min | 93.2±18.4 | 96.6±18.6 | 90.2±18.1 | 0.21 |
| Lowest MAP, mmHg | 91.0(17.9) | 88.4(16.6) | 93.4(18.9) | 0.31 |
| Highest RR, times/min | 25[20-36] | 25[21-31] | 24[20-30] | 0.19 |
| Lowest $SPO_2$, % | 93[88-98] | 93[81-98] | 93[90-97] | 0.93 |
| APACHE II score | 13.5[10.3-15.8] | 14.0[11.0-16.0] | 13.0[9.5-15.0] | 0.24 |
| GCS score | 15.0[14.5-15.0] | 15.0[13.0-15.0] | 15.0[15.0-15.0] | 0.75 |
| **Comorbidities, n, %** | | | | |
| Diabetes | 16(29.6) | 7(26.9) | 9(32.1) | 0.77 |
| Hypertension | 24(44.4) | 10(38.5) | 14(50.0) | 0.42 |
| Coronary heart disease | 12(22.2) | 4(15.40 ) | 8(28.6) | 0.33 |
| Chronic lung disease | 3(5.6) | 1(3.8) | 2(7.1) | 1.00 |
| Chronic renal failure | 1(1.85) | 1(3.8) | 0(0.0) | 0.48 |
| Malignant tumor | 3(5.6) | 3(11.5) | 0(0.0) | 0.11 |
| Nervous system diseases | 11(20.4) | 7(26.9) | 4(14.3) | 0.32 |
| **Median duration of symptoms before** | 17.0[11.0-25.0] | 22.0[11.0- | 15.0[11.0- | 0.18 |

| | | | | |
|---|---|---|---|---|
| **HDIVC therapy, days** | | 33.0] | 22.0] | |
| **Other treatments during 7-days HDIVC therapy** | | | | |
| Corticosteroid use, n, % | 18(33.3) | 8(36.4) | 109(38.5) | 1.00 |
| Antibiotic, n, % | 51(94.4) | 24(92.3) | 27 (96.4) | 1.00 |
| Net fluid balance, mL/kg/24 h | | | | |
| Day 1 | 190[-1487-662] | 252[-252-810] | 155[-520-499] | 0.39 |
| Day 2 | 156[-349 -653] | 192[-508-883] | 121[-90 -577] | 0.94 |
| Day 3 | 62[-703-768] | -240[-1004 -233] | 463[5-1351] | 0.02 |
| | | | | |

Data were expressed as mean ± standard deviation, as median [interquartile range], or as numbers (percentage). Comparisons were performed using Student's t test, Wilcoxon–Man–Whitney, Chi square, or Fischer's exact.

Abbreviations: SD, standard deviation; IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow coma scale; HDIVC: high dose intravenous vitamin C.

**Table 2 Outcomes in a Trial of HDIVC in patients with Covid-19.**

| Variable | Day | Vitamin C(n=26) | Placebo(n=28) | Difference, Coefficient (95% CI) | P Value |
|---|---|---|---|---|---|
| SOFA scores | 1 | 3.5[3-6.8] | 2.0[3.0-5.0] | 0.7(-0.9 to 2.3) | 0.37 |
| | 3 | 4.0[2.0-8.0] | 4.0[3.0-7.0] | -0.3(-2.6 to 1.9) | 0.50 |
| | 7 | 3.0[2.0-5.8] | 6.0[2.50-8.0] | -1.14(-3.1 to 0.8) | 0.24 |
| Lowest P/F | 1 | 188.7±95.4 | 210.6±128.5 | 34.6(-91.9 to 48.0) | 0.53 |
| | 3 | 217.3±96.5 | 189.5±101.9 | 30.7(-34.3 to 89.9) | 0.37 |
| | 7 | 228.5±72.6 | 150.7±75.3 | 22.1(33.2 to 122.5) | 0.01 |
| **Advanced life support, n, %** | | | | | |
| CRRT | 1 | 1(3.8) | 3(10.7) | OR0.3(0.0 to 3.5) | 0.61 |
| | 7 | 3(12.5) | 1(3.8) | OR3.57(0.4 to 36.9) | 0.34 |
| ECMO | 1 | 1(3.8) | 2(7.1) | OR0.5(0.0 to 6.0) | 1.00 |
| | 7 | 0(0.0) | 2(9.1) | OR0.5(0.4 to 0.7) | 0.50 |
| Vasopressor use | 1 | 9(36.0) | 6(21.4) | OR2.1(0.6 to 6.9) | 0.36 |
| | 7 | 4(16.7) | 4(17.4) | OR1.2(0.4 to 3.8) | 1.00 |
| Oxygen-support category | | | | | |
| HFNC | 1 | 7(26.9) | 11(39.3) | OR0.6(0.2 to 1.8) | 0.40 |
| | 7 | 11(47.8) | 9(39.1) | OR14.3(0.4 to 4.6) | 0.77 |
| NIV | 1 | 7(26.9) | 7(25.0) | OR1.1(0.3 to 3.7) | 1.00 |
| | 7 | 7(30.4) | 2(8.7) | OR4.6(0.8 to 25.2) | 0.14 |
| IMV | 1 | 10(38.5) | 11(39.3) | OR1.0(0.3 to 2.9) | 1.00 |
| | 7 | 10(43.5) | 11(47.8) | OR0.8(0.3 to 2.7) | 1.00 |
| **Complications, n, %** | | | | | |
| Septic shock | | 9(34.6) | 8(28.6) | OR1.3(0.4 to 2.4) | 0.77 |
| Acute cardiac injury | | 7(26.9) | 13(48.1) | OR0.4(0.1 to 1.3) | 0.16 |
| Acute liver injury | | 12(48.0) | 13(48.1) | OR1.0(0.3 to 3.0) | 1.00 |

| | | | | |
|---|---|---|---|---|
| Acute kidney injury | 3(12.0) | 6(22.2) | OR0.5(0.1 to 2.2) | 0.50 |
| Coagulation disorders | 9(34.6) | 7(25.9) | OR1.5(0.5 to 5.0) | 0.56 |
| **Outcomes** | | | | |
| HFNC days to day 28, days | 0.5[0.0 -8.3] | 2.0[0.0 -7.0] | 0.2(-2.9 to 3.3) | 0.85 |
| NIV days to day 28, days | 0.0[0.0 -3.3] | 0.0[0.0 -1.8] | 1.2(-1.2 to 3.7) | 0.68 |
| IMV days to day 28, days | 1.5[0.0 -19.0] | 6.0[0.0-16.0] | -0.8(-6.4 to 4.9) | 0.60 |
| IMV- free days to day 28, days [c] | 26.5[1.5-28.0] | 10.5[0.0 -28.0] | 4.8(-2.3 to 11.9) | 0.56 |
| Patients' condition deterioration, n, % [d] | 3(11.5) | 6(24.0) | 0.4(0.1 to 1.7) | 0.19 |
| Patients' condition improvement, n, % [e] | 5(19.2) | 6(21.4) | 0.9(0.2 to 3.3) | 0.84 |
| ICU mortality, n, % | 5(19.2) | 10(35.7) | HR0.6(0.7 to 1.6) | 0.23 |
| ICU mortality of patients with SOFA ≥3, n, % | 4(18.2) | 10(50.0) | HR0.2(0.1 to 0.9) | 0.03 |
| ICU stay, days | 23.6±14.6 | 18.4±13.2 | 5.2(-2.4 to 12.8) | 0.17 |
| Hospital mortality, n, % | 5(19.2) | 10(35.7) | HR0.6(0.7 to 1.6) | 0.23 |
| Hospital mortality of patients with SOFA ≥3, n, % | 4(18.2) | 10(50.0) | HR0.2(0.1 to 0.9) | 0.03 |
| Hospital stay, days | 36.3±16.2 | 33.8±16.4 | 2.4(-7.1 to 11.9) | 0.61 |
| 28-day mortality, n, % | 5(19.2) | 9(32.1) | HR0.5(0.1 to 1.8) | 0.36 |
| 28-days mortality of patients with SOFA ≥3, n, % | 4(18.2) | 9(45.0) | HR0.3(0.1 to 1.1) | 0.06 |

Data were expressed as mean ± standard deviation, as median [interquartile range], or as numbers (percentage). Hazard ratio and 95% CI were estimated by Cox proportional risk model. Odd ratio with 95% CI were calculated by binary logistic regression for the rest. Absolute diference was expressed as a percentage with the 95% CI range. P values were calculated by logistic regression.

[a] Acute cardiac injury was defined as the serum levels of troponin I were above the 99th percentile upper reference limit or new abnormalities were shown in electrocardiography and echocardiography.

[b] Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition.

[c] IMV-free days were defined as the number of days a patient was extubated from mechanical ventilation, after ICU admission to day 28. Days requiring reintubation were subtracted. If the patient died in the hospital post extubation, a value of zero was assigned.

[d] Patients' condition deterioration was defined that the patient required HFNC or NIV on day 1, and transferred to ECMO, or IMV, or dead on day 7.

[e] Patients' condition improvement was defined that the patient required ECMO or IMV on day 1 and transferred to HFNC, or NIV, or discharged from ICU on day 7.

Abbreviations: HDIVC: high dose intravenous vitamin C; COVID-19, coronavirus disease 2019; SD, standard deviation; IQR, interquartile range; HR, hazard ratio; OR, odd ratio; CI, confidence interval; SOFA: sequential organ failure assessment; P/F, $PaO_2/FiO_2$; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFNC, high flow nasal cannula; IV, invasive ventilation; IMV, invasive mechanical ventilation; NIV, noninvasive mechanical ventilation; ICU, intensive care unit.

**Table 3 Laboratory findings in a Trial of HDIVC in patients with Covid-19.**

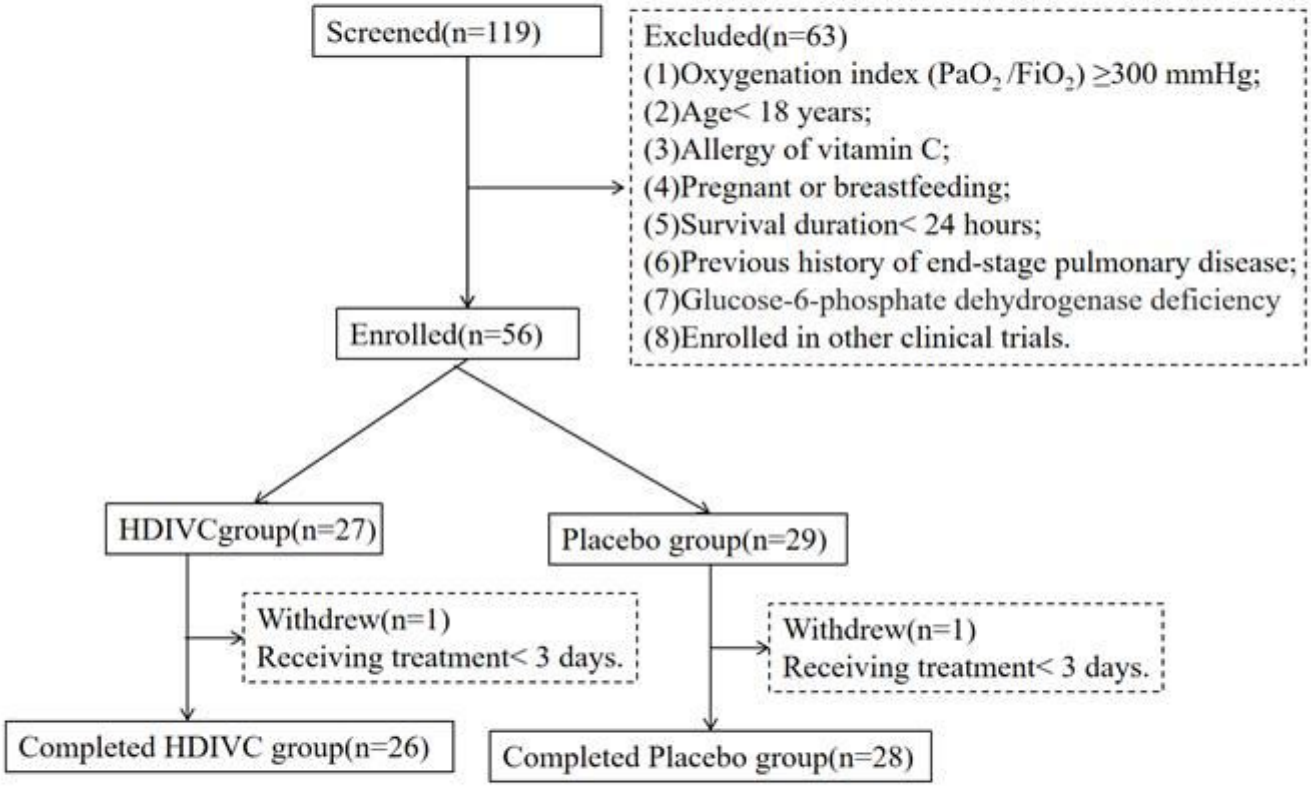
| Variable | Day | Vitamin C(n=26) | Placebo(n=28) | Difference, Coefficient (95% CI) | P Value |
|---|---|---|---|---|---|
| Leukocyte count, 10^9 | 1 | 9.50±5.04 | 11.45±7.22 | -1.95(-5.38 to -1.47) | 0.26 |
| | 3 | 8.59[5.74-11.48] | 8.44[7.09-12.23] | -0.40(-3.50 to 2.70) | 0.67 |
| | 7 | 10.23±6.73 | 9.64±5.41 | 0.59(-2.96 to 4.14) | 0.74 |
| Neutrophil count, 10^9 | 1 | 8.21±4.81 | 10.19±7.08 | -1.98(-5.31 to 1.35) | 0.24 |
| | 3 | 6.19[4.52-10.45] | 7.07[5.68-9.94] | -0.51(-3.48 to 2.47) | 0.50 |
| | 7 | 8.05±6.47 | 8.15±5.45 | -0.11(-3.58 to 3.37) | 0.95 |
| Neutrophil ratio, % | 1 | 83.50±9.63 | 85.83±9.92 | -2.33(-7.74 to -3.07) | 0.39 |
| | 3 | 85.65[77.05-91.42] | 83.30[75.53-91.78] | 4.03(-6.32 to 14.38) | 0.70 |
| | 7 | 78.45±15.76 | 81.66±11.45 | -3.21(-11.22 to 4.79) | 0.42 |
| IL-6 | 1 | 22.56[8.87-85.54] | 54.73[12.34-145.47] | -6.21(-129.71 to 117.29) | 0.61 |
| | 3 | 113.10[21.80-288.73] | 37.24[5.59-85.28] | 92.44(-25.13 to 210.01) | 0.07 |
| | 7 | 19.42[10.59-29.16] | 158.00[15.29-259.60] | -165.76(-301.72 to -29.79) | **0.04** |
| Lymphocyte count, 10^9 | 1 | 0.55[0.36-0.99] | 0.53[0.37-0.95] | 0.09(-0.17 to 0.36) | 0.49 |
| | 3 | 0.56[0.33-0.95] | 0.71[0.47-1.05] | -2.61(-8.59 to 3.37) | 0.50 |
| | 7 | 0.81[0.43-1.05] | 0.65[0.42-0.97] | 1.11(-0.76 to 2.98) | 0.25 |
| Lymphocyte ratio, % | 1 | 9.68±6.97 | 8.12±7.33 | 1.62(-2.32 to 5.57) | 0.41 |
| | 3 | 10.08±9.22 | 8.71±4.90 | 1.37(-2.67 to 5.40) | 0.88 |
| | 7 | 13.14±11.31 | 6.83[5.05 -13.42] | 3.34(-2.13 to 8.81) | 0.23 |
| PCT, ng/mL | 1 | 0.16[0.08-0.6] | 0.19[0.05-0.53] | -9.94(-29.28 to 9.41) | 0.80 |
| | 3 | 0.35[0.09-3.22] | 0.31[0.08-1.11] | -6.59(-20.46 to 7.28) | 0.84 |
| | 7 | 0.26[0.13-14.79] | 0.20[0.07-0.74] | 13.28(-17.91 to 44.48) | 0.18 |
| CRP, mg/L | 1 | 39.86[3.91-86.85] | 56.84[40.19-100.20] | -23.16(-69.46 to 23.14) | 0.19 |
| | 3 | 43.52[3.41-65.72] | 66.34[29.76-107.39] | -4.78(-68.08 to 58.53) | 0.28 |
| | 7 | 29.47[10.95-110.93] | 30.20[2.3-131.70] | -12.60(-75.34, 50.14) | 0.68 |

| | | | | | |
|---|---|---|---|---|---|
| Total bilirubin, umol/L | 1 | 8.55[6.78-15.60] | 10.80[7.40-18.30] | -1.45(-7.30 to 4.41) | 0.28 |
| | 3 | 8.40[6.70-16.10] | 14.85[9.85-25.48] | -9.46(-18.33 to -0.59) | **0.03** |
| | 7 | 8.30[6.53-16.15] | 15.30[9.03-27.68] | -4.19(-15.88 to 7.50) | 0.11 |
| , umol/L | 1 | 64.20[46.58-85.45] | 64.20[52.00 -81.70] | 26.35(-50.86 to 103.56) | 0.57 |
| | 3 | 60.30[37.65-80.38] | 70.35[49.80-100.88] | 2.52(-39.89 to -44.93) | 0.15 |
| | 7 | 57.50[39.95-71 ] | 63.50[51.70-104.50] | -12.43(-45.59 to 20.73) | 0.13 |
| BUN, mmol/L | 1 | 7.11[4.48-11.10] | 6.50[4.90-9.94] | 9.34(-8.75 to 27.44) | 0.84 |
| | 3 | 7.58±5.01 | 8.56[5.13-11.39] | -2.10(-5.22 to -1.02) | 0.11 |
| | 7 | 8.48±5.69 | 7.80[5.10-10.50] | -0.73(-4.12 to 2.66) | 0.48 |
| PT, s | 1 | 13.25[12.35-14.63] | 12.90[12.50-13.80] | -0.58(-2.35 to 1.19) | 0.97 |
| | 3 | 13.90±3.24 | 13.25[12.70-15.05] | -0.29(-1.97 to 1.39) | 0.33 |
| | 7 | 12.99±2.55 | 13.05[12.35-14.60] | -0.27(-1.67 to 1.14) | 0.08 |

Data were expressed as mean ± standard deviation, as median [interquartile range]. Odd ratio with 95% CI were calculated by binary logistic regression for the rest. P values were calculated by logistic regression.

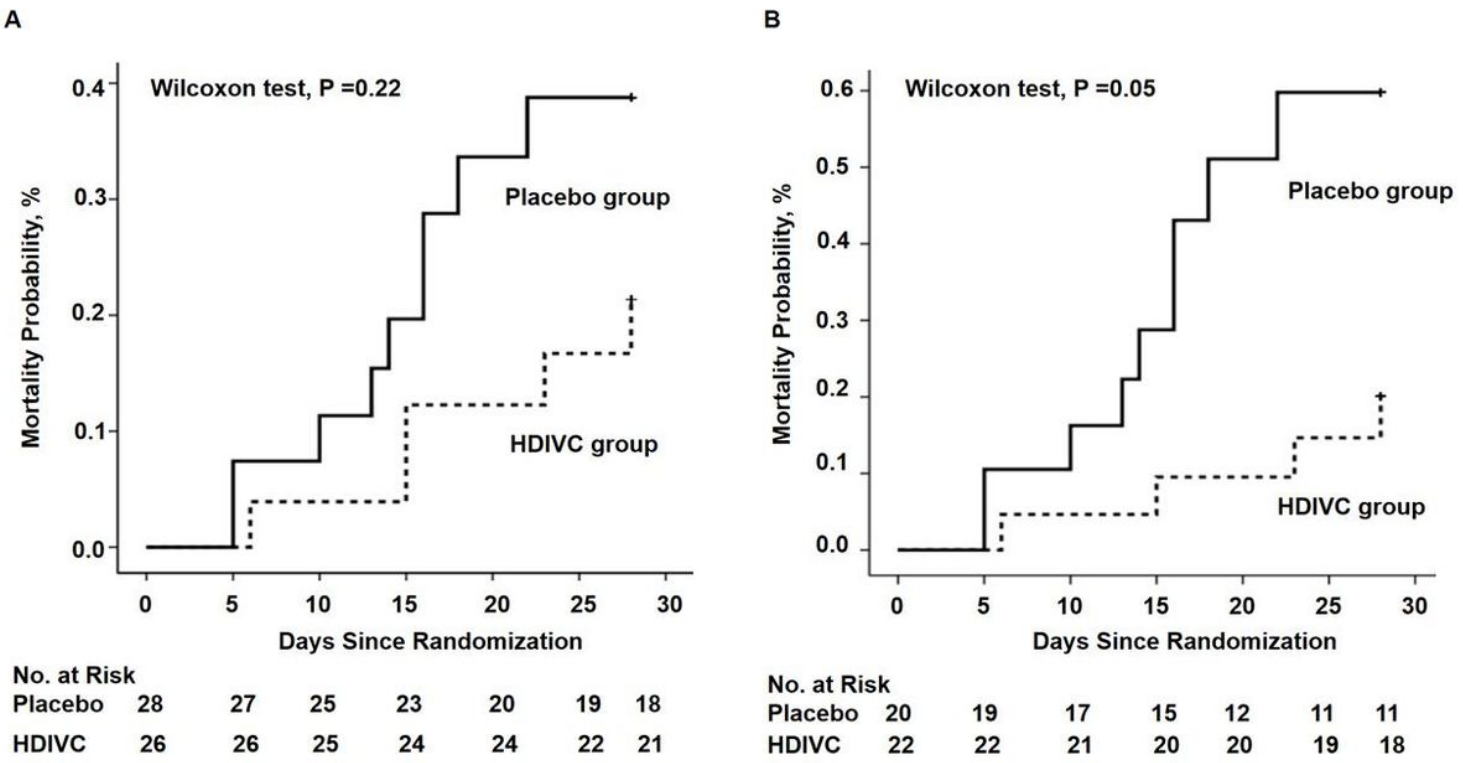
Abbreviations: SD, standard deviation; IQR, interquartile range; HR, hazard ratio; OR, odd ratio; CI, confidence interval; HDIVC: high dose intravenous vitamin C; COVID-19, coronavirus disease 2019; SD, standard deviation; IQR, interquartile range; PCT, procalcitonin; CRP, C-reactive protein; BUN, blood urea nitrogen; PT, prothrombin time,IL-6, interleukin-6.

# Figures



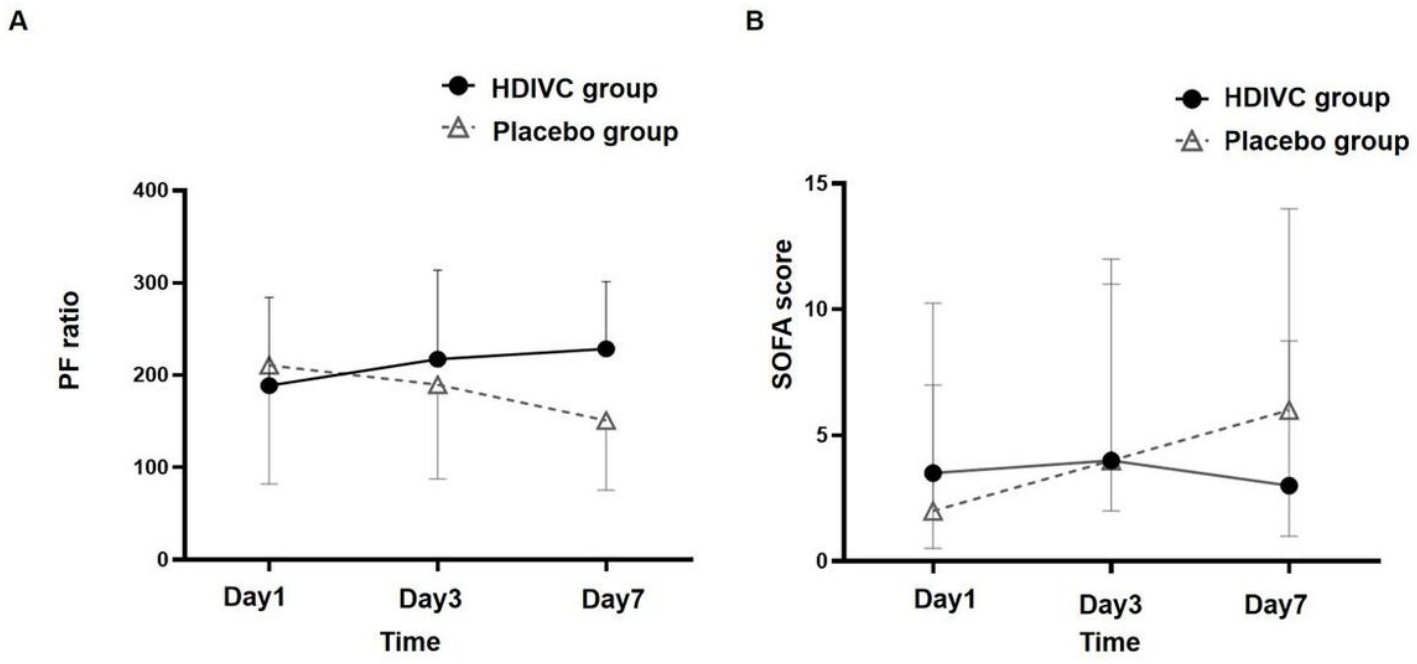

## Figure 1

Flow chart of patients. Abbreviations: HDIVC: high-dose intravenous vitamin C.




## Figure 2

The 28-day mortality from randomization (day 1) to day 28. A Kaplan-Meier analysis was used to estimate the 28-day mortality, and survival curves were compared with the Wilcoxon test (P=0.22) among patients with COVID-19. Cox regression was used for multiple comparisons (P=0.06, HR, 0.50 [95% CI 0.14-1.77]). B Kaplan-Meier analysis was used to estimate the 28-day mortality and survival curves were compared with the Wilcoxon test(P=0.05) among severe COVID-19 patients (baseline SOFA score≥3). Cox regression was used as multiple comparisons (P=0.06, HR, 0.32[95%CI, 0.10-1.06]). Abbreviations: HDIVC: high dose intravenous vitamin C; COVID-19, coronavirus disease 2019; SOFA: sequential organ failure assessment.




## Figure 3

P/F and SOFA scores following high-dose intravenous vitamin C treatment. A The bars show the standard deviation (SD) of the mean. The P/F in both groups was approximately 200 at enrollment. After initiation of treatment, there was a steady rise in the P/F in the HDIVC group and a decline in the P/F in the placebo group (day 3: 217 vs. 189, 95% CI -34 to 90, P=0.37; day 7: 229 vs. 151, 95% CI 33 to 122, P=0.01). B The bars showed the interquartile range (IQR) of the median. There was no difference in the initial Sequential Organ Failure Assessment (SOFA) scores of the 2 groups at baseline (vitamin C vs placebo, median, 3.5[3.0-6.8] vs 2.0 [3.0-5.0]). After 7-day treatment, the median of SOFA score increased from 2.0 to 6.0 in the placebo group and slightly decreased from 3.5 to 3.0 in the HDIVC group, but there were no difference between the 2 groups. Abbreviations: HDIVC: SOFA, sequential organ failure assessment; P/F, PaO2/FiO2; high dose intravenous vitamin C; COVID-19, coronavirus disease 2019.