

# Adjunctive Therapy with Ascorbic in Critically Ill Patients with COVID-19: A Multicenter Propensity Score Matched Study

Khalid Al Sulaiman (✉ [alsulaimankh@hotmail.com](mailto:alsulaimankh@hotmail.com))

King Abdulaziz Medical City <https://orcid.org/0000-0002-5547-2043>

Ohoud Al Juhani

King Abdulaziz University

Hisham A. Badreldin

King Saud bin Abdulaziz University for Health Sciences

Khalid Bin Salah

King Saud bin Abdulaziz University for Health Sciences

Abdullah Al Harthi

King Abdulaziz Medical City

Mohammed Alenazi

King Saud bin Abdulaziz University for Health Sciences

Aisha Alharbi

King Abdulaziz University Hospital

Rahmah Algarni

King Abdulaziz University Hospital

Shmeylan Al Harbi

King Saud bin Abdulaziz University for Health Sciences

Ramesh Vishwakarma

King Abdullah International Medical Research Center

Sarah Aldekhyl

King Abdulaziz Medical City

Yaseen M Arabi

King Abdulaziz Medical City

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## Research

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# Abstract

## Background:

Due to its supposed clinical efficacy, relative safety, and low cost, ascorbic acid represents an appealing option for clinicians to utilize in the context of a global health pandemic of COVID-19 patients.

**Objectives:** The aim of this study was to evaluate the efficacy and safety of using ascorbic acid as adjunctive therapy in critically ill patients with COVID-19.

## Methods:

This was a multi-center, non-interventional, retrospective cohort study. All critically ill adult patients admitted to ICU with a confirmed COVID-19 between March 1st to December 31<sup>st</sup>, 2020 were included in the final analysis. The study was conducted at two large governmental tertiary hospitals in Saudi Arabia. The purpose was to investigate the association between clinical outcomes with ascorbic acid use as an adjunctive therapy in COVID-19 after propensity score matching using baseline severity scores, systemic use of corticosteroids and study centers.

**Results:** A 739 patients were included in this study; 296 patients were included after propensity score matching. There was no association between the administration of ascorbic acid and in-hospital mortality nor 30-day ICU mortality (OR (95%CI): 0.77 (0.476, 1.234), p-value=0.2738 and OR (95%CI): 0.73 (0.438, 1.204), p-value=0.215 respectively). Using ascorbic acid was associated with lower incidence of thrombosis compared with the non-ascorbic acid group (6.1% vs. 13% respectively); OR (95%CI): 0.42 (0.184, 0.937), p-value=0.0342).

**Conclusion:** Ascorbic acid use as an adjunctive therapy in COVID19 critically ill patients was not associated with mortality benefits; but associated with lower incidence of thrombosis. Further studies are required to confirm these findings.

## Introduction

Coronavirus Disease 2019 (COVID-19) and its related Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) represents one of the most serious healthcare challenges known to the mankind. To date, most of the available investigated treatments are supportive measures with few proposed preventive measures.<sup>1</sup> There are several agents proposed to have a role in treatment and prevention of COVID-19. Due to its known antioxidant effects and role in enhancing immune function, ascorbic acid (Vitamin C) was assumed to have beneficial effect in COVID-19. This is mainly via supporting lymphocyte activity, stimulating interferon- $\alpha$  production, reducing inflammation, and improving endothelial function; thus, it might exert an antiviral effect<sup>2-4</sup>

Ascorbic acid is a well-known water-soluble vitamin that is believed to have clinical benefits for patients with severe illnesses. Due to its antioxidant properties, it has been evaluated in severe oxidative stress

status such as serious infection, sepsis and ARDS. COVID-19 infections can lead to serious oxidative stress leading to a state where patients might require more ascorbic acid. Several reports addressed vitamin C's potential effect in ameliorating the inflammation and vascular injury in COVID-19 patients.<sup>5,6</sup> In light of its proposed efficacy, relative safety, and low cost, ascorbic acid represents an appealing agent for researchers and clinicians to utilize in the context of a global health pandemic.

There are several studies with mixed results regarding the clinical use of ascorbic acid in non-COVID-19 critically ill patients. A pilot study compared intravenous (IV) ascorbic acid in two different regimens with placebo arm in 24 critically ill patients with sepsis. This study showed that patients who received IV ascorbic acid had lower sequential organ failure assessment (SOFA) scores and lower levels of proinflammatory compared to the placebo group.<sup>7</sup> Another randomized controlled study conducted in critically ill patients with sepsis induced ARDS found no difference in SOFA scores and levels of inflammatory markers between the groups. However, the 28-day mortality was lower in the treatment group.<sup>8</sup>

Ascorbic acid has also been evaluated in some studies as part of a combination regimen with thiamine and hydrocortisone. There were two small retrospective studies that found some improvement in the clinical outcomes (i.e., reduced mortality, reduced risk of progression to organ failure, and improved radiographic findings) in patients with sepsis or severe pneumonia who received ascorbic acid as part of combination regimen with thiamine, and hydrocortisone<sup>9,10</sup>. One meta analysis evaluated ascorbic acid use in intensive care unit (ICU) patients without COVID-19 and found that high-dose intravenous ascorbic acid infusions (i.e., 200 mg/kg/day) shortened the ICU length of stay by 7.8%.<sup>11</sup> A similar experiment was conducted in critically ill patients with severe influenza in which ascorbic acid was shown to reduce oxidative stress related lung injury.<sup>12,13</sup> A recent report that investigated the use of high-dose intravenous ascorbic acid in treatment of 50 moderate to severe COVID-19 patients, showed an improvement in the oxygenation index.<sup>28</sup>

Overall, there is limited data to support the use of ascorbic acid in critically ill patients with COVID-19. In this context, this study aims to investigate the safety and efficacy of ascorbic acid use as adjunctive therapy in COVID-19 critically ill patients.

## Methods

### Study design:

This was a retrospective, multi-center, non-interventional study with retrospective analysis of prospectively collected data in consecutive critically ill patients aged  $\geq 18$ -year who admitted to ICUs with a confirmed diagnosis of COVID-19 in Saudi Arabia. The diagnosis of COVID-19 was confirmed by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) on nasopharyngeal and/or throat swabs. All the patients who met our inclusion criteria during the study period (01/03/2020–31/12/2020) were included. Included patients were divided into 2 groups based on ascorbic acid use as adjunctive therapy

during ICU stay. All patients were followed until they were discharged from the hospital or died during in-hospital stay whichever occurred first. The study was approved by the Ministry of National Guard Health Affairs Institutional Review Board, Riyadh, Saudi Arabia (Study Number: RC20/589/R).

Propensity score matching Procedure (Proc PS match) (SAS, Cary, NC) was used to match patients who received ascorbic acid to patients who did not. A greedy nearest neighbor matching method was used in which one non ascorbic acid (control) is matched with each patient in the ascorbic acid (active) group which eventually produced the smallest within-pair difference among all available pairs with treated patients. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups was less than or equal to 0.5 times the pooled estimate of the standard deviation.

## **Eligibility criteria:**

Patients were enrolled in the study if they were deemed to be critically ill, aged 18 years or older and admitted to the ICU with confirmed diagnosis of COVID-19 using the PCR test. Patients were excluded if the ICU length of stay (LOS) was  $\leq 1$  day or  $\geq 60$  days, and/or labeled as “Do-Not-Resuscitate” status within 24 hours of ICU admission.

## **Setting:**

This study was conducted in two tertiary governmental hospitals; King Abdulaziz Medical City, Riyadh and King Abdulaziz University Hospital, Jeddah. The primary site for this multicenter study was King Abdulaziz Medical City (Riyadh).

## **Data collection:**

The following information were collected: demographic data (See additional file-1), comorbidities, vital signs and laboratory tests, severity baseline scores (i.e. Acute Physiology And Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Nutrition Risk in Critically ill (NUTRIC)), Glasgow Coma Score (GCS), acute kidney injury, fluid balance, needs for mechanical ventilation (MV) and MV settings within 24 hours of ICU admission. Additionally, renal profile, liver function tests (LFTs), coagulation profile (i.e., INR, aPTT, fibrinogen), and inflammatory markers (CRP, procalcitonin) within 24 hours of ICU admission were collected. Lastly corticosteroids and tocilizumab use were recorded for the eligible patients and followed due to their potential benefits.

## **Endpoints:**

The major endpoint was estimate the in-hospital mortality in critically ill patients with COVID-19 who received versus those who didn't receive ascorbic acid as adjunctive therapy. The minor endpoints were the following, 30-days ICU mortality, ICU LOS, hospital LOS, MV duration. We also reported the following complications during ICU stay, acute kidney injury (AKI), liver injury, respiratory failure, thrombosis and infraction.

## Definition (s)

- The acute kidney injury (AKI) was defined using AKIN definition<sup>29</sup>, which is a sudden decrease of renal function within 48 hours, defined by an increase in absolute SCr of at least 26.5  $\mu\text{mol/L}$  (0.3 mg/dL) or by a percentage increase in SCr  $\geq 50\%$  (1.5 $\times$  baseline value), or by a decrease in the urine output (UOP) (documented oliguria  $< 0.5 \text{ mL/kg/h}$  for more than 6 hours).
- Thrombosis/infraction was defined using ICD10-CM code (i.e. Myocardial infraction (MI), ischemic stroke, pulmonary embolism, deep vein thrombosis) during ICU stay<sup>30</sup>.
- Liver injury was defined as alanine aminotransferase (ALT) exceeding 3 times the upper limit of normal or double in patients with elevated baseline ALT during hospital stay.

## Statistical analysis:

Data was entered in Microsoft Excel 2010. Categorical variables were reported using numbers and percentages. Continuous variables were reported using mean with standard deviation (SD), or median with interquartile range (IQR) when appropriate. We compared categorical variables using the Chi square or Fisher exact test. Continuous variables were compared using numerical the student-t test (for the normally distributed variables) or other quantitative variables with the Mann-Whitney U test (for the non-normally distributed variables). The normality assumptions were assessed for all numerical variables using statistical test (i.e., Shapiro–Wilk test) and also using graphical representation (i.e., histograms and Q-Q plots). A Kaplan–Meier plot was used to describe survival rates and compared using log rank test. Baseline characteristics, baseline severity and endpoints variables were compared between the two treatment groups. Multivariate logistic regression and generalized linear regression were used to find out the relationship between zinc use and different outcomes considered in this study. We considered a P value of  $< 0.05$  statistically significant and used SAS version 9.4 for all statistical analyses.

We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. Generalized linear regression was also used to find out the relationship between zinc sulfate use and the different study outcomes considered in this study. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection.

## Result Section

A total of 739 patients met the inclusion criteria. Of those included, 158 (21.3) % patients received ascorbic acid whereas 581(78.7%) patients did not. A total of 296 patients were included after propensity score matching using baseline severity scores (i.e., APACHE II, SOFA score, NUTRIC scores), systemic use of corticosteroids and study centers.

A fixed dose of 1000 mg of ascorbic acid enterally was administered per day with a median duration of administration of 11 days (IQR 7–18). Ascorbic acid was administered within 3 days of ICU admission in

(74.5%) of the patients.

## Demographic and Clinical Characteristics

The majority of the included patients in both arms were male (72%) with a mean age of 60.65 ( $\pm$  14.81) (Additional file 1). The predominant comorbidities were diabetes mellitus (59 %) followed by hypertension (56 %) and dyslipidemia (29 %). Most of the comorbidities were similar between the two groups (Additional file 2).

Patients who didn't receive ascorbic acid as adjunctive therapy had higher baseline severity scores (i.e., APACHE II, SOFA, and NUTRIC scores), AKI, requiring MV within 24 hours of ICU admission, and higher baseline laboratory tests (Additional file 1). Conversely, patients who received ascorbic acid as adjunctive therapy had significantly higher systemic corticosteroid use during ICU, estimated glomerular filtration rate (eGFR), and pH. Following the propensity score matching, most of these baseline and demographic characteristics were shown to be similar between the two groups. (Additional file 1).

## Endpoints

During hospital stay, patients who received ascorbic acid had less death in comparison to the non-ascorbic acid group (33.6% vs. 49.3% respectively). In another word, patients who received ascorbic acid as adjunctive therapy during ICU stay are less likely to die by 23 %. and 30-days ICU mortality by 27 %. However, it statistically insignificant after propensity matching between the two groups with OR (95%CI): 0.77 (0.476, 1.234), p-value = 0.2738 and OR (95%CI): 0.73 (0.438 ,1.204), p-value = 0.215 and respectively (Table 1).

Table 1  
Regression analysis for the outcomes

Outcomes	Ascorbic Acid group			Odds Ratio (OR) (95%CI)	P-value
	n of outcomes/Total no- of patients				
	NO	Yes	P-value		
<b>In-hospital mortality, n (%)</b>					
Analysis on all eligible patients	275/558 (49.3)	50/149 (33.6)	0.0006 <sup>^^</sup>	0.50 (0.330 ,0.759)	0.0011 <sup>**</sup>
Propensity score matched	59/142 (41.6)	46/142 (32.4)	0.11 <sup>^^</sup>	0.77 (0.476 ,1.234)	0.27 <sup>§</sup>
<b>ICU mortality within 30 days</b>					
Analysis on all eligible patients	235/540 (43.5)	40/146 (27.4)	0.0004 <sup>^^</sup>	0.51 (0.332 ,0.794)	0.0027 <sup>**</sup>
Propensity score matched	48/136 (35.3)	37/139 (26.6)	0.11 <sup>^^</sup>	0.73 (0.438 ,1.204)	0.21 <sup>§</sup>
				<b>beta coefficient (Estimates) (95%CI)</b>	<b>P-value</b>
<b>MV duration during ICU stay Days, Median (IQR)</b>					
Analysis on all eligible patients	8.0(3.00, 16.00)	6.0(1.00, 16.50)	0.0892 <sup>^</sup>	2.28 (1.78 ,2.77)	< .0001 <sup>**</sup>
Propensity score matched	6.0 (2.00, 14.00)	6.0 (1.00, 17.00)	0.88 <sup>^</sup>	0.37 (0.05 ,0.69)	0.02 <sup>§*</sup>
<b>ICU Length of Stay Days, Median (IQR)</b>					
Analysis on all eligible patients	10.0 (6.00, 18.00)	10 (6.00, 19.00)	0.74 <sup>^</sup>	2.60 (2.13 ,3.08)	< .0001 <sup>**</sup>
Propensity score matched	9.0 (5.00, 16.50)	10.0 (6.00, 18.00)	0.22 <sup>^</sup>	0.41 (0.19 ,0.62)	0.0003 <sup>§*</sup>
<b>Hospital Length of Stay Days, Median (IQR)</b>					
Analysis on all eligible patients	17.0 (10.00, 25.00)	18.0 (12.00, 26.00)	0.20 <sup>^</sup>	3.06 (2.44 ,3.67)	< .0001 <sup>**</sup>

Outcomes	Ascorbic Acid group			Odds Ratio (OR) (95%CI)	P-value
	n of outcomes/Total no- of patients				
	NO	Yes	P-value		
Propensity score matched	14.5 (10.00, 23.00)	18 (12.00, 26.00)	0.02	0.50 (0.29 ,0.71)	<.0001\$*

-Denominator of the percentage is the total number of patients

\*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

^^Chi-square test is used to calculate the P-value.

\*\*Fisher Exact test is used to calculate the P-value.

\$\*propensity score adjusted Generalized linear model is used to calculate estimates and p-value.

\$ propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

^^Multivariate Logistic regression is used after adjusting for patient's baseline severity scores, systemic use of corticosteroids and hospital center to calculate Odds ratio and p-value

Critically ill patients who received ascorbic acid as adjunctive therapy had a longer ICU length of stay (LOS), mechanical ventilation duration and hospital LOS with Est. (95%CI): 0.41 (0.19, 0.62), p-value = 0.0003, Est. (95%CI): 0.37 (0.05, 0.69), p-value = 0.0224 and Est. (95%CI): 0.50 (0.29, 0.71), p-value = < 0.001 respectively (Table 1).

## ICU Complications during ICU stay

Patients who received ascorbic acid as adjunctive therapy during ICU stay had significantly lower incidence of thrombosis/infraction compared with the non-ascorbic acid group (6.1% vs 13% respectively); (OR (95%CI): 0.42 (0.184, 0.937), p-value = 0.0342) (Table 2).

Table 2  
Regression analysis for ICU complication (s) during ICU stay

Outcomes	Ascorbic Acid group		P-value	OR/Estimates (95%CI)	P-value <sup>\$</sup>
	n of outcomes/Total no-of patients				
	No	Yes			
<b>Acute Kidney Injury (AKI), n (%)</b>					
Analysis on all eligible patients	277/570 (48.6)	58/156 (37.2)	0.01 <sup>^^</sup>	0.66 (0.444 ,0.984)	0.04 <sup>**</sup>
Propensity score matched	51/146 (34.9)	56/148 (37.8)	0.60 <sup>^^</sup>	1.34 (0.837 ,2.150)	0.22 <sup>\$</sup>
<b>Liver Injury, n (%)</b>					
Analysis on all eligible patients	63/568 (11.1)	14/156 (9.0)	0.44 <sup>^^</sup>	0.52 (0.277 ,0.989)	0.04 <sup>**</sup>
Propensity score matched	9/146 (6.2)	13/148 (8.8)	0.39 <sup>^^</sup>	1.17 (0.517 ,2.653)	0.70 <sup>\$</sup>
<b>Respiratory Failure Required MV, n (%)</b>					
Analysis on all eligible patients	400 /568 (70.4)	104/156 (66.7)	0.36 <sup>^^</sup>	1.00 (0.662 ,1.525)	0.98 <sup>**</sup>
Propensity score matched	94/146 (64.4)	98/148 (66.2)	0.74 <sup>^^</sup>	1.47 (0.929 ,2.335)	0.09 <sup>\$</sup>
<b>Thrombosis During ICU, n (%)</b>					
Analysis on all eligible patients	64/565 (11.3)	9/5.8 (2.3)	0.04 <sup>^^</sup>	0.35 (0.167 ,0.717)	0.0043 <sup>**</sup>
Propensity score matched	19/146 (13.0)	9/147 (6.1)	0.04 <sup>^^</sup>	0.42 (0.184 ,0.937)	0.03 <sup>\$</sup>

-Denominator of the percentage is the total number of patients.

OR: Odds Ratio

\*T -Test / ^ Wilcoxon rank sum test is used to calculate the P-value.

^^Chi-square /\*\*Fisher Exact test is used to calculate the P-value.

\$ propensity score adjusted Logistic regression is used to calculate Odds ratio and p-value.

\*\*Multivariate Logistic regression is used after adjusting for patient's baseline severity scores, systemic use of corticosteroids and hospital center to calculate Odds ratio and p-value

The ascorbic acid group was shown to have significantly higher incidence of acute kidney injury (AKI), liver injury and respiratory failure requiring MV; however, it was not statistically significant (Table 2). The overall survival probability during hospital stay was statistically significant before propensity score matching among patients who used ascorbic acid; however, after propensity score matching there was no significant difference. (Fig. 1a, 1b).

## Discussion

Patients with severe COVID-19 are known to have higher inflammatory markers and cytokine storm. In this retrospective and multi-center observational study for critically ill patients with COVID-19, patients received enteral ascorbic acid in a dose of 1000 mg daily for a median of 11 days (IQR 7–18 days).

Ascorbic acid with its proposed anti-inflammatory activity through its antioxidant effect associated with lower 30-days and in-hospital mortality in our overall cohort. However, after matching patients based on the severity of illness (i.e., APACHE II, SOFA score, NUTRIC scores), center, and steroid use, both 30-days and in-hospital mortality were similar in both groups. However, patients who received ascorbic acid had longer ICU LOS, mechanical ventilation duration and hospital LOS in both matched and unmatched groups. This might be secondary to the survival benefits of ascorbic acid which was associated longer hospitalization and using invasive MV modalities. Interestingly, we also observed a significant reduction in the risk of thrombosis during ICU stay in the ascorbic acid group. This could be as result of its anti-inflammatory properties. Moreover, DVT prophylaxis was used as a standard of care in our cohort

Several pharmacological regimens have been proposed to impact the outcomes for patients with COVID-19 positively. Out of these regimens, only dexamethasone has been shown to improve survival<sup>(15)</sup>. In our study, more patients in the ascorbic acid group received a systemic steroid than in the non-ascorbic acid group 92.9 vs. 86.5 (P-value 0.0312), respectively. This could justify the survival benefit of ascorbic acid prior to controlling for the effect of steroid use. However, the ascorbic acid group showed no mortality benefits after controlling for the potential impact of steroid use.

In critically ill patients, ascorbic acid deficiency is commonly observed despite receiving proper vitamin C intake<sup>(16)</sup>. Furthermore, in critically ill patients, ascorbic acid deficiency is associated with multi-organ failure and increased mortality<sup>(17,18)</sup>. A bioinformatic study highlighted the potential role of ascorbic acid in sepsis. By suppressing inflammatory response and oxidative stress, which are key pathophysiological mechanisms of sepsis, ascorbic acid may have a beneficial effect against sepsis<sup>(19)</sup>.

Large randomized controlled studies using ascorbic acid for COVID-19 in ICU patients are lacking. However, ascorbic acid in non-COVID-19 patients has been studied extensively, and the results have been mixed. **One explanation for these mixed results is the differences in the baseline characteristics of the enrolled patients.** Moreover, there was a lack of consistency in terms of the ascorbic acid dose, route, timing, and frequency of administration in these studies.

Multiple studies reported positive results for ascorbic acid therapy in respiratory infections including upper respiratory tract infection (URTI) and pneumonia <sup>(20,21)</sup>. Ascorbic acid has been widely used in the literature for critically ill and septic patients. In a phase I trial, 16 patients with severe sepsis received IV ascorbic acid (50-200mg/kg/day) for 4 days. Ascorbic acid use showed reduction in sequential organ failure assessment (SOFA) score, and proinflammatory biomarkers while being well tolerated <sup>(7)</sup>. Nathens et al. used IV ascorbic acid 1 g every eight hours for 28 days in 594 critically ill surgical patients and found a significantly lower incidence of multi-organ failure, shorter mechanical ventilation duration and ICU length of stay <sup>(22)</sup>. A retrospective study reported the use of IV ascorbic acid 1.5g every 6 hours for 4 days with thiamine and hydrocortisone in 47 septic ICU patients. This study showed a significant reduction in mortality rate and vasopressor requirement in the group treated with IV ascorbic acid <sup>(23)</sup>. Multiple other trials showed positive outcomes with ascorbic acid in critically ill septic patients <sup>(8,24,25)</sup>. However, several other trials did not show improvement in clinical outcomes using ascorbic acid in septic patients with ARDS <sup>(26,27)</sup>. Compared to these trials, our study used a consistent and lower dose (1000 mg orally once daily).

A pilot study randomized patients in the ICU with COVID-19 to receive high dose ascorbic acid 12g every 12 hours for 7 days or placebo. Only 56 patients were included in the study in which 26 patients received ascorbic acid. This study showed no benefit of using ascorbic acid in the 28-days mortality or duration of mechanical ventilation. However, oxygenation was significantly improved in the ascorbic acid patients<sup>(28)</sup>.

Our study is the first study to describe the association of ascorbic acid with clinical outcomes in a matched-controlled ICU COVID-19 patients. This research is providing a hypothesis-generating idea of the potential benefit of using ascorbic acid in critically ill patients with COVID-19. This study is suggesting that using ascorbic acid could potentially reduce the risk of ICU thrombosis. We believe that this hypothesis needs to be further investigated at a larger scale using stronger and more validated modalities and study designs in order to eliminate the risk of bias.

Our study has several limitations in terms of the retrospective design and the heterogeneity in the comorbid conditions and disease severity. This was eliminated via using the propensity score. Moreover, there were a dynamic change in the clinical practice of managing patients with COVID-19 as evidence continued to emerge over time. Furthermore there was no consensus on when to start ascorbic acid, and it was mainly at the discretion of the treating team. In the future, there is a plan to investigate the difference in clinical outcomes in the early versus late ascorbic acid initiation.

## Conclusion

The use of ascorbic acid was not associated with in-hospital nor 30-days ICU mortality reduction. Using ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19 was associated with lower incidence of thrombosis. Further studies are warranted to confirm these findings.

# Abbreviations

Intensive care units (ICUs), Coronavirus disease (COVID-19), Mechanical ventilation (MV), Length of Stay (LOS).

# Declarations

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Not applicable.

Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

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None.

Availability of data and material

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

Ethics approval and consent to participate

The study was approved in November 19th, 2020 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/589/R).

Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the policy of the governmental and local research center.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

Author details

<sup>1</sup>Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia

<sup>2</sup>Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

<sup>3</sup>Pharmaceutical Care Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

<sup>4</sup>College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center

<sup>5</sup>Intensive Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia

<sup>6</sup>College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

<sup>7</sup>King Abdullah International Medical Research Center, Biostatistics and Bioinformatics Department, Riyadh, Saudi Arabia.

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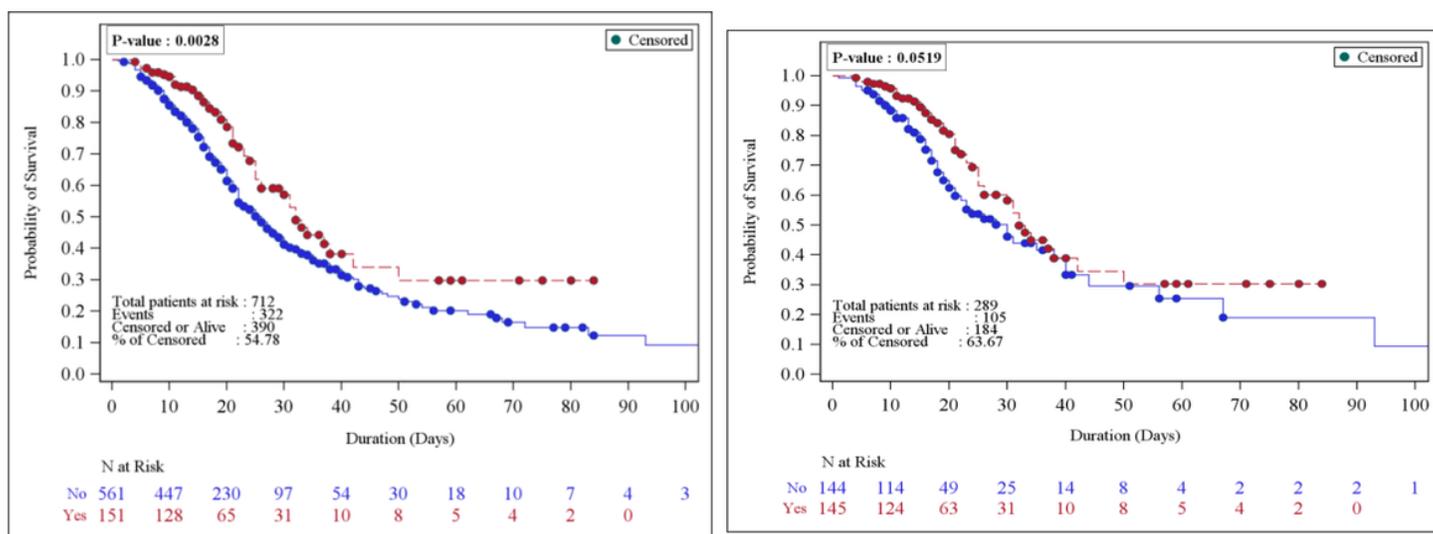
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## Figures



A

B

Figure 1

a: Time to hospital discharge in patients received ascorbic acid and those who did not (All cohort) b: Time to hospital discharge in propensity score matched patients who received ascorbic acid and those who did not

## Supplementary Files

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