

# Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection

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## Abstract

**Introduction:** The pathophysiology for Coronavirus Disease 2019 (COVID-19) infection is characterized by cytokine oxidative stress and endothelial dysfunction. Intravenous (IV) vitamin C has been utilized as adjuvant therapy in critically ill patients with sepsis for its protective effects against reactive oxygen species and immunomodulatory effects. The primary objective of this study was to evaluate the effects of IV vitamin C in critically ill patients with COVID-19 infection. **Methods:** Retrospective observational cohort study with propensity score matching of intensive care unit (ICU) patients who received 1.5 grams IV vitamin C every 6 hours for up to 4 days for COVID-19 infection. The primary study outcome was in-hospital mortality. Secondary outcomes included vasopressor requirements in norepinephrine equivalents, ICU length of stay, and change in Sequential Organ Failure Assessment (SOFA) score. **Results:** Eight patients received IV vitamin C and were matched to 24 patients. Patients in the IV vitamin C group had higher rates of hospital mortality [7 (88%) vs. 19 (79%),  $P = 0.049$ ]. There was no difference in the daily vasopressor requirement in the treatment group or between the 2 groups. The mean SOFA scores post-treatment was higher in the IV vitamin C group ( $12.4 \pm 2.8$  vs.  $8.1 \pm 3.5$ ,  $P < 0.005$ ). There was no difference in ICU length of stay between the treatment and control groups. **Conclusion:** Adjunctive IV vitamin C for the management of COVID-19 infection in critically ill patients may not decrease the incidence of mortality, vasopressor requirements, SOFA scores, or ventilator settings.

## Keywords

COVID-19, vitamin C, sepsis, infection

## Introduction

The pathophysiology for Coronavirus Disease 2019 (COVID-19) infection is complex and characterized by cytokine storm, oxidative stress, and endothelial dysfunction leading to multiorgan failure and mortality.<sup>1-3</sup> Furthermore, lactic acidosis and a dysregulated host response to infection have been attributed to thiamine deficiency and adrenal insufficiency, respectively.<sup>4,5</sup> Vitamin C is a water-soluble vitamin that exerts a multitude of beneficial effects on cellular function and has been described to have antioxidant, anti-inflammatory, and immunomodulatory properties leading to enhancement of neutrophil chemotaxis and phagocytosis, decreased lipopolysaccharide-induced generation of pro-inflammatory cytokines, and amelioration of respiratory symptoms in acute infection.<sup>6</sup>

Prior to the COVID-19 pandemic, intravenous (IV) vitamin C has been utilized experimentally in combination with hydrocortisone and thiamine as adjunctive therapy to attenuate the circulatory and metabolic abnormalities characteristic of septic shock.<sup>7-9</sup> In a retrospective before-after study of 47 patients, critically-ill patients treated with a combination of IV vitamin C 1.5 grams every 6 hours, IV hydrocortisone 50 mg every 6 hours, and IV thiamine 200 mg every 12 hours demonstrated

significantly significant decreases in mortality and Sequential Organ Failure Assessment (SOFA) scores.<sup>7</sup> The dramatic decrease in mortality and organ dysfunction was attributed to the synergistic effect of the combination therapy in reversing the pathophysiology of sepsis through downregulation of inflammatory mediators, preservation of endothelial function, and promotion of aerobic metabolic processes.<sup>10</sup> However, the decrease in SOFA scores and mortality were not reproduced in 2 subsequent multicenter randomized controlled trials evaluating the effects of combination therapy in septic shock.<sup>8,10</sup>

A prospective observational cohort study during the COVID-19 surge in New York City between March and April 2020 reported that 66% of patients had a component of shock requiring vasopressor therapy, 39% of patients expired, and

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elevated inflammatory biomarkers were an independent predictor of mortality.<sup>11</sup> Given similar characteristics and potential overlap in pathogenesis, we postulated that combination IV vitamin C with hydrocortisone and thiamine may play significant role in the management of COVID-19 infection.

Few studies have evaluated the effect of IV vitamin C on the clinical course of COVID-19 patients.<sup>12,13</sup> The purpose of this study was to evaluate the effects of IV vitamin C in critically-ill patients with COVID-19 infection compared to standard of care.

## Methods

### Patients

We performed a single-center retrospective preliminary observational cohort study with propensity matching at an urban community teaching hospital. The Icahn School of Medicine at Mount Sinai institutional review board determined this study was exempt human research. Adult intensive care unit (ICU) patients with confirmed COVID-19 infection between April 1st, 2020 and May 30th, 2020 were included in the study. Patients were excluded if they were pregnant or incarcerated.

### Treatment

Our institution utilized IV vitamin C 1.5 grams every 6 hours in combination with hydrocortisone 50 milligrams every 6 hours and thiamine 200 mg every 12 hours for a total course of 4 days.<sup>7,10</sup> IV vitamin C was prepared by the pharmacy department as an IV infusion over 30 minutes in 100 mL of dextrose 5% water. The decision to initiate IV vitamin C was not guided by clinical practice guidelines and was made on a case-by-case basis through provider assessment of various clinical parameters such as organ dysfunction and vasopressor requirement.

### Study Outcomes

The primary outcome of the study was in-hospital mortality. Secondary outcomes included ventilator requirements, SOFA scores post-treatment, vasopressor requirement in norepinephrine equivalents, resolution of diagnostic imaging, and ICU length of stay. Total norepinephrine equivalents was calculated based on the following formula: norepinephrine (mcg/min) + dopamine [(mcg/kg/min)/2] + epinephrine (mcg/min) + phenylephrine [(mcg/min)/10].<sup>14</sup>

### Statistical Analysis

All eligible patients were included in a propensity score model with initiation of IV vitamin C being the dependent variable and age, sex, diabetes, and hypertension being the independent variables in order to perform global optimal matching to create propensity score matched cohort in a 1:3 ratio. Covariate balance was assessed using standardized mean differences, with a standardized mean difference between -0.10 and +0.10 representing good covariate balance between the

2 groups. Dichotomous study outcomes were compared using the Fisher's Exact Test, continuous outcomes were compared using the Student's t test, and ordinal outcomes were compared using the Wilcoxon rank sum test. Laboratory value trends were analyzed through linear regression analyses. Statistical analyses were performed using SAS Studio (SAS Corporation, Cary, NC, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA).

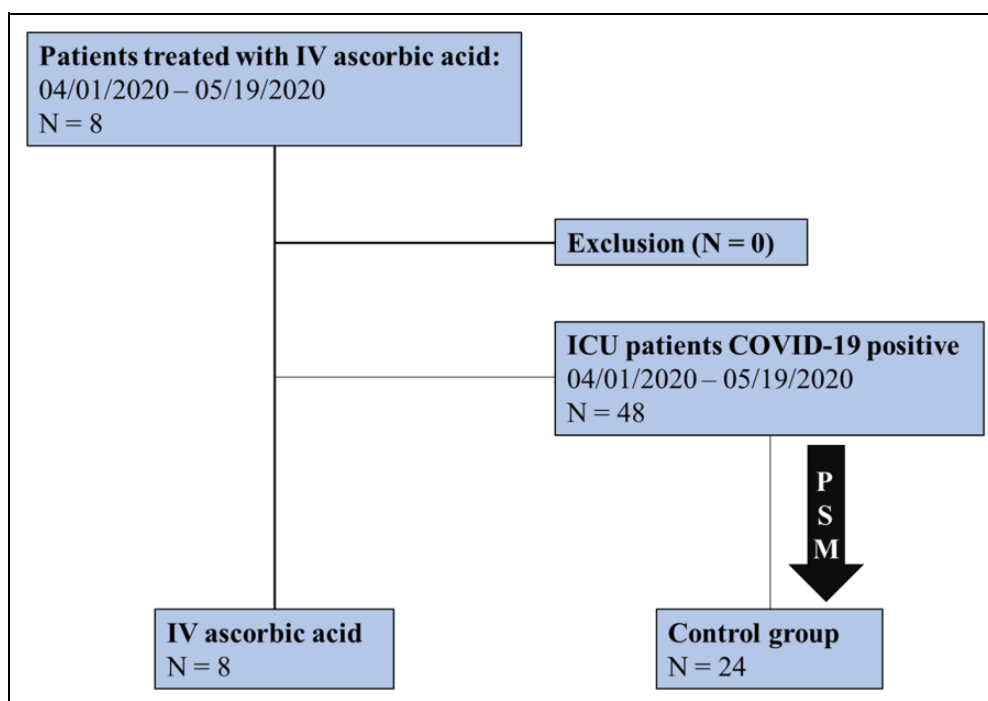
## Results

A total of 8 patients received IV vitamin C and were matched in a 1:3 ratio to 24 critically-ill COVID-19 patients (Figure 1). Data was determined to be normally distributed based on the Kolmogorov-Smirnov test. Baseline characteristics for the IV vitamin C and control groups are shown in Table 1. There were no statistically significant differences noted in any of the baseline characteristics. Standardized mean differences were all between -0.10 and +0.10 except for hypertension (SMD = 0.35).

Patient treatment and outcomes are shown in Table 2. There were no differences in receipt of convalescent plasma, corticosteroids, therapeutic anticoagulation, or remdesivir. More patients in the control group received tocilizumab ( $P < 0.005$ ). A greater percentage of patients in the IV vitamin C group received IV thiamine ( $P = 0.01$ ). On average, the IV vitamin C group were initiated on therapy  $7.1 \pm 4.6$  days from admission and received  $13.4 \pm 3.6$  total doses.

Patients in the IV vitamin C group had significantly higher rates in-hospital mortality (88% vs. 79%,  $P = 0.05$ ). There was no difference in ICU length of stay ( $P = 0.71$ ). There was no difference in the incidence of chest radiographs demonstrating bilateral opacities, infiltrates, or consolidations at baseline or over the next 4 days of therapy. Mean SOFA scores were significantly higher in the IV vitamin C group when compared to the control group ( $12.4 \pm 2.8$  vs.  $8.1 \pm 3.5$ ,  $P < 0.005$ ). A paired-samples t-test was conducted to compare mean SOFA scores before and after the treatment periods in both groups. There was a statistically significant increase in mean SOFA scores in the IV vitamin C group ( $P = 0.04$ ) and no difference in the control group ( $P = 0.13$ ).

Mean clinical parameter trends pre-treatment (denoted time zero) through post-treatment are highlighted in Table 3 and Figure 2. Patients in the control group had a statistically significant increase in tidal volume requirements when over time ( $P < 0.005$ ) and when compared to the IV vitamin C group ( $P < 0.005$ ). The control group patients had decreased fraction of inspired oxygen (FiO<sub>2</sub>) and positive end-expiratory pressure (PEEP) requirements over time ( $P = 0.03$  and  $P = 0.05$ , respectively) and when compared to the IV vitamin C ( $P = 0.02$  and  $P = 0.03$ , respectively). Serum lactate concentrations were significantly increased in the IV vitamin C group throughout the treatment course ( $P = 0.05$ ) and when compared to the control group ( $P = 0.01$ ). There was no difference in lymphocyte concentration, vasopressor requirement over time, or chest radiographical findings between the 2 treatment groups.



**Figure 1.** Patient identification and inclusion.

**Table 1.** Baseline Characteristics.

Characteristic	IV Vitamin C (N = 8)	Control (N = 24)	P-value
Mean age, years $\pm$ SD	64.1 $\pm$ 8.3	64.9 $\pm$ 11.8	0.87
Sex, female	5 (63%)	15 (63%)	1.0
Weight (kg)	85.1 $\pm$ 27.3	88.8 $\pm$ 26	0.73
Asthma	0	1 (4%)	1.0
Cancer	0	2 (8%)	1.0
Congestive heart failure	1 (13%)	0	0.25
Coronary artery disease	1 (13%)	1 (4%)	0.44
Diabetes mellitus	4 (50%)	11 (46%)	1.0
Hypertension	6 (75%)	13 (54%)	0.42
Smoking	0	1 (4%)	1.0
C-reactive protein (mg/L)	233.6 $\pm$ 58.7	213.1 $\pm$ 68.9	0.52
D-dimer (ng/mL)	1708.6 $\pm$ 1969.7	5500.1 $\pm$ 8792.4	0.36
IL-6 (pg/mL)	692.4 $\pm$ 1291.5	346.7 $\pm$ 707.6	0.42
Lactate dehydrogenase (U/L)	724.8 $\pm$ 152.6	703.7 $\pm$ 231.8	0.84
Mean SOFA score $\pm$ SD	9.4 $\pm$ 3.2	6.6 $\pm$ 3.5	0.06

## Discussion

In a preliminary observational cohort study from a single center community teaching hospital we found that adjunctive IV vitamin C did not decrease the incidence of mortality in critically ill patients with COVID-19 infection. Vitamin C is a water-soluble molecule that serves as a free radical scavenger, a cofactor for several enzymes that facilitate the production of catecholamines, and an immunomodulating agent.<sup>15</sup> COVID-19 infection has been described to cause changes in redox homeostasis leading to oxidative stress, profound

inflammation and tissue damage, ultimately leading to acute respiratory distress syndrome and mortality.<sup>16</sup> Thus, we hypothesized the potent antioxidant and anti-inflammatory effects of vitamin C may be valuable in the management of COVID-19 infection.

The utility of IV vitamin C in critically ill patients was initially reported by Marik et al in a retrospective before-and-after study that reported significant mortality, SOFA score, and vasopressor requirement reduction utilizing a combination of IV vitamin C, hydrocortisone, and thiamine.<sup>7</sup> However, the subsequent prospective multicenter CITRIS-ALI and VITAMINS trials did not find any reductions in mortality.<sup>8,9</sup> We adapted the treatment regimens utilized in these studies for our patients due to the lack of available literature supporting alternative regimens for COVID-19 infection. Additional studies are now underway investigating various dosing and duration regimens.<sup>13,17,18</sup> The multicenter prospective trial conducted by Liu et al will utilize IV vitamin C 24 grams daily for 7 days, while the longitudinal study by Corrao will administer IV vitamin C 10 grams.<sup>13,17</sup> The optimal dosing and duration of IV vitamin C is not known and it is unclear if an inadequate treatment course contributed to the lack of benefit in this study.

Time to initiation of IV vitamin C may have also played a role in our results. Profound inflammation and cytokine storm has been implicated to be one of the contributing factors for the severe ARDS and subsequent mortality seen in COVID-19.<sup>3,19,20</sup> Early therapy may be required to prevent and attenuate the cytokine storm since the clinical benefit of select therapy such as corticosteroids in ARDS are dependent upon time to initiation in the disease course.<sup>21</sup> Although the optimal

**Table 2.** Patient Treatment and Outcomes.

Outcome	IV Vitamin C (N = 8)	Control (N = 24)	P-value
Mean time from admission to initiation of IV Vitamin C, days $\pm$ SD	7.1 $\pm$ 4.6	—	—
Number of doses of IV Vitamin C, mean $\pm$ SD	13.4 $\pm$ 3.6	—	—
Convalescent plasma	0	8	0.08
Corticosteroids	8 (100%)	18 (75%)	0.30
• Dexamethasone	7 (88%)	9 (38%)	—
• Mean dexamethasone dose, mg $\pm$ SD	18.6 $\pm$ 3.8	18.2 $\pm$ 5.3	—
• Methylprednisolone	1 (12%)	9 (38%)	—
• Mean methylprednisolone dose, mg $\pm$ SD	100	91.1 $\pm$ 34.8	—
• Mean duration, days $\pm$ SD	4.6 $\pm$ 2.7	6.5 $\pm$ 4.2	—
IV thiamine	8 (100%)	11 (46%)	0.01
• Mean thiamine dose, mg $\pm$ SD	200	164 $\pm$ 50.5	—
• Mean duration, days $\pm$ SD	6 $\pm$ 4.7	16.8 $\pm$ 15	—
Tocilizumab	1 (12.5%)	18 (75%)	<0.005
Remdesivir	0	2 (8.3%)	1.0
Therapeutic anticoagulation	8 (100%)	24 (100%)	1.0
Chest radiograph bilateral opacities, infiltrates, or consolidation	8 (100%)	23 (96%)	1.0
• Worsened chest radiograph day 1	1 (13%)	4 (17%)	1.0
• Worsened chest radiograph day 2	0	6 (25%)	0.30
• Worsened chest radiograph day 3	0	4 (17%)	0.55
• Worsened chest radiograph day 4	0	4 (17%)	0.55
Mean $\pm$ SD SOFA score post-treatment	12.4 $\pm$ 2.8	8.1 $\pm$ 3.5	<0.005
Mean ICU length of stay, days $\pm$ SD	18 $\pm$ 13	16 $\pm$ 14	0.71
Hospital mortality	7 (88%)	19 (79%)	0.05

timing is still unknown and requires further investigation, IV vitamin C was administered on average within 7 days of admission which may have been too late in the patient's disease course to make a significant impact.

Oxidative stress may play a role in the progression of COVID-19 infection to ARDS and IV vitamin C has been proposed as a potential therapeutic modality to attenuate this process.<sup>22</sup> The daily trend of ventilator settings did not reflect significant improvements in respiratory status in our study as there was no statistically significant difference in tidal volume, FiO<sub>2</sub>, or PEEP from pre-treatment through post-treatment. This is a similar finding to the CITRIS-ALI trial which reported no difference in oxygenation index at baseline and through 168 hours post-treatment.<sup>9</sup> It is possible for the delayed timing of IV vitamin C to have blunted the beneficial effects as these patients may have already progressed to the late fibroproliferative phase or ARDS.

The combination of IV vitamin C, corticosteroids, and thiamine has been shown to have important roles such as

preservation of endothelial function and microcirculatory flow, thereby improving sepsis and decreasing vasopressor requirements.<sup>23</sup> Treatment with IV vitamin C did not lead to a statistically significant decrease in vasopressor requirements when compared to the control group. This finding is similar to lack of difference in vasopressor-free days reported in the CITRIS-ALI and VITAMINS studies.<sup>8,9</sup> Our results should be interpreted within the context of not having patient data on intravascular volume status, cardiac function, and concomitant use of inotropic agents or vasopressin.

As a corollary to the persistent vasopressor requirement in the treatment group, the statistically significant increase in lactate concentrations in the IV vitamin C group may be reflective of ongoing hypoperfusion and unresolved shock. Furthermore, it is unclear if patients in this study received an adequate dose of thiamine to facilitate lactate clearance as some studies report utilizing higher doses of 500 mg every 8 hours.<sup>4</sup>

There was no statistically significant change in lymphocyte concentration in the IV vitamin C group. Vitamin C has been implicated in the activation and differentiation of lymphocytes and may play a role in preventing viral disease progression.<sup>24</sup> One possible explanation for stable lymphocyte concentrations is the high utilization of glucocorticoids in the IV vitamin C group and control group (100% and 75%, respectively).

At the conception of this study, the available literature supporting the routine use of tocilizumab in COVID-19 patients was controversial as there was inconsistent evidence reporting improved survival or other clinical outcomes such as requirement of mechanical ventilation, oxygen requirements over time, and successful discharge.<sup>25-28</sup> Subsequently, a large randomized controlled trial of adult patients with COVID-19 infection reported decreased 28-day mortality and greater probability of discharge from hospital alive in patients allocated to tocilizumab.<sup>29</sup> Although more patients in the control group received tocilizumab, the overall mortality rates in the control group remained high (79%). The higher mortality rates in this study may be attributable to the higher severity of illness of our study population. It remains unclear if the higher percentage of patients receiving tocilizumab had a significant role in our results.

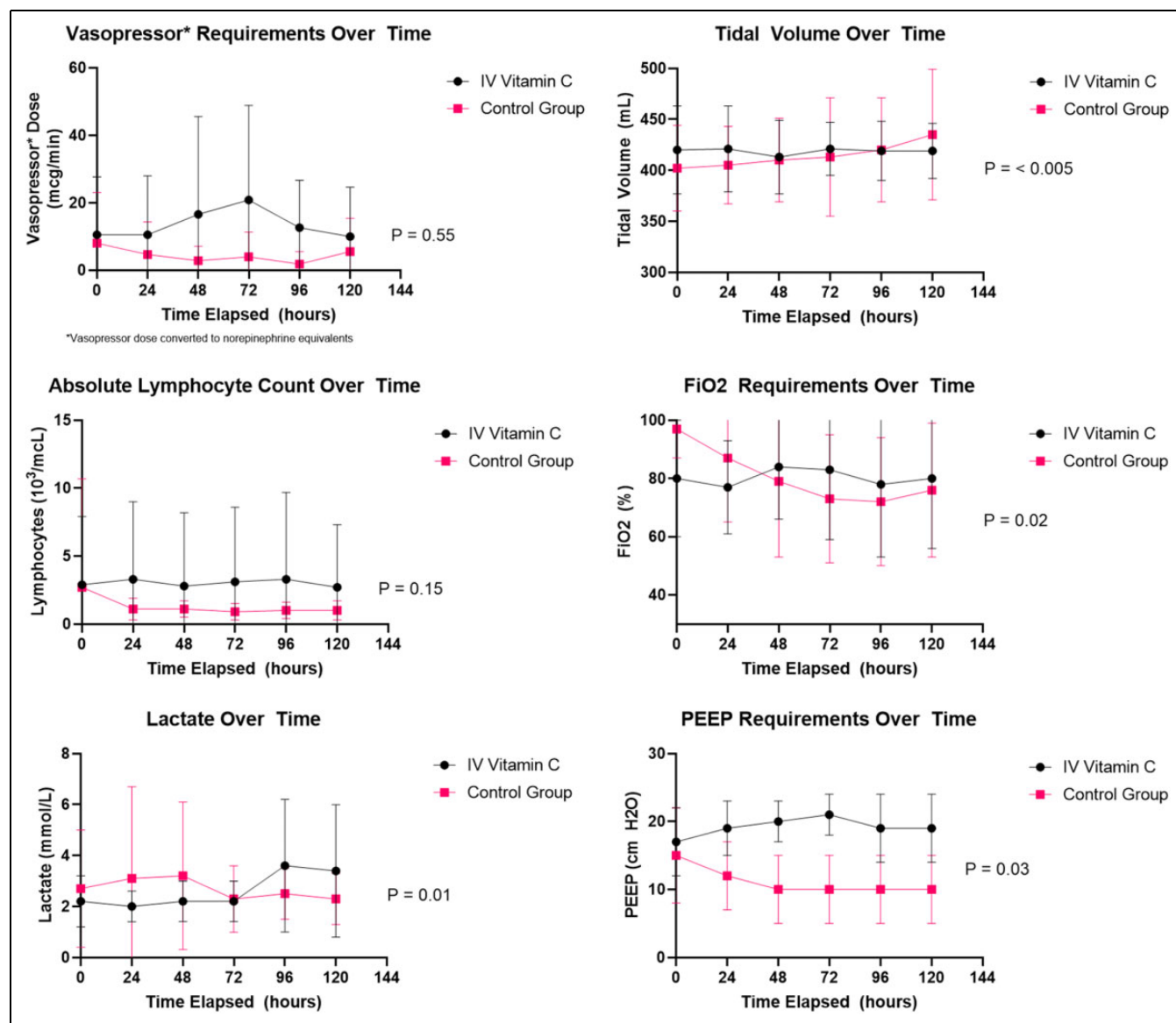
There are additional considerations regarding the preparation of IV vitamin C. Each multi-dose vial of IV vitamin C contains 25 grams and doses must be dispensed from the vial within 4 hours.<sup>30</sup> In an effort to reduce pharmaceutical waste and streamline workflow, doses for patients being treated with IV vitamin C should be prepared as a batch to be administered on standardized institutional schedules. Once diluted, each bag of IV vitamin C is stable for up to 96 hours at room temperature.<sup>31</sup>

Our study has a number of limitations that we acknowledge. First, given its retrospective design, we were unable to fully account for all confounding variables. Second, although we performed propensity score matching to form a control group, some residual imbalance was noted between the 2 groups with could have led to bias and may have influenced our results. Third, the lack of sample size calculation and small sample size

**Table 3.** Clinical Parameter Trends (Mean  $\pm$  SD).

Laboratory parameter	Group	Pre-treatment	Day 1	Day 2	Day 3	Day 4	Post-treatment	P-value	P-value
Tidal volume (mL)	IV Vitamin C	420 $\pm$ 43	421 $\pm$ 42	413 $\pm$ 36	421 $\pm$ 26	419 $\pm$ 29	419 $\pm$ 27	1.0	<0.005
	Control	402 $\pm$ 42	405 $\pm$ 38	410 $\pm$ 41	413 $\pm$ 58	420 $\pm$ 51	435 $\pm$ 64	<0.005	
FiO <sub>2</sub> (%)	IV Vitamin C	80 $\pm$ 20	77 $\pm$ 16	84 $\pm$ 18	83 $\pm$ 24	78 $\pm$ 25	80 $\pm$ 24	0.94	0.02
	Control	97 $\pm$ 10	87 $\pm$ 22	79 $\pm$ 26	73 $\pm$ 22	72 $\pm$ 22	76 $\pm$ 23	0.03	
PEEP (cm H <sub>2</sub> O)	IV Vitamin C	17 $\pm$ 5	19 $\pm$ 4	20 $\pm$ 3	21 $\pm$ 3	19 $\pm$ 5	19 $\pm$ 5	0.38	0.03
	Control	15 $\pm$ 7	12 $\pm$ 5	10 $\pm$ 5	10 $\pm$ 5	10 $\pm$ 5	10 $\pm$ 5	0.05	
Lactate (mmol/L)	IV Vitamin C	2.2 $\pm$ 1	2 $\pm$ 0.6	2.2 $\pm$ 0.8	2.2 $\pm$ 0.8	3.6 $\pm$ 2.6	3.4 $\pm$ 2.6	0.05	0.01
	Control	2.7 $\pm$ 2.3	3.1 $\pm$ 3.6	3.2 $\pm$ 2.9	2.3 $\pm$ 1.3	2.5 $\pm$ 1	2.3 $\pm$ 1	0.17	
Lymphocytes (10 <sup>3</sup> /mCL)	IV Vitamin C	2.9 $\pm$ 5	3.3 $\pm$ 5.7	2.8 $\pm$ 5.4	3.1 $\pm$ 5.5	3.3 $\pm$ 6.4	2.7 $\pm$ 4.6	0.78	0.15
	Control	2.7 $\pm$ 8	1.1 $\pm$ 0.8	1.1 $\pm$ 0.6	0.9 $\pm$ 0.6	1 $\pm$ 0.6	1 $\pm$ 0.7	0.12	
Vasopressor requirement*	IV Vitamin C	10.6 $\pm$ 17.1	10.6 $\pm$ 17.4	16.6 $\pm$ 29	20.9 $\pm$ 28	12.7 $\pm$ 14	10 $\pm$ 14.7	0.86	0.55
	Control	8.1 $\pm$ 15	4.7 $\pm$ 9.7	2.9 $\pm$ 4.3	4 $\pm$ 7.3	1.9 $\pm$ 3.7	5.6 $\pm$ 9.8	0.33	

\*Norepinephrine equivalents.

**Figure 2.** Comparison of clinical parameters over time.

of our study population limits the external validity of our results and increases the chance of type II error.

## Conclusion

In summary, the results of our study suggest the use of adjunctive IV vitamin C for the management of COVID-19 infection in critically ill patients does not decrease the incidence of mortality, vasopressor requirements, SOFA scores, or ventilator settings. Additional studies are needed to establish the optimal dose, duration, and potential role of IV vitamin C.

## Declaration of Conflicting Interests

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