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High-dose intravenous vitamin C decreases rates of mechanical ventilation and cardiac arrest in severe COVID-19

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Abstract

Intravenous vitamin C (IV-VitC) has been suggested as a treatment for severe sepsis and acute respiratory distress syndrome; however, there are limited studies evaluating its use in severe COVID-19. Efficacy and safety of high-dose IV-VitC (HDIVC) in patients with severe COVID-19 were evaluated. This observational cohort was conducted at a single-center, 530 bed, community teaching hospital and took place from March 2020 through July 2020. Inverse probability treatment weighting (IPTW) was utilized to compare outcomes in patients with severe COVID-19 treated with and without HDIVC. Patients were enrolled if they were older than 18 years of age and were hospitalized secondary to severe COVID-19 infection, indicated by an oxygenation index < 300. Primary study outcomes included mortality, mechanical ventilation, intensive care unit (ICU) admission, and cardiac arrest. From a total of 100 patients enrolled, 25 patients were in the HDIVC group and 75 patients in the control group. The average time to death was significantly longer for HDIVC patients ($P=0.0139$), with an average of 22.9 days versus 13.7 days for control patients. Patients who received HDIVC also had significantly lower rates of mechanical ventilation (52.93% vs. 73.14%; $OR_{IPTW}=0.27$; $P=0.0499$) and cardiac arrest (2.46% vs. 9.06%; $OR_{IPTW}=0.23$; $P=0.0439$). HDIVC may be an effective treatment in decreasing the rates of mechanical ventilation and cardiac arrest in hospitalized patients with severe COVID-19. A longer hospital stay and prolonged time to death may suggest that HDIVC may protect against clinical deterioration in severe COVID-19.

Keywords Ascorbic acid · Vitamin C · Treatment · Intensive care · SARS-CoV-2

Introduction

COVID-19 infection is an ongoing global pandemic that has affected more than 109 million patients worldwide and caused more than 2.4 million deaths so far [1]. Dexamethasone is currently available as a potential treatment for COVID-19, and Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of severe COVID-19 [2]. Acute respiratory distress syndrome (ARDS) is a frequent complication of COVID-19 infection and 61–81% of COVID-19 cases complicated by ARDS require intubation and mechanical ventilation [3].

Low levels of vitamin C have been described in critically ill patients, and prior studies have found that septic shock patients have low levels of vitamin C [4]. Vitamin C is an antioxidant and can aid in maintaining the lung epithelial barrier function, allowing it to be of potential benefit in patients with sepsis-induced ARDS [5]. Early use of intravenous vitamin C (IV-VitC) (along with glucocorticoids and

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thiamine) has been described to provide a mortality benefit in septic shock patients [6]. Recently, IV-VitC administration has been suggested as a potential treatment for COVID-19 infection [7]. Unfortunately, in recent studies in patients with sepsis and ARDS, the use of IV-VitC did not improve organ dysfunction scores or decrease inflammatory markers. However, this clinical trial did identify a lower death rate at 28 days in treated patients [8].

The inconclusive evidence behind the benefit of IV-VitC in patients with COVID-19 infection and the relative safety of its use has led to the start of a new clinical trial in Wuhan, China; however, the trial was terminated given the lack of qualifying patients due to the control of the pandemic in China [9]. A recent pilot trial showed that high-dose intravenous vitamin C failed to improve invasive mechanical ventilation-free days in 28 days, but might show a potential signal of benefit in oxygenation for critically ill patients with COVID-19 [10]. We aimed to investigate the efficacy and safety of high-dose IV-VitC (HDIVC) in patients with severe COVID-19.

Methods

Study design and setting

This retrospective cohort study was conducted at a single-center, large (530 bed) community teaching hospital, and took place from March 24, 2020 through July 2, 2020. Two cohorts of patients with severe COVID-19 were identified, and outcomes from each cohort were compared via inverse probability treatment weighting (IPTW). One cohort was treated with HDIVC while the second cohort did not receive this treatment.

COVID-19 illness severity has been defined by the Infectious Diseases Society of America as non-severe, severe, or critical. Severe COVID-19 (sCOVID-19) illness has been defined as an oxygen saturation of less than or equal to 94% while breathing room air, and this includes those on supplemental oxygen [11, 12].

Patients were followed through hospital discharge (home or to another institution) or death.

Participants

All patients 18 years or older with sCOVID-19, admitted to the hospital with hypoxic respiratory failure [oxygenation index < 300] were eligible for study enrollment. This oxygenation index was calculated based on inspiratory oxygen level requirement and arterial blood oxygen level. All sCOVID-19 patients, whether or not they were treated with HDIVC, were included in this study.

Variables

Patient information was reviewed and the following information was collected: patient age, demographics, Body Mass Index (BMI), past medical history, Charlson Comorbidity Index (CCI) [13], laboratory values, respiratory values, dates of various events, medications, admission to the intensive care unit (ICU), ICU length of stay (LOS), mechanical ventilation, time on the ventilator, vasopressor requirement, development of acute kidney injury (AKI), cardiac arrest, and survival. AKI was diagnosed based on the Acute Kidney Injury Network (AKIN) classification of an acute rise in serum creatinine within 48 h [14]. Cardiac arrest was noted for patients that had a cardiopulmonary resuscitation documented by a physician. If care was withdrawn due to an advanced directive on file, this did not qualify as a cardiac arrest.

Four variables were utilized to evaluate a time-to-event setting: ICU admission, mechanical ventilation, cardiac arrest, and death. Patients who did not have an event of interest were considered censored either at the date of hospital discharge or date of death.

Data sources/measurement

After receiving approval from the Institutional Review Board, patient data were extracted through the Electronic Health Record (EHR; EPIC system, Verona, WI, USA). Mechanical ventilation outcomes included the time in days to intubation from admission, the total number of days on the ventilator, and if reintubation was required following successful extubation.

Intervention

One treatment of HDIVC contained three grams of IV-VitC every 6 h for seven consecutive days. High-dose IV vitamin C is considered a supplementation of at least 10 g per day [15] that would lead to supra-normal plasma concentrations of vitamin C. The IV-VitC dosing for this study was modeled based on prior literature that showed a dosage of one to six grams per day of vitamin C shortened ventilation time on average by 25% [16].

Study size

We have included all available patients that met the inclusion criteria at the time of data collection.

Bias

Selection and ascertainment bias were avoided by including all the patients that received HDIVC that were available at the time of data collection. Selection bias may have been

introduced at the time of HDIVC prescription as the therapy was prescribed at the physician's discretion. Regular meetings with the data collectors were done throughout the study to minimize information bias. Researcher bias was limited via strict adherence to the research protocol. Standardized protocols for data collection were implemented to minimize the inter-observer variability among the four data collectors. The propensity score was utilized to minimize confounding factors between patient characteristics that may affect outcomes.

Statistical methods

Continuously measured variables were displayed in terms of mean/average with standard deviation in parentheses while categorical variables were displayed in terms of frequencies with percentages in parentheses. Two Samples Independent *T* Tests (or its non-parametric equivalent, Wilcoxon rank-sum) and Pearson's Chi-Square Tests were used to evaluate continuous and categorical variables, respectively. Odds Ratios (ORs) were generated with categorical variables and the control group was always treated as the reference group. Kaplan–Meier Survival Estimates were used to display survival outcomes. To minimize the effect of confounding bias given our study design, an Inverse Probability Treatment Weighting (IPTW) Propensity Score Methodology was employed. In the first step, a propensity model was built to predict the probability of receiving HDIVC treatment. The variables included in the propensity score model were extensively discussed and agreed upon by all authors based on clinical relevance. These variables included age, CCI, BMI, serum creatinine upon admission, N:L Ratio upon admission, history of diabetes mellitus (DM), and history of hypertension (HTN). In the second step, doubly robust propensity score outcome models were generated. In all outcome models, robust or sandwich standard errors were used. Marginal, or adjusted, means and proportions were generated for the HDIVC and control groups in the outcome models. The Fisher's Exact Test was implemented to compare groups with numerosity less than six, and univariate/unadjusted logistic regression when a subgroup had a value of zero.

Any P value < 0.05 indicates statistically significant associations. All analyses were done in both SAS 9.4 (SAS Institute Inc. Cary, NC, USA) and Stata 13.1 (StataCorp, LP, College Station, Texas).

Results

A total of 100 patients were enrolled during the study period, 25 patients in the HDIVC group and 75 patients in the control group. The average age of patients in each group was 68 years and the majority of patients were male (55%) and Caucasian (57%). There were notable patient populations of both Black or African American (15%) as well as Arabic or Middle Eastern descent (16%) in the study. The average BMI of patients was 31.7 kg/m^2 and half (50%) of all patients were considered obese. The average CCI was 4.3 and 52% of patients had DM, 79% of patients had HTN, and 28% of patients had chronic kidney disease (CKD). A minority of patients (15%) were on angiotensin-converting enzyme inhibitors (ACEI) prior to admission. The overall LOS in the cohort was 20.72 days. Baseline patient characteristics between both groups are described in Table 1.

The average serum creatinine on admission was 1.74 and the average N:L ratio upon admission was 9.99. The vast majority of patients were treated with steroids (99%), azithromycin (84%), antibiotics other than azithromycin (84%), and hydroxychloroquine (88%). A minority of patients were given remdesivir (4%) and tocilizumab (11%).

Patients who received HDIVC, on average, were significantly younger than the control group patients (58.3 years vs. 71.2 years; $P \leq 0.0001$) and had higher BMI (35.9 vs. 30.3; $P = 0.0073$). A lower average CCI was seen in those treated with HDIVC (3.0 vs. 4.8; $P = 0.0090$), which may partially be attributed to lower rates of HTN (60% vs. 85.3%; $P = 0.0071$) and CKD (8% vs. 34.7%; $P = 0.0101$) (Table 1). In addition, the average baseline SCr was lower in HDIVC patients (0.99 vs. 1.41; $P = 0.2376$), which translated to lower SCr upon admission (1.20 vs. 1.92; $P = 0.0248$) (Appendix Table 5). HDIVC patients were more likely to be treated with remdesivir (16% vs. 0%; $P = 0.0032$) and tocilizumab (28% vs. 5.33%; $P = 0.0047$) than control patients (Appendix Table 6).

A total of 19/25 patients (76%) completed at least 7 days of HDIVC. One of the patients was transferred to another facility for extracorporeal membrane oxygenation and the HDIVC was stopped after 2 days. Another patient was changed to comfort care and expired after 5 days of HDIVC. One patient received only 5 days of HDIVC because they were discharged home. One patient expired after 2 days, one after 3 days and one after 4 days of HDIVC.

Unadjusted outcome data

A majority of patients (85%) were admitted to the ICU and the average ICU LOS was 11.3 days, with 10.8% of patients were subsequently readmitted to the ICU. Mechanical ventilation was required for a majority of patients (72%), with the average time to ventilation of 5.3 days and an average of 9.3 days on the ventilator. Of those ventilated, 18.7% patients were transferred out of the ICU to a long-term acute care hospital while remaining on a ventilator. A minority of patients (15.9%) required reintubation. A majority of patients required vasopressors (63%) and developed AKI

Table 1 Demographics and baseline comorbidities stratified by vitamin C (data are reported prior to the hospital admission)

	IV-VitC ($n=25$)	Control ($n=75$)	P value
Age (years)			
Mean (standard deviation)	58.3 (14.2)	71.2 (13.0)	< 0.0001
Biological sex			
Female	12 (48.0%)	33 (44.0%)	0.7277
Male	13 (52.0%)	42 (56.0%)	
Race/ethnicity			
White or Caucasian	16 (64.0%)	41 (54.7%)	0.3185
Black or African American	2 (8.0%)	13 (17.3%)	
Asian	2 (8.0%)	2 (2.7%)	
Arabic or middle eastern Descent	2 (8.0%)	14 (18.7%)	
Other	3 (12.0%)	5 (6.7%)	
BMI (kg/m^2)			
Mean (standard deviation)	35.9 (9.7)	30.3 (7.1)	0.0073
BMI categories			
Underweight	0 (0.0%)	3 (4.0%)	0.1843
Normal weight	2 (8.0%)	12 (16.0%)	
Overweight	6 (24.0%)	27 (36.0%)	
Obese	17 (68.0%)	33 (44.0%)	
History of DM without complications			
No	13 (52.0%)	52 (69.3%)	0.1156
Yes	12 (48.0%)	23 (30.7%)	
History of DM with end-organ damage			
No	23 (92.0%)	60 (80.0%)	0.1666
Yes	2 (8.0%)	15 (20.0%)	
History of hypertension			
No	10 (40.0%)	11 (14.7%)	0.0071
Yes	15 (60.0%)	64 (85.3%)	
History of smoking			
No	18 (72.0%)	45 (60.0%)	0.2818
Yes	7 (28.0%)	30 (40.0%)	
History of CAD			
No	20 (80.0%)	48 (64.0%)	0.1375
Yes	5 (20.0%)	27 (36.0%)	
History of MI			
No	25 (100.0%)	66 (88.0%)	0.0694
Yes	0 (0.0%)	9 (12.0%)	
History of stroke			
No	21 (84.0%)	68 (90.7%)	0.3562
Yes	4 (16.0%)	7 (9.3%)	
History of PAD			
No	21 (84.0%)	64 (85.3%)	0.8715
Yes	4 (16.0%)	11 (14.7%)	
History of CHF			
No	22 (88.0%)	61 (81.3%)	0.4422
Yes	3 (12.0%)	14 (18.7%)	
History of COPD			
No	24 (96.0%)	62 (82.7%)	0.0961
Yes	1 (4.0%)	13 (17.3%)	

Table 1 (continued)

	IV-VitC ($n=25$)	Control ($n=75$)	P value
History of asthma			
No	22 (88.0%)	69 (92.0%)	0.5450
Yes	3 (12.0%)	6 (8.0%)	
History of liver disease			
No	25 (100.0%)	73 (97.3%)	0.4095
Yes	0 (0.0%)	2 (2.7%)	
History of kidney disease			
No	23 (92.0%)	49 (65.3%)	0.0101
Yes	2 (8.0%)	26 (34.7%)	
History of DVT or PE			
No	22 (88.0%)	67 (89.3%)	0.8536
Yes	3 (12.0%)	8 (10.7%)	
Immunosuppressed state upon admission			
No	22 (88.0%)	65 (86.7%)	0.8637
Yes	3 (12.0%)	10 (13.3%)	
History of cancer			
No	23 (92.0%)	59 (78.7%)	0.1329
Yes	2 (8.0%)	16 (21.3%)	
History of metastasis	($n=20$)	($n=16$)	
No	19 (95.0%)	13 (81.3%)	0.1921
Yes	1 (5.0%)	3 (18.8%)	
History of dementia			
No	25 (100.0%)	65 (86.7%)	0.0543
Yes	0 (0.0%)	10 (13.3%)	
History of hemiplegia			
No	25 (100.0%)	73 (97.3%)	0.4095
Yes	0 (0.0%)	2 (2.7%)	
History of peptic ulcer disease			
No	24 (96.0%)	68 (90.7%)	0.3946
Yes	1 (4.0%)	7 (9.3%)	
History of mild liver disease (hepatitis)			
No	25 (100.0%)	75 (100.0%)	––
Yes	0 (0.0%)	0 (0.0%)	
Moderate to severe liver disease			
No	25 (100.0%)	73 (97.3%)	0.4095
Yes	0 (0.0%)	2 (2.7%)	
History of AIDS			
No	25 (100.0%)	75 (100.0%)	––
Yes	0 (0.0%)	0 (0.0%)	
ACEI use prior to admission			
No	23 (92.0%)	62 (82.7%)	0.2577
Yes	2 (8.0%)	13 (17.3%)	
Charlson comorbidity index			
Mean (standard deviation)	3.0 (2.3)	4.77 (3.0)	0.0090

BMI body mass index, *DM* diabetes mellitus, *CAD* coronary artery disease, *MI* myocardial infarction, *PAD* peripheral artery disease, *CHF* congestive heart failure, *COPD* chronic obstructive pulmonary disease, *DVT* deep venous thrombosis, *PE* pulmonary embolism; *AIDS* acquired immune deficiency syndrome, *ACEI* angiotensin-converting enzyme inhibitor

(71%). Only 10.1% experienced cardiac arrest and the average time to cardiac arrest was 14.4 days. In addition, 47% of patients died in the cohort, with an average time to death of 15.7 days.

On average, patients who received HDIVC had a prolonged hospital stay (26.7 vs. 18.7 days; $P=0.0140$), prolonged ICU stay (16.9 vs. 9.2 days; $P=0.0535$), and prolonged time to death (22.9 vs. 13.70 days; $P=0.0139$) (Appendix Table 7). CRP levels were lower in the HDIVC group while other inflammatory markers (d-dimer and ferritin) were similar in both groups ($P \geq 0.05$).

Main results—IPTW analysis

HDIVC patients had significantly lower rates of mechanical ventilation (52.9% vs. 73.1%; $OR_{IPTW}=0.27$; $P=0.0499$). There also were significantly lower rates of cardiac arrest (2.5% vs. 9.1%; $OR_{IPTW}=0.23$; $P=0.0439$) in those treated with HDIVC (Table 2). These significant findings were confirmed in a time-to-event setting, showing a modest benefit for HDIVC treatment in terms of mechanical ventilation ($HR_{IPTW}=0.47$; $P=0.0254$) and cardiac arrest ($HR_{IPTW}=0.21$; $P=0.0082$) (Table 3).

IPTW analysis also shows that HDIVC patients had a significantly longer average LOS (24.0 vs. 18.5 days; $P=0.0393$). However, unlike the unadjusted analysis, there was not enough evidence to conclude that there was a prolonged ICU LOS ($P=0.1415$) or prolonged time to death ($P=0.0644$) for the HDIVC group (Table 4).

CRP levels were significantly lower in the HDIVC patients on the fifth day of treatment ($Diff_{IPTW}=-- 68.68$; $P=0.0348$). Ferritin levels were also significantly lower in the HDIVC patients on the seventh day of treatment ($Diff_{IPTW}=-2500$; $P=0.0042$).

Table 3 Inverse probability treatment weighting survival estimates

	HR_{IPTW} (95% CI)	*P* value
ICU admission	0.7 (0.4, 1.2)	0.1863
Mechanical ventilation	0.5 (0.2, 0.9)	0.0254
Cardiac arrest	0.2 (0.1, 0.7)	0.0082
Death	0.8 (0.4, 1.6)	0.5425

ICU intensive care unit

Discussion

Patients who received HDIVC had significantly lower rates of mechanical ventilation and cardiac arrest compared to the control group. Furthermore, those treated with HDIVC had a significantly longer average length of stay than the patients with COVID-19 that did not receive HDIVC. These findings are consistent with results recently reported in a meta-analysis which found strong evidence that vitamin C shortens the duration of mechanical ventilation in critically ill patients. [16] To our knowledge, our study is one of the few studies that show the benefit of HDIVC in patients with sCOVID-19. Lower rates of mechanical ventilation and cardiac arrest could have a significant impact on overall mortality, length of stay, and healthcare expenses related to COVID-19 admissions if applied at a larger scale. Furthermore, a longer average time to death in patients with sCOVID-19 treated with HDIVC might allow other pharmacologic interventions to take effect, especially in the critically ill patients, therefore potentially having a positive impact on their outcomes. The evidence to date suggests that HDIVC (6–24 g/day) may reduce mortality, ICU and hospital stay, and time on mechanical ventilation for severe respiratory infections [17].

Table 2 Inverse probability treatment weighting survival estimates for outcomes stratified by IV-VitC

	IV-VitC ($n=25$)	Control ($n=75$)	OR_{IPTW} (95% CI)	*P* value
Cardiac arrest	2.5% (0.0%, 5.5%)	9.1% (3.4%, 14.8%)	0.2 (0.1, 1.0)	0.0439
ICU admission	67.3% (55.0%, 79.7%)	79.5% (70.3%, 88.8%)	0.3 (0.1, 1.3)	0.1054
Mechanical ventilation	52.9% (36.8%, 69.1%) ($n=18$)	73.1% (61.8%, 84.5%) ($n=54$)	0.3 (0.1, 1.0)	0.0499
Transfer on ventilator	10.9% (1.1%, 20.7%)	14.0% (4.1%, 23.9%)	0.7 (0.2, 3.1)	0.6815
Reintubation	12.2% (0.5%, 23.9%) ($n=25$)	12.0% (3.2%, 20.9%) ($n=75$)	1.0 (0.1, 7.2) D_{IPTW} (95% CI)	0.9853
Overall LOS (days)	24.0 (20.4, 27.7) ($n=22$)	18.5 (15.4, 21.5) ($n=63$)	5.6 (0.3, 10.9)	0.0393
ICU LOS (days)	11.8 (7.9, 15.8) ($n=18$)	7.9 (5.1, 10.7) ($n=54$)	4.0 (−7.4, 9.3)	0.1415
Days on ventilator	13.6 (8.9, 18.3)	8.6 (6.3, 11.0)	5.0 (−0.2, 10.6)	0.0843

ICU intensive care unit, *LOS* length of stay

Table 4 Inverse probability treatment weighting survival estimates for time to outcomes, stratified by IV-VitC

	IV-VitC ($n=25$)	Control ($n=75$)	D_{IPTW} (95% CI)	*P* value
ICU admission	4.07 (1.73, 6.42)	3.8 (2.8, 4.9)	0.3 (− 2.4, 2.9)	0.8483
Cardiac arrest	45.3 (0.0, 313)	7.1 (0.0, 74.4)	38.2 (− 293, 370)	0.3817
Death	21.1 (15.4, 26.9)	14.6 (11.2, 18.1)	6.5 (− 0.4, 13.4)	0.0644
Mechanical ventilation	6.3 (3.3, 9.2)	4.5 (3.3, 5.8)	1.7 (− 1.5, 5.0)	0.2915
Reintubation	5.1 (0.0, 10.6) ($n=18$)	7.4 (1.6, 13.1) ($n=54$)	− 2.3 (− 10.7, 6.1)	0.4877

ICU intensive care unit

The ICU admission rates were lower in our HDIVC group with longer times to ICU admission and death but were not significantly different when compared with the control group. This might be due to type II error, caused by the small sample size which did not allow for enough power to detect a difference. Additionally, early COVID-19 treatment options, such as remdesivir and tocilizumab, were not readily available to clinicians. Prior to medication approval, there were strict criteria that had to be met by the patient. This posed an obstacle to administer these medications in a timely manner to hospitalized patients with sCOVID-19 that needed an immediate treatment option. HDIVC was available for prompt administration and therefore was given to severely ill patients as a novel treatment option. These circumstances may have also contributed to the lack of significant difference in ICU admission and death, despite the longer duration to ICU admission and death seen in the HDIVC group.

We were not able to show any difference in the AKI development and in the need for CRRT for AKI, which also may be due to the small sample size. Previous literature showed that HDIVC, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including AKI, and in reducing the mortality of patients with severe sepsis and septic shock [8]. Safety concerns were initially raised regarding the administration of HDIVC in patients with underlying CKD as reports of oxalate nephropathy have been published in patients with COVID-19 receiving HDIVC [18]. Interestingly, our data demonstrate that HDIVC may not be more harmful to patients with pre-existing CKD. Two patients that had CKD at baseline received HDIVC as a treatment for sCOVID-19. Both of these patients developed an AKI; however, neither progressed to renal failure that would require continuous renal replacement therapy (CRRT). On the other hand, 26 patients had CKD at baseline in the control group, and 20 developed an AKI. Five of these patients subsequently developed renal failure during their hospitalization that required CRRT as a result of the AKI.

Each dose of HDIVC was administered in combination with 500 ml of normal saline, which resulted in these patients receiving a daily excess of two liters of fluid from the treatments alone. Initially, there was concern regarding the administration of excess fluid in these patients with sCOVID-19, therefore the healthcare team attempted to otherwise maintain a neutral net fluid balance. In the typical management of ARDS, excess fluid can lead to complications and potentially be detrimental to lung function. Therefore, in ARDS a conservative fluid strategy is generally agreed upon within the medical community [19]. We did observe; however, that the excess fluid was tolerated fairly well by the lungs of those treated with HDIVC. This is indicated through the significantly lower rates of mechanical ventilation in the HDIVC cohort, and the lack of data demonstrating adverse effects from the excess fluid. These findings suggest that fluids in sCOVID-19 may be handled differently than typically seen in acute respiratory failure.

Our IPTW analysis showed that CRP was significantly lower on day 5 and ferritin was significantly lower on Day 7 in the HDIVC group compared to the control group. This is consistent with prior literature demonstrating HDIVC might be beneficial in the inflammatory response, immune and organ function for aggravation in sCOVID-19 [20, 21].

Our data demonstrate no measurable occurrences of direct harm to those who were treated with HDIVC. The data further demonstrate that this population did not experience less favorable outcomes compared to those who did not receive HDIVC. These data are similar to previous research that found that HDIVC has an excellent safety profile. It also has low cost and potential for rapid upscaling of production; therefore, its usage appears warranted in COVID-19 [22]. Our study supports the continuation of investigations of HDIVC in hospitalized patients with sCOVID-19.

Limitations

The main limitation of this study is the sample size. Furthermore, not every patient in the HDIVC cohort completed the full seven days of treatment; however, each patient in this cohort received at least two full days of HDIVC. Additionally, the tests ordered on a given day for each patient in the control group vary based upon individual physician preference and practice of medicine, which resulted in missing

data in the control group. The IPTW analysis could not include any other pharmacologic interventions and adjusted analysis was not performed based on the other treatments (remdesivir) as they were only given to the HDIVC group and would create complete statistical separation. Therefore, the differences in the outcomes could have been influenced by these treatments and not by HDIVC alone. The overall care provided to the patients could have been different, as different physicians cared for the patients that received HDIVC than for the patients that were in the control group. While an IPTW propensity score analysis was thoughtfully conducted and variables were included based on previously published data as well as clinical relevance, there could still be unmeasured confounders that were not collected or adjusted for.

Table 5 Baseline lab values and labs upon admission, stratified by IV-VitC

	IV-VitC	Control	*P*-value
Baseline lab values	(*n* = 20)	(*n* = 66)	
Serum Cr			
Mean (standard deviation)	1.0 (0.3)	1.4 (1.4)	0.2376
GFR			
Mean (standard deviation)	75.6 (21.3)	64.6 (29.2)	0.0831
Lab values upon admission	(*n* = 25)	(*n* = 75)	
WBC count			
Mean (standard deviation)	7.4 (2.4)	8.3 (5.8)	0.6760
Neutrophil count			
Mean (standard deviation)	5.9 (2.5)	6.7 (5.1)	0.9492
Lymphocyte count			
Mean (standard deviation)	1.0 (0.7)	0.9 (0.5)	0.8199
N:L ratio			
Mean (standard deviation)	9.1 (7.0)	10.3 (11.6)	0.6500
Serum Cr			
Mean (standard deviation)	1.2 (0.6)	1.9 (1.7)	0.0248
GFR			
Mean (standard deviation)	69.0 (26.9)	49.8 (28.2)	0.0046
CRP	(*n* = 24)	(*n* = 48)	
Mean (standard deviation)	126.0 (76.3)	165.3 (98.5)	0.1308
D-Dimer	(*n* = 24)	(*n* = 29)	
Mean (standard deviation)	1,968.3 (3186.0)	2,553.3 (2720.0)	0.0166
Ferritin	(*n* = 24)	(*n* = 47)	
Mean (standard deviation)	2668.8 (4938.7)	2271.3 (2996.5)	0.6485
P/F ratio	(*n* = 24)	(*n* = 75)	
Mean (standard deviation)	106.7 (36.9)	118.5 (66.2)	0.7470

Cr creatinine *GFR* glomerular filtration rate *WBC* white blood cell *N:L ratio* neutrophil:lymphocyte ratio *CRP* C-reactive protein *P/F ratio* PaO_2/FiO_2 ratio

Conclusion

HDIVC was associated with decreased rates of mechanical ventilation and cardiac arrest, as well as increased length of survival in patients with sCOVID-19. A longer hospital stay and prolonged time to death may suggest that HDIVC protects against the clinical deterioration in sCOVID-19. These results should guide future randomized clinical trials regarding HDIVC treatment in patients with sCOVID-19.

Appendix

See Tables 5, 6, and 7.

Table 6 Treatment modalities, stratified by IV-VitC

Treatment	IV-VitC (*n* = 25)	Control (*n* = 75)	*P* value
Plaquenil			
No	5 (20.0%)	7 (9.3%)	0.1552
Yes	20 (80.0%)	68 (90.7%)	
Azithromycin			
No	7 (28.0%)	9 (12.0%)	0.0588
Yes	18 (72.0%)	66 (88.0%)	
Steroids			
No	0 (0.0%)	1 (1.3%)	0.5617
Yes	25 (100.0%)	74 (98.7%)	
Antibiotics (other than azithromycin)			
No	2 (8.0%)	6 (8.0%)	0.9999
Yes	23 (92.0%)	69 (92.0%)	
Anticoagulation treatment			
No	3 (12.0%)	21 (28.0%)	0.1048
Yes	22 (88.0%)	54 (72.0%)	
Anticoagulation prophylaxis			
No	7 (28.0%)	1 (1.3%)	< 0.0001
Yes	18 (72.0%)	74 (98.7%)	
Remdesivir			
No	21 (84.0%)	75 (100.0%)	0.0032
Yes	4 (16.0%)	0 (0.0%)	
Tocilizumab			
No	18 (72.0%)	71 (94.7%)	0.0047
Yes	7 (28.0%)	4 (5.3%)	

Table 7 Unadjusted outcomes, stratified by IV-VitC

Outcome	IV-VitC	Control	OR (95% CI)	*P* value
ICU admission	(*n* = 25)	(*n* = 75)		
No	3 (12.0%)	12 (16.0%)	1.4 (0.4, 5.4)	0.6290
Yes	22 (88.0%)	63 (84.0%)		
Time to ICU (days)	(*n* = 22)	(*n* = 63)	– (–, –)	0.5240
Mean (Standard Deviation)	4.5 (4.2)	3.9 (4.4)		
ICU LOS (days)	(*n* = 22)	(*n* = 60)	– (–, –)	0.0535
Mean (Standard Deviation)	16.9 (15.7)	9.2 (9.0)		
Mechanical ventilation	(*n* = 25)	(*n* = 75)		
No	7 (28.0%)	21 (28.0%)	1.0 (0.4, 2.7)	0.9999
Yes	18 (72.0%)	54 (72.0%)		
Time to ventilation (days)	(*n* = 18)	(*n* = 54)		
Mean (standard deviation)	6.9 (5.0)	4.7 (4.6)	– (–, –)	0.0922
Time on ventilator (days)	(*n* = 11)	(*n* = 49)		
Mean (standard deviation)	15.6 (10.6)	7.9 (6.9)	– (–, –)	0.0097
Transfer out on ventilator	(*n* = 23)	(*n* = 52)		
No	18 (78.3%)	43 (82.7%)	1.3 (0.4, 4.5)	0.6503
Yes	5 (21.7%)	9 (17.3%)		
Reintubation	(*n* = 21)	(*n* = 48)		
No	18 (85.7%)	40 (83.3%)	0.8 (0.2, 3.5)	0.8758
Yes	3 (14.3%)	8 (16.7%)		
Time to reintubation (days)	(*n* = 4)	(*n* = 9)		
Mean (standard deviation)	6.5 (6.5)	5.7 (5.4)	– (–, –)	0.8132
Pressors requirement	(*n* = 25)	(*n* = 75)		
No	10 (40.0%)	27 (36.0%)	0.8 (0.3, 2.1)	0.7199
Yes	15 (60.0%)	48 (64.0%)		
Development of AKI				
No	11 (44.0%)	18 (24.0%)	0.4 (0.2, 1.0)	0.0602
Yes	14 (56.0%)	57 (76.0%)		
AKI needing RRT				
No	21 (84.0%)	57 (76.0%)	0.6 (0.2, 2.0)	0.4064
Yes	4 (16.0%)	18 (24.0%)		
Confirmed DVT/PE	(*n* = 24)	(*n* = 75)		
No	22 (91.7%)	69 (92.0%)	1.1 (0.2, 5.6)	0.9584
Yes	2 (8.3%)	6 (8.0%)		
ICU readmission	(*n* = 24)	(*n* = 59)		
No	19 (79.2%)	55 (93.2%)	3.6 (0.9, 14.9)	0.0747
Yes	5 (20.8%)	4 (6.8%)		
Cardiac arrest	(*n* = 24)	(*n* = 75)		
No	22 (91.7%)	67 (89.3%)	0.8 (0.2, 3.9)	0.7420
Yes	2 (8.3%)	8 (10.7%)		
Time to cardiac arrest (days)	(*n* = 2)	(*n* = 8)		
Mean (standard deviation)	21.5 (7.8)	12.6 (8.5)	– (–, –)	0.1497
Death	(*n* = 25)	(*n* = 75)		
No	15 (60.0%)	38 (50.7%)	0.7 (0.3, 1.7)	0.4193
Yes	10 (40.0%)	37 (49.3%)		
Time to death (days)	(*n* = 10)	(*n* = 37)		
Mean (standard deviation)	22.9 (11.2)	13.7 (10.7)	– (–, –)	0.0139
Overall LOS (Days)	(*n* = 25)	(*n* = 75)		
Mean (standard deviation)	26.7 (15.0)	18.7 (11.9)	– (–, –)	0.0140

ICU intensive care unit *LOS* length of stay *AKI* acute kidney injury *RRT* renal replacement therapy *DVT* deep venous thrombosis *PE* pulmonary embolism

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Declarations

Conflict of interest The authors have no competing interests to declare.

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