Original Article

The effectiveness of vitamin C for patients with severe viral pneumonia in respiratory failure

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Background: Vitamin C is a well-known antioxidant and essential cofactor for numerous biological reactions. Several studies reported that vitamin C can improve the symptoms and prognosis of patients with sepsis and respiratory infection. We aimed to examine the effect of vitamin C when used in viral pneumonia patients with severe respiratory failure.

Methods: Total 201 patients with viral pneumonia were included, of them 35 patients used vitamin C. We performed a statistical analysis through a propensity score matching of the age and baseline characteristics of these patients.

Results: There were differences between the vitamin C group and non-vitamin C group in terms of age (60±15 *vs.* 66±14, P=0.03), extracorporeal membrane oxygenation (28.6% *vs.* 5.4%, P<0.001), and procalcitonin (3±8 *vs.* 9±23, P=0.02). The 28-day mortality was not different between the two groups (20.0% *vs.* 24.7%, P=0.33). In the propensity-matched group, the 28-day mortality was not significantly different between the two groups (20.0% *vs.* 37.1%, P=0.07). Moreover, no difference was observed in shock reversal within 14 days (45.7% *vs.* 25.7%, P=0.08) and recovery after acute kidney injury (52.9% *vs.* 66.7%, P=0.41) between the two groups. Vitamin C was not a prognostic factor for 28-day mortality (P=0.33).

Conclusions: In this study adjunctive intravenous vitamin C therapy alone was not associated with improvement of the 28-day mortality and prognosis in patients with severe viral pneumonia with respiratory failure.

Keywords: Acute respiratory distress syndrome (ARDS); ascorbic acid; critical care; viral pneumonia

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Introduction

Severe viral pneumonia with respiratory failure requires intensive care unit (ICU) admission and is known to have a high mortality rate. The treatment of severe viral pneumonia remains a challenge to clinicians. The incidence of adult viral pneumonia determined via polymerase chain reaction (PCR) was 13.5–56.2% (1-4). In a previous study conducted in an ICU, 31.4% of the patients with severe community acquired pneumonia had viral pathogens (4).

Vitamin C has been known to help relieve and prevent

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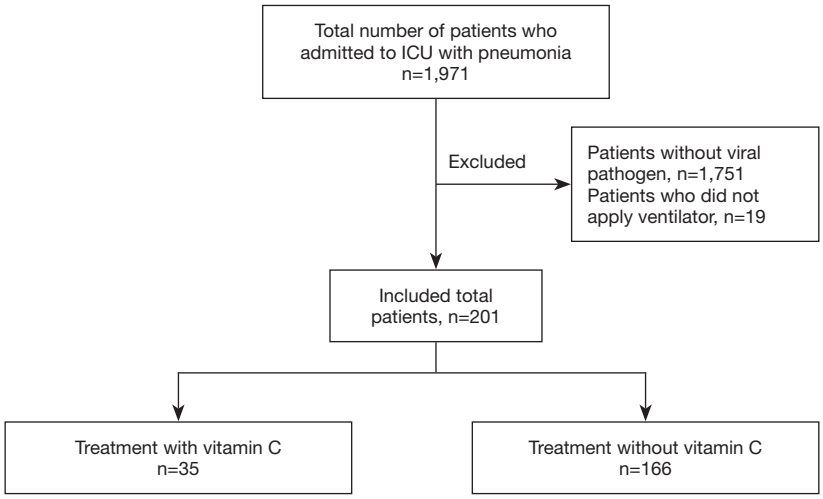

Figure 1 Flowchart of selected patients. ICU, intensive care unit.

symptoms of respiratory infection (5) for a long time, and several studies have reported the beneficial effects of vitamin C in the treatment of pneumonia (6) and sepsis (7). Previous studies suggested that vitamin C prevents the progression of sepsis to multiple organ failure, reduces the requirement for vasopressors, and improves patients' outcomes. It also has a synergistic effect when used in combination with thiamine and corticosteroid (8).

Plasma concentrations of vitamin C were decreased in patients with critical illnesses including sepsis, and a previous study suggested the relationship between such a decrease and the development of multiple organ failure (9-11). Vitamin C levels were found to be lower in patients with tuberculosis and pneumonia (12). The incidence of pneumonia was decreased in the group taking vitamin C (13), and symptoms of pneumonia were improved and hospital stay was shorter (6,13,14). The effect of vitamin C on H1N1 virus-induced pneumonia in restraint-stressed mice has been studied; results showed improvements in survival rates and prolonged survival time of virus-infected stressed mice in a dose-dependent manner (15). Recent studies reported that a combination of vitamin C, hydrocortisone, and thiamine therapy decreased the mortality rate in patients with severe pneumonia (16). These findings suggest vitamin C can improve the prognosis of patients with viral pneumonia.

2019 Novel Coronavirus (2019-nCoV) is rapidly spreading around the world. However, there are currently no specific effective antiviral agents or drug combinations supported by high levels of evidence (17,18). Therefore, we decided to analyze whether the effect of vitamin C on viral pneumonia could support the treatment.

We examined those patients with viral pneumonia admitted in the ICU to determine the efficacy of vitamin C treatment with respiratory failure and investigate the prognosis of patients with this condition after receiving the vitamin C treatment.

Methods

Patients and study design

We reviewed the medical records of patients with viral pneumonia admitted to Asan Medical Center (Seoul, Republic of Korea) medical intensive care unit (MICU) from January 2015 to April 2017. Of 1,971 patients admitted to the MICU, 201 were included. Patients who were younger than 18 years, those without viral pathogens (n=1,751), and those who did not use a ventilator (n=19) were excluded (*Figure 1*).

Viral pneumonia is a lung infection caused by a virus identified by sputum culture and PCR. The study patients were administered with 2 g of intravenous vitamin C every 8 hours for 4 days or until ICU discharge. We decided to give 6 grams of vitamin C (divided into three equal doses) per day because intravenous vitamin C normalizes leukocyte vitamin C levels in respiratory infections at a dose of 6 g/day (19). In addition, vitamin C 6 g/day has been used recently with reference to other studies (13) (Table S1). The ICU admission and treatment data of eligible patients were obtained from hospital electronic medical records. The data included age, sex, body weight, hospital and ICU

admission date, ICU admission diagnosis, site of admission, comorbidities, presence of immunosuppression, use of renal replacement therapy (RRT), hospital and ICU discharge date, date of death, Sepsis-related Organ Failure Assessment (SOFA) score (20), sputum and blood culture results, viral marker, laboratory data and radiologic results, usage of antibiotics and vitamin C, and outcomes. Continuous renal replacement therapy (CRRT) was initiated with the help of a nephrologist (21), and the initiation of extracorporeal membrane oxygenation (ECMO) was decided by two pulmonologists (22).

The primary outcome was 28-day mortality. The secondary outcomes included in-hospital mortality, ventilator-free days, recovery after acute kidney injury, shock reversal within 14 days, changes in the SOFA score within 3 days, and ICU and hospital lengths of stay.

Statistical analysis

To reduce the effect of selection bias and potential confounding factors in this observational study, we adjusted the age, malignancy, organ transplantation, procalcitonin, and CRRT with a P value <0.1 difference in baseline characteristics using propensity score matching.

After all the propensity score matches were performed, we compared the baseline covariates between the two groups. Continuous variables were compared using paired *t*-test or Wilcoxon signed-rank test, as appropriate, while categorical variables were compared using McNemar's test. Statistical significance and the effect of treatment on outcomes were estimated using appropriate statistical methods for matched data. Survival curves were constructed with Kaplan-Meier estimates.

All reported P values were two sided, and P values of less than 0.05 were considered significant. SPSS, version 21 (IBM Corporation, Armonk, NY, USA), was used for statistical analysis.

Results

Patients' characteristics

From January 2015 to April 2017, 1,971 patients with pneumonia were admitted in the ICU. Of them, 201 patients were included. Patients who were admitted pneumonia without vital pathogen (n=1,751) and those who did not use a ventilator (n=19) were excluded. Among the 201 patients included, 35 were using vitamin C (*Figure 1*).

The baseline characteristics of the study patients are shown in *Table 1*. Vitamin C group was younger (60±15 *vs.* 66±14, P=0.03), had lower procalcitonin level (3±8 *vs.* 9±23, P=0.02), and frequently used ECMO (28.6% *vs.* 5.4%, P<0.001). Patients in this group had slight differences in malignancy, organ transplantation, and frequency of CRRT but no statistical difference was found. There were no statistical differences in other baseline characteristics and laboratory data. There was no difference in the viral analysis except rhinovirus (28.6% *vs.* 14.5%, P=0.04) (Table S2).

Outcomes and prognosis of the unmatched patients

There was no significant difference between groups in terms of the 28-day mortality (20.0% *vs.* 24.7%, P=0.33) and in-hospital mortality (62.9% *vs.* 40.4%, P=0.57) (*Table 2*, *Figure 2*).

ICU length of stay (LOS) (34±32 *vs.* 17±17 days, P<0.001) and hospital LOS (65±57 *vs.* 43±42 days, P=0.04) were longer in the vitamin C group. There was no significant difference between groups in terms of shock reversal within 14 days, ventilator-free days, changes in the SOFA score within 3 days, and recovery after AKI (*Table 2*).

Baseline characteristics of matched patients

Age, malignancy, organ transplantation, procalcitonin, and CRRT were used for propensity score matching. We compared the baseline characteristics of patients treated with vitamin C and those who did not use vitamin C. In the vitamin C group, male patients were more predominant (77.1% *vs.* 51.4%, P=0.03) and APACHE score was lower (25±9 *vs.* 30±10, P=0.03). No significant difference was observed in other baseline characteristics and laboratory data between the two groups (*Table 3*). There was no significant difference in the viral analysis (Table S3).

Outcomes and prognosis for the matched patients

The 28-day mortality of the matched patients slightly decreased (20.0% *vs.* 37.1%, P=0.07) but it did not show a statistical significance. In-hospital mortality did not show a statistical significance (62.9% *vs.* 68.6%, P=0.14) (*Table 4*, *Figure 3*).

ICU LOS (34±32 *vs.* 17±14 days, P=0.005) was still longer in the vitamin C group. However, no significant differences were observed in the hospital LOS, shock reversal within 14 days, changes in the SOFA score within 3 days, and

Table 1 Baseline demographic, clinical characteristics and laboratory data of the unmatched patients

Characteristics	Total (n=201)	Vitamin C (n=35)	Non vitamin C (n=166)	P value
Age, years	65±15	60±15	66±14	0.03
Sex, male	134 (66.7)	27 (77.1)	107 (64.5)	0.15
Comorbidities				
Diabetes	50 (24.9)	6 (17.1)	44 (26.5)	0.24
Heart failure	7 (3.5)	1 (2.9)	6 (3.6)	0.82
Chronic kidney disease	9 (4.5)	2 (5.7)	7 (4.2)	0.70
Chronic lung disease	50 (24.9)	7 (20.0)	43 (25.9)	0.46
Liver cirrhosis	7 (3.5)	2 (5.7)	5 (3.0)	0.43
Stroke	15 (7.5)	2 (5.7)	13 (7.8)	0.67
Malignancy	24 (11.9)	1 (2.9)	23 (13.9)	0.07
Immunocompromised	98 (48.8)	18 (51.4)	80 (48.2)	0.73
Organ transplantation	7 (3.5)	3 (8.6)	4 (2.4)	0.07
Others	48 (23.9)	9 (25.7)	39 (23.5)	0.78
WBC, /μL	13,581±28,242	10,341±7,934	14,279±30,892	0.16
CRP, mg/dL	13±10	15±9	13±10	0.25
Procalcitonin, ng/mL	8±22	3±8	9±23	0.02
Acute kidney injury	80 (39.8)	17 (48.6)	63 (38.0)	0.24
CRRT	71 (35.3)	17 (48.6)	54 (32.5)	0.07
Vasopressors	130 (64.7)	26 (74.3)	104 (62.7)	0.19
Steroid	132 (65.7)	31 (88.6)	130 (78.3)	0.17
ECMO	19 (9.5)	10 (28.6)	9 (5.4)	<0.001
APACHE scores	27±9	25±9	27±9	0.26
Day 1 SOFA scores	9±4	10±4	9±4	0.66

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. WBC, white blood cell; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

recovery after AKI between the two groups (*Table 4*).

In the univariate Cox analysis, ventilator-free days [hazard ratio (HR) =0.91, 95% confidence interval (CI): 0.86–0.95, P<0.001], shock reversal within 14 days (HR =0.57, 95% CI: 0.29–1.09, P=0.09), and recovery from acute kidney injury (HR =2.85, 95% CI: 1.60–5.09, P<0.001) were prognostic factors for the 28-day mortality. Vitamin C was not a significant prognostic factor (P=0.33). In the multivariate Cox analysis, ventilator-free days (HR =0.91, 95% CI: 0.87–0.96, P=0.001) and recovery from acute kidney injury (HR =2.01, 95% CI: 1.12–3.63, P=0.02) were prognostic factors for 28-day mortality (*Table 5*).

There was no significant difference between day 3 SOFA scores and day 7 SOFA scores at the time of ICU admission. After comparing the changes in the renal SOFA scores, there was no significant difference between the initial score and the day 3 and day 7 scores (Table S4).

Discussion

In this study, we evaluated the therapeutic efficacy of adjunctive intravenous vitamin C in severe viral pneumonia patients with respiratory failure. The intravenous administration of 6 g/day of vitamin C was not associated

Table 2 Treatment outcomes and prognosis of the unmatched patients

Outcomes	Vitamin C (n=35)	Non vitamin C (n=166)	P value
28-day mortality	7 (20.0)	41 (24.7)	0.33
In hospital mortality	22 (62.9)	67 (40.4)	0.57
Shock reversal within 14 days	16 (45.7)	54 (32.5)	0.14
Ventilator free days	5±9	4±8	0.61
ICU length of stay (days)	34±32	17±17	<0.001
Hospital length of stay (days)	65±57	43±42	0.04
Changes in the SOFA score within 3 days	−0.8±2.3	−0.5±2.4	0.53
Recovery after acute kidney injury	9 (52.9)	30 (55.6)	0.85

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. ICU, intensive care unit; SOFA, sequential organ failure assessment.

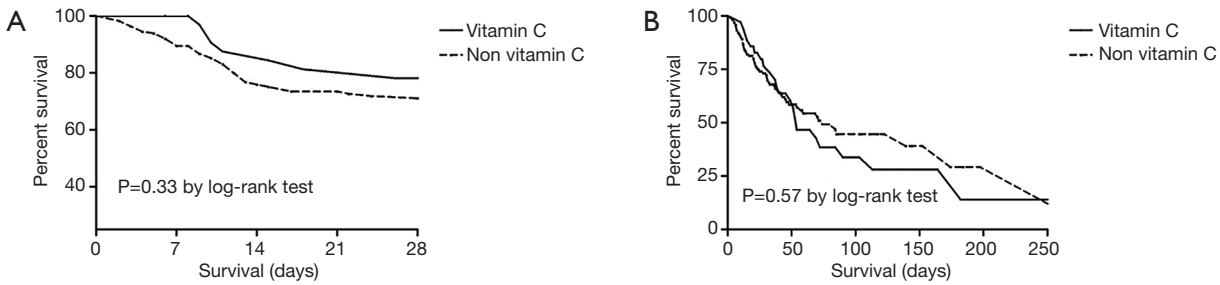

Figure 2 Survival time between the unmatched group. (A) 28-day mortality; (B) in-hospital mortality.

with decreasing in 28-day and in-hospital mortalities. In addition, there were no significant differences in shock reversal within 14 days, change in SOFA scores within 3 days, and recovery after AKI. We showed just trend to improve survival and shock reversal in limited patients.

Vitamin C is a well-known antioxidant and plays an important role in hormone production and immune response. Vitamin C plays a role in regulating immune cells, which increases the function of phagocytes and promotes the proliferation of T lymphocytes, which are important in bacterial and viral infections (14). Vitamin C has been found to be effective in killing bacteria (23,24), mycobacteria (25), HIV (26), and HCV (27) because it can generate free radicals and H_2O_2. As such, vitamin C plays a number of important roles in reducing oxidative stress caused by infection (13,28,29), balancing the immune system (14), and killing microorganisms by generating free radicals (23-27). For the reasons described above, we hypothesized that vitamin C would have positive effects in viral pneumonia. In our study, however, vitamin C did not have beneficial effects in patients with severe viral pneumonia with respiratory failure.

Vitamin C has been found to be effective in recovery and prevention from infection in animal experiments, and this effect is thought to be the same for humans (5,6,13). In some studies conducted in humans, vitamin C is also helpful for prevention and treatment of common colds, viral and bacterial infection (5,6,13,16,30,31). Hunt *et al.* found an 85% lower mortality in the vitamin C group compared with the placebo group. However, this comparison was made based on a small number of cases (six cases) (32). Mochalkin *et al.*'s study reported that the duration of recovery was reduced from 23.7 days in the control group to 4.6 days (19%) in the low-dose vitamin C group and 8.6 days (36%) in the high-dose vitamin C group (33). The use of vitamin C in restraint-stressed mice with H1N1 virus-induced pneumonia resulted in the improvement of survival rates and prolonged survival time (15). This finding suggests that vitamin C may be effective in improving the prognosis of patients with influenza. Fowler Iii *et al.* showed that administration of high-dose intravenous vitamin C

Table 3 Baseline demographic, clinical characteristics and laboratory data of the matched patients

Characteristics	Total	Vitamin C (n=35)	Non vitamin C (n=35)	P value
Age	59±17	60±15	59±18	0.95
Sex, male	45 (64.3)	27 (77.1)	18 (51.4)	0.03
Comorbidities				
Diabetes	15 (21.4)	6 (17.1)	9 (25.7)	0.38
Heart failure	2 (2.9)	1 (2.9)	1 (2.9)	>0.99
Chronic kidney disease	4 (5.7)	2 (5.7)	2 (5.7)	>0.99
Chronic lung disease	18 (25.7)	7 (20.0)	11 (31.4)	0.27
Liver cirrhosis	2 (2.9)	2 (5.7)	0 (0)	0.49
Stroke	2 (2.9)	2 (5.7)	0 (0)	0.49
Malignancy	2 (2.9)	1 (2.9)	1 (2.9)	>0.99
Immunocompromised	42 (60.0)	18 (51.4)	24 (68.6)	0.14
Organ transplantation	6 (8.6)	3 (8.6)	3 (8.6)	>0.99
Others	20 (28.6)	9 (25.7)	11 (31.4)	0.60
WBC, /μL	18,675±45,575	10,341±7,934	27,008±63,333	0.13
CRP, mg/dL	15±10	15±9	14±11	0.84
Procalcitonin, ng/mL	3±8	3±8	3±7	0.93
Acute kidney injury	35 (50.0)	17 (48.6)	18 (51.4)	0.81
CRRT	33 (47.1)	17 (48.6)	16 (45.7)	0.81
Vasopressors	47 (67.1)	26 (74.3)	21 (60.0)	0.20
Steroid	59 (84.3)	31 (88.6)	28 (80.0)	0.32
ECMO	14 (20.0)	10 (28.6)	4 (11.4)	0.07
APACHE scores	27±10	25±9	30±10	0.03
Day 1 SOFA scores	10±4	10±4	10±4	0.46

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. WBC, white blood cell; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

into a patient with enterovirus/rhinovirus-induced acute respiratory distress syndrome (ARDS) was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae (34). After influenza infection, bacterial pneumonia is likely to follow as a complication (35). It is thought that vitamin C can play a role in both bacterial and viral infections, so it is thought that it may be effective in preventing bacterial pneumonia and promoting prognosis in viral pneumonia. Kim *et al.* found that the use of red ginseng and vitamin C in influenza A infection increases immune cell activity and reduces lung inflammation (36). Recently, Kim *et al.* showed that the use of vitamin C, hydrocortisone, and thiamine in severe pneumonia resulted in the reduction of mortality (17% *vs.* 39%, P=0.04) and improvement in the chest radiologic findings (16). However, in our study, use of vitamin C in patients with severe viral pneumonia with respiratory failure did not showed the improvement of prognosis. In the vitamin C group, ECMO was frequently applied, and the group of patients who had ECMO was predicted to have high mortality (37), so we thought that this has influenced the results.

Moreover, shock reversal within 14 days and recovery after AKI did not improve in the vitamin C group. Several

Table 4 Treatment outcomes and prognosis of the matched patients

Outcomes	Vitamin C (n=35)	Non vitamin C (n=35)	P value
28-day mortality	7 (20.0)	13 (37.1)	0.07
In hospital mortality	22 (62.9)	24 (68.6)	0.14
Shock reversal within 14 days	16 (45.7)	9 (25.7)	0.08
Ventilator free days	5±9	6±10	0.59
ICU length of stay (days)	34±32	17±14	0.005
Hospital length of stay (days)	65±57	44±53	0.12
Changes in the SOFA score within 3 days	−0.8±2.3	0.0±2.9	0.21
Recovery after acute kidney injury	9 (52.9)	12 (66.7)	0.41

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. ICU, intensive care unit; SOFA, sequential organ failure assessment.

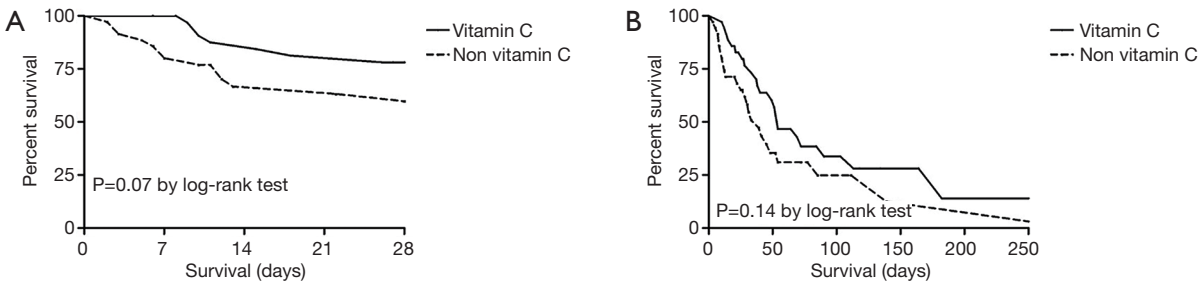

Figure 3 Survival time between the matched group. (A) 28-day mortality; (B) in-hospital mortality.

studies showed the beneficial effects the vitamin C in patients with sepsis and septic shock. Infusion with vitamin C resulted in an improvement in arteriolar responsiveness to hypotensive agents (38), improvement in endothelial and epithelial barrier function (39). In a phase I study investigating the safety of intravenous vitamin C in medical ICU patients with severe sepsis, Fowler *et al.* reported that the high-dose vitamin C group had a significant reduction in the daily SOFA score over 96 hours compared with the placebo group (11). As the study was performed only in a small number of patients (eight patients per group), this study failed to demonstrate the significant effect of vitamin C on 28-day mortality. Marik *et al.* reported that the use of a combination of vitamin C, hydrocortisone, and thiamine in patients with severe sepsis and septic shock reduced the hospital mortality rate by 32% (8). However, recent studies reported that vitamin C administration in patients with sepsis or septic shock did not improve their survival rate (40,41). Ahn *et al.* showed that adjunctive intravenous vitamin C therapy alone did not improve the hospital mortality rate associated with severe sepsis or septic shock (46% *vs.* 40%, P=0.62) (40). Shin *et al.* reported that a combination of vitamin C and thiamine in patients with septic shock did not improve the 28-day (16.6% *vs.* 17.5%, P=0.76) and in-hospital mortality (16.6% *vs.* 18.3%, P=0.55), respectively (41).

2019 Novel Coronavirus (2019-nCoV) is rapidly spreading around the world and was declared as a global concern (pandemic) by the World Health Organization (WHO). Since then, clinical trials have been conducted for various antiviral agent and vaccines, but there are no definite drugs that shown to be effective (17,18,42). Coronavirus infections can cause cytokine storms, which can increase oxidative stress and damage capillary endothelial cells (43,44). Vitamin C is a well-known antioxidant and reduces oxidative stress and improves in endothelial and epithelial barrier functions (39,45). The use of vitamin C for COVID-19 is being attempted (45,46) because it takes time to find effective vaccines and antiviral agents. The use of vitamin C 24 g/day for 7 days in severe COVID-19

Table 5 Prognostic factors for 28-day mortality in patients assessed using Cox proportional hazards model

Characteristics	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	1.02 (1.00–1.04)	0.13	–	–
Vasopressors	1.57 (0.83–2.97)	0.16	–	–
APACHE	1.02 (0.99–1.06)	0.24	–	–
SOFA scores	1.06 (0.98–1.16)	0.14	–	–
Diabetes	1.13 (0.59–2.17)	0.71	–	–
Malignancy	1.55 (0.73–3.31)	0.26	–	–
Immunocompromised	1.44 (0.81–2.56)	0.22	–	–
Organ transplantation	1.17 (0.29–4.84)	0.83	–	–
CRP	1.01 (0.98–1.04)	0.68	–	–
Procalcitonin	1.00 (0.99–1.01)	0.84	–	–
Vitamin C	0.67 (0.30–1.50)	0.33	–	–
Ventilator-free days	0.91 (0.86–0.95)	<0.001	0.91 (0.87–0.96)	0.001
Shock reversal within 14 days	0.57 (0.29–1.09)	0.09	0.89 (0.44–1.77)	0.73
Recovery after acute kidney injury	2.85 (1.60–5.09)	<0.001	2.01 (1.12–3.63)	0.02

Patients with P value <0.1 were included as multivariate models. APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment, CRP, C-reactive protein.

pneumonia patients is going on trial (46).

Our study has several limitations. First, plasma levels of vitamin C were not measured. Intravenous administration of high-dose vitamin C to severe patients can lead to restoration of normal plasma levels of vitamin C. However, it remains unknown how much vitamin C initially decreased and how quickly it recovered. Second, the administration of vitamin C was based on the allocation of patients to a specific primary care physician. Third, the baseline characteristics of patients in each group were different; even after propensity matching, still some differences in sex and severity of illness were still observed. Hence, our study should be interpretated carefully. Fourth, vitamin C levels were not measured in this study, so we did not know exact levels. But we gave vitamin C intravenously 2 g q8hrs, so therapeutic levels could be maintained. Finally, our results were less persuasive due to the retrospective nature of the study and the small sample size. However, large, multicenter randomized controlled trial is not easy for these patients, and this retrospective study can help until these results accumulate.

Conclusions

In conclusion, adjunctive intravenous vitamin C therapy alone did not reduce 28-day ICU mortality and in-hospital mortality in patients with severe viral pneumonia with respiratory failure. Our negative results do not mean that there is no potential for vitamin C in viral pneumonia. We showed just trend to improve survival and shock reversal in limited patients.

So a well-controlled randomized trial is needed to determine whether vitamin C is effective against viral pneumonia.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1306). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study was approved by the institutional review board of Asan Medical Center (IRB No. 2018-0429). The requirement for informed consent is waived by the ethics review board due to the retrospective nature of the study.

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Supplementary

Table S1 Variations in vitamin C dose in the control and vitamin C groups

Trial year, title	Vitamin C levels (g/day)		
	Participants	Vitamin C group	Control group
Mochalkin 1970, Ascorbic acid in the complex therapy of acute pneumonia (33)	70 in control group, 39 in low vitamin C group and 31 in high vitamin C group	High vitamin C: 0.5 to 1.6 G/day; Low vitamin C: 0.25 to 0.8 G/day	–
Hunt 1994, The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections (32)	28 vitamin C; 29 placebo, Hospitalised for acute bronchitis (n=40) or pneumonia (n=17)	Vitamin C 0.2 G/day	–
Tanaka 2000, Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study (47)	37 consecutive patients with burns over 30% of their total body surface area who were admitted to the ICU within 2 h after the injury	Intravenous vitamin C (66 mg/kg/h)	–
Flower 2014, Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (11)	24 patients with severe sepsis, 8 in placebo group, 8 in low ascorbic acid group, 8 in high ascorbic acid group	High vitamin C: 200 mg/kg/24 h Low vitamin C: 50 mg/kg/24 h	5% dextrose/ water
Marik 2017, Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock (8)	47 patients in both treatment and control groups	Vitamin C: 1.5 g every 6 h for 4 days or until ICU discharge	–
Kim 2018, Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study (16)	99 patients with severe pneumonia, 53 patients in vitamin C group, 46 patients in control group	Vitamin C: 6 g/day	–

Table S2 Virus strain identified in sputum culture and viral polymerase chain reaction

	Total (n=201) (%)	Vitamin C (n=35) (%)	Non vitamin C (n=166) (%)	P value
Rhinovirus	34 (16.9)	10 (28.6)	24 (14.5)	0.04
Parainfluenza virus	19 (9.5)	2 (5.7)	17 (10.2)	0.41
Influenza virus	66 (32.8)	10 (28.6)	56 (33.7)	0.55
Metapneumovirus	16 (8.0)	1 (2.9)	15 (9.0)	0.22
Respiratory syncytial virus	20 (10.0)	6 (17.1)	14 (8.4)	0.12
Cytomegalovirus	8 (4.0)	3 (8.6)	5 (3.0)	0.13
Corona virus	21 (10.4)	3 (8.6)	18 (10.8)	0.69
Adenovirus	15 (7.5)	5 (14.3)	10 (6.0)	0.09
Herpes simplex virus	9 (4.5)	3 (8.6)	6 (3.6)	0.20
Bocavirus	6 (3.0)	1 (2.9)	5 (3.0)	0.96

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Table S3 Virus strain identified in sputum culture and viral polymerase chain reaction in matched patients

	Vitamin C (n=35) (%)	Non vitamin C (n=35) (%)	P value
Rhinovirus	10 (28.6)	4 (11.4)	0.07
Parainfluenza virus	2 (5.7)	5 (14.3)	0.23
Influenza virus	10 (28.6)	8 (22.9)	0.58
Metapneumovirus	1 (2.9)	5 (14.3)	0.09
Respiratory syncytial virus	6 (17.1)	3 (8.6)	0.28
Cytomegalovirus	3 (8.6)	2 (5.7)	0.64
Corona virus	3 (8.6)	3 (8.6)	>0.99
Adenovirus	5 (14.3)	4 (11.4)	0.72
Herpes simplex virus	3 (8.6)	0 (0)	0.08
Bocavirus	1 (2.9)	2 (5.7)	0.56

Table S4 Serial change of SOFA score and renal SOFA score in the matched group during 7 days

	Total (n=70)	Vitamin C (n=35)	Non vitamin C (n=35)	P value
SOFA score				
D1	10.0±3.7	9.7±3.5	10.3±3.8	0.46
D3	9.5±4.1	8.9±3.7	10.2±4.5	0.17
D7	9.2±4.5	8.6±4.8	9.7±4.2	0.37
Renal score (SOFA)				
D1	0.7±1.2	0.7±1.2	0.8±1.1	0.84
D3	0.7±1.0	0.6±1.1	0.7±1.0	0.62
D7	0.7±1.1	0.8±1.1	0.7±1.0	0.60

Data are presented as mean ± standard deviation, unless otherwise indicated. SOFA, sequential organ failure assessment.

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