



INTRAVENOUS VITAMIN C (IVC) TREATMENT OUTCOME OF COVID 19 PATIENTS ADMITTED IN HOSPITAL: A SYSTEMATIC REVIEW

HASIL TERAPI VITAMIN C INTRAVENA TERHADAP KESEMBUHAN PASIEN COVID-19 DI RUMAH SAKIT : SISTEMATIK REVIEW

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is still becoming a problem in several countries with the emergence of new variants with the latest variant named Omicron. Studies show that patients with COVID-19 tend to have Acute Respiratory Distress Syndrome (ARDS) because of high pro-inflammatory cytokines and chemokines levels. Since its role as an antiviral agent, anti-cytokine, immunomodulator, antioxidant and has potential effect in maintaining body functions, vitamin C can be used as one of therapy. There is still arguable about giving treatment of COVID-19 patients with Intravenous Vitamin C (IVC). Previous research has not been discussed related to accelerating recovery and decreasing mortality. **Purpose:** To identify the impact of IVC intervention given to COVID-19 patients admitted in hospital by reviewing clinical outcomes particularly on complexity or mortality. **Review:** Literature information was sourced from PubMed, ScienceDirect, and Google Scholar databases through keywords to retrieve inclusion criteria published during 2019-2021. **Result:** We found that IVC influenced inflammatory biomarkers such as CRP, d-dimer, ferritin, and several inflammatory cytokines, mortality, length of stay, oxygenation, organ and immune system function but showed no significant difference between the control group. **Conclusion:** IVC treatment might be an essential adjuvant therapy in the aggravation of mild, severe, and critical COVID-19 patients, but did not understate complexity or mortality. Hence, further research and evaluation in clinical trials are needed.

ABSTRAK

Latar belakang: Pandemi virus corona (COVID-19) masih menjadi masalah di beberapa negara dengan munculnya beberapa varian serta varian terbaru bernama Omicron. Studi menunjukkan bahwa pasien dengan COVID-19 cenderung mengalami Sindrom Distres Pernapasan Akut (ARDS) karena tingginya kadar sitokin dan kemokin proinflamasi. Vitamin C berperan sebagai agen antivirus, antisitokin, imunomodulator, antioksidan, dan memiliki efek potensial dalam menjaga fungsi tubuh sehingga vitamin C dapat digunakan sebagai salah satu terapi. Pemberian vitamin C intravena (IVC) kepada pasien COVID-19 masih diperdebatkan. Penelitian terdahulu belum banyak membahas mengenai percepatan pemulihan dan penurunan angka kematian. **Tujuan:** Mengidentifikasi dampak intervensi IVC terhadap pasien COVID-19 yang dirawat di rumah sakit dengan meninjau hasil klinis terutama pada kompleksitas atau kematian. **Telaah pustaka:** Informasi literatur bersumber dari database Pubmed, ScienceDirect, dan Google Scholar melalui kata kunci untuk mengambil kriteria inklusi yang dipublikasikan selama 2019-2021. **Hasil:** Kami menemukan bahwa IVC memengaruhi biomarker inflamasi seperti CRP, d-dimer, ferritin, beberapa sitokin proinflamasi, kematian, lama rawat inap, oksigenasi, fungsi organ, dan sistem kekebalan, tetapi tidak menunjukkan perbedaan signifikan antara kelompok kontrol. **Kesimpulan:** Perawatan IVC mungkin merupakan terapi tambahan yang penting dalam peningkatan perburukan pasien COVID-19 dari ringan, berat, dan kritis tetapi tidak mengecilkan kompleksitas dan kematian. Oleh karena itu, diperlukan evaluasi klinis dan penelitian lebih lanjut.

Literature Review Studi Literatur

ARTICLE INFO

Received 14 December 2022

Revised 22 December 2022

Accepted 12 December 2023

Available online 30 July 2023

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Keywords:

Coronavirus, COVID-19, Drugs, Intravenous Vitamin C

Kata kunci:

Virus Corona, COVID-19, Obat, Vitamin C intravena



INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious virus originating from Wuhan, Hubei Province, China, since December 2019 (WHO, 2020). This virus has spread for more than two years and infected more than 100 million people globally. It becomes a problem in several countries with the emergence of new variants (*Alpha, Beta, Gamma, and Delta* variants). Recently, WHO designated the new SARS-CoV-2 strain named Omicron as a *Variant of Concern* (VOC), same as previous variants mentioned (WHO, 2021). This VOC was linked to greater transmissibility, enhanced infectivity, and possibly higher re-infection rates than the *Delta* variation, as well as a stronger affinity for human ACE2 (Kumar et al., 2021; WHO, 2021). High levels of ACE2 leads to higher risks of getting COVID-19, especially people with immune system defects (Sumantri et al., 2022).

Clinical manifestations of COVID-19 have ranged from absent or mild symptoms to severe respiratory illness or death. Majority of patients will have mild to moderate respiratory symptoms that recover without needing any specific therapy. Meanwhile, older people with comorbidities or organ function disorders have potential to more easily aggravate the development of diseases and even cause death, with characteristics such as decreasing oxygen saturation and lymphocytes, increasing white blood cells and CRP levels (Deng et al., 2020). Studies show that patients with COVID-19 exhibit high levels of pro-inflammatory cytokines and chemokines, the leading cause of *Acute Respiratory Distress Syndrome* (ARDS) (Coperchini et al., 2020). It revealed the strongest association with the requirement for mechanical ventilation in COVID-19 patients (Herold et al., 2020). Until now, there is no definite effective and recommended treatment up to declared cured for COVID-19 cases. The most commonly used standard therapy are chloroquine, hydroxychloroquine, and antiviral agents. Some also use adjuvant therapy such as corticosteroids, cytokine agents, immunomodulatory, and immunoglobulin therapy (Sanders et al., 2020).

Vitamin C can also be used for therapy because of its role as an antiviral agent, anti-cytokine, and immunomodulator. Under observational studies, vitamin C levels are practically inadequate and undetectable in COVID-19 patients with severe or critical illnesses, so vitamin C is undoubtedly needed (Chiscano-Camon et al., 2020; Tomasa-Irriguible and Bielsa-Berrocal, 2021). Vitamin C can increase the survival rate of COVID-19 patients with severe immune activation, reduce excessive inflammatory response, and enhance antiviral cytokines such interferon (IFN)- α/β (Bae and Kim, 2022). In pre-clinical studies (Erol et al., 2019). Vitamin C as an antioxidant has also been shown to reduce serum levels of TNF α , IL-1 β , increase superoxide dismutase levels, catalase and glutathione in ARDS. Some research stated large *Intravenous Vitamin C* (IVC) doses effectively cured over 50 individuals with mild to severe COVID-19

(Cheng, 2020). Treatment with a modest dosage of IVC, on the other hand, provided no significant benefit in terms of lowering the risk of mortality or achieving clinical improvement in patients with severe COVID-19 (Zheng et al., 2021). Further, other studies show that vitamin C supplementation had no effect on COVID-19 patients and did not significantly reduce the duration of symptoms when compared to standard care (Capone et al., 2020; Thomas et al., 2021) besides have few evidence role in susceptibility to COVID-19 and pneumonia (Hui et al., 2022). It is important to emphasize that findings of several ongoing clinical trials, particularly those using intravenous supplementation, are still pending and do not provide sufficient support for vitamin C as a COVID-19 therapy. Hence, the definite effect of IVC treatment on COVID-19 remains disputable. Based on this, researchers want to review further the potential of IVC therapy in patients with COVID-19 from some of current literature to obtain an overview of its effect and effectiveness as well as get more precise information.

LITERATURE STUDY

This review includes research articles from the database during 2019-2021, with the type of study are clinical trial, observational studies, pilot trial, and case series. Clinical research subjects on humans, men, and women aged over 18 years diagnosed with COVID-19 and hospitalized with interventions of given IVC in various doses. The exclusion criteria included experimental animal subjects, literature without full text and inaccessibility, literature review, systematic reviews, and meta-analysis. All data was extracted independently by two researchers in accordance with the pre-designed inclusion or exclusion criteria. The types of outcome were responses to inflammatory biomarkers, PaO₂/FiO₂, invasive mechanical ventilation-free days in 28 days, length of stay, mortality, and organ function improvement.

Search strategy

The literature research was performed electronically through *PubMed, ScienceDirect, and Google Scholar* databases released from March 2019 to August 2021. The search was limited only to the findings of the English language literature and the time of publication in the last two years. The keyword used is "Intravenous Vitamin C, COVID" or "Ascorbic acid, Intravenous, COVID" or "Intravenous Vitamin C, SARS-CoV-2". We included articles that reported any of the following inclusion criteria and any of the following outcomes.

Study selection

The literature was independently reviewed and assessed according to the inclusion and exclusion criteria by two researchers using the predefined

search strategy. Duplicate documentation or any other irrelevant article that does not meet the inclusion criteria that could be seen by name, year of publication, title, and abstract at the stage of feasibility analysis according to the criteria of inclusion (Figure 1).

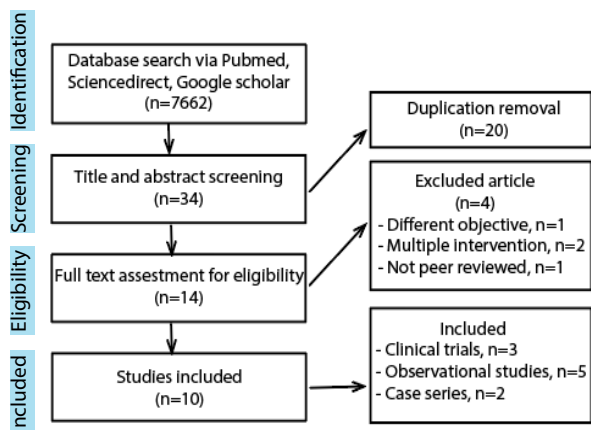


Figure 1. Flow chart of literature selection process

Data extraction

Literature that meets the inclusion criteria was collected and extracted independently by two researchers for inclusion in the review, starting with the title, author, year of publication, participant, IVC intervention (administration, dose and duration), comparator, and outcomes in tabular form.

RESULT

From the identification results based on a search on the database according to keywords found 34 journals. From 34 journals, screening was carried out to see duplication and then re-analyzed to ensure eligibility according to the predetermined inclusion criteria IVC and its effect on patients with COVID-19. It was obtained from the inclusion results of 10 journals (Table 1). Subject criteria, 1.702 total of patients, included men and women aged more than 18 years, diagnosed with COVID 19 in the moderate, medium, severe to critical stages with the main symptoms of respiratory system disorders such as *Severe Acute Respiratory Syndrome* (SARS) and pneumonia.

Follow-up duration ranging from 3 to 7 days is calculated from admission to hospitalization or admission to the ICU, some of them are treated at the *Medical Intensive Care Unit* (MICU) or *Progressive Care Unit* (PCU) and are being or will be given treatment with vitamin C. The duration of treatment with IVC was carried out for a maximum of 7 days and the shortest of 3 days With the highest dose of 24 g/day and the lowest 50 mg/kg. Some administer the IVC intervention by dissolving it in a bacteriostatic/sterile sea, 50 ml of saline solution, and 100 ml of dextrose.

The primary and secondary treatment outcomes are its effect on inflammatory biomarkers, PaO₂/FiO₂, invasive mechanical ventilation-free days in 28 days, mortality, length of stay and organ function improvement.

According to the results of the analysis from ten journals, we showed that several had an influence on inflammatory biomarkers in the form of decreasing inflammatory markers such as CRP, d-dimer, ferritin. Additionally, we showed the IVC treatment also have roles in some other inflammatory cytokines, reducing mortality, shortening the duration of hospitalization, potential in oxygenation, and improving organ and immune system function but show no significant difference between the control group.

DISCUSSION

In this systematic review, we involved three clinical trials, five observational studies and two case series to analyze the function of IVC therapy in COVID-19 patients. The resulting study of the literature proved the outcome in the form of an increase after the intervention. However, the increased experienced group was not significantly different from the control group in some literature or even had no effect. These results are nonetheless with another review. It turned out that the allotment of vitamin C did not significantly affect the length of stay, the need for mechanical ventilation and lessened mortality rates (Langlois *et al.*, 2019 ; Ozgunay *et al.*, 2021; Zhang and Jativa, 2018).

The leading cause of death in patients with COVID-19 is respiratory collapse in consequence of ARDS. Cytokine storm and oxidative stress are the two main factors involved in determining the progression of COVID-19 to ARDS. The complexity of COVID-19 experienced tends to be severe and critical. The age of each subject is relatively old and tends to have congenital diseases such as cardiovascular disease, diabetes, and respiratory disorders, and it increases the risk for accelerating disease progression. Generally, the intervention coincided with standard COVID-19 therapeutic such as dexamethasone, hydroxychloroquine, hydrocortisone, tocilizumab, lopinavir/ritonavir, antibiotics, corticosteroids, and other drugs. But some of the standard therapies mentioned later disapproved because these medicines showed no benefit on mortality or in speeding recovery of COVID-19 patients. Moreover, safety issues, including serious heart rhythm and other risky side effect has been evaluated (FDA, 2020). This outcome was consistent with other recent findings, such as the fact that the recommended dose for these medications is unlikely to kill or suppress the virus that causes COVID-19. As a consequence, we found that the EUA's legal criteria are no longer met.

Table 1. Descriptive analysis of ten literatures used in this study

Study design	Participants	Time and Location	Intervention	Comparator	Outcome	Reference
Retrospective study	323 COVID-19 patients, 204 men and 119 women with acute respiratory symptoms (153 /170)	Ankara,Turkey Hospital From 1th to 30th September 2020	IVC at dose of 2 g/ day within 3 days + standard therapy	Dexamethasone, Favipiravir, advanced oxygen support and medical treatment	<ul style="list-style-type: none"> • No difference in the level of length of stay, re-admission, ICU admission, advanced oxygen support, advanced medical care need and mortality • No reduction in CRP, d-dimer, and ferritin levels. 	Suna <i>et al.</i> , 2022
Case series	17 moderate and severe SARS-CoV-2 with severe acute respiratory symptoms requiring 30%/+ fraction inspired oxygen (FiO ₂) and receiving IVC treatment.	Albert Einstein Medical Center, Philadelphia, PA (USA)	IVC at dose of 1 g every 8 h within 3 days after hospital admission + standard therapy	Hydroxychloroquine, IV methylprednisolone, and/or tocilizumab	<ul style="list-style-type: none"> • Inpatient mortality rate 12% with intubation • Mechanical ventilation rate 17.6% • ↓ Inflammatory markers, ferritin, and d-dimer • ↓ FiO₂ requirement but not significant. 	Hiedra <i>et al.</i> , 2020
Multicenter, randomized trial	56 ICU patients severe and critical pneumonia COVID-19 with severe acute respiratory symptoms Having/at risk of multiple organs injury, P/F ratio <300 mmHg , admitted in the ICU, age ≥18 and <80 years (27/29)	3 hospitals in Hubei, China from 14th February 14, 2020 to 29th March 2020	High-dose intravenous vitamin C (24g/day)/12 g of vitamin C (diluted in 50 ml sterile water) /BD for 7 days, 12 ml/h + standard therapy	Bacteriostatic water for injection (same volume), Oseltamivir, azithromycin; LMWH; Piperacillin/tazobactam; hydrocortisone, lung protective ventilation	<ul style="list-style-type: none"> • No difference in Invasive mechanical ventilation-free (IMVFD28) • ↑ Oxygenation (PaO₂/FiO₂) • ↓ Inflammatory biomarker IL-6. • 28-day mortality, ICU and hospital mortality in patients with SOFA scores ≥3 	Zhang <i>et al.</i> , 2021
Open-label, non-blinded, randomized controlled trial	60 patients with COVID-19 >18 year, SpO ₂ <93%, at admission or >48h from the first COVID-19 treatment (30/30)	Ziaean Hospital, Tehran, Iran from April and May 2020	IVC 1.5 g/6 h, 6 g daily + standard therapy for 5 days	Oral lopinavir/ritonavir and single dose of oral hydroxychloroquine	<ul style="list-style-type: none"> • ↑ Level of SpO₂ (oxygen saturation) • ↓ Body temperature • No difference in the level of SpO₂ (oxygen saturation), length of stay, and mortality rate. 	Siahkali <i>et al.</i> , 2021

The continue of Table 1

Study design	Participants	Time and Location	Intervention	Comparator	Outcome	Reference
Retrospective study	110 patients moderate-grade pneumonia COVID 19 (55/55)	Shanghai Public Health Clinical Center, March 18 and april 18, 2020	High dose IVC at a dosage of 100 mg/kg/day. 1 g/h for 7 days, within following admission + standard therapy	Antiviral therapy, nutrition support, antibiotics, nasal tube oxygen, non-steroid antiinflammatory drugs or glucocorticoid	<ul style="list-style-type: none"> • ↓ Number of patients progressing to severe type • ↓ Duration and incidence of systemic inflammation (SIRS) • ↓ C-reactive protein levels and d-dimer • ↑ CD4⁺ (helper) T cells • ↓ APT (activated partial thromboplastin) time than the control group 	Zhao <i>et al.</i> , 2021b
Retrospective, case series	12 patients severe/critical pneumonia COVID 19 6 severe and 6 critical >18 year. PaO ₂ /FiO ₂ <lung radiological lesion enlargement of for 1–3 days	Shanghai Public Health Clinical Center from January 22, 2020 to April 11, 2020	HDIVC 162.7 mg/kg/day in severe cases and 178.6 mg/kg/day in critical cases for 7 days	Oxygen therapy of nasal cannula, mechanical ventilation (MV), vaso-active drug, glucocorticoid, antibiotics, low molecular heparin	<ul style="list-style-type: none"> • ↓ OFA score (organ failure assessment score), CRP, and body temperature • Level lymphocytes and CD4⁺ T cells in severe cases returned to normal • ↑ PaO₂/FiO₂ levels 	Zhao <i>et al.</i> , 2021a
Retrospective cohort studies	76 COVID 19 patients, (46/30)	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.hospital patients from January 31, 2020 to March 28, 2020	HDIVC dose of 6 /12 h (diluted in 50 ml of 5% glucose solution over 60 min) on the first day, and 6 g once for the following 4 days + standard therapy	Antibiotics, corticosteroids, immunomodulators and other antivirals (Lopinavir/Ritonavir, Ribavirin)	<ul style="list-style-type: none"> • ↓ 28-day risk of mortality • ↑ Oxygen support status • ↓ Serum hs-CRP, procalcitonin (PCT), interleukin-8 (IL) -8) 	Gao <i>et al.</i> , 2021
Randomized controlled trial	150 patients with COVID-19 (75/75)	A tertiary care hospital in Karachi, Pakistan From March to July 2020	50 mg/kg/day of IVC + standard therapy with duration same as length of stay	Antipyretics, dexamethasone, and prophylactic antibiotics	<ul style="list-style-type: none"> • Symptom-free earlier • Shorter length of stay • No difference in mechanical ventilation requirements • No difference in mortality 	Kumari <i>et al.</i> , 2020

The continue of Table 1

Study design	Participants	Time and Location	Intervention	Comparator	Outcome	Reference
Retrospective, cohort study	32 ICU patients with COVID-19 infection (8/24)	Adult intensive care unit (ICU) between April 1st, 2020 and May 30th, 2020	1.5 grams IV vitamin C (diluted in 100 mL of dextrose 5% water over 30 min) every 6 hours for up to 4 days + standard therapy	Corticosteroids hydrocortisone thiamine Tocilizumab antivoagulan	<ul style="list-style-type: none"> • ↑ Rates of hospital mortality and SOFA scores post-treatment • Not show a decrease in the incidence of mortality, SOFA score, vasopressors or ventilators need 	Li <i>et al.</i> , 2021
Retrospective, cohort study	236 patients with severe COVID 19 Respiratory rate >30 times/min; SpO ₂ <93% P/F ratio <300 mmHg 300 mm H (85/151)	Tongji Hospital of Huazhong University in Wuhan, China, between February 1 and March 10, 2020.	IVC at 100 mg/kg BW (diluted in 50 ml of saline solution over 30 min) every 6 hours on the first day, then 100 mg/kg BW every 12 h for the next 5 day	Antiviral, antibiotics, glucocorticoid, Immunoglobulin	• ↓hs-CRP; IL-6, TNF-α	Xia <i>et al.</i> , 2021

In patients with COVID-19, levels of inflammatory markers, CRP, increased correlate with disease severity, disease progression, the need for mechanical ventilation, and the duration of longer hospitalization (Chen *et al.*, 2020; Herold *et al.*, 2020; Sharifpour *et al.*, 2020). Procalcitonin (PCT) levels are also utilized to differentiate between severe or critical COVID-19 patients and moderate individuals and to predict prognosis better (Hu *et al.*, 2020). Both the CRP concentration and the PCT are important factors predicting an outcome in patients hospitalised with COVID-19 (Ming *et al.*, 2021). Worsening of the disease is also often characterized by the rapid development of a decrease in PaO₂/FiO₂ ratio, impaired organ function, and coagulation disorders (Zaim *et al.*, 2020)

Intravenous administration of vitamin C at a dose 2 g/day did not show a decrease in levels of inflammatory biomarkers such as CRP, D-dimer, and ferritin (Suna *et al.*, 2022). Same as other research, IVC at same dose show no differences between groups for inflammatory parameters (CRP, procalcitonin, d-dimer), length of stay or mortality (Ozgunay *et al.*, 2021), but an increased amount of oxygen saturation and decreased respiratory rate, reducing lung involvement and improving clinical symptoms (Darban *et al.*, 2021; Scholz *et al.*, 2021). In contrast, the administration of a dose of 1 g/8 hours with the duration of the same day showed a decrease in the markers of inflammation d-dimer and ferritin, the similarities in both of which the change in the duration of hospitalization and oxygen requirements (Hiedra *et al.*, 2020). Lymphocyte decrease, including CD4⁺ T cells, CD8⁺ and CD3⁺ reported correlating with the severity of

COVID-19 (Peng *et al.*, 2020). Administration of intravenous vitamin C for seven days with a dose of 100 mg/kg/day - 178.6 mg/kg/day has been proved to have an effect on CRP, which plays a role in the inflammatory process and organ function as seen from the decrease in SOFA scores, as well as CD4⁺ and lymphocytes that play a role in the immune system (Zhao *et al.*, 2021a; Zhao *et al.*, 2021b). Most of the infected patient's COVID 19 invades the lungs, characterized by respiratory disorders, hypoxia, and other respiratory disorders, affecting oxygenation, leading to a decrease in the SpO₂ level (Riviello *et al.*, 2016). PaO₂/FiO₂ and IL-6 levels are also potentially independent risk factors for mortality and prognosis in predicting severity in COVID-19 patients requiring intensive care (Gu *et al.*, 2021).

The results of the study prove that the administration of Vitamin C at high doses of 24 g/day for seven days, in addition to showing a decrease in inflammatory cytokines, vitamin C, has potential in oxygenation as indicated by an increase in PaO₂/FiO₂ as an indicator of oxygen levels in the body (Zhang *et al.*, 2021). Further, the doses of 1.5 g/6 hours for five days also have potential in oxygenation with increasing oxygen saturation but are not significant (Siahkali *et al.*, 2021). But at the same doses, show no decrease in the incidence of mortality, SOFA score, vasopressors or ventilators need. Meanwhile, hospital mortality rates and SOFA scores post-treatment increased (Li *et al.*, 2023). Intravenous administration of vitamin C 50 mg/day showed earlier symptom-free, shorter hospitalization period than controls but did not show a significant

difference in the need for mechanical ventilation and mortality (Kumari *et al.*, 2020). IVC treatment showed good results on vasopressors and requirements of mechanical ventilation need without affecting overall mortality. The task of vitamin C, in this case, is limited from mild to moderate cases of COVID-19, in which severe inflammation or cytokine storms are improbable ensued.

In this review about the use of IVC, we rivet on the risk of complexity and mortality from COVID-19. Hence, most of the patients involved our study were hospitalized patients who started IVC treatment after upturning to severe COVID-19. Thus, initiation of IVC was not early enough and the length of medication was relatively short. In a previous study, vitamin C administration to increase the concentration of vitamin C in critically ill patients also showed promising results in CRP levels, PCT, SOFA scores, and decreased 28 days-mortality events in patients with critical respiratory disorders pneumonia and sepsis (Mahmoodpoor *et al.*, 2021). Similar to the treatment of COVID-19 patients with respiratory disorders, intravenous administration of vitamin C, in addition to affecting inflammatory biomarkers and oxygen status, also reduces the incidence of 28 days mortality and duration of hospitalization (Gao *et al.*, 2021; Hiedra *et al.*, 2020).

Intravenous administration of vitamin C along with standard covid therapy generally does not show any significant side effects. While at high doses, the side effects probably can be thrombocytopenia, increased total bilirubin, and respiratory disorders (Gao *et al.*, 2021). *Acute Tubular necrosis* (ATI) and hyperoxaluria are also found in patients given high doses of vitamin C (Fontana *et al.*, 2020). Differences in outcomes that occur in addition to being suspected based on the previously mentioned subject factors may also be caused by differences in duration and the dose used. Interventions in each study were not the same, and it is suspected that earlier intervention duration might have a better effect before the development of more severe disease. However, in this case, the exact and effective dose and therapy provisions still do not exist.

Some studies mention a longer duration, at least seven days showing better results than the other, but some literature says the best duration of vitamin C administration is around 3-4 days, with lower efficacy if it is used for less than three days or more than five days (Marik *et al.*, 2021; Scholz *et al.*, 2021). Briefly, we are found that route of administration, VC dosage, initiation time, length of medication, type of disease, and progression of disease may define why the yield are discordant with those of previous studies.

This study has some inherent limitations described as follows. First, there is still a lack of participants and control groups as a comparison for effective results, so further inclusive research is needed in some of these aspects. In addition, the standard of COVID therapy in each study also uses relatively different drug interventions and does not enter into the observational

aspect of the study. In terms of dose, high doses of intravenous therapy are often used to treat various diseases, considering that most of the serum vitamin C levels are very low in critically ill patients, including critically ill patients with COVID 19. This high dose is used more often and it is believed to help more quickly in preventing disease severity.

Several studies on high-dose vitamin C intravenous therapy are still being carried out and are still ongoing, some of which have been registered with clinicaltrials.gov, one of which is: NCT04401150, NCT04357782, NCT04264533, NCT04323514, NCT04344184, with the main aim of seeing its effect on improving organ function, mortality and the need for a ventilator in the patient. Because of its potential benefit for several pathophysiological phases of COVID-19 in some study, vitamin C may be one of the adjuvant therapies that may be utilized to aid the patient with COVID-19 disease despite the type of variant (Miranda-Massari *et al.*, 2021). Second, despite only mild variability, the statistical results of studies with a high degree of heterogeneity may be due to clinical diversity. The definitions of COVID-19 severity were inconsistent among the enrolled studies. These effects, however, have only been recorded in a few reports and provides an opportunity in the future because there will be more data and clinical trials to analyze further its effect and correlation on the treatment of COVID-19 patients. Third, the studies involved in this systematic review, did not provide adequate data regarding the effect of IVC treatment with respect to time and duration of treatment on expected outcomes. These studies used IVC therapy for dissimilar durations and doses. For this reason, as an evaluation and optimization of the time, dose and duration of IVC treatment, a more intense RCT is needed so as to produce a precise understanding of the effects of this intervention on the prognosis in COVID-19 patients.

CONCLUSION

In summary, IVC treatment could be an essential therapy in the aggravation of mild, severe, and critical COVID-19 patients, but did not understate complexity or mortality. Due to the small sample and clinical study size, it is impossible to make a definitive statement about the potential effectiveness of intravenous vitamin C intervention, so these observations require further research and evaluation in clinical trials.

ACKNOWLEDGMENTS

This work was supported by a grant from the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia awarded to Nur Atik. The author reports no conflicts of interest in this work.

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