Literature Review

Effectiveness of Vitamin C Administration on Outcome in COVID-19 Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Numerous studies on the effectiveness of vitamin C against the COVID-19 infection have been widely carried out recently. However, the differences in dosage ranges and therapeutic efficacy in previous studies have prompted a systematic literature review on the effectiveness of vitamin C on outcomes in COVID-19 patients. In addition, this study aimed to determine the appropriate therapeutic dose of vitamin C for COVID-19 patients, either alone or in combination with other supplements, and to determine the side effects.

Methods: Gleaned from the search on Pubmed, Science Direct, and Google Scholar databases up to April 25, 2022, fourteen studies were relevant, namely five studies using vitamin C orally and nine studies administered intravenously. We assessed multiple outcomes, including mortality, hospitalization, and symptoms. The quality and risk of bias analyses were performed using JBI critical appraisal tools.

Results: The oral administration of vitamin C resulted in a significant difference in the mortality of COVID-19 patients (OR=0.66; 95% CI=0.45–0.97; *P*=0.04; I^2=0%) and a non-significant difference in the outcome. Duration of hospitalization (OR = -0.21; 95% CI = -2.70-2.28; *P*=0.87; I^2=94%). Regarding the cost-effectiveness and side effects manifested in digestive disorders such as nausea, diarrhea, stomach cramps, and vomiting, vitamin C with a dose of 500-1000 mg could be given orally.

Conclusion: Oral administration of vitamin C showed a reduction in the mortality of asymptomatic COVID-19 patients with moderate symptoms.

Keywords: ascorbic acid, mortality, SARS-CoV-2, supplements

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease characterized by severe acute respiratory syndrome.[1] It spread rapidly around the world and led to an increase in confirmed cases of COVID-19. Hence, the World Health Organization (WHO) declared a pandemic in 2020 due to this disease. The prevalence of COVID-19 in the world as of March 18, 2022, reached 480,170,572 confirmed cases with a death toll of 6,124,396. In Indonesia, the incidence of COVID-19 was 6,001,751 confirmed cases, with a death toll of 154,774. [2]

Since its first appearance, the high rate of confirmed COVID-19 by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and the death rate in COVID-19 patients have led to continued research on this subject, one of which is research on supplements for COVID-19 patients.[3] Additional supplementation in COVID-19 patients is necessary because the pathophysiological involvement is very complex and involves a decrease in the immune system. This additional supplement can act as an immunomodulator, anti-oxidant, and anti-inflammatory. [4]

The supplement for COVID-19 that has been widely studied is vitamin C. [5] Ascorbic acid, or vitamin C, is an anti-oxidant that can fight reactive oxygen species (ROS). In COVID-19 patients, there is excessive ROS production due to an impaired body defense system resulting in an increase in oxidative stress that contributes to tissue damage. [6] Apart from being an anti-oxidant, vitamin C also acts as an immunomodulator.[7,8] In the case of influenza, the administration of vitamin C has a symptom-

ameliorating effect, reduces hospitalization duration, and significantly reduces the risk of death.[9]

Several studies on the effectiveness of vitamin C in COVID-19 patients have been conducted, both in RCTs and cohort studies. The results show differences in the effectiveness of therapy and variations in the dose used. Therefore, further research studies are required to provide up-to-date information on the effectiveness, therapeutic dose, and side effects of vitamin C administration on outcomes in COVID-19 patients.

METHODS

We collected the data from articles published in Google Scholar, Pubmed, and Science Direct until April 25, 2022, using Coronavirus Disease, COVID-19, SARS-CoV-2, vitamin C, and ascorbic acid as the keywords. A critical analysis of the selected studies was performed using The Joanna Briggs Institute (JBI) Critical Appraisal Tools for risk assessment of bias by the researcher and three reviewers. The meta-analysis was generated in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The inclusion criteria used were: (1) randomized control trial (RCT) and cohort studies, from 2019 to 2022; (2) studies related to the administration of vitamin C to COVID-19 patients (primary or reinfection COVID-19 patients). The exclusion criteria were: (1) treatment of COVID-19 in the pregnant female population; (2) samples of less than 50; (3) incomplete information or full texts unavailable.

We used Review Manager Software version 5.3 to perform our meta-analysis to estimate the pooled odds ratio (OR), mean difference (MD), and 95% confidence interval (95% CI). The value of *P* less than 0.05 was considered to be statistically significant. The statistical heterogeneity was evaluated using the I^2 statistics. We performed a subgroup analysis among subjects who received vitamin C orally or intravenously, with mortality as the outcome of efficacious therapy, to minimize the impact of heterogeneity on the outcome of our results.

RESULTS

Based on the search of three databases, we found 1,222 studies. Subsequently, an eligibility assessment was conducted, and we excluded 1,208 studies, resulting in fourteen studies for further review. The study selection process is laid out in Figure 1.

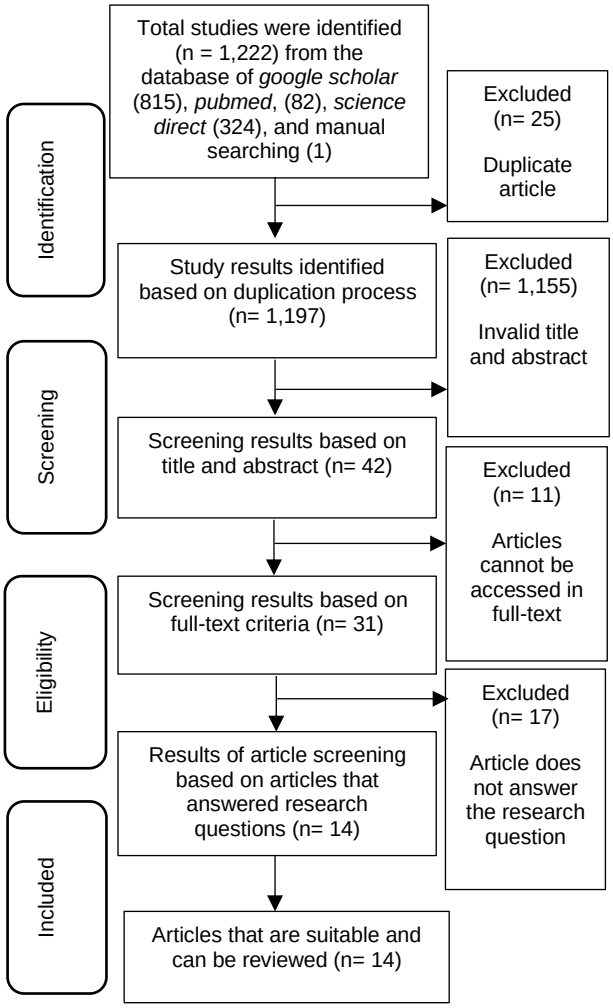

Figure 1. PRISMA flowchart of article selection

From the 14 studies reviewed, ten articles discussed the administration of vitamin C as a single supplement[10–19], and four studies examined the administration of a combination of vitamin C.[20–23] We analyzed the articles by extracting and synthesizing data. Outcomes obtained from this study were grouped into three types: mortality, hospitalization, and symptoms (duration of illness, fever, and anosmia). The results of data extraction and synthesis are shown in Table 1.

Table 1. Results of data extraction and synthesis

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
1	Jamali Moghadam, Saeidreza, et al., 2020, Iran	RCT	Administration of vitamin C to 60 severe COVID-19 patients at Ziaeian Hospital, Iran from April - May 2020 was divided into two groups	Group I: vitamin C lovinapir/ritonavir and HCQ Group II: only lovinapir/ritonavir and HCQ	IV	6 grams vitamin C per day	5 days	Primary	There was an improvement in temperature in both groups, can reduce fever (*P*=0.001)	Unknown
2	Kumari, Poona, et al., 2020, Pakistan	RCT	Administration of vitamin C to 150 COVID-19 patients at Karachi Hospital from March – to July 2020 which was divided into two groups	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	50 mg/kg BW/day	4 weeks	Primary	Symptoms improved (fever, dry cough, anosmia, and diarrhea) more quickly (5-9 days) (*P*=0.001) and hospitalization time (7-9 days) (*P*= 0.001) compared to the control group.	Unknown
3	Zhang, Jing, et al., 2020, China	RCT	Administration of vitamin C to 56 patients with severe COVID-19 in the ICU of three hospitals in China from February to March 2020 which was divided into two groups	Group I: vitamin C Group II: bacteriostatic infusion	IV	12 grams 2 times a day	7 days	Primary	Did not affect the use of mechanical ventilation (*P*=0.57)	Unknown
4	Li, Matthew, et al., 2021, United States of America	*Cohort Retrospective*	Administration of vitamin C to 56 COVID-19 patients from April – to May 2020	Group I: vitamin C, hydrocortisone, and thiamine Group II: only standard therapy	IV	1.3 grams 4 times a day	4 days	Primary	Did not affect mortality (*P*=0.05) and hospitalization duration (*P*=0.71)	Unknown
5	Gao, Dengfeng et al., 2021, China	*Cohort Retrospective*	Administration of vitamin C to 76 COVID-19 patients in the ICU of the China Hospital which was divided into two groups	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	Loading dose of 6 grams of vitamin C IV twice a day on the first day followed by 6 grams a day the next day	28 days	Primary	Reduced mortality (*P*=0.03)	Unknown

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
6	Hakamifard, Atousa, et al., 2021, Iran	RCT	Administration of vitamin C and vitamin E to 72 COVID-19 patients with pneumonia in Iran	Group I: vitamin C, vitamin E, and standard therapy Group II: only standard therapy	Oral	Vitamin C: 1000 mg per day Vitamin E: 400 IU per day	7 days	Primary	Vitamin C and vitamin E did not have a significant effect on COVID-19 patients (*P*=0.380)	Unknown
7	Suna, Kavurgaci, et al., 2021, Turkiye	*Cohort Retrospective*	Administration of vitamin C to 323 COVID-19 patients in Turkiye in September 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 grams per day	30 days	Primary	Did not affect hospitalization duration (*P*=0.05) and mortality (*P*=0.52)	Unknown
8	Zheng, Shaoping, et al., 2021, China	*Cohort Retrospective*	Administration of vitamins to 397 severe COVID-19 patients in China in February 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	2 – 4 grams per day	7 days	Primary	Did not affect mortality and symptom improvement (*P*>0.05)	Unknown
9	Liu, Fang, et al., 2020, China	RCT	IV administration of vitamin C to 308 patients in two ICUs in China	Group I: vitamin C and standard therapy Group II: only standard therapy	IV	12 grams 2 times a day	7 days	Primary		Unknown
10	Majidi, Nazanin, et al., 2021, Iran	RCT	Administration of vitamin C to 69 COVID-19 patients in Iran in May-June 2020	Group I: vitamin C and standard therapy Group II: only standard therapy	Oral	500 mg per day	14 days	Primary	Reduced the average duration of hospitalization in COVID-19 patients four days faster than the control group (*P*<0.01)	Unknown
11	Al Sulaiman, Khalid, et al., 2021, Saudi Arabia	*Cohort Retrospective*	Administration of vitamin C to 739 severe COVID-19 patients in Saudi Arabia from March – to December 2020	Group I: were given vitamin C Group II: were not given vitamin C	Oral	1000 mg per day	30 days	Primary	Did not affect mortality (*P*=0.11)	Unknown

No	Author, Year of Publication, Country	Study Design	Study Setting	Subject Characteristics					Results	
				Type of Intervention	Mode of administration	Dose	Duration of Study	Infection (Primary/ Reinfection)	Effectiveness	Side Effect
12	Thomas, Suma, et al., 2021, United States of America	RCT	214 COVID-19 patients were divided into four groups	Group I: Standard therapy (anti-viral) Group II: Vitamin C Group III: Zinc gluconate Group IV: Vitamin C and Zinc gluconate	Oral	50 mg zinc per day 8000 mg vitamin C (2-3 times a day)	10 days	Primary	There was no significant difference (*P*=0.45) in the treated group (reduction of symptoms such as fever, shortness of breath, or fatigue)	Nausea, diarrhea, and stomach cramps in the vitamin C group
13	Ried, Karin, et al., 2021, Australia and Turkiye	RCT	237 COVID-19 patients were divided into two groups	Group I: HCQ, AZM, zinc Group II: HCQ, AZM, zinc, and IV C + all groups were given vitamin D3	Oral zinc IV vitamin C	Zinc citrate: 30 mg Vitamin D: 5000 IU Vitamin C: 50 mg/kg (divided by 4 times on the first day); 100 mg/kg (divided 4 times per day on the next 6 days)	14 days	Primary	Significantly faster recovery in the group with IV vitamin C (*P*=0.0069)	Diarrhea, nausea, and vomiting in both groups
14	Margolin, Leon, et al., 2021, United States of America	*Cohort*	113 individuals were given over the counter (OTC) products as treatment and prophylaxis	Group I: were given OTC (zinc, vitamin C, vitamin D, vitamin E, quina, l-lysine, azithromycin, and doxycycline) Group II: were not given OTC drugs	Oral	Zinc: 25 mg Vitamin C: 1000 mg Vitamin D: 1000 IU	5 days	Primary	Effective in treating mild to moderate symptoms (*P*=0.04) at 2 doses/day, with no or only minimal addition to prescription (other standard antibiotics)	Unknown

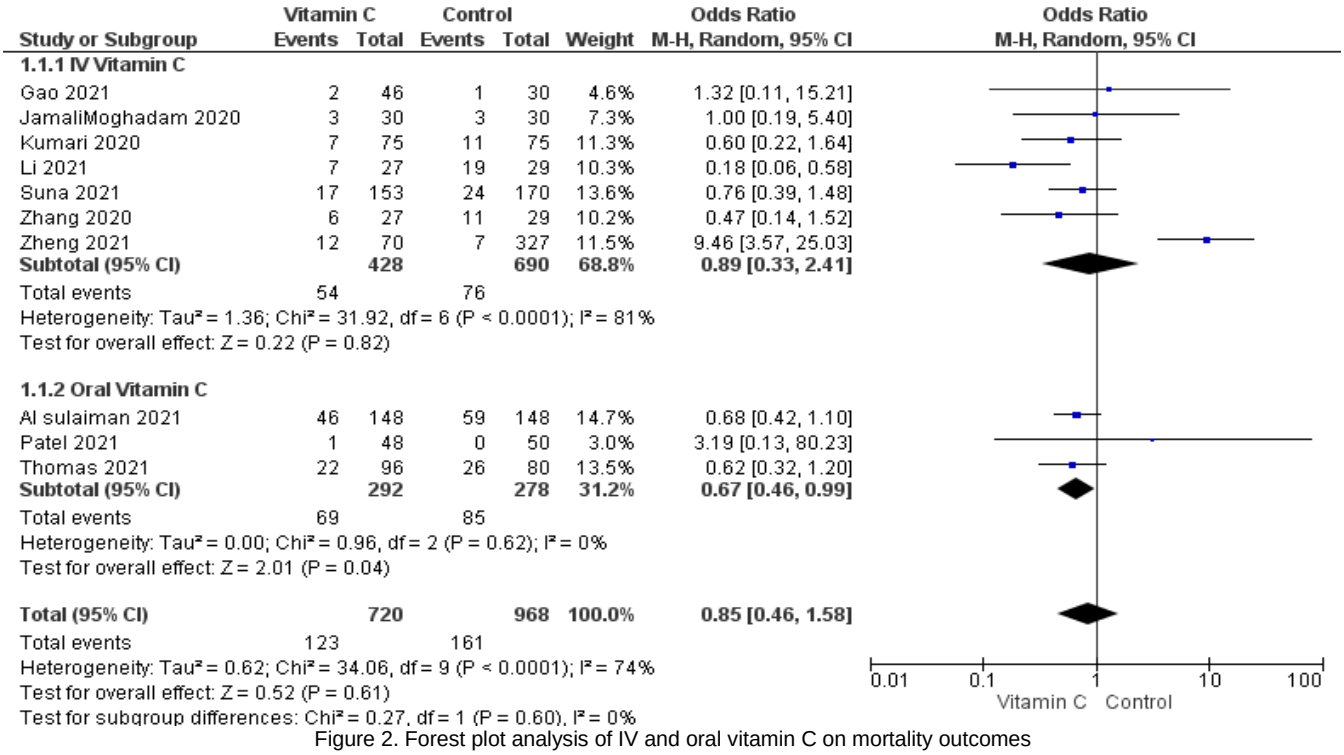

Figure 2. Forest plot analysis of IV and oral vitamin C on mortality outcomes

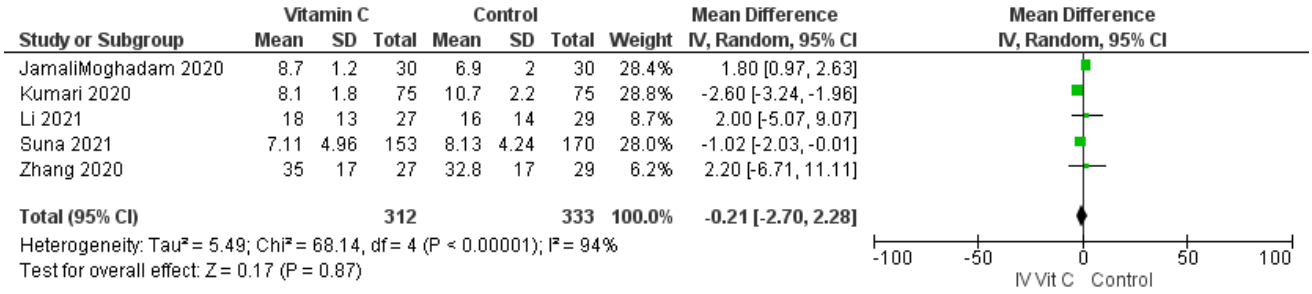

Figure 1. Forest plot analysis of vitamin C IV on inpatient outcomes

The meta-analysis design was performed on eleven articles with oral or IV vitamin C administration based on mortality outcomes and six articles with hospitalization outcomes. Eight articles using an IV vitamin C intervention and three using an oral vitamin C intervention were depicted through forest plot analysis in Figures 2 and 4. When viewed from the articles obtained, the IV vitamin C intervention did not significantly affect the mortality of severe COVID-19 patients (OR=0.80; 95% CI=0.31–2.09; *P*=0.66; I^2=79%). Conversely, oral vitamin C significantly affected the mortality of asymptomatic COVID-19 patients and patients with mild to moderate symptoms of COVID-19 (OR=0.66; 95% CI=0.45–0.97; *P*=0.04; I^2=0%). In this case, oral vitamin C intervention can reduce the mortality rate in COVID-19 patients by 66% compared to the control group.

The results of the second meta-analysis showed that the use of IV vitamin C had no effect (OR = -0.21; 95% CI = -2.70-2.28; *P*=0.87; I^2=94) on the duration of hospitalization for COVID-19 patients.

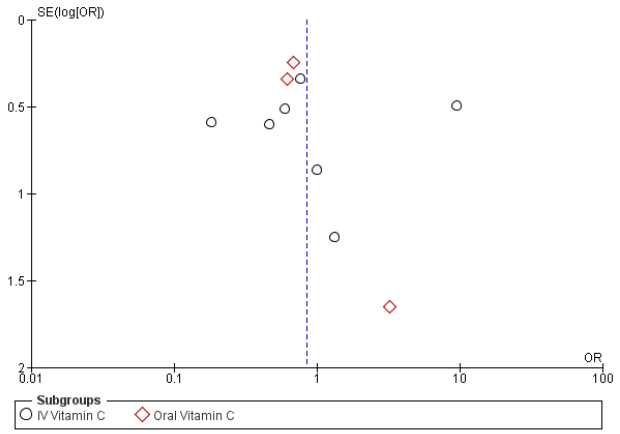

Figure 2. Results of funnel plot analysis of IV and oral vitamin C on mortality outcomes

Based on the funnel plot analysis results obtained in Figures 3 and 5, the asymmetric distribution of the data indicates a high publication bias. These results can be caused by many factors, such as the small number of studies used and the lack of databases used.[24]

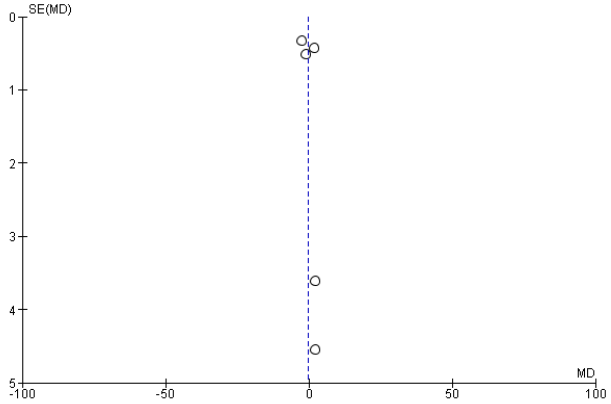

Figure 3. Results of the funnel plot analysis of vitamin C IV on inpatient outcomes

DISCUSSION

This systematic review assessed studies related to the effectiveness, dosage, and side effects of vitamin C administration either alone or in combination up to April 25, 2022. Based on these results, eight of the 14 studies showed notable results according to the significant values obtained from the statistical test.

The first outcome was the duration of hospitalization, and five studies assessed the variable duration of hospitalization as an outcome of the effectiveness of the therapy given. The meta-analysis results showed that the results were insignificant (*P*=0.87). One of the studies[11] discovered that giving IV vitamin C at a dose of 50 mg/kg BW/day significantly (*P*=0.0001) reduced hospitalization duration by six to ten days faster than the control group.

A prior study[22] supported this finding and revealed that administering a combination of oral vitamin C at a dose of 100 mg per day, vitamin D, and zinc showed a significant (*P*=0.00069) reduction in the duration of hospitalization compared to the control group. However, not all measurements of normal levels in the blood are carried out either before or after supplementation. Consequently, it cannot determine whether the levels in the blood are within normal limits.

The second outcome was symptoms, and five studies assessed this variable as an outcome of the effectiveness of the therapy given. The study[10] explained that giving IV vitamin C significantly (*P*=0.001) reduced symptoms in the form of fever. Other studies[11,22,23] revealed that giving IV vitamin C significantly (*P*<0.05) decreased symptoms in the form of fever and the duration of pain was shorter than in the control group.

The third outcome was mortality, and two studies showed a decrease in mortality rates.[12,18] These studies obtained a significantly reduced mortality (*P*=0.03 and *P*=0.05) in the treatment group. The meta-analysis results for mortality outcomes pointed out significant results (*P*=0.04) in the sub-group using oral vitamin C in asymptomatic to moderately symptomatic COVID-19 patients. In contrast to the previous meta-analysis,[25,26] it was explained that vitamin C administration had no effect on COVID-19 patients. The distinction between the findings of previous studies and our study could be due to differences in study design. The prior study only used one study design, an RCT. Other causes were found in the outcomes assessed.[26,27] Both studies looked at the outcome of using mechanical ventilation and duration of stay in the ICU. Because the patient's condition was already severe, the effectiveness of a supplement decreased, yielding insignificant results.[27]

Another reason for the difference in results could be due to many factors, such as the clinical classification of patients, advanced age, and comorbidities, which were groups prone to worsening symptoms and even death. Comorbidities that aggravated the patient's condition included metabolic diseases, for instance, diabetes mellitus and hypertension, a history of smoking, and chronic lung disease (asthma, COPD, and chronic bronchitis).[26]

Oral administration of vitamin C has been described in prior studies[14,19–21,23] that used vitamin C at a dose of 500-1000 mg and 8000 mg per day.

The IV administration of vitamin C in other studies[10,12,16–18,22,28] used doses of 1.3 grams per day, 2-12 grams per day, 50 mg/kg BW/day, and 100 mg/kg BW/day. Oral vitamin C comes in doses of 100 mg, 250 mg, 500 mg, and 1000 mg, while IV solutions are available in 100 mg/ml and 200 mg/ml.[16]

In general, dosing to get maximum results with minimal side effects needs to be considered based on the history of the disease, individual needs, over-the-counter drugs, and the costs involved. Based on cost-effectiveness considerations, oral administration of vitamin C with a dose range of 500-1000 mg was significantly (*P*=0.04) effective for reducing mortality in asymptomatic COVID-19 patients compared to COVID-19 patients with moderate symptoms.

Three of the 14 studies stated that there were side effects. These studies[12,21,22] revealed similar side effects of vitamin C when taken orally and intravenously. Side effects manifested in digestive disorders include nausea, diarrhea, stomach cramps, and vomiting. The IV administration of vitamin C still causes indigestion, even though it is not as common as oral administration.[29]

Digestive disorders in COVID-19 patients often occur because the ACE2 receptor is expressed in numerous body tissues. The digestive organs are receptors for the SARS-CoV-2 virus, which will activate ACE2 receptors in the digestive tract in the early stages of infection and cause digestive disorders. However, in the next phase, the symptoms of indigestion will decrease. On the condition that side effects arise, it is recommended to discontinue vitamin C since gastrointestinal disturbances might induce changes in gut microbes and increase pro-inflammatory cytokines.[30] Other side effects are lymphopenia, leukopenia, ARDS, shock, and sepsis. However, it has been confirmed that these side effects are not related to the administration of vitamin C.[12]

Apart from determining the dose and method of administering the drug, it is essential to consider the side effects due to supplementation. Multiple factors can induce side effects when consuming supplements, including the patient's medical history (such as gastritis), the degree of disease, reactions that may arise from each component, and the synergistic effect of the drug. The physician and other health professionals must ascertain this point to determine from which factor these side effects emerge. Whether it is purely due to supplementation in the absence of other factors, the supplementation administration should be reconsidered.[31]

LIMITATION

This systematic review had some limitations, such as the limited number of similar study designs, thus using a combination of RCT and cohort study designs. Furthermore, not all studies included complete data, such as expected levels of vitamin C in human blood samples, follow-up data for patients after treatment, and strategies for dealing with lost to follow-up patients.

Lastly, there was heterogeneity in the meta-analytical assessment of IV vitamin C due to the heterogeneous population. Despite these limitations, our study engaged a plentiful sample consisting of 2,870 participants from fourteen studies with a low risk of bias across all articles.

CONCLUSION

Based on the meta-analysis conducted in this study, we found that oral administration of vitamin C had a significant effect (*P*=0.04) on the mortality rate of COVID-19 patients, and the use of IV vitamin C showed no significant effect (*P*=0.87) on the duration of hospitalization for COVID-19 patients. Other outcomes, in particular symptoms, could not measure the effectiveness of therapy due to the limitations of the participants involved in the study. In consideration of cost-effectiveness, oral administration of vitamin C with a dosage range of 500-1000 mg demonstrated efficacy in reducing mortality rates in COVID-19 patients. Side effects due to supplementation consumption included digestive disorders such as nausea, diarrhea, stomach cramps, and vomiting.

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CONFLICT OF INTEREST

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REFFERENCES

1. WHO. Coronavirus [Homepage on the Internet]. 2021 [cited 2021 Sep 14];19–22. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1
2. Kemenkes. Protokol Tatalaksana Covid-19 [Homepage on the Internet]. Buku Saku. Jakarta: Kementerian Kesehatan RI, 2021; Available from: https://promkes.kemkes.go.id/buku-saku-protokol-tata-laksana-covid-19
3. Kumari P, Dembra S, Dembra P, et al. The Role of Vitamin C as Adjuvant Therapy in COVID-19. Cureus 2020;12(11):10–13.
4. Mrityunjaya M, Pavithra V, Neelam R, Janhavi P, Halami PM, Ravindra P V. Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19. Front Immunol 2020;11:1–12.
5. Bauer SR, Kapoor A, Rath M, Thomas SA. What is the role of supplementation with ascorbic acid, zinc, vitamin D, or N - acetylcysteine for prevention or treatment of COVID-19? . Cleve Clin J Med 2020;3–5.
6. Beltrán-García J, Osca-Verdegal R, Pallardó F V., et al. Oxidative stress and inflammation in covid-19-associated sepsis: The potential role of anti-oxidant therapy in avoiding disease progression. Antioxidants 2020;9(10):1–20.
7. Fantacone ML, Lowry MB, Uesugi SL, et al. The effect of a multivitamin and mineral supplement on immune function in healthy older adults: A double-blind, randomized, controlled trial. Nutrients 2020;12(8):1–15.
8. Pirabbasi E, Shahar S, Manaf ZA, Rajab NF, Manap RA. Efficacy of ascorbic acid (Vitamin C) and/N-acetylcysteine (NAC) supplementation on nutritional and antioxidant status of male chronic obstructive pulmonary disease (COPD) patients. J Nutr Sci Vitaminol (Tokyo) 2016;62(1):54–61.
9. Lee SI, Lim CM, Koh Y, Huh JW, Lee JS, Hong SB. The effectiveness of vitamin C for patients with severe viral pneumonia in respiratory failure. J Thorac Dis 2021;13(2):632–641.
10. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, et al. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. Eur J Med Res. 2021;26(1):1–9.
11. Kumari P, Dembra S, Dembra P, et al. The Role of Vitamin C as Adjuvant Therapy in COVID-19. Cureus 2020;12(11):10–13.
12. Gao D, Xu M, Wang G, et al. The efficiency and safety of high-dose vitamin C in patients with COVID-19: a retrospective cohort study. Aging (Albany NY) 2021;13(5):7020–7034.
13. Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. BMJ Open. 2020;10(7):e039519.
14. Sulaiman K Al, Aljuhani O, Saleh K Bin, et al. Ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19: a propensity score matched study. Sci Rep. 2021;11(1):1–8.
15. Suna K. Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia. Med Clin (Barc). 2022;158(8):356–360.
16. Zhang J, Rao X, Li Y, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care. 2021;11(1):3–14.
17. Zheng S, Chen Q, Jiang H, Guo C, Luo J, Li S. No signi fi cant bene fi t of moderate - dose vitamin C on severe COVID - 19 cases. 2021;1403–1414.

18. Li M, Ching TH, Hipple C, Lopez R, Sahibzada A, Rahman H. Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection. J Pharm Pract 2021;1–7.
19. Majidi N, Rabbani F, Gholami S, et al. The Effect of Vitamin C on Pathological Parameters and Survival Duration of Critically Ill Coronavirus Disease 2019 Patients: A Randomized Clinical Trial. Front Immunol. 2021;12:717816.
20. Hakamifard A, Soltani R, Maghsoudi A, et al. The effect of Vitamin E and Vitamin C on quality of life in patients with type 2 diabetes: A single-blind randomized clinical trial. Jundishapur J Nat Pharm Prod 2021;14(4):1–6.
21. Thomas S, Patel D, Bittel B, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. JAMA Netw open 2021;4(2):e210369.
22. Ried K, BinJemain T, Sali A. Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, and Vitamin D3 With or Without Intravenous Vitamin C: An International, Multicenter, Randomized Trial. Cureus 2021;13(11).
23. Margolin L, Luchins J, Margolin D, Margolin M, Lefkowitz S. 20-Week Study of Clinical Outcomes of Over-the-Counter COVID-19 Prophylaxis and Treatment. J evidence-based Integr Med. 2021;26:2515690X211026193.
24. Enst WA Van, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: A meta-epidemiological study. BMC Med Res Methodol 2014;14(1):1–11.
25. Rawat D, Roy A, Maitra S, Gulati A, Khanna P, Baidya DK. Vitamin C and COVID-19 treatment: A systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Syndr Clin Res Rev. 2021;15(6):102324.
26. Beran A, Mhanna M, Srour O, et al. Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: A comprehensive systematic review and meta-analysis. Clin Nutr ESPEN. 2022;48:167–177.
27. Rawat D, Roy A, Maitra S, Gulati A, Khanna P, Baidya DK. Vitamin C and COVID-19 treatment: A systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Syndr Clin Res Rev. 2021;15(6):102324.
28. Kumari P, Dembra S, Dembra P, et al. The Role of Vitamin C as Adjuvant Therapy in COVID-19. Cureus 2020;12(11):10–13.
29. Arifah IF, Novitasari D, Permatasari PS, Naomi EFF. Pengetahuan Tentang Injeksi Vitamin C Untuk Di Kalangan Mahasiswi Kampus B Universitas. J Farm Komunitas 2018;5(1):18–24.
30. Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res 2020;226:57–69.
31. Fowler AA, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12(1):1–10.