Inflammopharmacology (2023) 31:3357–3362
https://doi.org/10.1007/s10787-023-01200-5

Inflammopharmacology

SHORT COMMUNICATION

The effect of vitamin C on the risk of mortality in patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

Chia Siang Kow[1] · Syed Shahzad Hasan[2,3] · Dinesh Sangarran Ramachandram[4]

Received: 8 February 2023 / Accepted: 18 March 2023 / Published online: 18 April 2023

Abstract

Background and Aims Vitamin C appears to be a viable treatment option for patients with COVID-19.

Methods We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of vitamin C versus comparative interventions in patients with COVID-19. The outcome of interest was all-cause mortality.

Results The meta-analysis of eleven trials using a random-effects model revealed significant reduction in the risk of all-cause mortality with the administration of vitamin C among patients with COVID-19 relative to no vitamin C (pooled odds ratio = 0.53; 95% confidence interval 0.30–0.92). Subgroup analysis of studies that included patients with severe COVID-19 also produced findings of significant mortality reduction with the administration of vitamin C relative to no vitamin C (pooled odds ratio = 0.47; 95% confidence interval 0.26–0.84).

Conclusion Overall, evidence from RCTs suggests a survival benefit for vitamin C in patients with severe COVID-19. However, we should await data from large-scale randomized trials to affirm its mortality benefits.

Keywords Ascorbic acid · COVID-19 · Mortality · Vitamin C

Introduction

Vitamin C could modulate the immune response and has been hypothesized to mitigate organ dysfunction in patients with coronavirus disease 2019 (COVID-19). Hence multiple clinical trials have been conducted since the beginning of the COVID-19 pandemic to investigate the effects of vitamin C on the risk of mortality in patients with COVID-19. We undertook a systematic review and meta-analysis to synthesize evidence from randomized controlled trials that evaluated the mortality outcomes with the use of vitamin C in patients with COVID-19.

Methods

We performed a systematic literature search in the following electronic databases: PubMed, Scopus, and Web of Science, for published studies, and medRxiv, Research Square, and SSRN for preprints, from inception to November 18, 2022. The literature search was updated again on April 1, 2023. The literature search in these electronic databases was conducted based on the following keywords and their Medical Subject Heading terms (if applicable): "COVID-19", "SARS-CoV-2", "COVID", "corona", ascorbic acid", "vitamin C", "Sodium Ascorbate", and "L-ascorbic". We also hand-searched the reference lists of included articles and relevant reviews to retrieve additional relevant records. We limited the search to human and adult studies with no restrictions on publication date or publication status.

Two investigators (CSK and SSH) independently screened all the retrieved titles and abstracts for inclusion.

✉ Dinesh Sangarran Ramachandram
dineshsangarran.ramachandram@monash.edu

Chia Siang Kow
chiasiang_93@hotmail.com

1 School of Pharmacy, International Medical University, 126, Jalan Jalil Perkasa, Bukit Jalil, Kuala Lumpur, Malaysia

2 School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom

3 School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia

4 School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

The two investigators (CSK and SSH) also retrieved and appraised full texts of articles that were deemed potentially eligible for inclusion. The two investigators (CSK and SSH) resolved disagreement during the review process through a discussion with a third investigator (DSR) and by consensus.

We included randomized trials that evaluated the mortality outcome with the use of vitamin C against any comparative interventions in adult participants (≥ 18 years) who were infected with SARS-CoV-2. We excluded non-randomized trials, single-arm trials, observational studies, case reports, reviews, conference abstracts, animal studies, and non-English language publications.

Data extraction from each included trial was performed independently by two investigators (CSK and DSR) using a pre-specified and standardized data extraction form. Data extracted included characteristics of the included studies (first author's surname, year of publication, and country where the trial was performed), trial design, details of the population enrolled (mean/median age and illness severity), details of the study interventions (dose, frequency, and duration), details of the comparative interventions, and mortality events. We resolved discrepancies in the data extracted between the two investigators by discussion or, if necessary, by adjudication by a third investigator (SSH).

Two investigators (CSK and SSH) independently assessed the risk of bias for each of the included trials using the Cochrane Risk of Bias Tool version 2 [1]. Disagreements in the assessment were resolved by discussion with a third investigator (DSR) and by consensus. We adjudicated the overall risk of bias as 'low' only if all domains were assessed as low risk of bias.

The outcome of interest was all-cause mortality.

A random-effects model meta-analysis was used to estimate the pooled odds ratio for the development of outcomes of interest with the use of vitamin C relative to the use of comparative interventions, at 95% confidence intervals. To evaluate the robustness of the pooled estimate, we also fitted an inverse variance heterogeneity (IVhet) model. In addition, we conducted sensitivity analyses by excluding visible outliers studies. Subgroup analysis based on the COVID-19 severity of included patients was also performed. The heterogeneity between studies was quantified using the I^2 statistics and the χ^2 test, with substantial heterogeneity predetermined at 50% and $p < 0.10$, respectively. All analyses were conducted in Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our systematic literature search on electronic databases retrieved 697 records. After deduplication, a total of 258 records were identified, and 19 records were assessed for eligibility. Eight studies were excluded either due to observational study design or reported no mortality events. In total, we included eleven randomized controlled trials (Beigmohammadi et al. 2021; Cao et al. 2020; JamaliMoghadamSiahkali et al. 2021; Kumar et al. 2022; Kumari et al. 2020; Labbani-Motlagh et al. 2022; Leal-Martínez et al. 2022; Majidi et al. 2021; Tehrani et al. 2022; Thomas et al. 2021; Zhang et al. 2021) in our systematic review and meta-analysis, with 445 patients randomized to receive vitamin C and 494 patients randomized to receive comparative interventions.

The characteristics of the included randomized trials are shown in Table 1. The regimen of vitamin C in the intervention group differed across the included trials. Most of the included trials (n = 6) (Beigmohammadi et al. 2021; JamaliMoghadamSiahkali et al. 2021; Kumar et al. 2022; Labbani-Motlagh et al. 2022; Tehrani et al. 2022; Zhang et al. 2021) administered vitamin C intravenously at a fixed non–weight-based dose ranging from 2 to 24 g daily for a duration of 4 to 7 days. One trial (Kumari et al. 2020) administered vitamin C intravenously at a weight-based dose of 50 mg/kg daily. The remaining four trials (Cao et al. 2020; Leal-Martínez et al. 2022; Thomas et al. 2021; Majidi et al. 2021) administered vitamin C orally/enterally at a fixed non–weight-based dose ranging from 0.2 g to 8 g daily for a duration of 10 up to 21 days.

We adjudicated five trials (Kumar et al. 2022; Labbani-Motlagh et al. 2022; Leal-Martínez et al. 2022; Majidi et al. 2021; Thomas et al. 2021) as having a low risk of bias in all domains and, thus an overall low risk of bias. We rated the remaining trials as having overall some concerns of bias (some concerns of bias in at least one domain): the four trials reported by Zhang et al. (2021), by JamaliMoghadamSiahkali et al. (2021), by Tehrani et al. (2022), and by Beigmohammadi et al. (2021) respectively, had some concerns of bias in the domain of 'deviations from intervention' due to open-label/single-blind trial design; the trial reported by Kumari et al. (2020) had some concerns of bias in the domain of 'randomization' due to inadequate information on allocation concealment as well as in the domain of 'deviations from intervention' due to single-blind trial design; the trial reported by Cao et al. (2020) had some concerns of bias and in the domain of 'deviations from intervention' due to single-blind trial design as well as in the domain of 'selection of the reported results' since it was unclear whether the trial was analyzed as pre-specified.

The meta-analysis of eleven trials (Beigmohammadi et al. 2021; Cao et al. 2020; JamaliMoghadamSiahkali et al. 2021; Kumar et al. 2022; Kumari et al. 2020; Labbani-Motlagh et al. 2022; Leal-Martínez et al. 2022; Majidi et al. 2021; Tehrani et al. 2022; Thomas et al. 2021; Zhang et al. 2021) using a random-effects model reported reduction in the risk of all-cause mortality with the administration of vitamin C

Table 1 Characteristic of included studies

Study (year)	Study design	Country	Age (mean/median)	Severity of COVID-19	Regimen of study intervention	Regimen of comparative intervention	Mortality events		Risk of bias[1]
							Vitamin C (n/N; %)	Non-vitamin C (n/N; %)	
Zhang et al. (2021)	Randomized, single-blind, controlled trial	China	Vitamin C group = 66.3 Non-vitamin C group = 67.0	Severe (baseline $PaO_2/FiO_2 < 300$ mmHg)	12 g twice daily intravenously for 7 days	Placebo	6/27; 22.2	11/29; 37.9	Some concerns
Kumari et al. (2020)	Randomized controlled, open-label trial	Pakistan	Vitamin C group = 52.0 Non-vitamin C group = 53.0	Severe (mean baseline oxygen saturation < 90%)	50 mg/kg daily intravenously + standard of care	Standard of care (antipyretics, dexamethasone, prophylactic antibiotics)	7/75; 9.3	11/75; 14.6	Some concerns
JamaliMoghadamSiahkali et al. (2021)	Randomized controlled, open-label trial	Iran	Vitamin C group = 57.5 Non-vitamin C group = 61.0	Severe (baseline oxygen saturation < 93%)	1.5 g every 6 h intravenously for 5 days + standard of care	Standard of care (lopinavir/ritonavir, hydroxychloroquine)	3/30; 10.0	3/30; 10.0	Some concerns
Thomas et al. (2021)	Randomized controlled, open-label trial	United States	Vitamin C group = 45.6 Vitamin C + zinc group = 48.7 Zinc group = 44.1 Non-vitamin C/zinc group = 42.0	Mild (received outpatient care)	8 g daily orally for 10 days ± zinc gluconate + standard of care	Standard of care ± zinc gluconate	3/106; 2.8	0/108; 0	Low
Cao et al. (2020)	Randomized, single-blind, controlled trial	China	Vitamin C group = 64.0 Non-vitamin C group = 63.0	Severe (defined according to the Chinese management guideline for COVID-19)	0.1 g twice daily orally + standard of care	Standard of care (antiviral therapy, corticosteroid, antibiotics)	3/21; 32.6	0/20; 0	Some concerns
Tehrani et al. (2022)	Randomized controlled, open-label trial	Iran	Vitamin C group = 58.0 Non-vitamin C group = 61.0	Severe (mean baseline oxygen saturation < 90%)	2 g every 6 h intravenously for 5 days + standard of care	Standard of care (lopinavir/ritonavir, hydroxychloroquine, interferon beta-1a)	0/18; 0	4/26; 15.4	Some concerns
Beigmohammadi et al. (2021)	Randomized, single-blind, controlled trial	Iran	Vitamin C group = 51.0 Non-vitamin C group = 53.0	Severe (admitted to intensive care unit)	0.5 g four times daily intravenously for 7 days + vitamin A, vitamin B, vitamin D, and vitamin E	Placebo	0/30; 0	4/30; 13.3	Some concerns

Table 1 (continued)

Study (year)	Study design	Country	Age (mean/median)	Severity of COVID-19	Regimen of study intervention	Regimen of comparative intervention	Mortality events		Risk of bias[1]
							Vitamin C (n/N; %)	Non-vitamin C (n/N; %)	
Majidi et al. (2021)	Randomized, double-blind, controlled trial	Iran	Vitamin C group = 59.4 Non-vitamin C group = 63.8	Severe (admitted to intensive care unit)	0.5 g daily enterally for 14 days	Placebo	26/31; 83.9	67/69; 97.1	Low
Kumar et al. (2022)	Randomized, double-blind, controlled trial	India	Vitamin C group = 57.0 Non-vitamin C group = 63.3	Severe (admitted to intensive care unit)	1 g every 8 h intravenously for 4 days	Placebo	10/30; 33.3	13/30; 43.3	Low
Labbani-Motlagh et al. (2022a)	Randomized, double-blind, controlled trial	Iran	Vitamin C group = 57.8 Non-vitamin C group = 58.9	Moderate-to-severe	12 g every 12hoursintravenouslyfor 4 days	Placebo	4/37; 10.8	6/37; 16.2	Low
Leal-Martínez (2022b)	Randomized, double-blind, controlled trial	Mexico	Vitamin C group = 51.5 Non-vitamin C group = 53.9	Severe (baseline oxygensaturation < 90%)	1 g twice daily orally + vitamin B complex, Spirulina maxima, folic acid, glutamine, brewer's yeast, amaranth, zinc, selenium, cholecalciferol, resveratrol, omega-3 fatty acids, LArginine, magnesium, Probiotic	Standard of care	1/40; 2.5	7/40; 17.5	Low

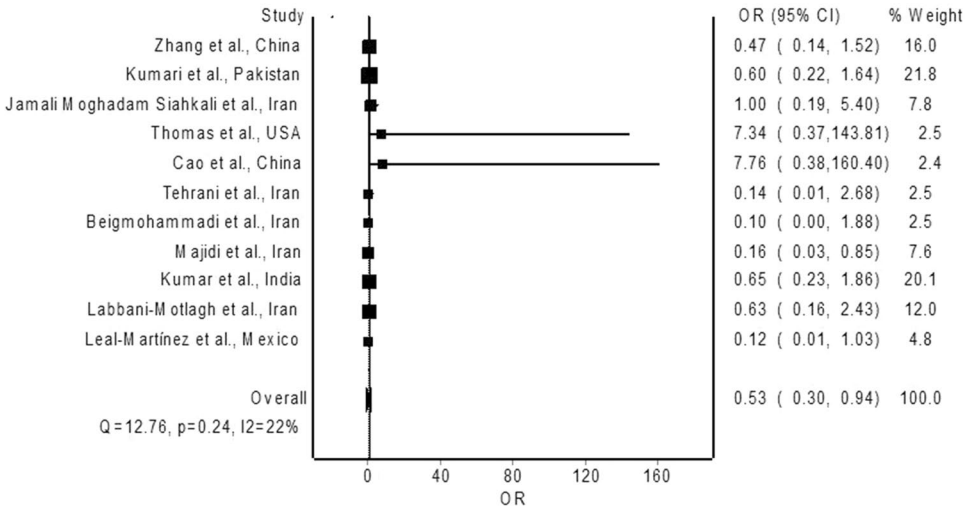

Fig. 1 Pooled odds ratio for all-cause mortality with the administration of vitamin C among patients with COVID-19 relative to comparative interventions

in patients with COVID-19 compared to non-administration of vitamin C; the pooled odds ratio is with significant evidence to indicate mortality benefits, at the current sample size (Fig. 1; pooled odds ratio = 0.53; 95% confidence interval 0.30 to 0.92; $I^2 = 22\%$). The IVhet model also produced-significant evidence of mortality reduction (pooled odds ratio = 0.53; 95% confidence interval 0.30 to 0.94; $I^2 = 22\%$).

The sensitivity analyses by excluding visible outliers studies (Cao et al. 2020; Thomas et al. 2021) also revealed mortality benefits with the use of vitamin C among patients with COVID-19 compared to non-use of vitamin C; the pooled odds ratio indicated significant mortality benefit (pooled odds ratio = 0.47; 95% confidence interval 0.29 to 0.75; $I^2 = 0\%$), in which, at the current sample size, there is adequate evidence to reject the null hypothesis of 'no significant difference'. The IVhet model with visible outliers studies (Cao et al. 2020; Thomas et al. 2021) removed, also produced significant evidence of mortality reduction (pooled odds ratio = 0.47; 95% confidence interval 0.29 to 0.75; $I^2 = 0\%$).

Subgroup analysis of studies (Beigmohammadi et al. 2021; Cao et al. 2020; JamaliMoghadamSiahkali et al. 2021; Kumar et al. 2022; Kumari et al. 2020; Leal-Martínez et al. 2022; Majidi et al. 2021; Tehrani et al. 2022; Zhang et al. 2021) which included patients with severe COVID-19, produced findings of significant mortality reduction with the administration of vitamin C relative to no vitamin C (pooled odds ratio = 0.47; 95% confidence interval 0.26 to 0.84; $I^2 = 17\%$). Likewise, significant evidence of mortality reduction (pooled odds ratio = 0.48; 95% confidence interval 0.27 to 0.87; $I^2 = 17\%$) is observed when an inverse variance heterogeneity (IVhet) model was fitted.

In this systematic review and meta-analysis, we found significant mortality benefits with the use of vitamin C in patients with COVID-19, especially in the subgroup of patients with severe illness. The findings of our review concur with the widely hypothesized benefits of vitamin C in patients with COVID-19 since the beginning of the COVID-19 pandemic. Vitamin C is deemed to have conducive effects in patients with COVID-19 by virtue of its immunomodulatory role. Vitamin C may have a role in various immunity pathways against COVID-19 by controlling the growth and function of innate and adaptive immune cells and producing antibodies. Besides, as a robust antioxidant, vitamin C can help ameliorate oxidative stress, which is considered a pivotal point in the pathophysiology of COVID-19. By scavenging reactive oxygen species produced in polymorphonuclear neutrophils, vitamin C may inhibit neutrophil extracellular traps (NET) production or NETosis, which contributes to the development of multiorgan injury in patients with COVID-19.

Nonetheless, we believe our findings are still inadequate to warrant the routine use of vitamin C in patients with COVID-19 for mortality reduction. Most of the randomized trials investigating the mortality outcomes with the use of vitamin C in patients with COVID-19 had some concerns of bias. In addition, other than the trial reported by Majidi et al. (2021), none of the individual trials (Beigmohammadi et al. 2021; Cao et al. 2020; JamaliMoghadamSiahkali et al. 2021; Kumar et al. 2022; Kumari et al. 2020; Labbani-Motlagh et al. 2022; Leal-Martínez et al. 2022; Tehrani et al. 2022; Thomas et al. 2021; Zhang et al. 2021) reported significant mortality reduction with the administration of vitamin C in patients with COVID-19. In addition, variation in the dosing regimen of vitamin C used across the included trials precludes recommendation of the most appropriate method(s) for the administration of vitamin C in patients with COVID-19 to reduce their risk of mortality. Therefore, further randomized trials with large sample sizes should be performed to confirm the mortality benefits of vitamin C and to determine the most optimal dosing strategy in this population of patients

Author contributions CSK participated in the study design, conduct, and, data collection, as well as writing and reviewing the manuscript; DSR participated in data collection as well as writing and reviewing the manuscript; SSH performed the data analysis and interpretation; and all authors provided final approval of the manuscript for submission.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of interest All authors have no conflicts of interest to declare.

References

Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Soltani D (2021) The effect of supplementation with vitamins A, B, C, D, and E on disease severity and inflammatory responses in patients with COVID-19: a randomized clinical trial. Trials 22:802

Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J (2020) Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 146:137-146.e3

JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, Sekhavati Moghadam E, Abbasian L, Dehghan Manshadi SA, Salehi M, Hasannezhad M, Ghaderkhani S, Meidani M, Salahshour F, Jafari F, Manafi N, Ghiasvand F (2021) Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. Eur J Med Res 26:20

Kumar V, Bhushan D, Supriya S, Ganapule AA, Lohani P, Shyama PS, Majhi PK, Anand U, Kumar R, Bhadani UK (2022) Efficacy of intravenous vitamin C in management of moderate and severe COVID-19: A double blind randomized placebo controlled trial. J Family Med Prim Care 11:4758–4765

Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, Sohail H, Kumar B, Memon MK, Rizwan A (2020) The role of vitamin C as adjuvant therapy in COVID-19. Cureus 12:e11779

Labbani-Motlagh Z, Amini S, Aliannejad R, Sadeghi A, Shafiee G, Heshmat R, Jafary M, Talaschian M, Akhtari M, Jamshidi A, Mahmoudi M, Sadeghi K (2022) High-dose intravenous vitamin C in early stages of severe acute respiratory syndrome coronavirus 2 infection: a double-blind, randomized, controlled clinical trial. J Res Pharm Pract 11:64-72

Leal-Martínez F, Abarca-Bernal L, García-Pérez A, González-Tolosa D, Cruz-Cázares G, Montell-García M, Ibarra A (2022) Effect of a nutritional support system to increase survival and reduce mortality in patients with COVID-19 in stage III and comorbidities: a blinded randomized controlled clinical trial. Int J Environ Res Public Health 19:1172

Majidi N, Rabbani F, Gholami S, Gholamalizadeh M, BourBour F, Rastgoo S, Hajipour A, Shadnoosh M, Akbari ME, Bahar B, Ashoori N, Alizadeh A, Samipoor F, Moslem A, Doaei S, Suzuki K (2021) The effect of vitamin C on pathological parameters and survival duration of critically Ill coronavirus disease 2019 patients: A randomized clinical trial. Front Immunol 12:717816

Tehrani S, Yadegarynia D, Abrishami A, Moradi H, Gharaei B, Rauofi M, Maghsoudi Nejad F, Sali S, Khabiri N, Abolghasemi S (2022) An investigation into the Effects of intravenous vitamin C on pulmonary CT Findings and clinical outcomes of patients with COVID 19 pneumonia a randomized clinical trial. Urol J 19:460–465

Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine ZJ, Mehra R, McWilliams C, Nissen SE, Desai MY (2021) 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 4:e210369

Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, Luo G, Meng Z, De Backer D, Xiang H, Peng Z (2021) Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 11:5