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NARRATIVE REVIEW

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Impact of high-dose vitamin C on the mortality, severity, and duration of hospital stay in COVID-19 patients: A meta-analysis

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Abstract

Background and Aims: Vitamin C has been predicted to be effective as an antioxidant in treating various ailments, including viral infections such as pervasive coronavirus disease (COVID-19). With this meta-analysis, we looked to ascertain the relationship between high-dose vitamin C administration and mortality, severity, and length of hospitalization of COVID-19 patients.

Methods: We collected articles from PubMed, Google Scholar, ScienceDirect, SAGE, and Cochrane databases between January 1, 2020, and May 30, 2022. Odds ratio (ORs) with corresponding 95% confidence interval (CI) and *p* value were calculated to assess the connection of high-dose vitamin C in COVID-19 patients' mortality and severity. The length of hospitalization was calculated and pooled with the mean difference (MD), 95% CI, and *p* value. Review manager 5.3 was used to carry out this meta-analysis.

Results: This meta-analysis included 15 complete studies involving 2125 COVID-19 patients. Our study demonstrated a significant correlation between vitamin C consumption and death. Vitamin C consumption significantly reduces mortality risk with COVID-19 patients (OR = 0.54, 95% CI = 0.42–0.69, $p < 0.00001$). Furthermore, there was a link between the severity of COVID-19 and the intake of vitamin C. Patients who consumed vitamin C showed 0.63 times less severity than those who did not take vitamin C (OR = 0.63, 95% CI = 0.43–0.94, $p = 0.02$). Patients taking vitamin C spent slightly more time in hospital than those who did not take vitamin C (MD = 0.19, 95% CI = −1.57 to 1.96, $p = 0.83$).

Conclusions: During COVID-19, there was a substantial advantage in taking supplementary vitamin C, at least in terms of severity and mortality.

KEYWORDS

COVID-19, meta-analysis, mortality, SARS-CoV-2, severity, vitamin C

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1 | INTRODUCTION

The highly contagious COVID-19 has already claimed the lives of more than five million individuals worldwide.[1,2] Since December 2019, when severe acute respiratory syndrome-2 (SARS-CoV-2) was first identified in Wuhan, Hubei Province, China, this respiratory viral infection has outstretched swiftly over the entire world, inducing the World Health Organization (WHO) to promulgate it as a ubiquitous epidemic on March 11, 2020.[3] Aged patients and those with pre-existing medical conditions, such as pulmonary disease or immunodeficiency, are at greater risk of developing this life-threatening respiratory condition that requires supplemental oxygen support.[4] The coronavirus that caused the severe acute respiratory syndrome pandemic of 2002–2003 has 70% of its genome resemblance to this new virus (SARS-CoV-2).[5] Chronic inflammation, oxidative stress, and endothelial dysfunction are the key possible pathophysiological pathways of COVID-19 that may cause multiple organ failures and mortality.[6]

To comprehend how SARS-CoV-2 enters the human body is a crucial challenge in thwarting its spread. Coronaviruses can enter host cells by receptor-mediated plasma membrane fusion, receptor-mediated endocytosis, or antibody-dependent viral entry. Both fusion and endocytosis of viruses are dependent on the presence of specific receptors on the host cell's surface.[7] The SARS-CoV-2 virus predominantly infects the respiratory system; however, other organ systems are also affected. Fever, dry cough, and dyspnea were documented as lower respiratory tract infection indicators.[8,9] SARS-CoV-2 is an encapsulated, positive-sense, single-stranded RNA virus of the betacoronavirus genus[10] and angiotensin-converting enzyme 2 (ACE2) is the obligatory receptor of this virus, permitting it to penetrate cells.[11–14]

Water-soluble ascorbic acid (vitamin C), a ubiquitous component in many fruits and vegetables,[15] possesses antioxidant, anti-inflammatory, and immunomodulatory effects. It has been demonstrated to have potential benefits in treating viral infections and inflammation. By inhibiting the generation of proinflammatory cytokines, it modulates nuclear transcription factor-κ B, neutralizes reactive oxygen species, and aids in immunomodulation as a cofactor of different metabolic processes in the immune system.[16–20] Oxidative stress is prominent with infection, particularly lung infection or pressing situations. Vitamin C lowers inflammation and enhances immunoregulatory function in pneumonia or severe disease patients.[21–25] Based on these biological functions, vitamin C may be advantageous to patients with COVID-19, at least those with urgent conditions.[26] Vitamin C can be administered either orally or intravenously. However, oral vitamin C's low absorption and plasma concentration rate limit its utility.[27] However, intravenous (IV) delivery of vitamin C bypasses the constraints of intestinal transporters to swiftly achieve therapeutic levels with 30–70 times greater peak plasma concentrations in comparison with oral vitamin C.[28]

Pro-inflammatory cytokines, or cytokine storms, are released during COVID-19, similar to MERS and SARS-CoV-1.[29] This cytokine storm can result in systemic pulmonary inflammation and numerous organ defeats.[30] Infections and sepsis can be alleviated by taking vitamin C supplements. Patients with COVID-19 may benefit from large doses of vitamin C supplementation to reduce inflammation, as severe COVID-19 can cause ARDS and sepsis. Systemic inflammation and severe respiratory infections have been found in vitamin C-deficient persons during COVID-19.[31,32] The efficacy of an elevated dose of vitamin C in individuals with SARS-CoV-2 has been studied in various contexts and clinical findings. The effects of high dose intravenous vitamin C (HDIVC) with a placebo in a randomized controlled trial pilot study to see if HDIVC infusion was effective against severe COVID-19 and found that HDIVC failed to reduce mortality in the hospital or improve the number of days without invasive mechanical breathing after 28 days of use.[33] A meta-analysis showed that vitamin C shortens the duration of automatic breathing in pneumonia patients by almost 8%.[34]

It was reported that COVID-19-related pneumonia sufferers might be effectively treated with HDIVC. The therapeutic effects of HDIVC on COVID-19 patients' mortality, severity, and duration of hospital stay are yet not fully established because previous research has produced comparable but conflicting results. This meta-analysis aims to present current research findings on the possible involvement of high-dose vitamin C in COVID-19 patients' mortality, severity, and length of hospitalization.

2 | METHODS

2.1 | Study search scheme

The following key terms were explored in the PubMed, Google Scholar, ScienceDirect, SAGE, and Cochrane databases to find articles published between January 1, 2020, and May 30, 2022. Key phrases include: “SARS-CoV-2,” “COVID-19 and Vitamin C,” “COVID-19,” “Ascorbic acid,” “Vitamin C and COVID-19 mortality,” “Vitamin C and COVID-19 severity,” “High dose of vitamin C in patients with COVID-19,” “Vitamin C and length of COVID-19-associated hospital stay,” “Effect of vitamin C on COVID-19 patients,” and so forth. We looked over the included articles' reference lists to see if there were any missing articles.

2.2 | Specifications for inclusion or exclusion

For studies to be considered for inclusion, the following requirements must be met: (1) Research articles published in English peer-reviewed journals; (2) only studies with proven COVID-19 infection; (3) retrospective and randomized controlled trial studies; (4) study used human subjects; (5) investigations with adequate data to compute the odds ratio (OR) or mean difference (MD) and 95% confidence interval (CI).

The following were exclusion criteria: (1) Research performed in other languages than English; (2) expert opinion, columns, conference

presentations, assessments, and correspondence; (3) nonessential information for extracting data; (4) investigations carried out on animals; (5) publications that duplicate or are identical.

2.3 | Data extraction

According to the inclusion criteria, two researchers (K. K. B. and M. A. B.) individually gathered data. They conducted their literature search, evaluation, and data extraction on an Excel datasheet. Conflicts in the research that developed during the procedure were resolved by other investigators (M. A. A. and M. S. I.). The studies used Rayyan QCRI, an internet platform for systematic reviews.[35]

2.4 | Evaluation of the methodological quality

The "Newcastle-Ottawa Scale (NOS)" is a methodological quality assessment tool used to evaluate research included in observational cohort studies, as previously indicated.[36] By talking things out, any dissenting views among the researchers were settled.

2.5 | Heterogeneity, publishing bias, and statistical calculation

The data was analyzed using Microsoft Excel and Review Manager 5.3 (The Cochrane Collaboration). We calculated high-dose vitamin C in COVID-19 patients' mortality and severity as the OR and used MD to assess the duration of hospitalization. The heterogeneity of the forest plot was measured using Cochran's χ^2 Q-test and the I^2 statistic. An $I^2 > 50\%$ indicated statistically substantial heterogeneity in the population. High heterogeneity was defined as an I^2 score of 75% or above. The random-effects model was employed throughout the study. Egger's regression test and Begg–Mazumdar's rank correlation were employed to examine publishing biases in the funnel plot. A p value of less than 0.05 was used as the threshold for statistical significance to rule out publication bias.

3 | RESULTS

3.1 | Literature selection and quality evaluation

Although 2840 papers from five databases (PubMed, Google Scholar, ScienceDirect, SAGE, and Cochrane databases) were found during the initial query, 1630 were eliminated because of duplicate entries. After reading the title and abstract, 1013 articles had to be removed, and 182 articles had to be eliminated for various reasons. Finally, 15 full-text studies involving 2125 COVID-19 patients were included in this meta-analysis, which strictly met inclusion criteria (Figure 1). The studies were from seven different countries around the globe; among them, nine studies were retrospective,[37–45] and the rest were randomized controlled trial studies.[33,46–50] Twelve studies retained data from severe COVID-19 patients, while only two studies integrated the data of nonsevere cases (Table 1). Only one study does not mention the severity of the included COVID-19 patients. The mean age of the vitamin C, COVID-19 group ranges from 35.68 to 70.50 years, and the age of control groups ranges from 36 to 71.20± 13.00 years. The male percentage ranges from 31.20% to 79% and 35% to 75.90% for vitamin C and control COVID-19 patients, respectively. The baseline characteristics of all included studies are portrayed in Table 1, and Figure 1 depicts the process of conducting the literature review, screening, and determining the eligibility of study articles.

3.2 | Patient treatment and outcomes

Thirteen studies show that patients are administered vitamin C via IV, while two studies are administered orally. Studies included in this meta-analysis had various vitamin C dosages and distinct durations. Patients also received additional therapy with vitamin C. A summary of all included studies' patient treatment and outcomes is provided in Table 2.

3.3 | Vitamin C intake and risk of mortality in patients with COVID-19

Among the 13 studies, the percentages of vitamin C and control COVID-19 patients were 35.44% and 64.56%, respectively, and showed insignificant heterogeneity compared with vitamin C exposure and mortality risk ($I^2 = 0\%$, $p = 0.70$). Moreover, it is discernible from Table 3 and Figure 2 that the mortality rate is 0.54 times lower with patients administered vitamin C than the patients without vitamin C, and the result is statistically significant (vitamin C group vs. control group 35.44% vs. 64.56%, OR = 0.54, 95% CI = 0.42–0.69, $p < 0.00001$).

3.4 | Vitamin C intake and risk of severity in patients with COVID-19

Seven studies compared the severity rate of vitamin C administered to patients with COVID-19 and a control group without vitamin C. These studies included 411 vitamin C COVID-19 patients and 464 patients without vitamin C. The pooled analysis indicated no substantial heterogeneity when comparing these groups ($I^2 = 26\%$, $p = 0.23$). Furthermore, from the forest plot, it is evident that there is a significant relationship between the vitamin C administration and the risk of severity in patients with COVID-19 because the vitamin C administered group had 0.63 times less severity than the control COVID-19 patients without vitamin C (vitamin C group and control group 46.97% and 53.03%, OR = 0.63, 95% CI = 0.43–0.94, $p < 0.02$) (Table 3 and Figure 3).

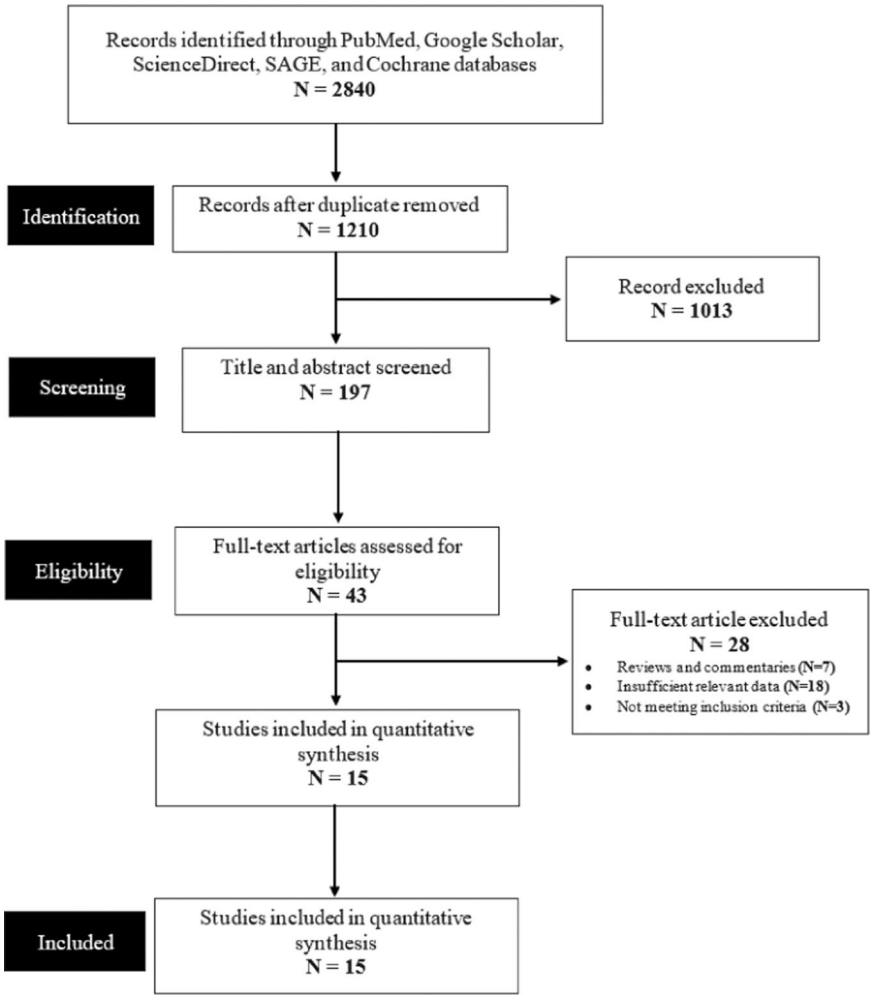

FIGURE 1 Study selection process according to PRISMA guideline

3.5 | Vitamin C intake and length of hospital stay in patients with COVID-19

Ten studies incorporating 632 vitamin C administered COVID-19 patients and 1118 COVID-19 patients without vitamin C. The forest plot demonstrated significant heterogeneity in terms of length of hospital stay between the vitamin C group and the control group (I^2 = 89%, p < 0.00001). Besides, from the forest plot, it is found that there is no significant association between length of hospital stay among vitamin C groups and control groups (vitamin C group vs. control group 36.11% vs. 63.89%, MD = 0.19, 95% CI = −1.57 to 1.96, p = 0.83). Table 3 and Figure 4 provide information about the forest plot of vitamin C patients and control groups for the length of hospital stay.

3.6 | Publication bias

This meta-analysis explored the publication bias using Begg–Mazumdar's and Egger's analysis. Both analyses found no significant publication bias (Table 3 and Figure 5).

4 | DISCUSSION

The COVID-19 pandemic resulting from SARS-CoV-2 infection is already looming large over the globe. The rapid spreading of this infection worldwide has blamed the death of millions of people. However, a significant factor affecting the spreading of COVID-19 and health systems' capability to retain it is vaccination rates, which will directly and critically impact both.[51] But vaccine skepticism is a crucial roadblock to implementing the COVID-19 vaccinations.[52] In individuals with COVID-19, respiratory failure owing to acute respiratory distress syndrome (ARDS) is the leading cause of death. COVID-19 progresses to ARDS because of a cytokine storm and oxidative stress; both play a critical role.[53,54] This meta-analysis evaluated the possible involvement of high-dose vitamin C in COVID-19 patients' mortality, severity, and length of hospitalization.

This contagious disease has already been treated with a variety of repurposed medicines.[55] Studies have shown that high doses of vitamin C can help individuals with inflammatory disorders, including ARDS and sepsis, improve their lung function.[56,57] There is a limited function for vitamin C in mild to moderate COVID-19 individuals who are unlikely to encounter a cytokine storm or severe inflammation.[58]

TABLE 1 Baseline characteristics of all included studies ($N = 15$)

SN	References	Ethnicity	Vitamin C group (n)	Control group (n)	Study design	Duration	Disease condition	Age (mean ± SD)		Gender male (%)		Nonsurvivor (n)		Severe condition (n)		Length of hospital stay (days ± SD)		NOS score
								Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	
1	Al Sulaiman et al.[37]	Saudi Arabia	149	558	Retrospective	March 1, 2020, to December 31, 2020	Sever	60.50 ± 15.09	60.70 ± 14.75	79.00	70.10	50	275	NIA	NIA	18.67 ± 11.23	15.50 ± 9.66	7
2	Beigmohammadi et al.[46]	Iran	30	30	RCT	NIA	Sever	51.00 ± 17.30	53.00 ± 7.00	50.00	53.30	0	4	NIA	NIA	NIA	NIA	8
3	Darban et al.[38]	Iran	10	10	Retrospective	NIA	Severe	59.00 ± 19.00	59.00 ± 19.00	65.00	35.00	2	2	NIA	NIA	NIA	NIA	8
4	Gao et al.[39]	China	46	30	Retrospective	January 31, 2020, to March 28, 2020	Sever	63.00	57.00	45.70	46.70	1	5	1	5	NIA	NIA	8
5	Gavrielatou et al.[40]	Greece	10	103	Retrospective	October 21, 2020, to March 8, 2021	Sever	70.50	69.00	70.00	75.70	2	49	NIA	NIA	NIA	NIA	8
6	Hess et al.[41]	USA	25	75	Retrospective	March 24, 2020, to July 2, 2020	Sever	58.30 ± 14.20	71.20 ± 13.00	52.00	56.00	10	37	13	55	26.7 ± 15.00	18.70 ± 11.90	7
7	Krishnan et al.[42]	USA	79	73	Retrospective	March 10, 2020 to April 15, 2020	NIA	NIA	NIA	NIA	NIA	40	52	NIA	NIA	7.67 ± 6.05	12.00 ± 6.80	8
8	Kumari et al.[47]	Pakistan	75	75	RCT	March 2020 to July 2020	Severe	52.00 ± 11.00	53.00 ± 12.00	NIA	NIA	7	11	12	15	8.10 ± 1.80	10.70 ± 2.20	8
9	Li et al.[43]	USA	8	24	Retrospective	April 1, 2020, to May 30, 2020	Severe	64.10 ± 8.30	64.90 ± 11.80	37.00	37.00	7	19	NIA	NIA	18.00 ± 13.00	16.00 ± 14.00	7
10	JamaliMoghadamSiahkali et al.[48]	Iran	30	30	RCT	April 2020 to May 2020	Severe	57.53 ± 18.27	61.00 ± 15.90	50.00	50.00	3	3	5	4	9.17 ± 3.89	7.50 ± 6.23	8

(Continues)

TABLE 1 (Continued)

SN	References	Ethnicity	Vitamin C group (*n*)	Control group (*n*)	Study design	Duration	Disease condition	Age (mean ± SD)		Gender male (%)		Nonsurvivor (*n*)		Severe condition (*n*)		Length of hospital stay (days ± SD)		NOS score
								Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	Vitamin C group	Control group	
11	Suna et al.[44]	Turkey	153	170	Retrospective	September 1, 2020, to September 30, 2020	Severe	60.16 ± 13.65	64.27 ± 14.49	66.70	60.00	17	24	11	12	8.13 ± 4.24	7.11 ± 4.96	7
12	Thomas et al.[49]	USA	48	50	RCT	April 27, 2020, to October 14, 2020	Nonsevere	45.60 ± 15.00	42.00 ± 14.60	31.20	38.00	1	0	NIA	NIA	2.00 ± 4.20	3.00 ± 6.00	8
13	Zhang et al.[33]	China	27	29	RCT	February 14, 2020, to March 29, 2020	Severe	66.30 ± 11.20	67.00 ± 14.30	55.60	75.90	6	11	10	11	35.00 ± 17.00	32.80 ± 17.00	8
14	Zhao et al.[45]	China	55	55	Retrospective	March 18, 2020, to April 18, 2020	Severe	36.00	36.00	33.00	35.00	NIA	NIA	4	12	NIA	NIA	7
15	Hakamifard et al.[50]	Iran	38	34	RCT	March 2020 to April 2020	Nonsevere	35.68	37.41	63.20	64.70	NIA	NIA	NIA	NIA	7.95 ± 3.18	8.03 ± 2.83	7

Abbreviations: NIA, no information available; RCT, randomized controlled trial.

TABLE 2 Patient treatment and outcomes stratified in all included studies ($N = 15$)

SN	References	Mode of administration	Dose of vitamin C	Intervention duration	Total cumulative dose of vitamin C	Treatment other than vitamin C	Final outcomes
1	Al Sulaiman et al.[37]	IV	1 g/day	NIA	NIA	– Tocilizumab – Corticosteroids	– No significant difference in mortality. – Lower the incidence of thrombosis.
2	Beigmohammadi et al.[46]	IV	2 g/day	7 days	14 g	– Vitamin A – Vitamin B – Vitamin D – Vitamin E	– Significant changes were detected in serum levels of vitamins, ESR, CRP, IL6, TNF-a, and SOFA score. – No significant difference in mortality. – The prolonged hospitalization rate to more than 7 days was significantly lower.
3	Darban et al.[38]	IV	8 g/day	10 days	80 g	– Azithromycin (250 mg daily) – Lopinavir/ritonavir (100 mg/25 mg daily) – Glucocorticoids – Oxygen therapy	– Reduce LDH, ESR, CRP, and Ferritin levels.
4	Gao et al.[39]	IV	12 g/day for 1st day, 6 g/day for the 2nd to 5th days	5 days	36 g	– Antibiotics – Corticosteroids, – Immunomodulators – Antivirals (e.g., Lopinavir/Ritonavir, Ribavirin)	– Reduce mortality and improve oxygen support status in patients.
5	Gavrielatou et al.[40]	IV	3 g/day for 4 days, 1.5 g/day for next 3 days, 1.0 g/day for next 3 days	10 days	19.5	– Thiamine	– No significant difference in mortality, hospitalization and other outcomes.
6	Hess et al.[41]	IV	12 g/day (3 g every 6 h)	7 days	84 g	– Steroids – Azithromycin – Antibiotics other than azithromycin – Hydroxychloroquine – Remdesivir – Tocilizumab	– Prolonged time to death. – Significantly lower rates of mechanical ventilation and cardiac arrest. – Decrease hospital stay.
7	Krishnan et al.[42]		NIA	NIA	NIA	NIA	NIA
8	Kumari et al.[47]	IV	50 mg/kg/day	NIA	NIA	– Antipyretics – Dexamethasone – Prophylactic antibiotics	– A shorter length of hospital stay. – No significant difference in the need for mechanical ventilation and mortality

(Continues)

TABLE 2 (Continued)

SN	References	Mode of administration	Dose of vitamin C	Intervention duration	Total cumulative dose of vitamin C	Treatment other than vitamin C	Final outcomes
9	Li et al.[43]	IV	9 g/day (1.5 g every 6 h)	4 days	36 g	– Hydrocortisone 50 mg/6 h – Thiamine 200 mg/12 h	– No significant difference in mortality rate and hospital stay
10	JamaliMoghadamSiahkali et al.[48]	IV	6 g/day (1.5 g every 6 h)	5 days	30 g	– Lopinavir/Ritonavir 400/100 mg twice daily – Hydroxychloroquine 400 mg on the first day	– No significant difference in mortality rate, length of ICU stay, and oxygen supply.
11	Suna et al.[44]	IV	2 g/day	NIA	NIA	– Dexamethasone 8 mg/day – Favipiravir 3.2 g/day for 1st day, 1.2 g/day for 2nd to 10th days – Oxygen support	– No significant difference in mortality rate, hospital stay
12	Thomas et al.[49]	Oral	8 g/day	10 days	80 g	– Antipyretics – NSAIDs – Bronchodilator – Gastrointestinal medication – Corticosteroids – Decongestant	– No significant difference in mortality rate, hospital stay
13	Zhang et al.[33]	IV	24 g/day	7 days	168 g	– Oseltamivir – Azithromycin – Piperacillin/tazobactam – Hydrocortisone	– Improvement in P/F ratio.
14	Zhao et al.[45]	IV	100 mg/kg	7 days	NIA	– Antiviral – Antibiotic – Low molecular heparin – Glucocorticoid	– Lower SIRS occurrence. – Lower C-reactive protein levels. – Improved activated partial thromboplastin time and D-dimer.
15	Hakamifard et al.[50]	Oral	1 g/day	NIA	NIA	– Hydroxychloroquine	– The duration of hospitalization was shorter. – No patients in both groups died during the study.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL6, interleukin-6; IV, intravenous; LDH: lactate dehydrogenase; NIA, no information available; P/F ratio, arterial partial pressure of oxygen (PaO_2)/inspired oxygen concentration (FiO_2); SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; TNF-α, tumor necrosis factor-alpha.

TABLE 3 Meta-analysis of the association of high dose vitamin C administration and mortality, severity, and length of hospitalization of COVID-19 patients.

	Test of association			Test of heterogeneity			Publication bias (*p* value)	
Studied parameters	**OR**	**95% CI**	***p* value**	**Model**	***p* value**	**I^2 (%)**	**Egger's test**	**Begg–Mazumdar's test**
Mortality	0.54	0.42–0.69	**<0.00001**	Fixed	0.70	0	0.755	0.583
Severity	0.63	0.43–0.94	**0.02**	Fixed	0.23	26	0.287	0.293
Hospital staying duration (days)	**MD**	**95% CI**	***p* value**	**Model**	***p* value**	**I^2 (%)**	**Egger's test**	**Begg–Mazumdar's test**
	0.19	−1.57 to 1.96	0.83	Random	**<0.00001**	89	0.535	0.788

Note: Bold values indicate statistically significant ($p < 0.05$).

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio.

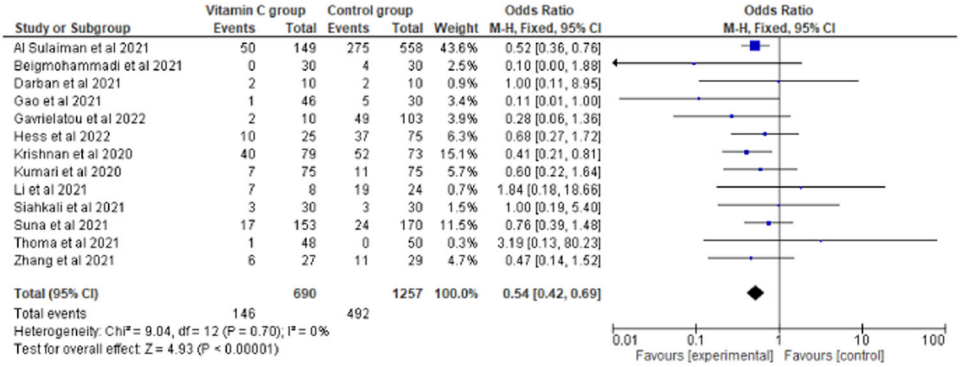

FIGURE 2 Vitamin C exposure and risk of mortality in patients with COVID-19

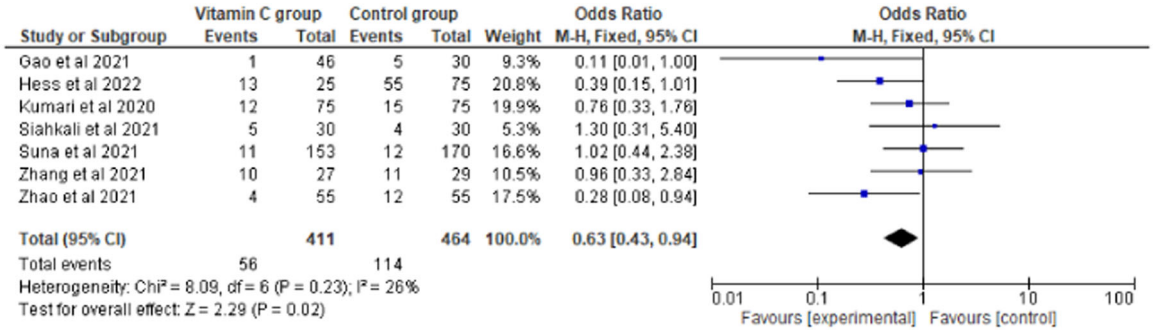

FIGURE 3 Vitamin C exposure and risk of severity in patients with COVID-19

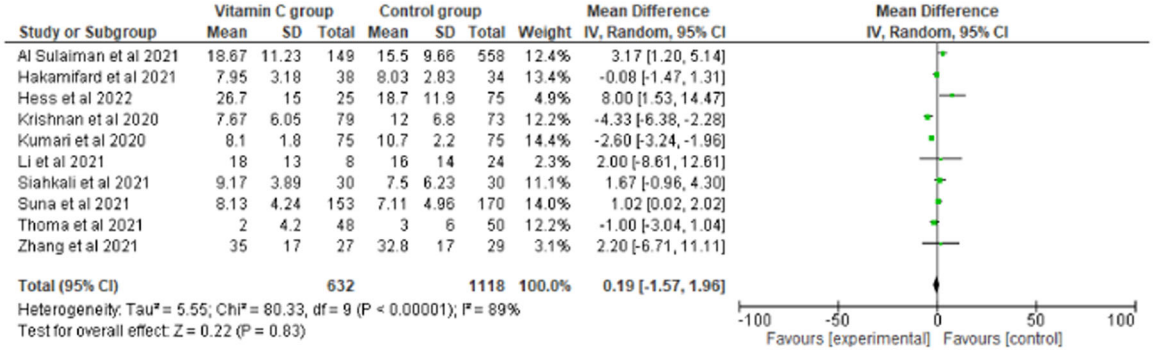

FIGURE 4 Vitamin C exposure and length of hospital stay in patients with COVID-19

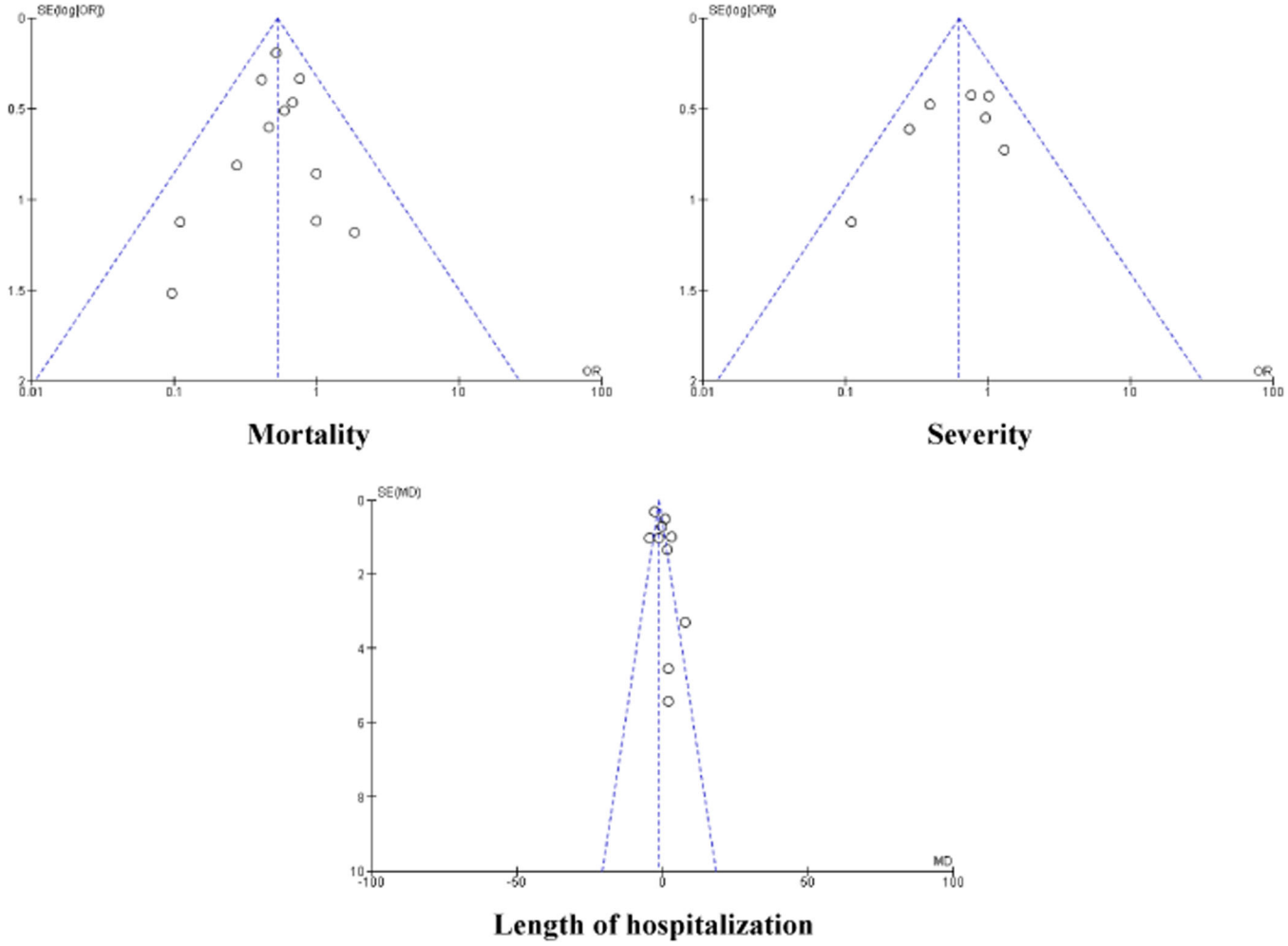

FIGURE 5 Funnel plots indicating the publication bias for detecting the association of high dose vitamin C administration and mortality, severity, and length of hospitalization of COVID 19 patients.

Vitamin C has been shown in several investigations to successfully inhibit various viruses, including influenza A, rhinovirus, avian influenza A virus H1N1, and poliovirus type 1.[59–61] Studies have demonstrated that IV vitamin C therapy in the ICU might improve health satisfaction.[62,63] COVID-19 patients who received vitamin C had a significantly lower death rate compared to those who did not receive vitamin C, according to this systematic review and meta-analysis (OR = 0.54, 95% CI = 0.42–0.69, $p < 0.00001$). This result is not congruent with other meta-analyses.[40,64,65]

Our meta-analysis found a significant correlation between COVID-19 severity and vitamin C supplementation (OR = 0.63, 95% CI = 0.43–0.94, $p < 0.02$). According to our findings, it is also inconsistent with the other meta-analysis in terms of COVID-19's severity and vitamin C intake.[64] Besides, this meta-analysis demonstrated that the MD in-hospital stay of vitamin C groups is insignificantly higher than control groups (MD = 0.19, 95% CI = −1.57 to 1.96, $p = 0.83$). One study concluded that the vitamin C group had to pass more time in the ICU than the control group. There was no difference in the length of mechanical ventilation between the vitamin C group and the control group.[40] This conclusion is also in line with other meta-analyses.[65,66] To overcome more advanced infectious diseases in the future and extend healthy life expectancy, it is recommended to maintain personal hygiene.[67]

However, besides the currently available data, detailed prospects and an indication of the effectiveness of vitamin C (IV) for COVID-19 treatment are still lacking. Therefore, it is required to collect all studies performed worldwide and carefully synchronize them to establish standard treatment options using vitamin C.[68] Moreover, to develop strong immunity against coronavirus infection, it is recommended that patients should administer vitamin C on a regular basis. A study by Uddin et al.[32] recently suggested that the requirement of vitamin C is enhanced in infected individuals and daily intake of vitamin C (1–2 g/day) is recommended in such conditions. It is also needed to be mentioned that 200 mg/day dose of vitamin C is a prerequisite to maintaining saturated blood levels in healthy subjects.[32]

This research has several limitations. In the first place, the total number of studies included in this meta-analysis is relatively small (15 studies). Second, the investigations involved just a small number of COVID-19 patients with or without vitamin C. Third, there is a great deal of variation in the populations, doses, and administration routes,

making the results difficult to interpret. Aside from these constraints, the quality of the literature employed in this research is quite high, the analysis is robust, and the findings generated from the study are highly credible and dependable.

5 | CONCLUSION

Our meta-analysis concludes that vitamin C usage significantly decreased the mortality rates and severity of COVID-19 patients. During the COVID-19 pandemic, patients experienced a substantial advantage from taking supplementary vitamin C. The findings of this study need to be substantiated by large-scale studies in the future to ensure its validity.

AUTHOR CONTRIBUTIONS

Conceptualization: Mohammad Safiqul Islam. *Data curation*: Khokon Kanti Bhowmik, Md. Abdul Barek, and Md. Abdul Aziz. *Formal analysis*: Mohammad Safiqul Islam. *Methodology*: Md. Abdul Barek and Mohammad Safiqul Islam. *Supervision*: Mohammad Safiqul Islam. *Validation*: Khokon Kanti Bhowmik and Mohammad Safiqul Islam. *Visualization*: Md. Abdul Aziz and Mohammad Safiqul Islam. *Writing—Original Draft*: Khokon Kanti Bhowmik and Md. Abdul Barek. *Writing—review and editing*: Md. Abdul Barek, Md. Abdul Aziz, and Mohammad Safiqul Islam.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

TRANSPARENCY STATEMENT

I, Mohammad S. Islam, the corresponding author of the referred article, declare that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained. All authors have read and approved the final version of the manuscript. Mohammad Safiqul Islam had full access to all of the data in this study and takes complete responsibility for the integrity of the data.

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