Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should vitamin C be used in the adjunctive treatment of COVID-19?

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RECOMMENDATION

There is insufficient evidence to recommend the use of vitamin C as adjunctive treatment for patients with COVID-19. *(Low certainty of evidence)*

Consensus Issues
The evidence still posed low certainty in terms of efficacy (i.e., reduction in length of hospital and ICU stay, need for mechanical ventilation for hospitalized patients, and mortality among both hospitalized and non-hospitalized patients) and safety. The panel could not suggest against the use of vitamin C since only one study for non-hospitalized patients showed inconclusive effects on mortality and adverse events.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of intravenous vitamin C as adjunct treatment for patients with COVID-19 infection. (Low quality of evidence)

Consensus Issues
Since there is insufficient evidence to recommend the use of vitamin C as adjunct treatment for COVID-19 and the quality of evidence is rated low, this means that more randomized controlled trials on vitamin C as adjunct treatment for COVID-19 need to be done.

Intravenous administration was the route used by the included studies in this review. According to the search for pricing, intravenous vitamin C costs Php 430 for 40 ampules of 500mg/2ml but this pricing was from an online selling source; there were no data on pricing of intravenous vitamin C on pharmaceutical websites searched.

What's new in this version?

This review contains four new additional randomized control trials, bringing to eight the studies included in this review. Data from four RCTs were pooled and analyzed in a meta-analysis, while the other four RCTs were individually reviewed and reported narratively for the relevant outcomes.

Key Findings

There are eight RCTs included in this review but only four, that used intravenous vitamin C for hospitalized patients with moderate to severe COVID-19, were pooled. For the outcome of mortality, there was a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One RCT using oral vitamin C in the outpatient setting and three RCTs using Vitamin C in addition to other adjunctive treatments showed inconclusive results. Adverse events reported were flushing, headache, nausea, vomiting, stomach pain, and diarrhea.

Introduction

Vitamin C (VC), also known as ascorbic acid, is an essential water-soluble vitamin that is required as a cofactor in many enzymatic reactions.[1] It promotes phagocytosis and chemotaxis of leukocytes and development and maturation of T-lymphocytes.[2,3] It also exhibits antioxidant properties through its effect on the NFKB activation that leads to the attenuation of inflammation and reduction in reactive oxygen species.[4] Early clinical trials show that VC can alleviate and prevent the common cold.[5,6] However, two observational studies on the effect of VC on COVID-19 showed no mortality benefit and increased hospitalization stay with VC treatment.[7,8]

Review Methods

We performed a comprehensive, systematic search for relevant literature in PubMed, Cochrane Library, *ClinicalTrials.gov*, *epistemonikos.com* and *medRxiv.com*, *covid-nma.com* as well as freehand search using Google Scholar. We used the search terms “COVID-19”, “SARS-CoV-2”, “nCOV-19”, “vitamin C”, “ascorbic acid” and “sodium ascorbate”. There was no limit as to the date, language and country of publication. We searched for randomized controlled trials. When systematic reviews were found, their individual component RCTs were tracked and assessed for eligibility. We excluded observational studies, case reports, case series and letters to the editor. Articles were included if they satisfied the following eligibility criteria:

Population	COVID-19 patients any age, co-morbidities and severity
Intervention/Exposure	Vitamin C or Sodium Ascorbate or Ascorbic Acid as adjunctive treatment
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, adverse effects
Methodological filter	Randomized controlled trials (RCTs)

Data from randomized control trials that included all hospitalized patients with moderate to severe COVID-19 and given intravenous vitamin C were pooled together in a meta-analysis. Outcomes that were analyzed included mortality, length of hospital stay, length of ICU stay, need for mechanical ventilation, and adverse events. When appropriate, pooling of the estimates was done using Review Manager 5.4; risk ratio was used for dichotomous outcomes while standard mean difference was used for continuous outcomes. GRADE PRO was used to evaluate the quality of evidence.

Other randomized control trials that had dissimilar population and intervention arms were excluded from the meta-analysis and reviewed individually for the same outcomes as in the pooled RCTs.

Results

We performed a meta-analysis of four RCTs, all of which included hospitalized patients with moderate to severe COVID.[9,10,12,13] Vitamin C was given via the intravenous route at doses ranging from 50mg/kg/day to 24g/day and compared with the study-defined control treatment or standard of care.

Data on mortality rate were pooled from all four RCTs with a total of 150 subjects in the treatment group and 160 subjects in the control group. The overall estimate showed a trend to benefit with negligible harm of vitamin C for the outcome of mortality (RR 0.59, 95% CI 0.34-1.03).

The estimate for length of hospital stay was also pooled from all four RCTs that studied the outcome, and the results were inconclusive (MD -0.96, 95% CI -3.84-1.92).

Length of ICU stay was measured in only two studies [9,12] and the overall estimate from the pooled analysis showed inconclusive results (MD 1.35; 95% CI -0.12-2.83).

For the outcome of need for mechanical ventilation, the pooled estimate from three studies [9,10,12] showed inconclusive results (RR 0.93, 95% CI 0.60-1.44).

Data on adverse events was reported in only two out of the four RCTs reviewed. One using high dose intravenous vitamin C [9] reported no adverse events, while the other using oral vitamin C [11] reported having adverse events in 17 out of 78 (21.7%) participants given vitamin C. Adverse events included flushing, headache, nausea, vomiting, stomach pain, and diarrhea.

Three randomized control trials gave vitamin C in conjunction with other adjunctive treatments. Results from these RCTs [14-16] were reviewed individually.

The study of Darban et al. [14] included ICU-admitted patients with severe COVID-19 given intravenous vitamin C (2g q6hr), oral melatonin (6mg q6hr), and oral zinc sulfate (50mg elemental zinc q6hr) for 10 days. The study results showed no significant improvement in hypoxemia and inflammatory markers in the case group versus the control group.

Beigmohammadi et. al. [16] also included ICU-admitted patients with severe COVID-19, and gave vitamin C 500mg four times daily together with vitamin A 25,000IU daily, vitamin D 600,000IU for 1 dose, vitamin E 300IU twice daily and B complex once daily. The study showed significantly shorter length of hospital stay and significantly lower inflammatory markers including ESR, CRP, IL-6 and TNF-a and SOFA score in the intervention group. The outcome for reduction in mortality was not significant.

The study by Hakamifard et al. [15] included hospitalized patients with non-severe COVID-19, and gave as an intervention oral vitamin C 1gram daily with oral Vitamin E 400IU daily in addition to standard treatment, showing inconclusive results for improvement in clinical response, duration of hospitalization and mortality.

One study, that of Thomas et al. [11], included COVID patients managed as out-patient, divided into treatment arms: patients received either oral vitamin C, oral zinc gluconate, both agents or standard of care. The study was discontinued for futility, and results were inconclusive for symptom reduction, hospitalization, mortality and adverse events.

Evidence to Decision

There are no cost-effectiveness studies available on use of vitamin C among COVID-19 patients. There are also no local studies tackling perspectives of relevant stakeholders on use of vitamin C among these patients. In a local drugstore, a tablet of ascorbic acid (500 mg) is approximately Php2.75.[17]

Recommendations from Other Groups

The World Health Organization (WHO) and IDSA did not mention the use of vitamin C for COVID-19 in their CPG. The US-NIH made no recommendation for or against use of vitamin C for COVID-19 due to insufficient evidence.

Research Gaps

Currently, there are 13 ongoing studies on the efficacy of vitamin C as an adjunctive treatment for COVID-19 (see Appendix 6). More studies are needed to examine the use of either intravenous or oral vitamin C in suppressing cytokine storms in COVID-19. Furthermore, studies on the most appropriate and effective dose and route of administration are also needed in order to make clearer recommendations on the use of vitamin C for patients with COVID-19.

References

[1] Padayatty SJ, Levine M. Vitamin C: The known and the unknown and Goldilocks. Oral Dis. 2016; 22:463–493

[2] Wang Y, Russo TA, Kwon O, Chanock S, Rumsey SC, Levine M. Ascorbate recycling in human neutrophils: Induction by bacteria. Proc. Natl. Acad. Sci. USA 1997; 94:13816–13819.

[3] Nualart FJ, Rivas CI, Montecinos VP, Godoy AS, Guaiquil VH, Golde DW, Vera JC. Recycling of vitamin C by a bystander effect. J. Biol. Chem. 2003; 278:10128–10133.

[4] Chen Y, Luo G, Yuan J, Wang Y, Yang X, Wang X, et al. Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages. Mediat. Inflamm. 2014; 2014:426740.

[5] Pauling L. Vitamin C and Common Cold. JAMA J. Am. Med. Assoc. 1971;216:332.

[6] Pauling L. Evolution and the need for ascorbic acid. Proc. Natl. Acad. Sci. USA. 1970; 67: 1643–1648.

[7] Patel M, Hong G, Schmidt B, Al-Janabi L, Kishan R, Tusha J, et al. The significance of oral ascorbic acid in patients with COVID-19. Chest Journal Org. 2020; 325A

[8] Al Sulaiman K, Al Juhani O, Badreldin H, Salah K, Al Harthi A, Alenazi M, et al. Adjunctive therapy with ascorbic in critically ill patients with COVID-19: A multicenter propensity score matched study. Research Square 2021 (preprint) 1-16.

[9] Jamalimoghadamsiahkali S, Zaresade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, et al. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. Eur J of Med Res. 2021; 26(1):20.

[10] Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, et al. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020; 12(11):e11779

[11] Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, 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 Network Open. 2021;4(2):e210369

[12] Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al. Pilot trial of high dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 2021; 11:5.

[13] Tehrani S, Yadegarynia D, Abrishami A, Moradi H, Gharaei B, Raoufi M, et al. 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. 2021.

[14] Darban M, Malek F, Memarian M, Gohari A, Kiani A, Emadi A, et al. Efficacy of high dose vitamin C, melatonin and zinc in Iranian patients with Acute Respiratory Syndrome due to Coronavirus Infection: A pilot randomized Trial. Journal of Cellular & Molecular Anesthesia (JCMA) 2021;6(2).

[15] Hakamifard A, Id R, Soltani, Id A, Maghsoudi, Id, et al. The effect of vitamin E and vitamin C in patients with COVID-19 pneumonia; a randomized controlled clinical trial *Correspondence to. Immunopathol Persa. 2021;8(1):8.

[16] Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Soltani D. 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. 2021 Nov 14;22(1).

[17] Watsons. Multivitamins and Overall Wellness: Ascorbic acid 500 mg 1 tablet [Internet]. Available from: https://www.watsons.com.ph/ascorbic-acid-500mg-1-tablet/p/BP_10096377

[18] 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 & Metabolic Syndrome: Clinical Research & Reviews [Internet]. 2021 Nov 1;15(6):102324. Available from: https://www.sciencedirect.com/science/article/pii/S1871402121003441

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 8)

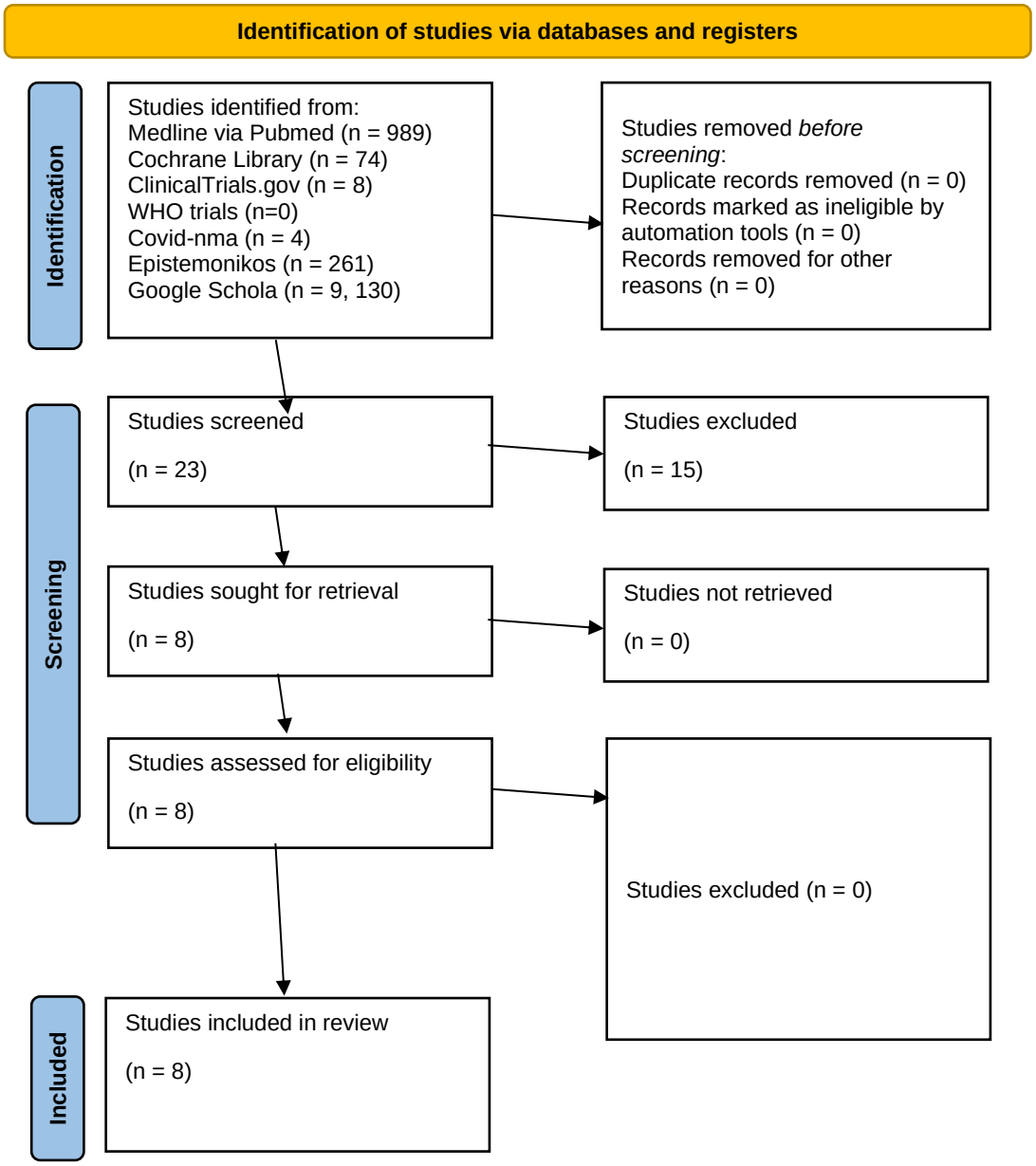
FACTORS	JUDGMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No	Yes (8)				• Early clinical trials show that VC can alleviate and prevent the common cold. However, two observational studies on the effect of VC on COVID-19 showed no mortality benefit and increased hospitalization stay with VC treatment.
Benefits	Large (1)	Moderate (2)	Small (3)	Uncertain (2)		• For the outcome of mortality there was trend towards benefit with small negligible harm (RR 0.59, 95 % CI 0.34 to 1.03). • For the outcomes of length of hospital stay, length of ICU stay and need for mechanical ventilation, the results were inconclusive.. • *Panelist: Patients are using double dose of the recommended daily intake. Will this also be considered as part of our recommendation?*
Harm	Large	Small (8)	Uncertain	Varies		• Adverse events reported from taking oral vitamin C were flushing, headache, nausea, vomiting, stomach pain, and diarrhea among COVID-19 outpatients. • There were no adverse events reported among hospitalized patients with COVID-19.
Certainty of Evidence	High	Moderate (1)	Low (7)	Very low		• The overall certainty of evidence is low primarily due to issues of inconsistency and imprecision.
Balance of effects	Favors vitamin C (7)	Does not favor vitamin C (1)	Uncertain	Varies		• For the outcome of mortality there was a trend towards benefit with small negligible harm (RR 0.59, 95 % CI 0.34 to 1.03). • For the outcomes of length of hospital stay, length of ICU stay and need for mechanical ventilation, the results were inconclusive • Adverse events reported from taking oral vitamin C were flushing, headache, nausea, vomiting, stomach pain, and diarrhea among COVID-19 outpatients. • There were no adverse events reported among hospitalized patients with COVID-19.

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Costs (3)	Negligible costs or savings (3)	Moderate savings (2)	Large savings	• There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients. In a local drugstore, a tablet of ascorbic acid (500 mg) is approximately Php2.75.
Certainty of evidence of required resources	No included studies (5)	Very low (2)	Low (1)	Moderate	High		• There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors vitamin C (3)			• There are no cost-effectiveness studies available on use of Vitamin C among COVID-19 patients.
Equity	Uncertain (4)	Reduced	Probably no impact (2)	Increased (2)			• No research evidence found.
Acceptability	Uncertain (2)	No	Yes (6)	Varies			• *Panelist who favors vitamin C: Encourage natural sources.*
Feasibility	Uncertain	No	Yes (8)	Varies			• No research evidence found.

Appendix 2. Search Yield and Results

Database	Date of Last Search	Search Strategy	Yield	Hit
MEDLINE via PubMed	11/30/21	((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND ((((((((vitamin C[MeSH Terms]) OR (ascorbic acid[MeSH Terms])) OR (sodium ascorbate[MeSH Terms])) OR (Vitamin C [tiab])) OR (sodium ascorbate [tiab])) OR (ascorbic acid [tiab])) OR (antioxidant[MeSH Terms])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (supplement[MeSH Terms]) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]) OR (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]	989	6
Cochrane Library	11/30/21	COVID-19 OR MeSH descriptor: [COVID-19] explode all trees OR coronavirus OR MeSH descriptor: [Coronavirus] explode all trees OR SARS-CoV-2 OR MeSH descriptor: [SARS-CoV-2] explode all trees AND "vitamin C"):ti,ab,kw OR MeSH descriptor: [Ascorbic Acid] explode all trees	74	4
covid-nma	11/30/21	Vitamin C	6	4
Epistemonikos	11/30/21	COVID-19 and Vitamin C	261	12
medRxiv	11/30/21	COVID-19 and (vitamin C or ascorbic acid)	360	0
Google Scholar	11/1/21	COVID-19 and Vitamin C and trial	9,130	10

PRISMA Flow Diagram



Appendix 3. Characteristics of Included Studies

Table 2. Randomized clinical trials on Vitamin C versus standard treatment or placebo among hospitalized patients with moderate to severe COVID-19

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Jamalimoghadamsiahkali 2021	COVID-19 confirmed patients by RT-PCR or by clinical symptoms, chest CT/HRCT, low oxygen saturation (n=60)	Vitamin C 1.5g Q6 x 5 days (6g/day) with lopinavir/ritonavir and HCQ	Lopinavir/ritonavir and HCQ with no Vitamin C	No significant difference in terms of mortality (p>0.05), patients on vitamin C had longer length of hospital stay (median 8.5 vs 6.5 days, p=0.028). Patients on vitamin C had higher SpO2 on 3rd day of admission (90.5% vs 88%; p=0.014)	Randomized controlled trial, open label
Kumari et al	Severe COVID-19 patients (n=150)	50mg/kg/day intravenous vitamin C with standard therapy (antipyretics, dexamethasone, and prophylactic antibiotics)	Standard therapy, no vitamin C	There were no statistically significant differences between the two groups in terms of mortality and need for mechanical ventilation. Patients on HDIVC group had earlier symptom free status (7.1 ± 1.8 vs 9.6 ± 2.1 days, p<0.001) and spent fewer days in the hospital (8.1±1.8 vs 10.7±2.2 days, p<0.0001) compared to patients without vitamin C	Randomized controlled open label
Tehrani, et al., 2021 Single center clinical trial	Patients diagnosed with COVID-19 with moderate to severe symptoms (n=54)	Vitamin C 2g every 6 hours for 5 days in addition to standard treatment	Standard treatment (Hydroxicholoroquine (400 mg stat) and Kaletra (400/100 mg q 12 h) and Interferon beta-1a (44 micrograms three times)]	Oxygen saturation, respiratory rates, serum C-Reactive Protein (CRP) levels, lymphopenia and lung parenchymal involvement on CT, length of hospital stay, mortality Due to the effectiveness of high doses of intravenous vitamin C on reducing lung involvement and improving clinical symptoms, further studies with a larger sample size are recommended to demonstrate the effects of this drug supplement.	Single center clinical trial
Zhang et al 2021	Severe COVID-19 confirmed patients	Vitamin C 24g/day IV x 7 days (HDIVC)	No vitamin C	No statistically significant difference between the two groups in terms of invasive mechanical ventilation-free	Randomized, placebo controlled

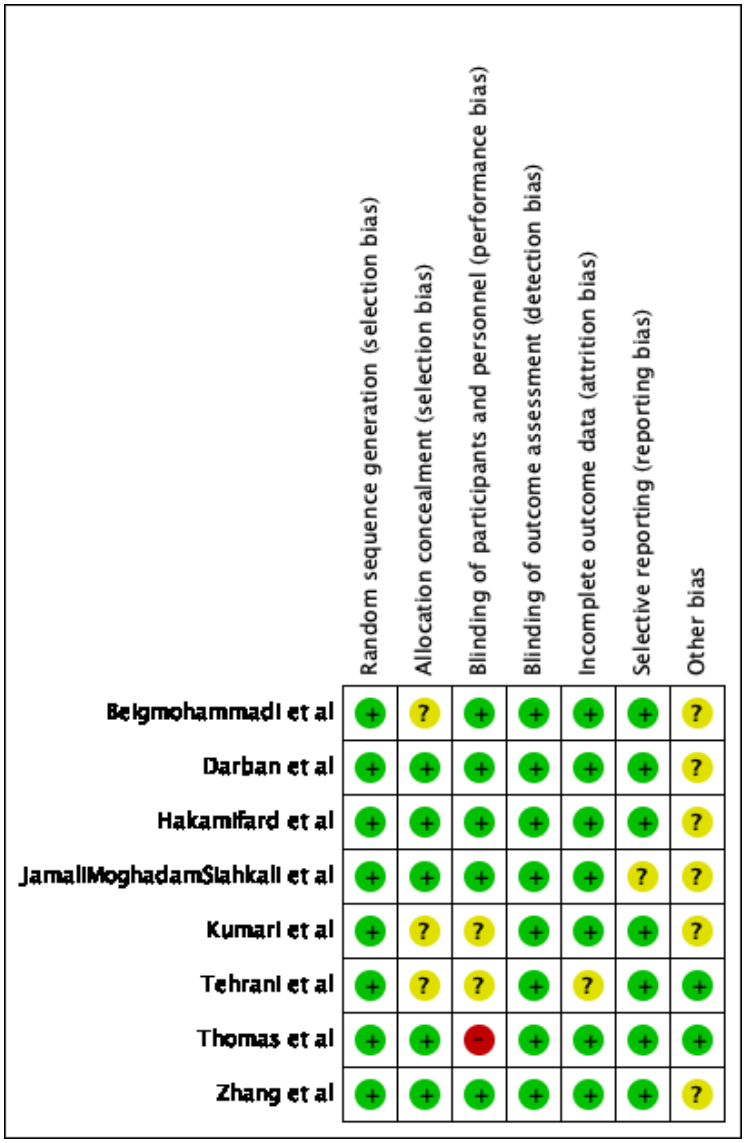
Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
	(n=56)	In addition, other general treatments followed the latest COVID-19 guidelines depending on the patient's situation: oseltamivir, azithromycin in the general ward; low-molecular weight heparin for those in ICU; piperacillin/tazobactam for patients on tracheal intubation		days, 28-day mortality, 28-day mortality for severe (SOFA ≥3). Patients on HDIVC had higher P/F ratio compared to the placebo group. The SOFA score increased in the placebo group and decreased in the HDIVC group. The delta P/F from day 1 to 7 was (20±96.7 in HDIVC and -51.9±150.7 in the control group No study related adverse events in the trial.	

Table 3. Clinical trials investigating effects of Vitamin C in combination with other dietary supplements among COVID-19 patients

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Darban, et al, 2021	Patients with severe COVID admitted to the ICU (n=20)	IV Vitamin C (2g q6hr), oral melatonin (6mg q6hr), oral zinc sulfate (220mg containing 50mg elemental zinc q6hr) for 10 days + standard of care	Standard of care	High-dose vitamin C, melatonin and zinc added to standard of care is not associated with improvement in hypoxemia (PaO2/FiO2 ratio), and inflammatory markers including LDH, ESR, ferritin, CRP	Randomized single-center, active-controleed, opne-label, parallel group, compassionate-use study
Hakamifard, et al, 2021	Hospitalized non-severe COVID-19 patients (n=72)	Oral Vitamin C 1g daily and oral vitamin E 400IU daily + standard treatment	Standard treatment	Co-administration of Vitamin C and E did not have a improvement in clinical response of patients at the end of treatment (either cure, improvement, or failure), the duration of hospitalization, and the mortality rate	Randomized controlled clinical trial
Beigmohammadi et al, 2021	ICU-admitted patients with COVID-19 (n=60)	25,000 IU daily of vitamins A, 600,000	No vitamins (placebo)	Significant changes were detected in serum levels of vitamins ($p < 0.001$ for all vitamins), ESR ($p < 0.001$),	Randomized, single-blinded clinical trial

		IU once during the study of D, 300 IU twice daily of E, 500 mg four times daily of C, and one amp daily of B complex for 7 days.		CRP (p = 0.001), IL6 (p = 0.003), TNF-a (p = 0.001), and SOFA score (p < 0.001) after intervention compared with the control group. The effect of vitamins on the mortality rate was not statistically significant (p=0.112). The prolonged hospitalization rate to more than 7 days was significantly lower in the intervention group than the control group (p=0.001). Supplementation with vitamins A, B, C, D, and E could improve the inflammatory response and decrease the severity of disease in ICU-admitted patients with COVID-19.	
Thomas et al, 2021	COVID-19 confirmed patients treated as outpatient (n=214)	Vitamin C 8,000mg/day Zinc gluconate 50mg Both zinc and vitamin c	Standard of care	The study was discontinued for futility. there was no significant difference among the 4 study groups in terms of days required to reach a 50% reduction in symptoms. Moreover, there was no significant difference in any of the secondary outcomes.	RCT, open label trial (with four treatment arms)

Appendix 4. Detailed Study Appraisal



Appendix 5. GRADE Evidence Profile

Author(s): Ina Chiu, MD and Mark Milan MD, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS Myzelle Anne J. Infantado, PTRP, MSc (cand.)
Question: Vit C with standard treatment compared to standard treatment alone for adjunctive treatment of COVID-19
Setting: Inpatient
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	16/150 (10.7%)	29/160 (18.1%)	**RR 0.59** (0.34 to 1.03)	**65 fewer per 1,000** (from 111 fewer to 4 more)	⊕⊕⊕◯ Moderate	CRITICAL
Length of hospital stay												
4	randomised trials	not serious	serious[b]	not serious	serious[a]	none	150	160	-	MD **0.96 lower** (3.84 lower to 1.92 higher)	⊕⊕◯◯ Low	CRITICAL
Length of ICU stay												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	57	59	-	MD **1.35 higher** (0.12 lower to 2.83 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Need for mechanical ventilation												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	28/132 (21.2%)	31/134 (23.1%)	**RR 0.93** (0.60 to 1.44)	**12 fewer per 1,000** (from 79 fewer to 72 more)	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Adverse events from vitamin C (oral vitamin C: flushing, headache, nausea, vomiting, stomach pain, and diarrhea)												
2	randomised trials	not serious	serious	not serious	serious	none	17/78 (21.8%)	0/50 (0%)	**RR 36.43** (2.25 to 589.34)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Confidence interval crosses the null value
b. I2 = 71%
c. Low number of included studies
d. Variability in patient population: outpatient and severe
e. Wide confidence interval

Appendix 6. Forest Plots

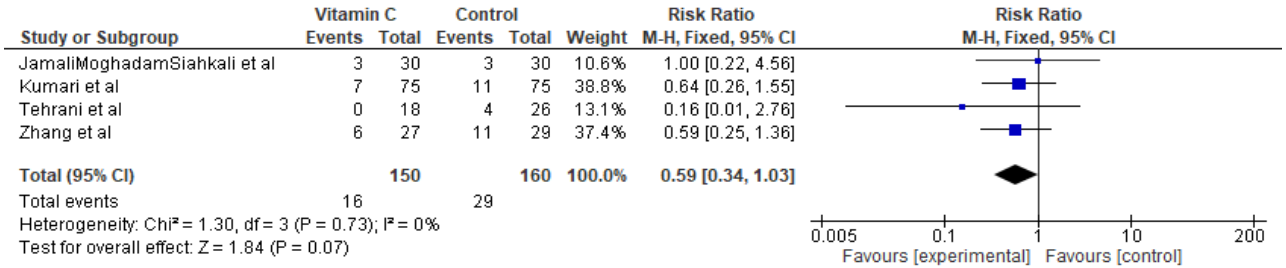


Figure 1. Mortality Outcome

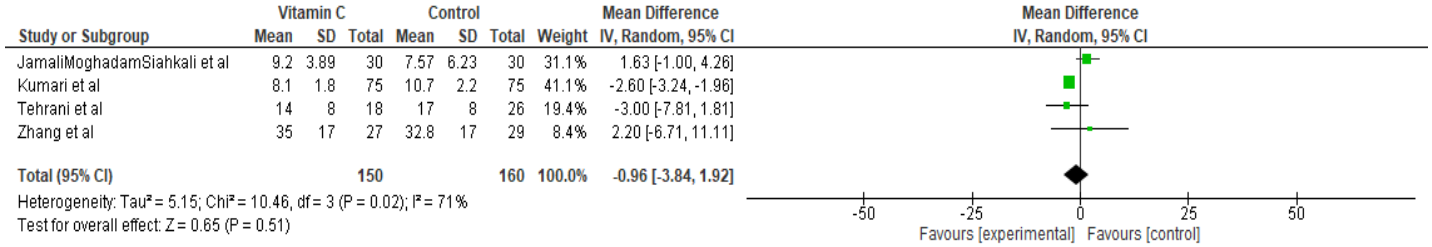


Figure 2. Length of hospital stay

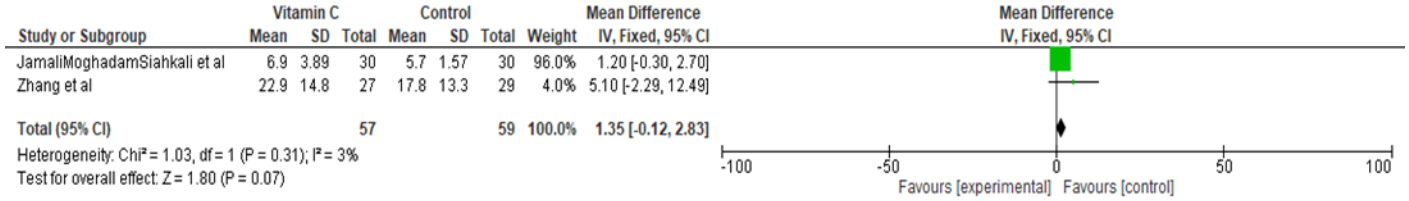


Figure 3. Length of ICU stay

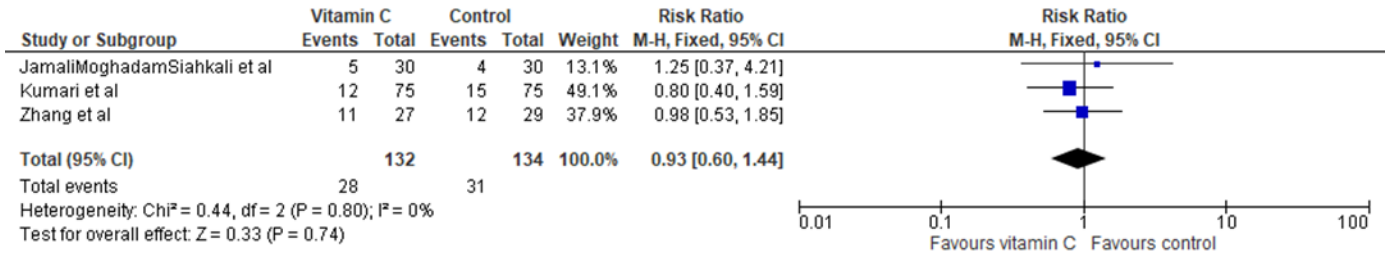


Figure 4. Need for mechanical ventilation

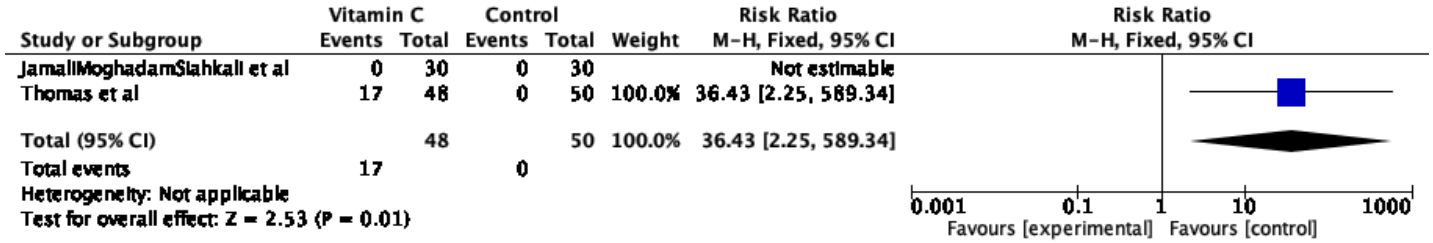


Figure 5. Adverse events

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
(1) NCT04664010 Efficacy and Safety of High-dose Vitamin C Combined With Traditional Chinese Medicine in the Treatment of Moderate and Severe Coronavirus Pneumonia (COVID-19)	Randomized Controlled Trial, parallel assignment	China	COVID-19	High dose Vitamin C in combination with traditional Chinese Medicine	Primary Outcome: Recovery time Secondary outcome: Relief of Symptoms Conversion time from positive to negative COVID-19	January 31, 2021 (no results posted yet)
(2) NCT04363216 Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment	Randomized sequential Assignment	USA	COVID-19	Ascorbic Acid vs routine care	Primary Outcome: Clinical Improvement Secondary Outcome: Patient status upgraded to ICU level, Oxygen supplementation, days with fever, days to discharge, SAEs	May 2021 not yet recruiting
(3) NCT04710329 High-Dose Vitamin C Treatment in Critically Ill COVID-19 Patients, A Retrospective Cohort Study	Retrospective Cohort Study	Turkey	ARDS Covid-19	Ascorbic Acid	Primary Outcome: Short term mortality Length of ICU stay	Feb 10, 2021 (no results posted yet)
~~(4)~~ ~~NCT04584437~~ The Treatment and Prevention of Covid-19 Pandemic Using Infrared and /or Vitamin C.	Single group assignment	Canada	All patients seeking prevention and treatment of COVID-19	Infrared Energy	Treatment and prevention of COVID-19	May 10, 2021 withdrawn -no financial support
(5) NCT04530539 The Effect of Melatonin and Vitamin C on COVID-19	Randomized parallel assignment	USA	COVID-19 patients	Ascorbic Acid Melatonin Vs Placebo	Primary Outcome: Symptom severity Secondary Outcome: Symptom progression	Dec. 1, 2021 still recruiting

(6) NCT04323514 Use of Ascorbic Acid in Patients With COVID 19	Single group assignment, open label	Italy	COVID-19 patients	Vitamin C	Primary Outcome: In-hospital Mortality Secondary Outcomes: PCR levels, lactate clearance, hospital stay, symptoms, positive swab, tomography imaging	Mar 13, 2021 (no results posted yet)
(7) NCT04558424 Randomized, Double -Blind, Placebo Controlled, Trial to Evaluate the Effect of Zinc and Ascorbic Acid Supplementation in COVID-19 Positive Hospitalized Patients in BSMMU	Randomized, Double -Blind, Placebo Controlled, Trial	Bangladesh	COVID-19	Vitamin C and Zinc	Primary outcome: Symptoms reduction time frame Secondary Outcome: Symptom resolution	Sept 1, 2021 (no results posted yet)
(8) NCT04468139 The Study of Quadruple Therapy Zinc, Quercetin, Bromelain and Vitamin C on the Clinical Outcomes of Patients Infected With COVID-19	Single group assignment	Saudi Arabia	COVID-19	Quercetin Bromelain Zinc Vitamin C	Primary Outcome: Hospital Stay after treatment	July 2020 (no results posted yet)
(9) NCT04395768 Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, Vitamin D, Vitamin B12 With or Without Vitamin C, a Multi-centre, International, Randomized Trial: The International ALLIANCE Study	Randomized parallel assignment	Australia	COVID 19	Vitamin C in combination with, Hydorxychloroquine, Azithromycin, Zinc, Vitamin B12 and Vitamin D3 vs control	Symptoms, length of hospital stay, invasive mechanical ventilation	Sept 30, 2021 (no results posted yet)
(10) NCT04357782 Administration of Intravenous with hypoxemia Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial	Non-Randomized, single group assignment, open label	USA	COVID-19 with hypoxemia	L-Ascorbic acid	Primary Outcome: Incidence of Adverse events, serious adverse reactions Secondary Outcome: Ventilator-free days, ICU-free days, hospital-free days, all-cause mortality, change in S/F ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin	Oct 13, 2020 (no results posted yet)

(11) NCT04682574 Efficacy of Mega Dose Vitamin C in Critically Ill COVID-19 Patients	Randomized parallel assignment	Pakistan	Critically Ill COVID-19 patients	Vitamin C vs placebo	Primary Outcome: Partial pressure of Oxygen in arterial blood to fraction of inspired Oxygen (P/F ratio) [Time Frame: 2 to 7 day Secondary Outcome: Duration of hospital stay	Jan 10, 2021 (no results posted yet)
(12) NCT04401150 Lessening Organ Dysfunction With VITamin C - COVID-19	multicentre concealed-allocation parallel-group blinded randomized controlled trial	Canada	Confirmed COVID-19	Vitamin C vs placebo	Primary Outcome: Death or persistent organ dysfunction	November 2021 on-going
(13) NCT04357782 Administration of Intravenous Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO): A Phase I/II Safety, Tolerability, and Efficacy Clinical Trial	Non Randomized Single Group Assignment	USA	COVID-19 patients with decreased oxygenation	Intravenous Vitamin C for mild hypoxemia, vs Intravenous Vitamin C for severe hypoxemia	Primary Outcome: Incidence of adverse events, serious adverse events, adverse reactions Secondary outcome: Ventilator free days, ICU free days, hospital free days, all cause mortality, change in SF ratio, CRP, LDH, D-dimer, lymphocyte count, NLR, serum ferritin	Oct 13, 2020 (no results posted yet)