# Vitamin C for SARS-COV-2 infection

**South African National Department of Health**
**Brief Report of Rapid Review**
**Component: COVID-19**

## TITLE: VITAMIN C FOR SARS-COV-2 INFECTION

**Date:** 28 May 2021

### Key findings

- We conducted a rapid review of available clinical evidence regarding the efficacy and safety of Vitamin C in patients with COVID-19.
- Following a search on four electronic databases we included one systematic review and five randomised controlled trials to answer the research question.
- We did not identify any reports on the use of Vitamin C in children, or in pregnant and breastfeeding women with COVID-19.
- Vitamin C compared to placebo, standard of care, zinc or ruxolitinib did not meaningfully reduce mortality, progression to hospitalisation, duration of hospitalisation, duration of ICU stay, progression to mechanical ventilation, or duration of mechanical ventilation. It may increase adverse events but the evidence is uncertain.
- The current evidence is insufficient to support the inclusion of vitamin C to treat confirmed SARS-CoV-2 infection – ongoing studies are expected to provide a stronger evidence base to better inform decision-making.

**NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:**

| Type of recommendation | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
|---|---|---|---|---|---|
| | | **X** | | | |

**Recommendation:** We do not recommend routine use of vitamin C for the treatment of COVID-19 in either ambulatory or hospital settings.
*Rationale:* The current evidence is insufficient to support the inclusion of vitamin C to treat confirmed SARS-CoV-2 infection.
**Level of Evidence: Low to very low certainty evidence**

*(Refer to Appendix 1 for the evidence to decision framework)*

**Therapeutic Guidelines Sub-Committee for COVID-19:** Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Gary Maartens, Jeremy Nel, Helen Rees.

**Note:** Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

## BACKGROUND

The ongoing COVID-19 (SARS-CoV-2) pandemic is a public health crisis. As there is currently no cure, interest in supportive treatment such as vitamin C (ascorbic acid or ascorbate) is high.

Vitamin C is widely promoted and used to treat respiratory infections. It has been postulated that it plays a role in strengthening the immune system by increasing the activity of phagocytes and lymphocytes and that it could decrease oxidative stress caused by Acute Respiratory Distress Syndrome (ARDS) (1, 2). However, best available evidence, fails to show clinically meaningful benefit as treatment for most respiratory infections. Although there is some evidence supporting its use in treating severe respiratory infection requiring ventilation (1, 3) and viral-induced ARDS (4), it is currently not considered as standard-of-care for any respiratory infections. These factors have led to vitamin C being considered for treatment of COVID-19.

A review was done of all currently available evidence on the efficacy of vitamin C in patients with COVID-19.

## RESEARCH QUESTION

Should Vitamin C be used to treat confirmed SARS-CoV-2 infection?

## METHODS

We conducted a rapid review of the evidence including comprehensive searching of four electronic databases – Epistemonikos and Cochrane Library COVID-19 study register on 23 April 2021, Pubmed on 26 April 2021, and the COVID-nma.com Living review database on 12 May 2021. Amongst others, these databases systematically search PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov. The search strategy is shown in Appendix 2.

We screened retrieved records against the eligibility criteria in the Covidence platform; we first screened the titles and abstracts in duplicate and then proceeded to screen relevant full text papers in duplicate.

Information on each included study in the COVID-nma.com Living review database, including the quality assessment using the Cochrane ROB 2 tool, was extracted into the Characteristics of Included Studies table (Table 1) and then checked by one reviewer. For data or risk of bias assessments not available in the database, one author extracted information and a second author checked it.

Meta-analyses were carried out in RevMan using random effects models. Results were reported as Risk Ratios in case of dichotomous outcomes or Mean Difference in terms of continuous outcomes, with 95% confidence intervals. Where necessary and possible, medians and IQRs were transformed into means and standard deviations using the quantile estimation methodology described by McGrath and colleagues (5).

All reviewers drafted the report before further evaluation by the NEMLC COVID-19 subcommittee.

### Eligibility criteria for review

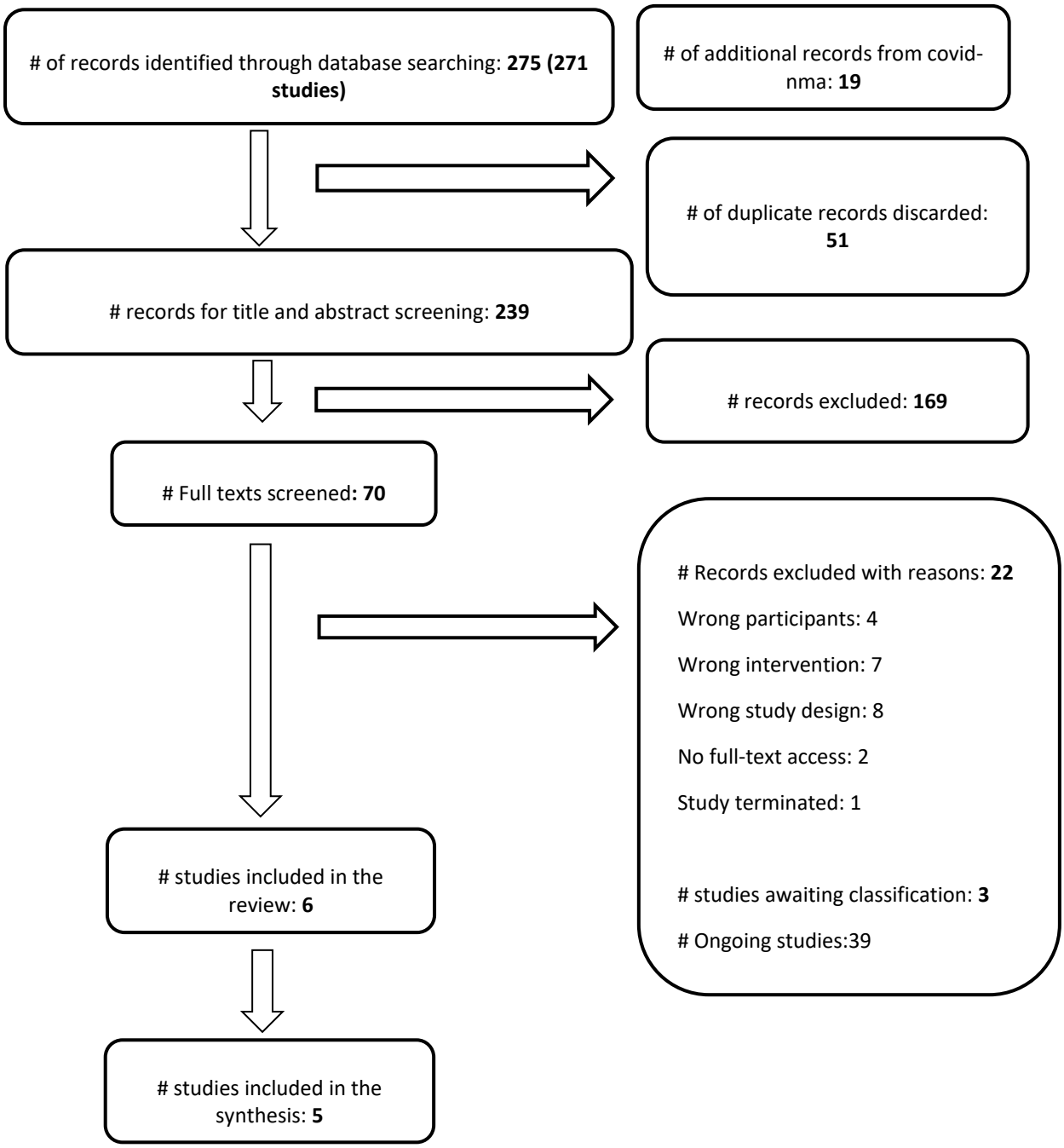
**Population:** All patients with confirmed SARS-CoV-2 infection, no restriction to age, disease severity or setting.
**Intervention:** Vitamin C. No restriction on dose, frequency or timing.
**Comparators:** Any comparator (e.g. standard of care; placebo; another intervention).
**Outcomes:** Mortality; progression to hospitalisation; duration of hospitalisation; progression to ICU admission; duration of ICU stay; progression to mechanical ventilation; duration of mechanical ventilation; adverse reactions
**Study designs:** Systematic reviews of randomized controlled studies (RCTs) and RCTs.

# RESULTS

## Results of the search

The databases search identified 290 records. After removing duplicates, we screened 239 titles and abstracts and then 70 potentially eligible full-texts against the eligibility criteria. Of the full-text articles screened 22 were excluded, three studies were classified as 'awaiting classification' because full-text versions could not be accessed, and 39 studies were identified as ongoing (see appendix 4 for the list of ongoing studies). Figure 1 below details the study selection process. Six publications were included in the review; one systematic review and five RCTs.

***Figure 1.*** **PRISMA flowchart of study selection process**



## Description of included studies

The included systematic review (6) is a living systematic review that aims to summarise the evidence available on the role of vitamin C in the treatment of patients with COVID-19. The review did not include any additional trials not identified in our search.

The characteristics of the five trials included are described in detail in Table 1. The five studies included 522 participants from China, Iran, Pakistan and the United States of America. All five trials considered males and females above 18 years and none included pregnant or breastfeeding patients. Four trials were done in an-inpatient setting and one trial in an outpatient setting (7). Of the studies carried out in an inpatient setting, three included patients classified as having severe disease and one included severe and critical disease severity patients. All trials included patients with confirmed SARS-CoV-2 based on local diagnostic criteria. All trials assessed the effects of vitamin C; two trials administered vitamin C orally while three trials administered vitamin C intravenously. Doses ranged from 2g per day to 24g per day, and the duration from 5-10 days. In one trial the vitamin C arm was the comparison arm, with ruxolitinib as the main intervention arm (8). Of the other trials, three compared vitamin C with standard of care and one with zinc and with placebo (7). All trials reported on mortality; one trial reported on progression to hospitalisation; four trials on duration of hospitalisation; two trials on duration of ICU stay; three trials on progression to mechanical ventilation; two trials on duration of mechanical ventilation; and three trials on adverse reactions. None of the trials reported on progression to ICU admission.

The overall risk of bias was judged as being high for one study (8) and there were some concerns for the remaining four studies. See figure 2 for a visual summary and Appendix 3 for the risk of bias assessments of each included study.

***Figure 2. Summary of risk of bias assessments of included trials***


## Effects of interventions

The included studies assessed three comparisons; the results for each are described below.

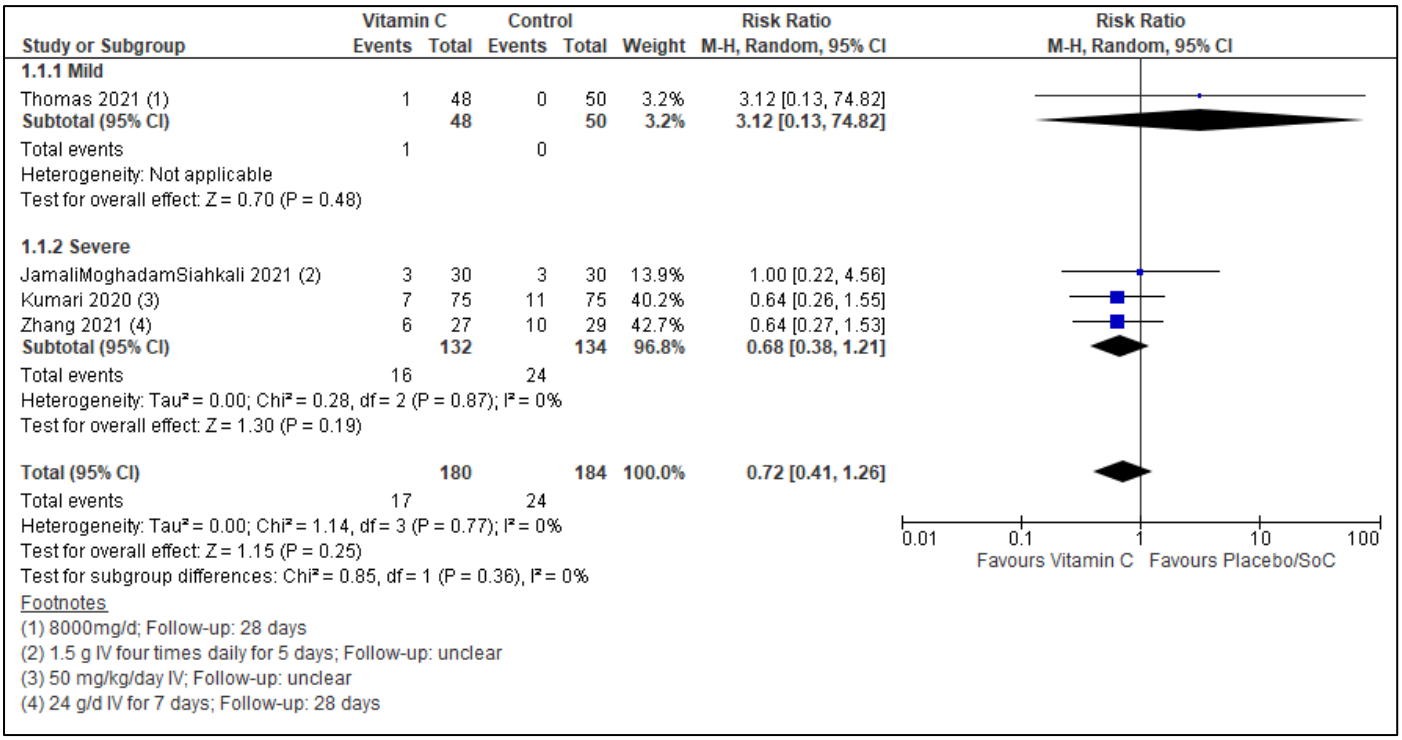
### Comparison 1: Vitamin C vs placebo/standard of care

Four trials reported this comparison (7, 9-11). The trials were conducted in China, USA, Pakistan and Iran; one included outpatients who received vitamin C orally and the others patients in severe clinical condition where vitamin C was provided intravenously. The GRADE evidence profile for this comparison is presented in Table 3.

**Mortality**

Evidence from these four trials indicates that vitamin C makes no difference to mortality (RR 0.72, 95% CI 0.41, 1.26, n=364 participants, low certainty of evidence). Figure 3 below indicates the results were similar for mild and severe patients. Two of these studies did not report clear follow-up times.

*Figure 3. Forest plot for Comparison 1, outcome: mortality*



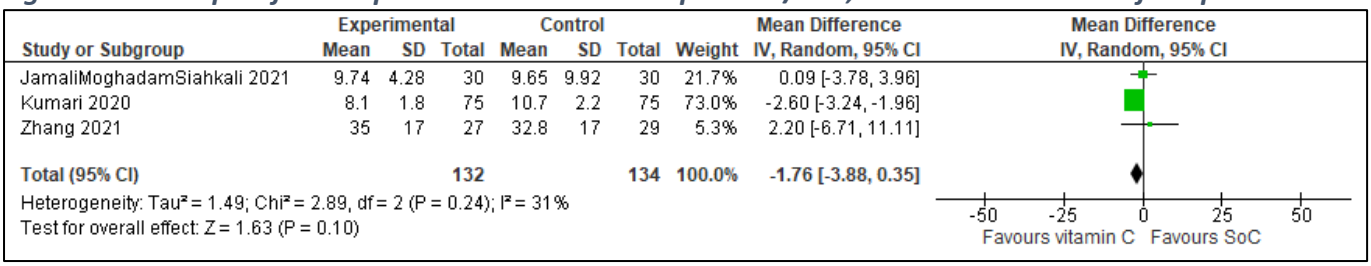

**Progression to hospitalisation**

Evidence from one trial (7) suggests that vitamin C makes no difference to progression to hospitalisation at day 10 after treatment initiation; a similar number of participants hospitalized during the study between the study arms; 2/48 in the intervention compared to 3/50 in control (RR 0.68, 95% CI 0.11, 4.27, n=98 participants, low certainty evidence).

**Duration of hospitalisation**

Evidence from three trials (9-11) is very uncertain regarding the effect of vitamin C on the mean number of days in hospital (MD -1.76, 95% CI -3.88, 0.35, n=266 participants, very low certainty evidence, Figure 4).

*Figure 4. Forest plot for comparison 1: vitamin C vs placebo/SoC; outcome: Duration of hospitalization*



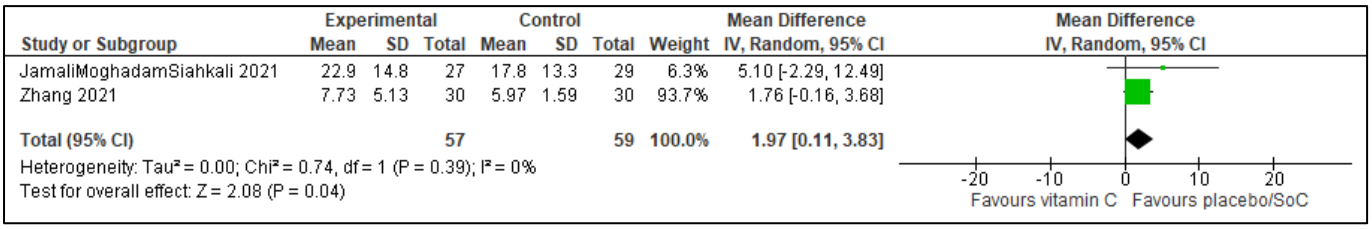

**Progression to ICU admission**

None of the included studies reported this outcome.

**Duration of ICU stay**

Evidence from two trials (9, 11) indicates that vitamin C made no difference to the duration of ICU stay compared with standard of care (MD 1.97, 95% CI 0.11, 3.83, n=116 participants, low certainty evidence, Figure 5).

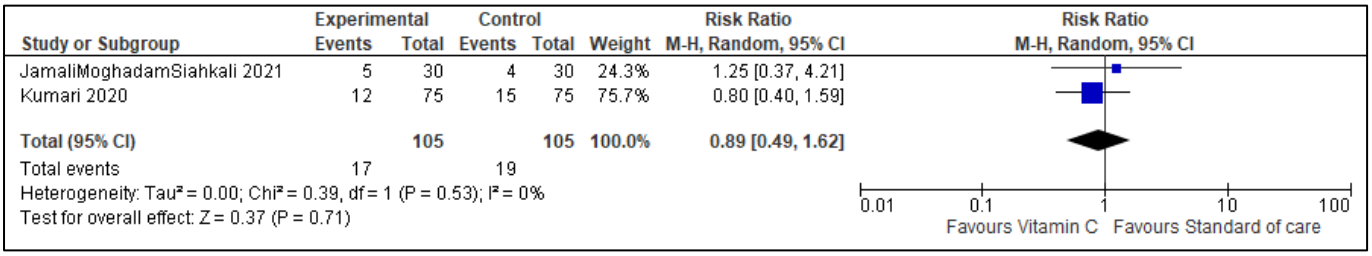
*Figure 5. Forest plot for comparison 1: vitamin C vs placebo/SoC; outcome: Duration of ICU stay*




**Progression to mechanical ventilation**

Data from two trials (10, 11) indicates the evidence is very uncertain regarding the effects of vitamin C on the progression to mechanical ventilation (RR 0.89 95% CI 0.49, 1.62, n=210 participants, very low certainty evidence).

*Figure 6. Forest plot for comparison 1; outcome: Progression to mechanical ventilation*




**Duration of mechanical ventilation**

Evidence from one trial (9) indicates that vitamin C may make little to no difference in the median number of days on mechanical ventilation; 1.5 (IQR 0.0-19.0) in the vitamin C group and 6.0 (IQR 0.0–16.0) in the control group (Median difference −0.8 , 95% CI −6.4, 4.9, n=56 participants, low certainty evidence).

**Adverse reactions**

Two trials reported on adverse reactions (7, 11) however, only one provided numerical results. Evidence from Thomas 2021 indicates that vitamin C may increase occurrence of adverse reactions (including flushing, headache, nausea, vomiting, tingling, numbness, stomach cramps, diarrhoea or dizziness) but the evidence is very uncertain (RR 37.39, 95% CI 2.32, 603.17, n=89 participants, very low certainty evidence). JamaliMoghadamSiahkali 2021 reported in the text of the paper that “During treatment with HDIVC, none of the patients experienced adverse events such as headache, nausea, bloating, or abdominal discomfort”.

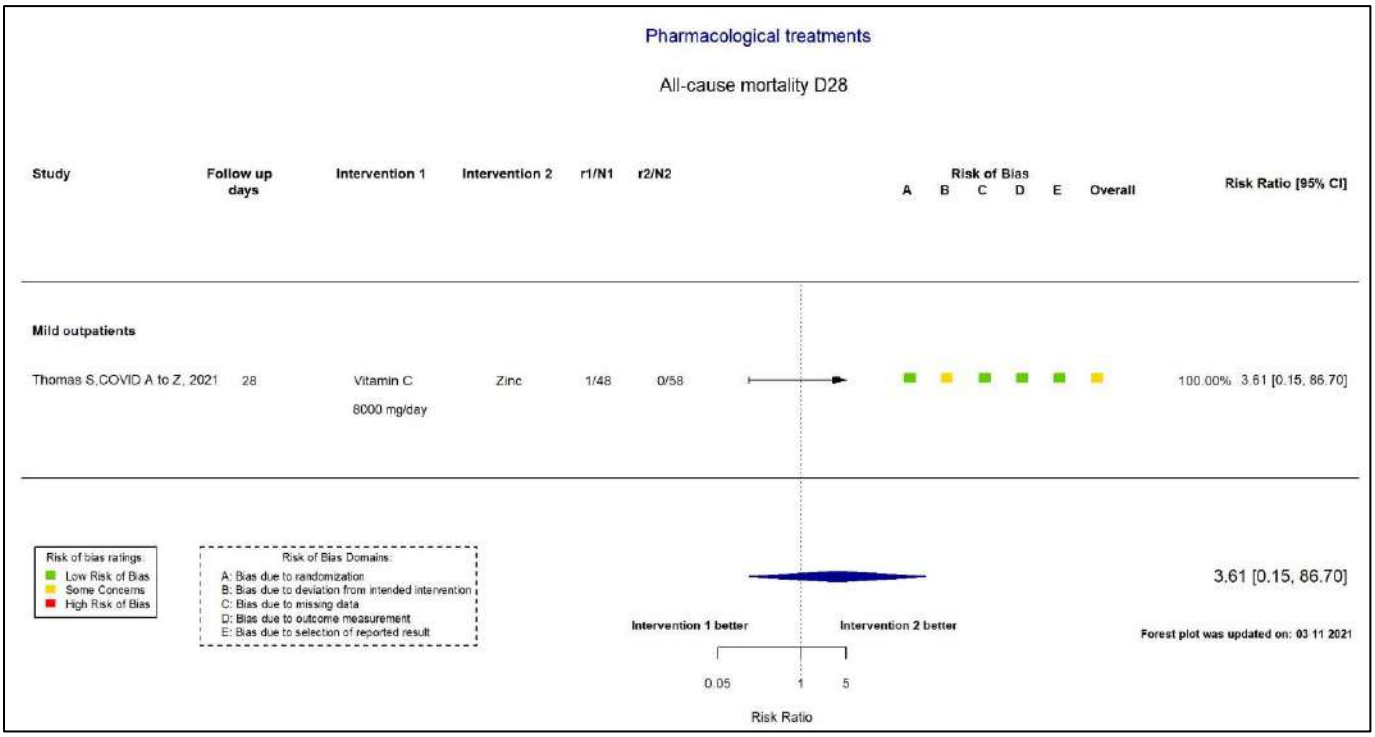
## Comparison 2: Vitamin C vs Zinc

One unblinded trial in the USA with 214 participants newly diagnosed with COVID-19 in an outpatient setting reported on this comparison (7). It compared the provision of 8000mg per day of oral vitamin C to zinc, for 10 days. This study’s overall risk of bias was classified as having some concerns. The GRADE evidence profile for this comparison is presented in Table 4.

**Mortality**

Evidence from one trial (7) indicates that the effect of vitamin C on mortality compared to zinc is very uncertain (RR 3.61, 95% CI 0.15, 86.7, n=106 participants, very low certainty evidence, Figure 7).

*Figure 7. Forest plot for comparison 2: Vitamin C vs Zinc; outcome: Mortality*




**Progression to hospitalisation**

Evidence from one trial (7) found no difference in the progression to hospitalisation with vitamin C compared to zinc (RR 0.48 95% CI 0.10, 2.38, n=106 participants, low certainty evidence).

**Duration of hospitalisation**

The study did not report on this outcome.

**Progression to ICU admission**

The study did not report on this outcome.

**Duration of ICU stay**

The study did not report on this outcome.

**Progression to mechanical ventilation**

The study did not report on this outcome.

**Duration of mechanical ventilation**

The study did not report on this outcome.

**Adverse reactions**

Evidence from one study (7) suggests that vitamin C increases the risk of adverse reactions (RR 2.13 95% CI 1.09, 4.17, n = 97 participants, low certainty evidence). This study reported that 17/43 participants reported adverse effects in the vitamin C group compared to 10/54 in the zinc only group.

## Comparison 3: Ruxolitinib vs Vitamin C

One unblinded RCT(8) in China evaluating ruxolitinib (a JAK1/2 inhibitor), used oral vitamin C as the control medication, and reported this comparison. The GRADE evidence profile for comparison is presented in Table 5.

**Mortality**

Evidence from one study (8) indicates that ruxolitinib may reduce mortality at 28 days compared to vitamin C (RR 0.14, 95% CI 0.01, 2.61, n=42 participants, low certainty evidence). In this study no deaths were reported in the group receiving ruxolitinib (0/21) and 3 deaths were reported in the group receiving vitamin C (3/21). The study was at high overall risk of bias.

**Progression to hospitalisation**
Not applicable as all patients enrolled were hospitalised.

**Duration of hospitalisation**
One trial reported no difference in effect on the number of days of hospitalisation (measured as median time to discharge from enrolment) between those receiving ruxolitinib and those receiving vitamin C [median number of days (IQR) 17 (11-21) vs 16 (11-20), p=0.941, low certainty of the evidence].

**Progression to ICU admission**
Not reported.

**Duration of ICU stay**
Not reported.

**Progression to mechanical ventilation**
The included study did not report this outcome.

**Duration of mechanical ventilation**
One trial (8) reported that patients in the ruxolitinib spent 0 days on invasive mechanical ventilation compared to a median of 5 days (IQR 2-8) among those in the vitamin C group (n=42 participants, low certainty evidence).

**Adverse reactions**
Evidence from one study (8) indicates that ruxolitinib may increase adverse events compared to vitamin C (RR 1.23, 95% CI 0.50, 3.02, n=41 participants, low certainty evidence).
This study also reported that serious adverse events were less likely in the ruxolitinib group compared to the vitamin C group (RR 0.12, 95% CI 0.01, 2.03, n=41 participants).

## CONCLUSION

In conclusion, in RCTs, vitamin C (compared to placebo, standard of care, zinc or ruxolitinib) has not demonstrated an important reduction in clinically relevant outcomes. Its use may increase adverse events.

The current evidence is insufficient to support the inclusion of vitamin C to treat confirmed SARS-CoV-2 infection. This review will be updated as further evidence becomes available.

**Reviewers**: Gary Reubenson, Elsie-Marie van Straten, Solange Durao

**Declaration of interests**: None to declare in respect of this topic. GR (Department of Paediatrics & Child Health, University of the Witwatersrand), EvS (ANOVA Health Institute), SD (Cochrane South Africa, South African Medical Research Council, SA GRADE Network).

## Table 1. Characteristics of included trials

| Citation | Study design | Population | Intervention | Comparator | Main findings | Risk of Bias |
|---|---|---|---|---|---|---|
| Cao Y<br>J Allergy Clin Immunol 2020; 146:137-46(8) | Parallel group RCT<br>Date: 9 Feb to 28 Feb 2020<br>Setting: multicentre<br><br>Follow-up: 28 days | China<br><br>N=42 (21 intervention; 21 placebo) median age of patients was 63 years (IQR, 58-68 years) Gender: 58.5% males Severity: Mild: n=0 / Moderate: n=0/ Severe: n=41 Critical: n=0<br><br>*Inclusion criteria*: (1) met the diagnostic criteria for COVID-19; (2) 18 years or older and younger than 75 years; (3) severe cases. The diagnosis and the illness severity of COVID-19 were defined according to the Chinese management guideline for COVID-19 (version 5.0) and the full translated edition of diagnostic criteria is available in Supplementary Methods section in the Online Repository at www.jacionline.org.<br><br>*Exclusion criteria*: (1) patients with concomitant malignant tumors; (2) patients with severe cardiovascular and metabolic disease that is not medically controlled; (3) patients with a mental or severe psychiatric disorder; (4) patients in need of invasive mechanic ventilation at recruitment; (5) patients who could not guarantee to complete all the scheduled treatment plans and follow-ups; (6) women of child-bearing age with positive pregnancy tests or those in the lactating period; (7) patients whose condition was further complicated with other active infections. | Ruxolitinib (5mg) twice/day + standard of care (SoC)<br><br>The SoC treatment included antiviral therapy, supplemental oxygen, noninvasive and invasive ventilation, corticosteroid, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation. | Vitamin C (100mg) twice/day + SoC | Mortality (All cause) d14-d28: 0/21 in intervention and 3/21 in control. RR 0.14 (95% CI 0.01 to 2.50). "Median time from randomization to death was 15 days (IQR, 4;19) in the control group."<br><br>Progression to hospitalization: NR<br><br>Duration of hospitalization: median number of days (IQR) from randomisation to discharge: 17 (11-21) in intervention group and 16 (11-20) in vitamin C group.<br><br>Progression to ICU admission: NR<br><br>Duration of ICU stay: NR<br><br>Progression to mechanical ventilation: NR<br><br>Duration of mechanical ventilation: 0 d in the control and 5 d (IQR 2-8) in intervention<br><br>Adverse events: 16/22 in intervention and 15/21 in control; RR 1.02 (0.70, 1.48). Serious adverse events: 0/22 in intervention and 4/21 in control; RR 0.11 (95% CI 0.01, 1.86) | High<br>(see Appendix 3 for details) |
| JamaliMoghadamSiahkali SEur J Med Res, 2021, 26:20(11) | Unblinded RCT<br>Date: April and May 2020 – recruitment<br><br>Setting: single-centre | Iran<br><br>N=60 (intervention: 30, control: 30)<br>Mean age (SD): 57.5 years (18.3) in intervention and 61 years (15.9) in control<br>Gender: 50% female | Vitamin C + Standard of care<br><br>1.5 g IV four times daily for 5 days | Standard care<br><br>Standard care: participants treated with oral Lopinavir/Ritonavir (Kaletra, Abbott Laboratories) 400/100 mg | Measured on admission, 3rd day after admission and at discharge<br><br>Mortality (decrease in mortality): 3/30 in intervention and 3/30 in control; p>0.05; RR 1.00 [0.22, 4.56] | Some concerns<br>(see Appendix 3 for details) |

| Citation | Study design | Population | Intervention | Comparator | Main findings | Risk of Bias |
|---|---|---|---|---|---|---|
| | Follow-up: unclear | Severity : Mild: n=0 / Moderate: n=0/ Severe: n=60 Critical: n=0<br><br>Inclusion criteria: Age older than 18 years; Positive COVID-19 polymerase chain reaction (PCR) test or COVID-19 suspicion based on clinical findings (mainly fever, dyspnea, dry cough); Imaging findings of COVID-19 on spiral chest computer tomography (CT) or high resolution CT (HRCT) imagings validated by a trained radiologist; Clinical manifestations of ARDS or myocarditis; and oxygen saturation lower than 93% from admission or after 48 hours from the first COVID-19 treatment<br><br>Exclusion criteria: Receiving anti-retroviral therapy or immune system booster medications in the last three months; No proven and confirmed COVID-19 disease based on the inclusion criteria; Patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency; Patients with end stage renal diseases (ESRD); Pregnancy | | twice daily and daily dose of oral Hydroxychloroquine (400 mg) according to the Iranian COVID-19 treatment protocol at time of this study. Some of the patients deteriorated during the admission and received corticosteroid (methylprednisolone 125 mg daily for three days) and IVIG (5 to 10 gr daily for three to five days). | Progression to hospitalization: n/a<br><br>Duration of hospitalization: median number of days (IQR): 8.5 (7.0–12.0) in intervention and 6.5 (4.0–12.0) in control; p=0.028<br><br>Progression to ICU admission: NR<br><br>Duration of ICU stay: median days (IQR): 5.5 (5.0-10.0) in intervention and 5 (5.0-7.0) in control, p=0.381.<br><br>Progression to mechanical ventilation-(intubation): 5/30 in intervention and 4/30 in control; p>0.09.<br><br>Duration of mechanical ventilation: NR<br><br>Adverse reactions: "During treatment with HDIVC, none of the patients experienced adverse events such as headache, nausea, bloating, or abdominal discomfort" | |
| Kumari P Cureus 2020; 12(11): e11779. DOI 10.7759/cureus.11779 (10) | Unblinded RCT<br>Date: 1 March 2020 to30 July 2020<br><br>Setting: single center<br><br>Follow-up: unclear | Pakistan<br><br>N=150 (intervention: 75, control: 75)<br>Mean age (SD): 52 (11) years in intervention and 53 (12) in control.<br>Gender: 56.9& male<br>Severity : Mild: n=0 / Moderate: n=0/ Severe: n=150 Critical: n=0<br><br>*Inclusion criteria*:<br>Patients who were admitted with severe COVID-19 infection diagnosed based on the national health guidelines of Pakistan. | Vitamin C + Standard care<br><br>50 mg/kg/day IV | Standard care<br><br>Standard care: Standard therapy for COVID-19 infection, which included antipyretics, dexamethasone, and prophylactic antibiotics | Mortality: 7/75 in intervention and 11/75 in control; p=0.31<br><br>Progression to hospitalization;<br><br>Duration of hospitalization: mean days (SD): 8.1 (1.8) in intervention and 10.7 (2.2) in control; p<0.0001<br><br>Progression to ICU admission: NR | Some concerns (see Appendix 3 for details) |

| Citation | Study design | Population | Intervention | Comparator | Main findings | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Guidelines: In adults, clinical signs of pneumonia (fever/ cough) plus, any of the following: Respiratory rate > 30, Severe respiratory distress, SpO2 ≤ 90% on room air, Chest X-ray involving >50% of lung fields<br><br>*Excluded*: Patients who needed mechanical ventilation within 12 hours of admission | | | Duration of ICU stay: NR<br><br>Progression to mechanical ventilation: 12/75 in intervention and 15/75 in control; p=0.406<br><br>Duration of mechanical ventilation: NR<br><br>Adverse reactions: NR | |
| Thomas JAMA network open. 2021;4(2):e210369 (7) | Unblinded RCT.<br><br>Date: 27 April 2020 to 14 October 2020<br><br>Setting: multi centre<br><br>Follow-up: unclear | United States of America<br><br>N=214<br>Mean age : 45.2<br>Gender: 82 males, 132 females<br>Severity : NR<br><br>Inclusion criteria:<br>1. New diagnosis in an outpatient setting;<br>2. Aged 18 years or older;<br>3. A menstrual period within the past 30 days or previous sterilization;<br>4. Negative pregnancy test<br><br>Exclusion criteria:<br>1. Hospitalized;<br>2. Resided outside of Ohio or Florida; pregnant;<br>3. Actively lactating<br>4. Advanced chronic kidney disease;<br>5. Liver disease awaiting transplantation;<br>6. History of calcium oxalate kidney stones | 1)Vitamin C + standard of care.<br><br>2) Vitamin C + standard of care<br><br>3) Zinc + standard of care*<br><br>Vitamin C: 8000mg orally per day<br><br>Zinc: 50mg orally per day<br><br>Duration: 10 days | 1) Standard care<br><br>2) Zinc + standard of care<br><br>3) Zinc + Vitamin C + standard of care * | Mortality: 1/48 in in vitamin C arm; 0/58 in zinc arm; 2/58 in vitamin C and zinc arm; 0/48 in standard care arm. p=0.40<br><br>Progression to hospitalization: 2/48 in in vitamin C arm; 0/58 in zinc arm; 7/58 in vitamin C and zinc arm; 3/48 in standard care arm. p=0.50<br><br>Duration of hospitalization: NR<br><br>Progression to ICU admission: NR<br><br>Duration of ICU stay: NR<br><br>Progression to mechanical ventilation: NR<br><br>Duration of mechanical ventilation: NR<br><br>Adverse reactions: 0/50 in SoC; 2/48 in vit C only group; 2/58 in Zn only group | Some concerns (see Appendix 3 for details) |
| Zhang J. Ann. Intensive Care (2021) 11:5 (9) | Single-blinded, placebo-controlled RCT<br><br>Date: 14 February 2020 | China<br><br>N=56 (Intervention: 27, control: 29)<br>Mean age (SD): 66.3 years (11.2) in intervention and 67.0 years (14.3) in control<br>Gender: 66.1% (37/56) male | Vitamin C (high dose) + Standard of care<br><br>24g/day administered 12g IVI 12 hourly (50mL)<br><br>Duration: 7d | Placebo + standard of care<br><br>50 ml of bacteriostatic water infused every 12 h at the same rate as vit C | Failed to reach planned enrolment as numbers declined.<br><br>28-day Mortality: 6/27 in intervention and 10/29 in control; HR (95% CI) 0.5 (0.2 to 1.8) p=0.31; RR 0.64 [0.27, 1.53] | Some concerns (see Appendix 3 for details) |

| Citation | Study design | Population | Intervention | Comparator | Main findings | Risk of Bias |
|---|---|---|---|---|---|---|
| | to 29 March 2020<br><br>Multi (3) centre study<br><br>Follow-up: 28 days | Severity: Mild: n=0 / Moderate: n=0/ Severe & Critical: 56<br><br>Inclusion criteria:<br>1. Age ≥18 and <80 years<br>2. RT-PCR positive for SARS-CoV-2<br>3. Pneumonia confirmed by chest imaging<br>4. Admission to ICU<br>5. Enrolled within 48 hours of ICU admission<br><br>Excluded:<br>1. Allergy to vitamin C, pregnancy or breastfeeding<br>2. Expected survival duration <24 hours<br>3. History of glucose-6-phosphate dehydrogenase deficiency<br>4. End-stage pulmonary disease<br>5. Already enrolled in another clinical trial<br><br>Removed from trial if actual treatment time <3 days due to death or discharge from the ICU. | | Standard of Care: "other general treatments followed the latest COVID-19 guidelines" | Progression to hospitalisation: NR<br><br>Duration of hospitalisation – mean days (SD) : 35.0 (17.0) in intervention and 32.8 (17.0) in control; HR (95% CI) 2.2 (− 7.5, 11.8) p= 0.65<br><br>Progression to ICU admission: NR<br><br>Duration of ICU stay: mean days (SD): 22.9 (14.8) in intervention and 17.8 (13.3) in control; MD (95% CI) 5.0 (− 2.5, 12.7) p=0.20<br><br>Progression to mechanical ventilation: NR<br><br>Duration of mechanical ventilation – median days (IQR): 1.5 [0.0-19.0] in intervention and 6.0 [0.0–16.0] in control; MD (95% CI) − 0.8 (− 6.4, 4.9) p=0.60<br><br>Adverse reactions: NR | |

*RCT: randomized controlled trials; NR: not reported; *this comparison is not reported in this review*

## Table 3. GRADE evidence profile for comparison 1: vitamin C vs placebo/standard of care

**Setting**: in patients and outpatient

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vitamin C | placebo/SoC | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality (follow up: 28 days)** | | | | | | | | | | | |
| 4 | RCTs | serious [a] | not serious | not serious | serious [b] | none | 17/180 (9.4%) | 24/184 (13.0%) | **RR 0.72** (0.41 to 1.26) | **37 fewer per 1,000** (from 77 fewer to 34 more) | ⊕⊕◯◯ LOW |
| **Progression to hospitalisation (follow up: 10 days; assessed with: number of patients requiring hospitalisation)** | | | | | | | | | | | |
| 1 | RCT | serious [a,b] | not serious | not serious | serious [b] | none | 2/48 (4.2%) | 3/50 (6.0%) | **RR 0.68** (0.11 to 4.27) | **19 fewer per 1,000** (from 53 fewer to 196 more) | ⊕⊕◯◯ LOW |
| **Duration of hospitalisation (follow up: 28 days)** | | | | | | | | | | | |
| 3 | RCTs | serious [a] | serious [c] | not serious | serious [b] | none | 132 | 134 | - | MD **1.76 days fewer** (3.88 fewer to 0.35 more) | ⊕◯◯◯ VERY LOW |
| **Progression to ICU admission** | | | | | | | | | | | |
| 0 | | | | | | | No study reported this outcome | | | | - |
| **Duration of ICU stay (follow up: 28 days; assessed with: days)** | | | | | | | | | | | |
| 2 | RCTs | serious [a] | not serious | not serious | serious [b] | none | 57 | 59 | - | MD **1.97 days more** (0.11 more to 3.83 more) | ⊕⊕◯◯ LOW |
| **Progression to mechanical ventilation (assessed with: number requiring intubation/mechanical ventilation)** | | | | | | | | | | | |
| 2 | RCTs | serious [d] | serious [e] | not serious | serious [f] | none | 17/105 (16.2%) | 19/105 (18.1%) | **RR 0.89** (0.49 to 1.62) | **20 fewer per 1,000** (from 92 fewer to 112 more) | ⊕◯◯◯ VERY LOW |
| **Duration of mechanical ventilation (assessed with: median number of days)** | | | | | | | | | | | |
| 1 | RCT | serious [g] | not serious | not serious | serious [h] | none | 27 | 29 | - | median **0.8 days fewer** (6.4 fewer to 4.9 more) | ⊕⊕◯◯ LOW |
| **Adverse events (assessed with: patients experiencing nausea, vomiting, bloating, abdominal discomfort or NR)** | | | | | | | | | | | |
| 1 | RCT | serious [g] | not serious | not serious | very serious [i] | none | 17/43 (39.5%) | 0/46 (0.0%) | **RR 37.39** (2.32 to 603.17) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW |

***CI:*** *Confidence interval; RCT: randomized controlled trial;* ***RR:*** *Risk ratio;* ***MD:*** *Mean difference*

**Explanations**

a. Downgraded by 1 level due to risk of bias: one study at high risk of bias and three studies' risk of bias judged as having some concerns
b. Downgraded by 1 level due to imprecision: overall estimate had wide confidence interval and small sample size
c. Downgraded by 1 level due to inconsistency: two trials with very different point estimates
d. Downgraded by 1 level due to risk of bias: both studies had some concerns
e. Downgraded by 1 level due to inconsistency: the point estimates of the two studies were very different, ranging from a 20% reduction in risk in one and a 25% increase in risk in the other
f. Downgraded due to 1 level due to imprecision: both trials had a small sample size and the 95% CI of the pooled analysis was very wide

g. Downgraded by 1 level due to risk of bias: one study at some concerns of bias
h. Downgraded by 1 level due to imprecision: small sample size and wide confidence interval
i. Downgraded by 2 levels due to imprecision: small sample size and very wide confidence interval

## Table 4. GRADE evidence profile for comparison 2: vitamin C vs zinc

**Setting**: Inpatient

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vitamin C | Zinc | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality (follow up: 28 days)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | very serious [b] | none | 1/48 (2.1%) | 0/58 (0.0%) | **RR 3.61** (0.15 to 86.70) | **0 fewer per 100** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW |
| **Progression to hospitalisation (follow up: 28 days; assessed with: number of participants hospitalised)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [c] | none | 2/48 (4.2%) | 5/58 (8.6%) | **RR 0.48** (0.10 to 2.38) | **4 fewer per 100** (from 8 fewer to 12 more) | ⨁⨁◯◯ LOW |
| **Duration of hospitalisation** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Progression to ICU admission** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Duration of ICU stay** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Progression to mechanical ventilation** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Duration of mechanical ventilation** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Adverse reactions (follow up: 28 days; assessed with: proportion of patients experiencing nausea, diarrhoea, and stomach cramps, other)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [c] | none | 17/43 (39.5%) | 10/54 (18.5%) | **RR 2.13** (1.09 to 4.17) | **209 more per 1,000** (from 17 more to 587 more) | ⨁⨁◯◯ LOW |

***CI:*** *Confidence interval; RCT: randomized controlled trial;* ***RR:*** *Risk ratio*

**Explanations**

a. Downgraded by 1 level due to risk of bias: study classified as having some concerns

b. Downgraded by 2levels due to imprecision: small sample size and very wide confidence interval

c. Downgraded by 1 level due to imprecision: small sample size and wide confidence interval

## Table 5. GRADE evidence profile for comparison 3: ruxolitinib vs vitamin C

**Setting**: inpatient

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Ruxolitinib | vitamin C | Relative (95% CI) | Absolute (95% CI) | |
| **Mortality (follow up: 18 days)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [b] | none | 0/21 (0.0%) | 3/21 (14.3%) | **RR 0.14** (0.01 to 2.61) | **123 fewer per 1,000** (from 141 fewer to 230 more) | ⊕⊕◯◯ LOW |
| **Progression to hospitalisation** | | | | | | | | | | | |
| 0 | | | | | | | The included study did not report this outcome | | | | - |
| **Duration of hospitalisation (assessed with: median number of days)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [b] | none | One trial (Cao 2021) reported a similar number of days of hospitalisation in the group receiving ruxolitinib and in the group receiving vitamin C (median (IQR) 17 (11-21) vs 16 (11-20), p=0.94 | | | | ⊕⊕◯◯ LOW |
| **Progression to ICU admission** | | | | | | | | | | | |
| | | | | | | | The included study did not report this outcome | | | | - |
| **Duration of ICU stay** | | | | | | | | | | | |
| | | | | | | | The included study did not report this outcome | | | | - |
| **Progression to mechanical ventilation** | | | | | | | | | | | |
| | | | | | | | The included study did not report this outcome | | | | - |
| **Duration of mechanical ventilation** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [b] | none | One trial (Cao et al., 2020) reported that patients in the ruxolitinib spent 0 days on invasive mechanical ventilation compared to a median of 5 days (IQR 2-8) among those in the vitamin C group | | | | ⊕⊕◯◯ LOW |
| **Adverse reactions (follow up: 28 days; assessed with: participants experiencing adverse events of any grade)** | | | | | | | | | | | |
| 1 | RCT | serious [a] | not serious | not serious | serious [b] | none | 7/20 (35.0%) | 6/21 (28.6%) | **RR 1.23** (0.50 to 3.02) | **66 more per 1,000** (from 143 fewer to 577 more) | ⊕⊕◯◯ LOW |

***CI:*** *Confidence interval; RCT: randomized controlled trial;* ***RR:*** *Risk ratio*

**Explanations**

a. Downgraded by 1 level due to risk of bias: one study at high overall risk of bias

b. Downgraded by 1 level due to imprecision: small sample size and very wide confidence interval

## Appendix 1: Evidence to decision framework

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| EVIDENCE OF BENEFIT | **What is the size of the effect for beneficial outcomes?**<br>Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X] | The available evidence demonstrates no benefit from vitamin C for the management of COVID-19 compared to placebo, zinc or Ruxolitinib, based on low certainty of evidence.<br>***Mortality D28:*** (vitamin C vs placebo)<br>• RR 0.72 (95% CI 0.41 to 1.26), low certainty<br>***Progression to hospitalisation:*** (vitamin C vs placebo)<br>• RR 0.68 (95% CI 0.11 to 4.27),, very low certainty |
| EVIDENCE OF HARMS | **What is the size of the effect for harmful outcomes?**<br>Large [ ] Moderate [ ] Small [X] None [ ] | The evidence demonstrates some minor harms associated with vitamin C for the management of COVID-19, very low certainty of evidence.<br>***Adverse events:*** (vitamin C vs placebo)<br>• RR 37.39 (95% CI 2.32 to 603.17), low certainty |
| BENEFITS & HARMS | **Do the desirable effects outweigh the undesirable harms?**<br>Favours intervention [ ] Favours control [X] Intervention = Control *or* Uncertain [ ] | Vitamin C compared to placebo was shown to be associated with more adverse events, with uncertain benefit for mortality and prevention of hospitalisation outcomes. |
| QUALITY OF EVIDENCE | **What is the certainty/quality of evidence?**<br>High [ ] Moderate [ ] Low [X] Very low [ ]<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | Evidence is of low to very low certainty - see above. |
| FEASABILITY | **Is implementation of this recommendation feasible?**<br>Yes [ ] No [X] Uncertain [ ] | Vitamin C (oral or injection), not part of a multi-component preparation, is not currently available on contract in the public sector. |
| RESOURCE USE | **How large are the resource requirements?**<br>More intensive [X] Less intensive [ ] Uncertain [ ] | **Price of medicines:**<br>**Medicine** / **Public sector price*** / **Private sector price****<br>Vitamin C, 100mg/ 5ml injection / R 14.47* / n/a<br>Vitamin C, oral 500mg, 300 tablets / n/a / R144.00<br>*Buy-out price sourced from Western Cape DoH, 24 May 2021 (Data on file)<br>**Clicks vitamin C tablets 500mg , 300 tabs – price accessed 24 May 2021. https://clicks.co.za/clicks_vitamin-c-300-tablets/p/109743 |
| VALUES, PREFERENCES, ACCEPTABILITY | **Is there important uncertainty or variability about how much people value the options?**<br>Minor [ ] Major [ ] Uncertain [X]<br>**Is the option acceptable to key stakeholders?**<br>Yes [ ] No [ ] Uncertain [X] | No survey data could be sourced, but the Committee was of the opinion that prescribers and patients would consider vitamin C acceptable if it was found to be beneficial. |
| EQUITY | **Would there be an impact on health inequity?**<br>Yes [X] No [ ] Uncertain [ ] | As single-component vitamin C (injection or oral formulations) is not nationally accessible in the public sector, access would be inequitable. |

## Appendix 2: Search strategy

**Database: Epistemonikos (using the COVID-19 specific interface: L·OVE Platform (https://app.iloveevidence.com/)**

*Search strategy:* using their curated interface for any COVID-19 studies; *Type of question:* any treatment or prevention; *Intervention:* vitamin C

*Output:* 10 systematic reviews, 63 randomised trials (1 duplicate)

*Date: 23 April 2021*

**Database Cochrane COVID-19 study register (**https://covid-19.cochrane.org/)

*Search strategy:* "vitamin c" OR "ascorbic acid"

*Output:* 149 studies *(*193 records; 39 duplicates)

*Date:* 23 April 2021

**Database: PubMed**

*Search strategy:* see table below

*Output:* 9 records (7 duplicates)

*Date:* 26 April 2021

| Search | Query | Results |
|---|---|---|
| #6 | **Search:** (#1 AND #2) NOT (animals[mh] NOT humans[mh]) **Filters:** Randomized Controlled Trial, Systematic Review **Sort by:** Most Recent | 9 |
| #4 | **Search:** (#1 AND #2) NOT (animals[mh] NOT humans[mh]) **Sort by:** Most Recent | 178 |
| #3 | **Search:** #1 AND #2 **Sort by:** Most Recent | 180 |
| #2 | **Search:** ascorbic acid[mh] OR "ascorbic acid"[tiab] OR "vitamin C"[tiab] OR "vit C"[tiab] **Sort by:** Most Recent | 67,112 |
| #1 | Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus*[tiab] OR COVID-19[mh] OR covid-19[tiab] OR covid19[tiab] OR covid 2019[tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2[tiab] OR SARS-CoV2[tiab] OR SARSCoV2[tiab] OR SARsCov-2[tiab] OR SARS-coronavirus*[tiab] OR severe acute respiratory syndrome coronavirus 2[nm] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR nCov2019[tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov[tiab] OR ncov*[tiab] **Sort by:** Most Recent | 137,330 |

**Database: Living mapping and living systematic review of Covid-19 studies (www.covid-nma.com)**

**Reviewed ongoing trials and living SR data,** https://covid-nma.com/networks/

Output: Five eligible studies (4 duplicates) and 39 ongoing studies

*Date:* **12 May 2021**

## Appendix 3. Risk of bias assessments

### 3.1 Cao 2021(8)

| Bias | Author's judgement | Support for judgement |
|---|---|---|
| Randomization |  Low | Quote: "The enrolled patients were randomly allocated into two groups (1:1 allocation ratio) by an independent statistician using permuted blocks of 4 for all sites. The whole process of randomization was masked to all treating physicians. Patient unique identification number and treatment allocation codes were provided by a clinical research associate in sequentially numbered opaque envelopes."<br>Comment: The allocation sequence was concealed. |
| Deviations from intervention |  Low | Comment: participants and staff were blinded except for the treating physicians. There was a slight imbalance in the receipt of biologic co-interventions (7 vs 11 participants in the treatment and the control arm, respectively). |
| Missing outcome data |  High | Comment: 43 patients randomized; 41 patients analyzed.<br>1 patient excluded due to humoral immune deficiency post CAR T therapy and 1 patient withdrew consent.<br>For outcome time to viral negative conversion, 17 participants analyzed; the remaining participants tested negative at baseline.<br>Missingness due to documented reasons unrelated to the outcome.<br>Risk assessed to be low for the outcomes: Mortality. Time to death. Time to viral negative conversion. Incidence of clinical improvement. Time to clinical improvement. Adverse events. Serious adverse events.<br>For WHO score ≥6 and WHO score ≥7, 38 participants analyzed at day 28 (retrieved from contact with authors).<br>Reason for missingness unclear. It could depend on its true value but there is no information.<br>Risk assessed to be high for outcomes: WHO score 6 and above. WHO score 7 and above. |
| Measurement of the outcome |  Some concerns | Comment: No information on blinding of outcome assessors<br>Mortality and viral negative conversion are observer-reported outcomes not involving judgement. For WHO score 7 and above, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment.<br>Risk assessed to be low for the outcomes: Mortality. Time to death. WHO score 7 and above. Time to viral negative conversion.<br>Clinical improvement (defined as 2-point improvement on scale) and WHO score 6 and above requires clinical judgement and could be affected by knowledge of intervention receipt. Also, the authors reported on adverse events and serious adverse events that may contain both clinically- and laboratory-detected outcomes. All these outcomes can |

| | | |
|---|---|---|
| | | be influenced by knowledge of the intervention assignment, but is not likely in the context of the pandemic.<br>Risk assessed to be some concerns for the outcomes: Incidence of clinical improvement. Time to clinical improvement. WHO score 6 and above. Adverse events. Serious adverse events. |
| Selection of the reported results | Some concerns | Comment: The protocol was available but did not provide enough information about the planned statistical analysis. The statistical analysis plan was not available.<br>Risk assessed to be some concerns for the outcomes: Mortality. Clinical improvement incidence. Time to clinical improvement. Time to viral negative conversion. WHO score 6 and above. WHO score 7 and above. Adverse events. Serious adverse events. |
| Overall risk of bias | Some concerns | |

## 3.2 JamaliMoghadamSiahkali S 2021(11)

| **Bias** | **Author's judgement** | **Support for judgement** |
|---|---|---|
| Randomization | Some concerns | Quote: "The patients were divided into two subgroups equally by block randomization."<br>Comment: Allocation sequence random. No information on allocation concealment. |
| Deviations from intervention | Some concerns | Quote: "Open label and nonblinded study"<br>Comment: Unblinded study.<br>No participant cross-over.<br>Insufficient information on administration of co-interventions of interest: Biologics and corticosteroids use reported, but not by study arm. Antivirals were reported and were balanced across groups. Overall, little to no information on deviations that arose due to the trial context.<br>Data were analyzed using appropriately to estimate the effect of assignment to intervention; participants analyzed according to their randomized groups. |

| | | |
|---|---|---|
| Missing outcome data | Low* | No attrition reported; all patients randomised were analysed. |
| Measurement of the outcome | Low* | All outcomes probably measured appropriately and outcomes are derived from observation and hospital records so less subjective to bias. |
| Selection of the reported results | Some concerns | The information in the trial registry differs slightly from the published paper. |
| Overall risk of bias | Some concerns | |

## 3.3 Kumari 2020(10)

| **Bias** | **Author's judgement** | **Support for judgement** |
|---|---|---|
| Randomization | Some concerns | Quote: "Patients were randomized to the interventional arm or placebo arm using a randomizer software"<br>Comment: Allocation sequence random. No information on allocation concealment. |
| Deviations from intervention | Some concerns | Quote: “open-label RCT”<br>Comment: Unblinded study.<br>No participant cross-over.<br>No information on administration of co-interventions of interest: antivirals and biologics. Corticosteroids were administered and were reported to be "comparable between both groups", however, numbers were not reported. Hence no information on deviations that arose due to the trial context. |

| | | |
|---|---|---|
| | | Data were analyzed appropriately to estimate the effect of assignment to intervention; participants analyzed according to their randomized groups. |
| Missing outcome data |  Low | All patients randomised were analysed. No attrition. |
| Measurement of the outcome |  Low | All outcomes probably measured appropriately. |
| Selection of the reported results |  Some concerns | There is no available protocol or trial registration record. |
| Overall risk of bias |  Some concerns | |

## 3.4 Thomas 2021(7)

| **Bias** | **Author's judgement** | **Support for judgement** |
|---|---|---|

| | | |
|---|---|---|
| Randomization |  Low | Quote: "The randomization grid was designed via the REDCap database and based on 25% of anticipated enrolled patients in each of the 4 groups. An automatically created link in REDCap randomized the patient to the supplement group based on the randomization grid."<br>Comment: Allocation sequence random. Allocation sequence concealed. |
| Deviations from intervention |  Some concerns | Quote: "Open-label"<br>Comment: Unblinded study (participants and personnel/carers).<br>Deviations from intended intervention arising because of the study context:<br>No information on participant cross-over.<br>No information on co-interventions of interest: antivirals and biologics. Corticosteroids were reported.<br>Hence, no information on whether deviations arose because of the trial context.<br>/Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.<br>Risk assessed to be some concerns for the outcomes: Mortality (D28). Adverse events. |
| Missing outcome data |  Some concerns | Comment: 214 participants randomized; 214 participants analyzed for mortality outcome; 196 patients analyzed for adverse events.<br>Data available for all or nearly all participants randomized for mortality.<br>Risk assessed to be low for the outcome: Mortality (D28).<br><br>Data not available for all or nearly all participants randomized for adverse events.<br>Reasons for missing data: not reported.<br>No information on whether missingness could depend on the true value of the outcome.<br>Not likely that missingness depended on the true value of the outcome (equal proportion of missing data among arms).<br>Risk assessed to be some concerns for the outcome: Adverse events. |
| Measurement of the outcome |  Some concerns | Comment: Method of measuring the outcome probably appropriate.<br>Measurement or ascertainment of outcome probably does not differ between groups.<br>Mortality is an observer-reported outcome not involving judgement.<br>Risk assessed to be low for the outcome: Mortality (D28).<br><br>The authors reported on adverse events that contain clinically-detected events. All these outcomes can be influenced by knowledge of the intervention assignment, but is not likely in the context of the |

| | | |
|---|---|---|
| | | pandemic.<br>Risk assessed to be some concerns for the outcome: Adverse events |
| Selection of the reported results | Some concerns | Comment: Protocol & statistical analytical plan & registry available:<br>Adverse events were pre-specified. Mortality outcome was not pre-specified, however, we do not consider the reporting of this outcome to be selective since mortality should be reported even if not planned.<br>Results were probably not selected from multiple outcome measurements or analyses of the data.<br>Trial analyzed as pre-specified.<br>Risk assessed to be low for the outcomes: Mortality (D28). Adverse events. |
| Overall risk of bias | Some concern | Some concerns in several domains |

## 3.5 Zhang 2021(9)

| **Bias** | **Author's judgement** | **Support for judgement** |
|---|---|---|
| Randomization | Low | Quote: "Each ICU was assigned with an independent random numeric table generated by Microsoft Excel 2019 by the primary investigator alone. Each table had equal numbers of 1 and 2, which represented the placebo group (bacteriostatic water infusion) and treatment group (HDIVC), respectively. The generated random list was stored by the principal investigator who was not involved in the treatment of patients and hidden to the other investigators. When a patient was transferred to the ICU and met the enrolment criteria, the clinician on duty would inform the principal investigator and obtain a number from the list. Then, participants were enrolled in the corresponding group according to the chronological order of ICU recruitment. The grouping and intervention were unknown to the participants and investigators who were responsible for data collection and statistical analysis"<br>Comment: Allocation sequence random. Allocation sequence probably concealed. |

| | | |
|---|---|---|
| Deviations from intervention |  Some concerns | Quote: "The study is unblinded for dosing nurses, attending physicians and investigators in charge of enrolling participants, but blinding will be maintained for patients and all other members of the clinical and research team, such as statistical staff, to minimise bias."<br>Comment: Participants blinded. Personnel/carers unblinded.<br>Deviations from intended intervention arising because of the study context:<br>No participant cross over.<br>No information on administration of co-interventions of interest: corticosteroids, antivirals and biologics.<br>Hence, no information on whether deviations arose because of the trial context.<br>Data for the outcome were analyzed using intention-to-treat analysis. This method was considered appropriate to estimate the effect of assignment to intervention.<br>Risk assessed to be some concerns for the outcomes: Mortality (D28). Time to death. |
| Missing outcome data |  Low | Comment: 56 participants randomized, 56 participants analyzed.<br>Data available for all or nearly all participants randomized.<br>Risk assessed to be low for outcomes: Mortality (D28). Time to death. |
| Measurement of the outcome |  Low | Comment: Method of measuring the outcome probably appropriate.<br>Measurement or ascertainment of outcome probably does not differ between groups.<br>Unblinded study (outcome assessor).<br>Mortality is an observer-reported outcome not involving judgement.<br>Risk assessed to be low for outcomes: Mortality (D28). Time to death. |
| Selection of the reported results |  Low | Comment: The protocol, statistical analysis plan and registry were available. The original February 8th, 2020 version of the registry was utilized as this was considered to be acceptable for assessing pre-specification of outcomes and selection of reported result (study start date February 2nd, 2020).<br>Mortality outcome was pre-specified.<br>Result was not selected from multiple outcome measurements or analyses of the data.<br>Trial analyzed as pre-specified.<br>Risk assessed to be low for the outcomes: Mortality (D28).<br><br>Time to death was not pre-specified.<br>No information on whether the result was selected from multiple outcome measurements or analyses of the data. |

| | | |
|---|---|---|
| | | Trial probably not analyzed as pre-specified.<br>Risk assessed to be some concerns for the outcome: Time to death. |
| Overall risk of bias | <br>Some concerns | |

## Appendix 4. Planned and ongoing studies (source: www.covid-nma.com 12 May 2021)

| N | Treatment (per arm) | Sample size | Severity at enrolment | Sponsor/Funder | Reg. number |
|---|---|---|---|---|---|
| 1 | (1) Vitamin C vs (2) Placebo | 140 | Severe | ZhiYong Peng | NCT04264533 |
| 2 | (1) Vitamin C vs (2) Placebo | 800 | Severe | Universitâ—Ž de Sherbrooke | NCT03680274 |
| 3 | (1) Chloroquine vs (2) Vitamin C vs (3) Placebo | 1020 | Health workers | Government body - Defence Materiel Technology Centre (DMTC) | ACTRN12620000417987 |
| 4 | (1) Hydroxychloroquine vs (2) Vitamin C | 1250 | Mild | Providence Health & Services | NCT04334967 |
| 5 | (1) Vitamin C vs (2) Placebo | 110 | No restriction on type of patients | Tehran University of Medical Sciences | IRCT20200411047025N1 |
| 6 | (1) Vitamin C vs (2) Placebo | 40 | Moderate | Abadan University of Medical Sciences | IRCT20200324046850N5 |
| 7 | (1) Vitamin C vs (2) Placebo | 60 | Moderate/severe | Tehran University of Medical Sciences | IRCT20190917044805N2 |
| 8 | (1) Vitamin C vs (2) Placebo | 200 | Severe | Virginia Commonwealth University | NCT04344184 |
| 9 | (1) Chloroquine vs (2) Vitamin C | 400 | Close contacts to covid patients | Health Systems Research Institute (HSRI) | TCTR20200404004 |
| 10 | (1) Hydroxychloroquine vs (2) Vitamin C | 1212 | Health workers | Stony Brook University | NCT04347889 |
| 11 | (1) Methylene blue + vitamin C + N-acetyl cysteine vs (2) Standard of care | 20 | Critical | Mashhad University of Medical Sciences | NCT04370288 |
| 12 | (1) Vitamin C vs (2) Standard of care | 66 | Moderate | Thomas Jefferson University | NCT04363216 |
| 13 | (1) Hydroxychloroquine + azithromycin + vitamin D3/B12 + vitamin C + zinc vs (2) Hydroxychloroquine + azithromycin + vitamin D3/B12 + zinc | 200 | No restriction on type of patients | AProf Dr Karin Ried | ACTRN12620000557932 |
| 14 | (1) Artemisinin + curcumin + frankincense + vitamin C vs (2) Placebo | 50 | Moderate | MGC Pharmaceuticals d.o.o | NCT04382040 |
| 15 | (1) Vitamin C vs (2) Vitamin D vs (3) Standard of care | 30 | No restriction on type of patients | Sabzevar University of Medical Sciences | IRCT20140305016852N4 |
| 16 | (1) Azithromycin + doxycycline + vitamin C + metformin vs (2) Standard of care | 40 | Mild/moderate | Kermanshah University of Medical Sciences | IRCT20200418047121N1 |
| 17 | (1) Vitamin C vs (2) Standard of care | 200 | No restriction on type of patients | National Institute of Integrative Medicine, Australia | NCT04395768 |
| 18 | (1) Vitamin C vs (2) Placebo | 800 | Moderate/severe/critical | Universitâ—Ž de Sherbrooke | NCT04401150 |
| 19 | (1) Vitamin C vs (2) Placebo | 50 | Severe | Shahid Beheshti University of Medical Sciences | IRCT20200516047468N1 |
| 20 | (1) Melatonin + sulfate + vitamin C vs (2) Standard of care | 30 | Severe | Semnan University of Medical Sciences | IRCT20151228025732N52 |
| 21 | (1) Artesunate vs (2) Artesunate + vitamin C vs (3) Placebo | 60 | Moderate | Malagasy government | PACTR202006899597082 |
| 22 | (1) Hydroxychloroquine vs (2) Povidone-Iodine vs (3) Zinc + vitamin C vs (4) Vitamin C vs (5) Ivermectin | 5000 | Healthy volunteers | National University Hospital, Singapore | NCT04446104 |
| 23 | (1) Vitamin C + vitamin E vs (2) Standard of care | 80 | Severe | Esfahan University of Medical Sciences | IRCT20180425039414N3 |
| 24 | (1) Desferal + vitamin C vs (2) Standard of care | 78 | No restriction on type of patients | Shahid Beheshti University of Medical Sciences | IRCT20190121042444N3 |
| 25 | (1) Melatonin vs (2) Vitamin C vs (3) Placebo | 150 | Mild/moderate | Lancaster General Hospital | NCT04530539 |
| 26 | (1) Unfractioned heparin OR Low molecular weight heparin (LMWH) vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine + lopinavir + ritonavir vs (4) Oseltamivir vs (5) Lopinavir + ritonavir vs (6) Interferon beta-1a vs (7) Convalescent plasma treatment vs (8) Simvastatin vs (9) Anakinra vs (10) Tocilizumab vs (11) Sarilumab vs (12) Hydrocortisone vs (13) Vitamin C vs (14) Ceftriaxone + macrolide vs (15) Levofloxacin OR Moxifloxacin vs (16) Piperacillin-tazobactam + macrolide vs (17) Ceftaroline + macrolide vs (18) Amoxicillin-clavulanate + macrolide vs (19) Standard of care | 1000 | No restriction on type of patients | University Medical Center Utrecht | NCT02735707 |
| 27 | (1) Vitamin C + methylprednisolone vs (2) Standard of care | 40 | Severe/critical | Tabriz University of Medical Sciences | IRCT20190312043030N2 |
| 28 | (1) Centrum adult (under 50) multivitamin vs (2) Zinc + vitamin C/E + copper + beta-carotene | 4500 | Health workers | Mayo Clinic | NCT04551339 |
| 29 | (1) Methylene blue + vitamin C + N-acetyl cysteine vs (2) Standard of care | 80 | Critical | Mashhad University of Medical Sciences | IRCT20191228045924N1 |
| 30 | (1) Vitamin C vs (2) Standard of care | 100 | Mild/moderate | Not reported | CTRI/2020/10/028695 |
| 31 | (1) Artemisinin + vitamin C + noscapine + hesperidin + resveratrol + N-acetylcysteine vs (2) Standard of care | 100 | No restriction on type of patients | Sirjan Faculty of Medical Science | IRCT20181030041504N1 |

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| 32 | (1) Vitamin C vs (2) Placebo | 80 | Moderate/severe | All India Institute Of Medical Sciences, Patna | CTRI/2020/11/029230 |
| 33 | (1) Vitamin C vs (2) Placebo | 15 | Critical | University of Lahore | NCT04682574 |
| 34 | (1) Vitamin C + brewer's yeast vs (2) Standard of care | 50 | Moderate/severe/critical | Tehran University of Medical Sciences | IRCT20201004048923N1 |
| 35 | (1) Vitamin D3 + Vitamin C/Zinc + Vitamin K2/D vs (2) Placebo | 200 | Mild | The Canadian College of Naturopathic Medicine | NCT04780061 |
| 36 | (1) Artemisinin + curcumin + boswellia + vitamin C vs (2) Artemisinin + curcumin + boswellia + vitamin C vs (3) Placebo | 252 | Moderate | MGC Pharmaceuticals d.o.o | NCT04802382 |
| 37 | (1) Ivermectin vs (2) Vitamin C | 50 | Health workers | AIIMS Rishikesh | CTRI/2021/03/031665 |
| 38 | (1) Omega DHA/EPA vs (2) Vitamin C + vitamin B complex + zinc acetate vs (3) Vitamin D vs (4) Omega DHA/EPA vs (5) Vitamin C, Vitamin B complex and Zinc Acetate vs (6) Vitamin D | 3600 | High risk patients | Hospital de la Soledad | NCT04828538 |
| 39 | (1) Vitamin A + Vitamin B + Vitamin C + Vitamin D + Vitamin E vs (2) Standard of care | 135 | Critical | Sabzevar University of Medical Sciences | IRCT20151226025699N5 |

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| First | 28 May 2021 | GR, EVS, SD | Routine use of vitamin C for the treatment of COVID-19 in either ambulatory or hospital settings is not recommended, as there is currently insufficient evidence. |

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