Vitamin C for SARS-CoV-2: a systematic review

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BACKGROUND

Despite limited evidence[1], supportive treatments such as vitamin C are widely used in the prevention and treatment of respiratory infections, including COVID-19. The National Essential Medicines List (NEMLC) Subcommittee on COVID-19 prioritised that the evidence for vitamin C be reviewed to inform treatment guidelines.

OBJECTIVES

To review available evidence from randomised controlled trials (RCTs) to determine the effects of vitamin C on confirmed SARS-CoV-2 infection.

We followed pre-specified methodology outlined in the NEMLC Subcommittee on COVID-19 approved protocol[1].

ELIGIBILITY CRITERIA

Study designs: RCTs

Participants: Patients with confirmed SARS-CoV-2 infection, with no restriction to age, disease severity or setting

Intervention: Vitamin C (with no restriction on dose, frequency or timing)

Comparison: Any control, including standard of care, placebo or 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; and adverse reactions.

SEARCH METHODS

- Three electronic databases searched up to 16 May 2022 – Epistemonikos, Cochrane Library COVID-19 Study Register, and COVID-nma.com Living review database
- No language or date restrictions were applied.

DATA COLLECTION AND ANALYSIS

- One author extracted data from each study, either from the COVID-nma.com Living review database or using the full-text of the paper, and another reviewer checked it.
- Risk of bias was carried out using the Cochrane ROB 2 tool for three key outcomes: mortality, progression to hospitalisation, progression to ICU admission, and adverse reactions.
- We conducted random effects meta-analysis if two or more studies reported the same outcome under the same comparison, and if they were sufficiently homogeneous.
- We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence for the key review outcomes.

SEARCH RESULTS

We included 10 RCTs assessing 1234 patients, mostly in in-patient settings.

Studies were conducted in:

- USA (n=3)
- Iran (n=3)
- China (n=2)
- Pakistan (n=1)
- Turkey (n=1)

Studies assessed Vitamin C **vs.**

- No vitamin C (n=8)
- Zinc (n=1)
- Hydroxychloroquine (HCQ) (n=1)
- Ruxolitinib (n=1)

Vitamin C administration:

- Most intravenously
- Dose range: 200mg to 50 000mg/day
- Duration: 5 to 14 days

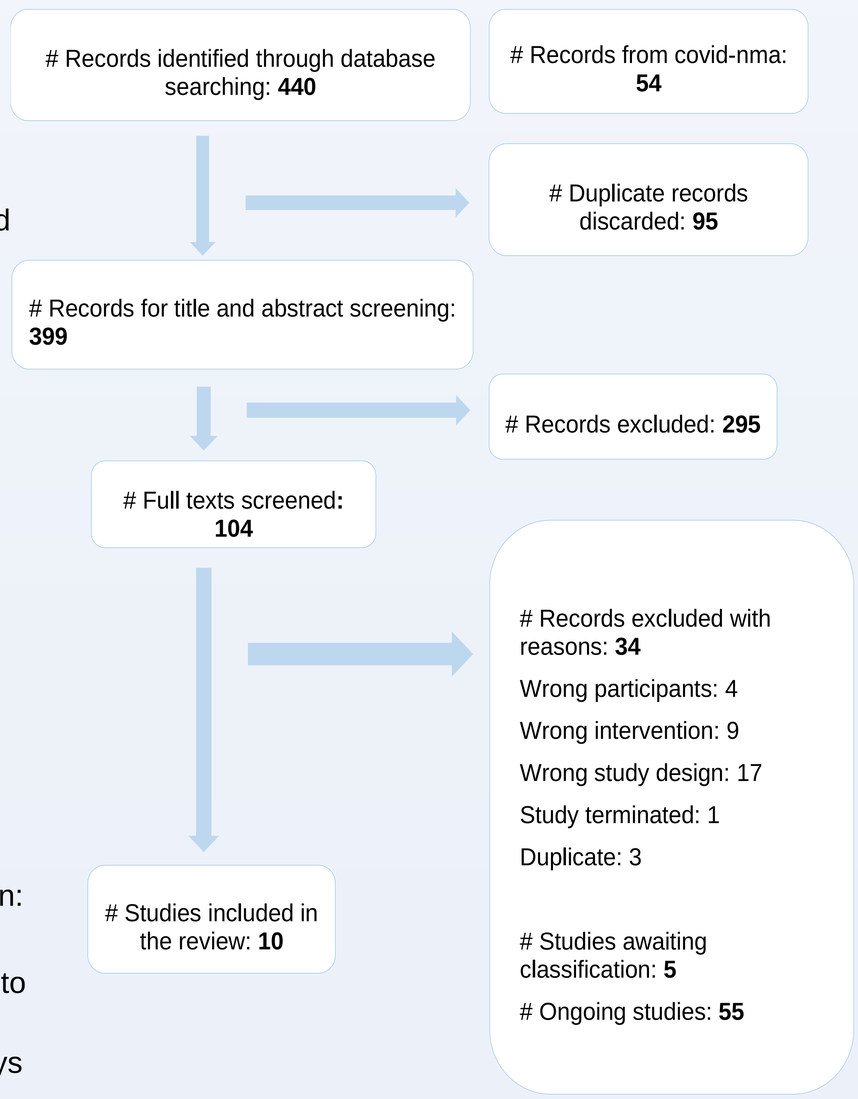


Figure 1. PRISMA flowchart of study selection

EFFECTS OF INTERVENTIONS

VITAMIN C vs. NO VITAMIN C (8 RCTs)

Table 1. GRADE SOF table for comparison: Vitamin C vs. no intervention for SARS-CoV-2 infection

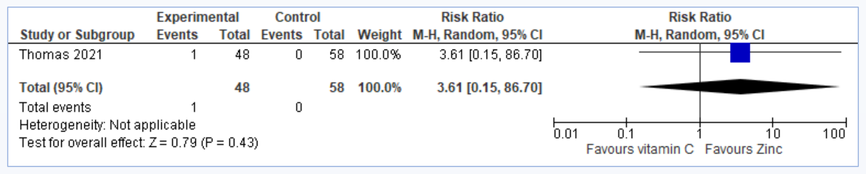
Patient or population: Outpatients and hospitalized adults with SARS-CoV-2 infection
Setting: Healthcare settings in China, USA, Pakistan, Turkey and Iran
Intervention: Vitamin C (mostly high dose and intravenous)
Comparison: no vitamin C (Standard of care provided to both arms)

Outcomes	Anticipated absolute effects* (95% CI) Risk with placebo/SoC	Risk with Vitamin C	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Mortality follow-up: range 6 days to 28 days	108 per 1,000	**102 per 1,000** (48 to 219)	**RR 0.95** (0.45 to 2.04)	508 (6 RCTs)	⨁⨁◯◯ Low[a,b]	Vitamin C may result in little to no difference in mortality.
Progression to hospitalisation follow-up: 10 days	60 per 1,000	**41 per 1,000** (7 to 239)	**RR 0.69** (0.12 to 3.98)	98 (1 RCT)	⨁⨁⨁◯ Moderate[a,b]	Vitamin C likely results in little to no difference in progression to hospitalisation.
Progression to ICU admission	91 per 1,000	**87 per 1,000** (15 to 526)	**HR 0.95** (0.16 to 7.84)	66 (1 RCT)	⨁⨁◯◯ Low[c,d]	Vitamin C may result in little to no difference in progression to ICU admission.
Adverse events assessed with: patients experiencing nausea, vomiting, bloating, abdominal discomfort	29 per 1,000	**251 per 1,000** (6 to 1,000)	**RR 8.54** (0.21 to 353.79)	155 (2 RCTs)	⨁◯◯◯ Very low[c,e,f]	Vitamin C may increase adverse events but the evidence is very uncertain.

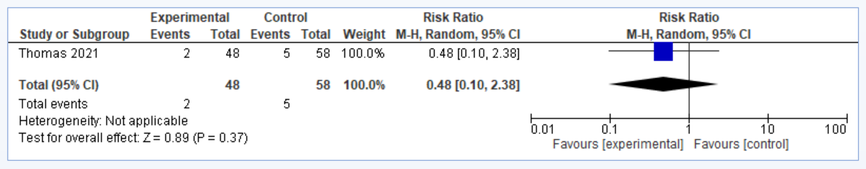
VITAMIN C vs. ZINC (1 RCT)

- The evidence is very uncertain about the effect of vitamin C on mortality
- Low certainty evidence that Vitamin C may
  - result in little to no difference in progression to hospitalization
  - increase adverse reactions (low certainty evidence)
- Progression to ICU admission not reported

Outcome: mortality



Outcome: Progression to hospitalization



Outcome: Adverse events

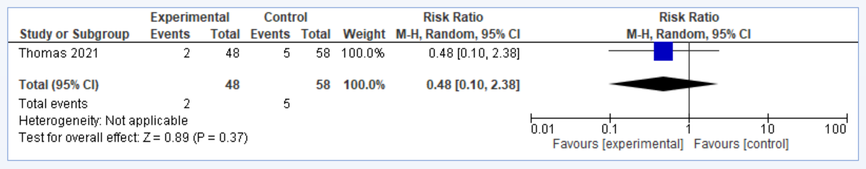


Figure 2. Forest plots of comparison: Vitamin C vs. Zinc

VITAMIN C vs. RUXOLITINIB (1 RCT)

- The evidence is very uncertain about the effect of vitamin C on mortality
- Ruxolitinib may result in little to no difference in adverse reactions (low certainty evidence)
- Progression to hospitalization and to ICU admission not reported

VITAMIN C vs. HYDROXYCHLOROQUINE (1 RCT)

- Moderate certainty evidence that vitamin C likely results in little to no difference to
  - mortality
  - progression to hospitalization
  - adverse reactions
- Progression to ICU not reported

CONCLUSION

Evidence from RCTs indicates that vitamin C, compared to placebo, standard of care, zinc, ruxolitinib, or hydroxychloroquine, has not demonstrated an important reduction in clinically relevant outcomes.

Its use may increase adverse events such as headache, nausea, vomiting, among others when compared to zinc or placebo.

REFERENCES

[1]Fowler A, Truwit JD, Hite RD, et al. 2019. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. Jama, 322, 1261-1270

[2]http://www.health.gov.za/wp-content/uploads/2021/03/NEMLC-Protocol-Template-for-rapid-reviews-of-COVID-19_v2.0_9March2021.pdf