# Therapeutic efficacy of zinc in the treatment of COVID-19 patients: A systematic review

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## Introduction

Novel therapeutic interventions are of utmost importance to alleviate the clinical symptoms caused by inflammation in COVID-19 patients. The beneficial role of zinc has been suggested due to its ability to mitigate the effects of the inflammatory cascade[1,3]. Hence it has been hypothesized that patients with zinc deficiency may benefit symptomatically from treatment with zinc. The primary goal of this systematic review of randomized controlled trials (RCTs) conducted between February and March 2021 is to determine the efficacy of zinc as a treatment for COVID-19 infection[2,4].

## Aims & Objectives

Aim: To gain an understanding of the beneficial effects of zinc treatment in patients with COVID-19.

Objectives:

1. To develop search terms that will gather articles relevant to this study's aim.
2. To screen articles with appropriate inclusion and exclusion criteria.
3. To gather data pertaining to the effects of zinc on symptomatic improvement in patients with COVID-19.
4. To present data in a clinically relevant manner that can be easily accessible to providers in the midst of the pandemic.

## Methods

Using key search words, 178 articles were collected from databases including PubMed, Cochrane, and Embase. Inclusion criteria for screening included randomized controlled trials (RCTs) with COVID-positive patients treated with zinc. Exclusion criteria included articles that were not RCTs, animal studies, zinc used for prevention, and unrelated studies. Screening was performed according to the algorithm shown below, in Figure 1. Then, pertinent information was gathered and prepared in Table. Finally, the data was analyzed and conclusions were drawn.

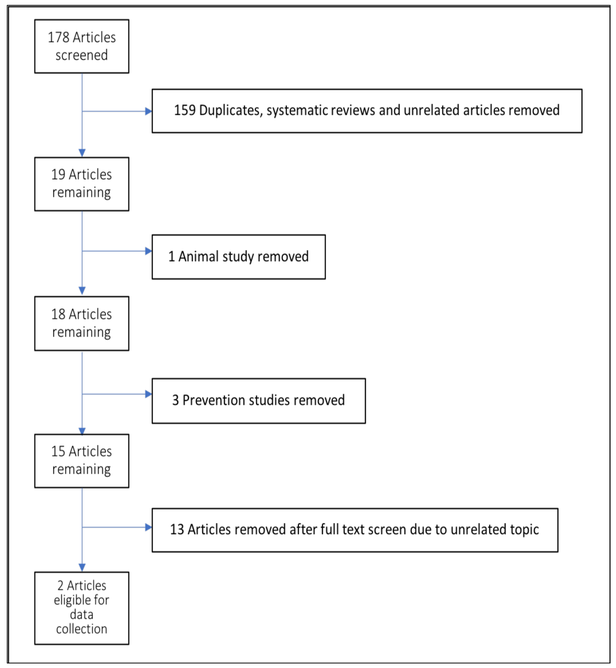


Figure 1 showing the method of screening that occurred.

## Acknowledgements

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## Results

In the first RCT[2], it was shown that hospitalized COVID-19 patients who were treated with IV zinc were successfully treated for their zinc deficiency by day six of hospitalization. However, due to limitations in target enrollment, the primary outcome investigating the reduction in oxygenation in non-ventilated patients and improvement in PaO2/FiO2 in ventilated patients was not assessed. The second RCT[4] revealed that there was no significant difference in the number of days required for patients to reach a 50% reduction in symptoms severity between patients treated with zinc gluconate and placebo.

### Table 1: Summary of Data Collected

| | | |
|---|---|---|
| PMID | 33629384 | 33576820 |
| Title | A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients | 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 |
| Authors | Patel O, Chinni V, El-Khoury J, Perera M, Neto AS, McDonald C, See E, Jones D, Bolton D, Bellomo R, Trubiano J, Ischia J. | Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine ZJ, Mehra R, McWilliams C, Nissen SE, Desai MY. |
| Location | Australia | United States |
| N total | 33 (15 HDIVZn, 18 placebo) | 214 (50 placebo, 48 ascorbic acid, 58 zinc, 58 both treatments) |
| Males | 21 | 82 |
| Females | 12 | 132 |
| Inclusion criteria | Ventilated or non-ventilated, hospitalized COVID-19 patients with SaO2: ≤94% | New COVID-19 diagnosis in outpatient setting, over 18yo, women of childbearing age had to confirm period within past 30 days or have proof of prior sterilization, perimenopausal women had to have negative pregnancy test |
| Exclusion criteria | Oxygen saturation > 94%, eGFR ≤30 mL/min/1.73 m2, kidney or liver transplant, cardiac surgery, placement into palliative care, poor prognosis, short term admission | Hospitalized, outside of Ohio or Florida, pregnant, actively lactating, or had advanced CKD, liver disease awaiting transplantation, or history of calcium oxalate kidney stones |
| Experimental group intervention | Pharmaceutical grade zinc chloride diluted in 250cc normal saline (HDIVZn) at a concentration of 0.5 mg/kg/day infused for 7 days, or until discharge or death | Given over 28 days:<br>Group 1: 8000mg of ascorbic acid<br>Group 2: 50mg zinc<br>Group 3: both therapies |
| Control group intervention | Saline solution infused for 7 days, or until discharge or death | Group 4: standard of care without intervention |
| Adverse effects (AE) | Three HDIVZn patients reported infusion site irritation | Less than 10% of experimental group patients experienced an AE |
| Primary outcome | The primary outcome of this study was to assess whether or not HDIVZn could lower oxygen flow or ventilation requirements to maintain SaO2 > 94%. This could not be assessed due to an inability to reach target enrollment. | Mean number of days (SD) for 50% reduction in symptom severity score:<br>Group 1: 5.5 (3.7) days<br>Group 2: 5.9 (4.9) days<br>Group 3: 5.5 (3.4) days<br>Group 4: 6.7 (4.4) days<br>Overall P-value = 0.45 |
| Secondary outcome | Mean serum zinc levels on Day 6 with cutoff for zinc deficiency being 10.7 umol/L:<br>HDIVZn: 12.5 umol/L<br>Placebo: 8.5 umol/L<br>P-value = < 0.001 | There was no significant difference in the symptom severity score at day 5 between any of the groups. Additionally, there was not a significant difference between the total number of hospitalizations and deaths between the groups. |
| Limitations to study | Reduced hospitalizations secondary to strict public health measures led to an inability to reach target enrollment | This study was stopped in October 2020 due to futility |

## Conclusions

The results do not support the hypothesis that zinc shortens the number of days between COVID-19 symptoms onset and 50% reduction in symptoms[4]. Additionally, more research will be required to investigate whether or not intravenous zinc can effectively decrease the oxygenation and ventilation requirements in COVID-19 patients, as public health measures at the time of the study limited the ability of researchers to reach target enrollment[2]. This systematic review highlights the necessity of well-designed RCTs to increase the quality of evidence.

## References

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3. Shakoor H, Feehan J, Al Dhaheri AS, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?. *Maturitas*. 2021;143:1-9.
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